Methadone Hydrochloride Intensol Oral Concentrate (methadone hydrochloride) dose, i... 1/5/2018

CLASSES
Drugs Used In Opioid Dependence
Opioid Agonists

BOXED WARNING

Angina, bradycardia, cardiac arrhythmias, cardiac disease, coronary artery disease, diabetes mellitus, females, heart failure, hypertension, hypocalcemia, hypokalemia, hypomagnesemia, hypotension, hypovolemia, long QT syndrome, malnutrition, myocardial infarction, orthostatic hypotension, QT prolongation, thyroid disease

Methadone is associated with an increased risk for QT prolongation and torsade de points (TdP). Although the risk of QT prolongation appears to be dose-related, most increases of QT prolongation and torsade de points occurring in patients receiving large doses for pain management (i.e., > 100 mg/day), it is important to note that smaller doses for maintenance of opiate addiction have also been implicated. A public health advisory was issued concerning cardiac-related deaths, which have been reported during initiation of methadone treatment as well as during conversion to methadone from alternative opioids. Extreme caution of treatment in one patient is recommended from one patient to another, and dose titrations. An understanding of methadone pharmacokinetic parameters is critical. In addition to slowing the rate of cardiac repolarization thus shortening the QT interval, methadone may produce cholinergic side effects (by stimulating medullary vagal nuclei) causing bradycardia and inducing the release of histamine causing peripheral vasodilation. Use methadone with extreme caution, if at all, in patients whose ability to maintain blood pressure has not been previously evaluated or in patients whose pressure has already been compromised by hypovolemic, operative, or in patients receiving medications known to cause electrolyte imbalances. Females, elderly patients, patients with diabetes mellitus, thyroid disease, malnutrition, a history of alcohol abuse, or hepatic impairment may also be at increased risk for QT prolongation. A 2009 clinical guideline for cardiac safety with methadone treatment recommends that prescribers: (1.) discuss the risk of arrhythmia with patients; (2.) take a complete cardiac clinical history; (3.) screen patients for QT prolongation with ECG monitoring prior to the initiation of methadone, at 3 months, and annually thereafter; (4.) use the ECG findings to stratify patient risk (i.e., patients with a QTc interval of 451—499 ms should receive more frequent monitoring and discuss the potential risks vs. benefits of treatment, patients with a QTc interval of >= 500 ms should receive intervention to lower cardiac risk either by discontinuing or lowering the methadone dose or by eliminating contributing factors); and (5.) be aware of methadone-drug interactions. Drugs known to prolong the QT interval, potentiate hypokalemia, or reduce methadone elimination should be coadministered with a careful assessment of risks versus benefits.

Alcoholism, depression, substance abuse

Methadone is an opioid agonist and therefore has abuse potential and risk of fatal overdose from respiratory failure. Addiction may occur in patients who obtain methadone illicitly or in those appropriately prescribed the drug. The risk of addiction in any individual is unknown. However, patients with mental illness (e.g., major depression) or a family history of substance abuse (including alcoholism) have an increased risk of opioid abuse. Assess patients for risks of addiction, abuse, or misuse before drug initiation, and monitor patients who receive opioids routinely for development of these behaviors or conditions. A potential risk of abuse should not preclude appropriate pain management in any patient, but requires more intensive counseling and monitoring. Abuse and addiction are separate and distinct from physical dependence and tolerance; patients with addiction may not exhibit tolerance and symptoms of physical dependence. The misuse of methadone by crushing, chewing, snorting, or injecting the dissolved product can result in overdose and death. To discourage abuse, the smallest appropriate quantity of methadone should be dispensed, and proper disposal instructions for unused drug should be given to patients.

Asthma, chronic obstructive pulmonary disease (COPD), coadministration with other CNS depressants, cor pulmonale, hypoxemia, obesity, pulmonary disease, respiratory depression, respiratory insufficiency, scoliosis, sleep apnea, status asthmaticus

Methadone is contraindicated in patients with significant respiratory depression and/or acute or severe bronchial asthma (e.g., status asthmaticus) in unmonitored settings or in the absence of resuscitative equipment. Additionally, avoid coadministration with other CNS depressants when possible as this significantly increases the risk for respiratory depression, low blood pressure, and death. Reserve concomitant use of these drugs for patients in whom alternative treatment options are inadequate. If concomitant use is necessary, use the lowest effective dose and minimum treatment durations possible and monitor patients closely for signs and symptoms of respiratory depression and sedation. Careful monitoring is also required with concomitant use of drugs that may inhibit the metabolism of methadone; an increase in methadone concentrations could cause potentially fatal respiratory depression. The potential risk of serious adverse effects with concomitant use of methadone and other CNS depressants should not preclude the appropriate treatment of opioid addiction with methadone, but requires more intensive counseling and monitoring. Methadone may significantly decrease respiratory drive and cause hyperventilation. Respiratory depression, if left untreated, may cause respiratory arrest and death. Symptoms of respiratory depression include a reduced urge to breathe, a decreased respiratory rate, or deep breaths separated by long pauses (a “sighing” breathing pattern). Serious or fatal respiratory depression can occur at any time during the use of methadone; however, the risk is greatest during the first 24 to 72 hours after therapy initiation or dose titration. It is important to note respiratory depressant effects occur later and persist longer than peak analgesic effects. Extreme caution is recommended during initiation of therapy, conversion from one opioid to another, and dose titrations; dose overestimation may lead to fatal overdose. Deaths have been reported during conversion to methadone from chronic, high-dose opioid treatment and during initiation of methadone treatment of addiction in patients previously abusing high doses of opioid agonists. Of healthcare professionals who are knowledgeable about methadone pharmacokinetics and pharmacodynamics should prescribe the drug, particularly during conversions to methadone from other opioids and in the use of methadone for chronic pain. Methadone should be reserved for patients in whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Do not use as a “prn” or “as needed” analgesic, for acute pain, or as a painkiller to replace an opioid. The use of methadone by crushing, chewing, snorting, or injecting the dissolved product can result in overdose and death. To discourage abuse, the smallest appropriate quantity of methadone should be dispensed, and proper disposal instructions for unused drug should be given to patients.

http://www.pdr.net/drug-summary/Methadone-Hydrochloride-Intensol-Oral-Concentrate-m...
even usual therapeutic doses may decrease respiratory drive and cause apnea in these patient populations. Extreme caution should also be used in patients with chronic asthma, kyphoscoliosis (a type of scoliosis), hypoxemia, or paralysis of the phrenic nerve. Patients with advanced age, cachexia, debilitation, severe obesity, or sleep apnea are at an increased risk for the development of respiratory depression associated with methadone; monitor these patients closely. Respiratory depression may persist for a significant period of time following discontinuation of methadone and patients require close monitoring until their respiratory rate has stabilized. Management of respiratory depression should include observation, necessary supportive measures, and careful use of an opioid antagonist (e.g., naloxone) if appropriate.

**Labor, neonatal opioid withdrawal syndrome, obstetric delivery, pregnancy**

There are no adequate and well-controlled studies with methadone in pregnant women. Use methadone for severe pain during pregnancy only if the potential benefit justifies the potential risk to the fetus. Medical withdrawal of pregnant, opioid-dependent women from methadone is not recommended. When methadone is used during pregnancy as part of a supervised, therapeutic regimen, it is unlikely to pose substantial teratogenic risk. Changes in methadone maintenance programs may reduce incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes and risk of continued or relapsing illicit opioid use. Consider these risks in pregnant women treated with methadone for maintenance treatment of opioid addiction. No increased risk of miscarriage in the second trimester or premature delivery in the third trimester was noted by a retrospective review of data from 101 opioid-dependent women. Benefits of methadone therapy during pregnancy include assisting women staying free of heroin or other opioids, increasing prenatal care, lessening the possibility of fetal death, and reducing the risk of HIV and hepatitis infection. Infants born to narcotic-addicted women treated with methadone during pregnancy have been found to have decreased fetal growth with reduced birth weight, length, or head circumference. The growth deficit does not appear to persist into later childhood. Children born to mothers who received methadone during pregnancy demonstrate mild but persistent performance deficits on psychometric and behavioral tests and may have an increased risk of visual development anomalies. Administration of methadone to pregnant animals during organogenesis through lactation resulted in decreased litter size, increased pup mortality, decreased pup body weights, developmental delays, and long-term biochemical changes in the brain which correlate with altered behavioral responses at exposures comparable to and less than the human daily dose of 120 mg. Methadone clearance may be increased during pregnancy. The methadone dose or interval may need to be increased as the pregnancy progresses due to changes in plasma volume and renal blood flow; due to an increased metabolism of methadone during pregnancy, close monitoring of pregnant women is recommended. Methadone is not recommended for analgesia during labor and obstetric delivery due to its long duration of action and potential for respiratory depression in the newborn. Women maintained on methadone require appropriate obstetric pain management, as methadone maintenance does not provide analgesia. Narcotics with mixed agonist/antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal. Prolonged maternal use of opioids, such as methadone, during pregnancy may result in neonatal opioid withdrawal syndrome (NOWS). This syndrome can be life-threatening. Severe symptoms may require pharmacologic therapy managed by clinicians familiar with neonatal opioid withdrawal. Monitor the neonate for withdrawal symptoms including irritability, hyperactivity, abnormal sleep pattern, high-pitched crying, tremor, vomiting, diarrhea, and failure to gain weight. Onset, duration, and severity of opioid withdrawal may vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination by the newborn.

**Accidental exposure, opioid-naive patients, potential for overdose or poisoning**

All forms of methadone have the potential for overdose or poisoning. Methadone is a long-acting opioid that should only be used as an analgesic in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment. When used for analgesia, methadone should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release, short-acting opioids) are ineffective, not tolerated, or would otherwise be inadequate to provide sufficient pain management. Due to the risk of respiratory depression, use methadone with caution in opioid-naive patients. Patients tolerant to other opioids may be incompletely tolerant to methadone; use caution when converting patients from other opioids to methadone. Special care should be taken to keep it out of the reach of patients for whom it was not prescribed, particularly pediatric patients, as accidental exposure may cause fatal overdose.

**Intravenous administration**

Methadone oral concentrate solution is for oral administration only; do not give via intravenous administration.

**Requires an experienced clinician**

Methadone therapy requires an experienced clinician when used for the treatment of opioid addiction in detoxification or maintenance programs. Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). An exception may be made for the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of their stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

**DEA CLASS**

Rx, schedule II

**DESCRIPTION**

A phenylethylamine synthetic opiate agonist; is structurally unrelated to morphine

Used in medically supervised opiate withdrawal and maintenance programs; effective for the relief of severe or chronic pain

For the treatment of opiate dependence, prescriber must register and comply with the Narcotic Addict Treatment Act (NATA) [21USC 823(g)]

**COMMON BRAND NAMES**

Dolophine, Methadose

**HOW SUPPLIED**

Dolophine/Methadone Hydrochloride Intramuscular Inj Sol: 1mL, 10mg
Dolophine/Methadone Hydrochloride Intravenous Inj Sol: 1mL, 10mg
Dolophine/Methadone Hydrochloride Subcutaneous Inj Sol: 1mL, 10mg
Dolophine/Methadone Hydrochloride/Methadose Oral Tab: 5mg, 10mg, 40mg
Methadone Hydrochloride/Methadose Oral Sol: 1mL, 5mL, 5mg, 10mg
Methadone Hydrochloride/Methadose Oral Tab for Susp: 40mg

http://www.pdr.net/drug-summary/Methadone-Hydrochloride-Intensol-Oral-Concentrate-... 1/5/2018
**DOSAGE & INDICATIONS**

For the treatment of opiate agonist withdrawal during detoxification treatment.

**NOTE:** Patients need to show withdrawal symptoms but no signs of sedation or intoxication.

**NOTE:** For the treatment of narcotic addiction in detoxification programs, methadone may be dispensed only by pharmacies and clinics approved by the FDA and state authorities according to treatment requirements stipulated in the Federal Methadone Regulations.

**NOTE:** Detoxification shall not exceed 21 days or be repeated earlier than 4 weeks after completion of a preceding course.

**NOTE:** Loss of opioid tolerance should be considered for a patient who has not taken opioids for more than 5 days.

**Withdrawal of methadone following detoxification treatment.**

**Oral dosage**

**Adults**

Medical withdrawal from methadone should be done in decrements as tolerated by the patient on a daily basis or at 2-day intervals. The dose should be sufficient to keep withdrawal symptoms at a tolerable level. Many hospitalized patients may tolerate a daily dosage reduction of 20%. In ambulatory patients, a somewhat slower schedule may be required. Patients should be allowed to discontinue withdrawal at anytime, for any reason, without feelings of guilt. They should then be placed into a methadone maintenance program at an appropriate dose. Any decrease in methadone dosage could precipitate a relapse to drug use. Methadone use is preferable to the use of illegal street drugs.

**Pregnant women**

Medical withdrawal of methadone maintenance is generally not recommended during pregnancy. If required, methadone withdrawal is done in decrements of 2 to 2.5 mg every 7 to 10 days. This should be done in conjunction with an obstetrician who can monitor the effects on the fetus.

**Oral dosage**

**Adults, including pregnant women**

20 to 30 mg PO initially unless low opioid tolerance is expected; use a lower initial dose for these patients. Additional doses of 5 to 10 mg of methadone PO may be given 2 to 4 hours after the initial dose if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily oral dose on Day 1 should not ordinarily exceed 40 mg. Dosage adjustments on subsequent days should be based on withdrawal symptom control at the time of expected peak methadone activity (2 to 4 hours after dosing). Due to the extended half-life of methadone, it may take up to 5 days to achieve a steady-state dose that controls symptoms of opiate withdrawal. Prior to achieving steady state, adequate total daily doses may not hold patients for a full 24 hours. Deaths have occurred in early treatment due to the cumulative effects of methadone. The stabilizing dose is continued for 2 to 3 days.

**Intravenous, Subcutaneous or Intramuscular dosage**

**NOTE:** Intravenous methadone should only be used on a temporary basis for patients who cannot take oral medication, such as hospitalized inpatients.

**Adults**

Initially, use a 2:1 dose ratio (e.g., 10 mg oral methadone to 5 mg parenteral methadone) when converting from oral to parenteral methadone. Conservative dose selection is recommended for opioid-tolerant patients due to dose conversion ratio uncertainty and incomplete cross-tolerance.

**For the maintenance treatment of opiate agonist dependence.**

**For the management of iatrogenic opiate agonist dependence in pediatric patients†.**

**Oral dosage**

**Neonates†, Infants†, Children†, and Adolescents†**

Initially, 0.05 to 0.1 mg/kg PO every 6 hours. Titrate by 0.05 mg/kg/dose until symptoms are controlled. Once symptoms are controlled, taper dosage incrementally (10% to 20% of initial dose every 1 to 2 days), lengthening interval (e.g., every 12 to 24 hours) prior to discontinuation; most patients can be tapered to off within 10 days. Dosage, interval, length of treatment, and taper schedule must be individualized based on the patient's previous opioid dose and symptoms of withdrawal. Various dosing regimens have been reported and some practitioners suggest the daily dosage of opioid infusion (e.g., fentanyl) be converted to an equianalgesic daily dosage of methadone, however this may lead to unnecessarily high doses. Monitor patients frequently for CNS and respiratory depression, particularly during the first 24 to 72 hours after initiation or dose escalation.

**Oral dosage**

**Adults**

Following induction therapy and detoxification, titrate patients to a dose that prevents opioid withdrawal symptoms for a full 24 hours, reduces drug craving, and blocks/attenuates the euphoric effects of self-administered opioids, ensuring that the patient is tolerant to the sedative effects of methadone. Clinical stability is usually achieved at doses between 80 to 120 mg/day PO. Pregnant women may require dose adjustments during pregnancy to provide effective dosing. MAINTENANCE: In the U.S., administer in accordance with the Code of Federal Regulations (CFR), Title 42, Section 8.12. Continue as long as desired by the patient and continued benefit is derived; maintenance reductions. A relapse to illicit drug use is a risk upon discontinuation.

**Intravenous, Subcutaneous, or Intramuscular dosage**

**Adults**

Initially, use a 2:1 dose ratio (e.g., 10 mg oral methadone to 5 mg parenteral methadone) when converting from oral to parenteral methadone. Conservative dose selection is recommended for opioid-tolerant patients due to dose conversion ratio uncertainty and incomplete cross-tolerance. NOTE: Intravenous methadone should only be used on a temporary basis for patients who cannot take oral medication, such as hospitalized inpatients. Injectable methadone is not approved for the outpatient treatment of opioid dependence.
For the treatment of moderate pain or severe pain.


NOTE: Methadone tablets or oral solution should be reserved for patients in whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would otherwise provide inadequate pain management. Discontinue all other around-the-clock opioid drugs upon initiation of methadone.

Oral dosage

**Adults**

Initially, 2.5 mg PO every 8 to 12 hours in the opioid-naive patient; titrate to pain relief. For the relief of severe, chronic pain in opioid-tolerant patients, convert the current total daily dose of all opioids to an oral morphine equivalent dose, then multiply the morphine equivalent dose by the corresponding percentage in the dose conversion table provided in the FDA-approved labeling. Divide the total daily methadone dose into an appropriate daily regimen. Clinical guidelines suggest that methadone should be initiated at a dose that is 75% to 90% lower than the calculated equianalgesic dose and no higher than 30 to 40 mg/day in patients with opioid tolerance. If patients experience breakthrough pain, dose adjustment or a small rescue dose of an immediate-release analgesic should be considered. Use extreme caution to avoid overdosage; it is safer to underestimate a patient's daily oral methadone requirement. Due to the potential for delayed toxic effects (e.g., respiratory depression), clinical guidelines recommend dose titration every 5 to 7 days, although the manufacturer suggests adjustments may be made every 3 to 5 days. Titrate the dosage by no more than 5-10 mg/day in patients on relatively low doses of other opioids prior to methadone treatment (less than 40 to 60 mg/day of oral morphine equivalent) and by no more than 10 mg/day in patients taking higher doses of morphine equivalent. Patients previously prescribed methadone who have not taken opioids for 1 to 2 weeks should be considered opioid-naive for the purposes of methadone reinitiation. Monitor patients closely for respiratory depression, especially during the first 24 to 72 hours after initiation or dosage increase. When the patient no longer requires methadone, taper the dose gradually every 2 to 4 days to prevent withdrawal in the physically-dependent patient.

**Pediatrics**

The following initial interval adjustments have been recommended for pediatric patients (normal interval every 4 to 12 hours):

- **CrCl less than 10 mL/minute**: Administer dosage every 12 to 24 hours.
- **CrCl 10 to 30 mL/minute**: Administer dosage every 8 to 12 hours.
- **CrCl 30 to 50 mL/minute**: Administer dosage every 6 to 8 hours.
- **CrCl less than 10 mL/minute**: Administer dosage every 12 to 24 hours.

**Maximum Dosage**

With appropriate dosage titration, there is no maximum dose of methadone. Safety and efficacy in pediatric patients have not been established; however, methadone is used off-label in these populations.

**Dosing Considerations**

**Hepatic Impairment**

Start these patients on lower doses and titrate slowly while carefully monitoring for signs of respiratory and CNS depression. Adjust dosage based upon clinical response; no specific quantitative recommendations are available.

**Renal Impairment**

**Adults**

Dose adjustments may be necessary in adult patients with renal impairment; guide adjustments based on clinical response. Methadone has not been extensively evaluated in patients with renal insufficiency. Since unmetabolized methadone and its metabolites are excreted in urine to a variable degree, start these patients on lower doses and with longer dosing intervals and titrate slowly while carefully monitoring for signs of respiratory and CNS depression. For example, for CrCl less than 10 mL/minute, one source recommends that the adult initial dose be reduced by 50 to 75%.

**Pediatrics**

Methadone has not been extensively evaluated in patients with renal insufficiency. Since unmetabolized methadone and its metabolites are excreted in urine to a variable degree, start these patients on lower doses and with longer dosing intervals and titrate slowly while carefully monitoring for signs of respiratory and CNS depression. The following initial interval adjustments have been recommended for pediatric patients (normal interval every 4 to 12 hours):

- **CrCl 30 to 50 mL/minute**: Administer dosage every 6 to 8 hours.
- **CrCl 10 to 30 mL/minute**: Administer dosage every 8 to 12 hours.
- **CrCl less than 10 mL/minute**: Administer dosage every 12 to 24 hours.

**Administration**

**Oral Administration**

When given as part of a methadone maintenance program, methadone may only be administered in an oral form and according to the requirements outlined in the Narcotic Addict Treatment Act (NATA) [21USC 823(g)]. The oral formulation is preferred for detoxification treatment. When administered as an analgesic, methadone may be dispensed by any licensed pharmacy. May be administered with food or milk to minimize GI irritation if needed.

**Oral Solid Formulations**

Dispersible tablets (Diskets): Do not chew or swallow the tablets without dispersal in liquid. Disperse tablets 3–4 ounces (90–120 ml) of water, orange juice, citrus Tang, citrus flavors of Kool-Aid, or other acidic fruit beverages prior to patient administration. This will take roughly 1 minute.
Insoluble excipients will be present after tablets are dissolved; they will not completely dissolve. Stir well and have patient drink all of the dosage dispersed.

**Oral Liquid Formulations**

Oral solution (1 mg/ml or 2 mg/ml solutions): Measure dosage using a calibrated measuring device. May administer undiluted.

Oral concentrates (10 mg/ml concentrates; e.g., Methadose, Methadone Intensol): Measure dosage using a calibrated measuring device. Because concentrates may numb the mouth or upset the stomach, it may be preferable to mix in 3–4 ounces (90–120 ml) of liquid (e.g., water or citrus fruit juice) prior to administration.

**Injectable Administration**

Methadone hydrochloride Injection may be administered intravenously, subcutaneously, or intramuscularly. Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

**Intravenous Administration**

Methadone has also been administered intravenously for patient controlled analgesia (PCA) via a rate controlled device as a bolus dose and as a continuous infusion.

**Intramuscular Administration**

Inject into a large muscle mass. Aspirate prior to injection to avoid injection into a blood vessel. The absorption of intramuscular (IM) methadone has not been well characterized and appears to be unpredictable.

Local tissue reactions may occur with IM use.

**Subcutaneous Administration**

Inject subcutaneously taking care not to inject intradermally. The absorption of subcutaneous (SC) methadone has not been well characterized and appears to be unpredictable.

Local tissue reactions may occur with SC use.

**STORAGE**

Generic:
- Store between 68 to 77 degrees F, excursions permitted to 59 to 86 degrees F

Dolophine:
- Protect from light
- Store at controlled room temperature (between 68 and 77 degrees F)
- Store in carton until contents are used

Methadose:
- Store at 77 degrees F; excursions permitted to 59-86 degrees F

**CONTRAINDICATIONS / PRECAUTIONS**

**General Information**

False positive urine drug screens for methadone have been reported for several drugs including diphenhydramine, doxylamine, clomipramine, chlorpromazine, thioridazine,quetiapine, and verapamil.

**Dental work, pain, surgery**

Methadone treatment for acute or chronic pain management should only be initiated if the potential analgesic or palliative care benefits outweigh the risks. Of particular concern are respiratory and cardiac related complications, including death, which may occur during treatment with the drug. Patients with cancer-related pain may have decreased clearance of methadone as compared to patients with chronic, benign pain. Patients receiving opioid dependence maintenance therapy with methadone are often under-treated or denied pain treatment. With long-term methadone therapy for opioid addiction, nearly complete tolerance develops to any analgesic effects of the medication. If a patient is taking methadone and experiences acute pain such as postoperative pain, analgesia may not be provided by the existing methadone dose; administration of another analgesic may be warranted. If another opioid is used, consider opioid tolerance induced by methadone. Whenever possible, pain management should be discussed with health care providers before any surgery or dental work takes place.

**Angina, bradycardia, cardiac arrhythmias, cardiac disease, coronary artery disease, diabetes mellitus, females, heart failure, hypertension, hypocalcemia, hypokalemia, hypomagnesemia, hypotension, hypovolemia, long QT syndrome, malnutrition, myocardial infarction, orthostatic hypotension, QT prolongation, thyroid disease**

Methadone is associated with an increased risk for QT prolongation and torsade de points (TdP). Although the risk of QT prolongation appears to be dose-related, with most incidences of QT prolongation and torsade de points occurring in patients receiving large doses for pain management (i.e., > 100 mg/day), it is important to note that smaller doses for maintenance of opioid addiction have also been implicated. A public health advisory was issued concerning cardiac-related deaths, which have been reported during initiation of methadone treatment as well as during conversion to methadone from other opiates. Extreme caution is recommended during initiation of treatment, conversion from one opiate to another, and dose titrations. An understanding of methadone pharmacokinetic parameters is critical. In addition to slowing the rate of cardiac repolarization thus lengthening the QT interval, methadone may produce cholinergic side effects (by stimulating medullary vagal nuclei) causing peripheral vasodilation. Use methadone with extreme caution, if at all, in patients whose ability to maintain blood pressure has already been compromised by hypovolemia or administration of certain CNS depressant medications such as phenothiazines or general anesthetics. Monitor patients for hypotension at the initiation of therapy and during dose titration. These effects can cause problems in patients with cardiac disease (e.g., angina, heart failure). Methadone should be used cautiously in patients with cardiac arrhythmias, hypokalemia, hypomagnesemia, hypotension, hypovolemia, or orthostatic hypotension. Opiate agonists can induce vasovagal syncope or orthostatic hypotension. A risk/benefit evaluation of methadone use in patients with congenital long QT syndrome or acquired QT prolongation syndromes, patients with a history of torsade de points, patients with unexplained syncope, and those with multiple risk factors for QT prolongation including family history and/or coadministration of contributing medications (i.e. drugs associated with QT prolongation and drugs that inhibit the cytochrome P450 enzymes). Use methadone with caution in patients with cardiac disease or other conditions that may increase the risk of QT prolongation including heart failure, bradycardia, myocardial infarction, hypertension, coronary artery disease, hypocalcemia, or in patients receiving medications known to cause electrolyte imbalances. Females, elderly patients, patients with diabetes mellitus, thyroid disease, malnutrition, a history of alcohol abuse, or hepatic impairment may also be at increased risk for QT prolongation. A 2009 clinical guideline for cardiac safety with methadone treatment recommends that prescribers: (1) discuss the risk of arrhythmia with patients; (2) take a complete cardiac clinical history; (3) screen patients for QT prolongation with ECG monitoring prior to initiation of methadone, at 3 months, and annually thereafter; (4) use the ECG findings to stratify patient risk (i.e., patients with a QTc interval of 451–499 ms should receive more frequent
monitoring and discuss the potential risks vs. benefits of treatment, patients with a QTc interval of >= 500 ms should receive intervention to lower cardiac risk either by discontinuing or lowering the methadone dose or by eliminating contributing factors; and (5) be aware of methadone-drug interactions. Drugs known to prolong the QT interval, potentiate hypokalemia, or reduce methadone elimination should be coadministered with a careful assessment of risks versus benefits.

Alcoholism, depression, substance abuse
Methadone is an opioid agonist and therefore has abuse potential and risk of fatal overdose from respiratory failure. Addiction may occur in patients who obtain methadone illicitly or in those appropriately prescribed the drug. The risk of addiction in any individual is unknown. However, patients with mental illness (e.g., major depression) or a family history of substance abuse (including alcoholism) have an increased risk of opioid abuse. Assess patients for risks of addiction, abuse, or misuse before drug initiation, and monitor patients who receive opioids routinely for development of these behaviors or conditions. A potential risk of abuse should not preclude appropriate pain management in any patient, but requires more intensive counseling and monitoring. Abuse and addiction are separate and distinct from physical dependence and tolerance; patients with addiction may not exhibit tolerance and symptoms of physical dependence. The misuse of methadone by crushing, chewing, snorting, or injecting the dissolved product can result in overdose and death. To discourage abuse, the smallest appropriate quantity of methadone should be dispensed, and proper disposal instructions for unused drug should be given to patients.

Anxiety
Methadone, as used in the treatment of opiate-dependent patients, does not have anxiolytic effects. Patients who are maintained on methadone will react to life problems and stresses with the same anxiety symptoms as other individuals. Health care professionals should not confuse such symptoms with those of opiate abstinence and should not treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of opiate withdrawal symptoms and is not effective in the treatment of anxiety.

Biliary tract disease, constipation, diarrhea, GI disease, GI obstruction, ileus, inflammatory bowel disease, pancreatitis, ulcerative colitis
Due to the effects of opiate agonists on the gastrointestinal tract, methadone is contraindicated in patients with known or suspected paralytic ileus. Use with caution in patients with GI disease including GI obstruction, ulcerative colitis, or pre-existing constipation. Opiate agonists may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Patients with acute ulcerative colitis (UC) or other inflammatory bowel disease may be more sensitive to the constipating effects of opiate agonists. Although opiate agonists are contraindicated for use in patients with diarrhea secondary to poisoning or infectious diarrhea, antimiobity agents have been used successfully in these patients. If possible, opiate agonists should not be used until the toxic substance has been eliminated. Morphine is well recognized to increase the tone of the biliary tract causing spasm in the sphincter of Oddi increasing biliary tract pressure. Biliary effects due to opiate agonists have resulted in plasma amylase and lipase concentrations up to 2—15 times the normal values. The clinical significance of these effects during methadone therapy specifically is not known. Nevertheless, methadone should be used with caution in patients with biliary tract disease, including acute pancreatitis, or in patients undergoing biliary tract surgery.

Asthma, chronic obstructive pulmonary disease (COPD), coadministration with other CNS depressants, cor pulmonale, hypoxemia, obesity, pulmonary disease, respiratory depression, respiratory insufficiency, scoliosis, sleep apnea, status asthmaticus
Methadone is contraindicated in patients with significant respiratory depression and/or acute or severe bronchial asthma (e.g., status asthmaticus) in unmonitored settings or in the absence of resuscitative equipment. Additionally, avoid coadministration with other CNS depressants when possible as this significantly increases the risk for respiratory depression, low blood pressure, and death. Reserve concomitant use of these drugs for patients in whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations possible and monitor patients closely for signs and symptoms of respiratory depression and sedation. Careful monitoring is also required with concomitant use of drugs that may inhibit or induce the metabolism of methadone; an increase in methadone concentrations could cause potentially fatal respiratory depression. The potential risk of serious adverse effects with concomitant use of methadone and other CNS depressants should not preclude the appropriate treatment of opioid addiction with methadone, but requires more intensive counseling and monitoring. Methadone may significantly decrease respiratory drive and cause hypoventilation. Respiratory depression, if left untreated, may cause respiratory arrest and death. Symptoms of respiratory depression include a reduced urge to breathe, a decreased respiratory rate, or deep breaths separated by long pauses (a "sighing" breathing pattern). Serious or fatal respiratory depression can occur at any time during the use of methadone; however, the risk is greatest during the first 24 to 72 hours after therapy initiation or dose titration. It is important to note respiratory depressant effects will continue and persist longer than peak analgesic effects (UC) or other inflammatory bowel disease may be more sensitive to the constipating effects of opiate agonists. Although opiate agonists are contraindicated for use in patients with diarrhea secondary to poisoning or infectious diarrhea, antimiobity agents have been used successfully in these patients. If possible, opiate agonists should not be used until the toxic substance has been eliminated. Morphine is well recognized to increase the tone of the biliary tract causing spasm in the sphincter of Oddi increasing biliary tract pressure. Biliary effects due to opiate agonists have resulted in plasma amylase and lipase concentrations up to 2—15 times the normal values. The clinical significance of these effects during methadone therapy specifically is not known. Nevertheless, methadone should be used with caution in patients with biliary tract disease, including acute pancreatitis, or in patients undergoing biliary tract surgery.

Brain tumor, CNS depression, coma, head trauma, increased intracranial pressure, intracranial mass
Patients with CNS depression, head trauma, intracranial mass, brain tumor, or increased intracranial pressure should be given methadone with extreme caution. Decreased respiratory drive and hypventilation can cause carbon dioxide (CO2) retention which can further increase intracranial pressure. In addition, opiate agonists may interfere with the evaluation of neurologic parameters. Avoid use in patients with impaired consciousness or coma.

Bladder obstruction, hepatic disease, oliguria, prostatic hypertrophy, renal disease, urethral stricture, urinary retention
Methadone and other opiate agonists can cause urinary retention and oliguria due to increasing the tension of the detrusor muscle. Patients more prone to these effects include those with bladder obstruction, prostatic hypertrophy, urethral stricture, or renal disease. Due to the absence of data regarding methadone use in patients with renal impairment, caution is recommended. Renal elimination is usually a minor elimination pathway, but methadone does undergo some renal elimination (see Pharmacokinetics). Drug accumulation or prolonged duration of action can occur in patients with hepatic disease. In acute situations, patients require close monitoring to avoid excessive toxicity. Patients with chronic liver disease may require less frequent dosing intervals.

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Seizure disorder, seizures

Seizures can be precipitated by opiate analgesics, particularly if used in high-doses and during opioid withdrawal. Methadone should be used cautiously in patients with a seizure disorder.

Geriatric

Use methadone with caution in geriatric or debilitated patients. Geriatric or debilitated patients are more susceptible to adverse reactions, especially sedation and respiratory depression, probably as a result of altered distribution of the drug or decreased elimination. Initial doses may need to be reduced, and doses should be carefully titrated taking into account analgesic effects, adverse reactions, and concomitant drugs that may depress respiration. According to the Beers Criteria, opioid agonists are considered potentially inappropriate medications (PIMs) in geriatric patients with a history of falls or fractures and risk of misuse or misadventure, with the exception of pain management due to recent fractures or joint replacement, since opioids can produce ataxia, impaired psychomotor function, syncope, and additional falls. If an opioid must be used, consider reducing use of other CNS-active medications that increase the risk of falls and fractures and implement other strategies to reduce fall risk. Individuals receiving palliative care or those in hospice settings are excluded from the Beers Criteria; the balance of benefits and harms of medication may be different for these patients. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). The Guidelines caution that opioids may cause constipation, nausea, vomiting, sedation, lethargy, weakness, confusion, dysphoria, and psychological dependency, hallucinations, and unintended respiratory depression, especially in individuals with compromised pulmonary function. These adverse effects can lead to other consequences such as falls. In addition, the initiation of longer-acting opioids, such as methadone, is not recommended unless shorter-acting opioids have been unsuccessful, or titration of shorter-acting doses has established a clear daily dose of opioid analgesic that can be provided by using a long-acting form.

Adrenal insufficiency, hypothyroidism, myxedema

Use methadone with caution in patients with adrenal insufficiency (i.e., Addison's disease), hypothyroidism, or myxedema. Such patients may be at increased risk of adverse events. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH); however, the thyroid stimulating hormone may be either stimulated or inhibited by opioids. Rarely, adrenal insufficiency has been reported in association with opioid use. Patients should seek immediate medical attention if they experience symptoms such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or hypotension. If adrenocortical insufficiency is suspected, confirm with diagnostic testing as soon as possible. If diagnosed, the patient should be treated with physiologic replacement doses of corticosteroids, and if appropriate, weaned off of opioid therapy. If the opioid can be discontinued, a follow-up assessment of adrenal function should be performed to determine if corticosteroid treatment can be discontinued. Other considerations: Additional opioids may be tried; some cases reported use of a different opioid with no recurrence of adrenocortical insufficiency. It is unclear which, if any, opioids are more likely to cause adrenocortical insufficiency. In addition, chronic opioid use may lead to symptoms of hypogonadism, resulting from changes in the hypothalamic-pituitary-gonadal axis. Monitor patients for symptoms of opioid-induced endocrinopathy, particularly those receiving a daily dose equivalent to 100 mg or more of morphine. Patients presenting with signs or symptoms of androgen deficiency should undergo laboratory evaluation.

Infants, neonates

The safety, effectiveness, and pharmacokinetics of methadone in pediatric patients below the age of 18 years have not been established. Methadone maintenance therapy has been an option for selected adolescents and is used off-label, though most methadone maintenance programs are not set up to manage patients. Methadone is not a drug of choice for pain management in opioid-naive pediatric patients, but off-label use of methadone has been described for children and adolescents who are opioid-experienced. Use in neonates and infants must be approached with caution. Neonates and infants younger than 6 months of age have highly variable clearance of opiate agonists. Therefore, infants younger than 6 months of age may be given opiate agonists but must be closely monitored for apnea for an extended period after their last dose. Clinical practice guidelines for acute pain management suggest close monitoring of children up to 1 year of age.

Labor, neonatal opioid withdrawal syndrome, obstetric delivery, pregnancy

There are no adequate and well-controlled studies with methadone in pregnant women. Use methadone for severe pain during pregnancy only if the potential benefit justifies the potential risk to the fetus. Medical withdrawal of pregnant, opioid-dependent women from methadone is not recommended. When methadone is used during pregnancy, it is unlikely to pose a significant teratogenic risk. Pregnant women in methadone maintenance programs may have reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes and risk of continued or relapsing illicit opioid use. Consider these risks in pregnant women treated with methadone for maintenance treatment of opioid use disorder. No increased risk of miscarriage or premature delivery in the second trimester was noted by a retrospective review of data from 101 opioid-dependent women. Benefits of methadone therapy during pregnancy include assisting women to stay free of heroin and other opioids, increasing prenatal care, lessening the possibility of fetal death, and reducing the risk of HIV and hepatitis infection. Infants born to narcotic-addicted women treated with methadone during pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and head circumference. The growth deficit does not appear to persist into later childhood. Children born to mothers who received methadone during pregnancy demonstrate mild but persistent performance deficits on psychometric and behavioral tests and may have an increased risk of visual development anomalies. Administration of methadone to pregnant animals during organogenesis through lactation resulted in decreased litter size, increased pup mortality, decreased pup body weights, developmental delays, and long-term neurochemical changes in the brain which correlate with altered behavior. Compared to animals with higher placental transfer rates, compared to animals with lower placental transfer rates, decreased pup survival has been demonstrated to a fetus. Methadone can be discontinued. Other opioids may be tried; some cases reported use of a different opioid with no recurrence of adrenocortical insufficiency. It is unclear which, if any, opioids are more likely to cause adrenocortical insufficiency. In addition, chronic opioid use may lead to symptoms of hypogonadism, resulting from changes in the hypothalamic-pituitary-gonadal axis. Monitor patients for symptoms of opioid-induced endocrinopathy, particularly those receiving a daily dose equivalent to 100 mg or more of morphine. Patients presenting with signs or symptoms of androgen deficiency should undergo laboratory evaluation.

Breast-feeding

Methadone is excreted in breast milk. According to the American Academy of Breastfeeding Medicine and previous American Academy of Pediatrics recommendations, therapeutic methadone use is usually compatible with breast-feeding. Consider the benefits of breast-feeding along with the mother’s clinical condition and whether the child from methadone or the underlying maternal condition. Women who received methadone maintenance therapy for opioid dependence during pregnancy who are stable may be encouraged to breast-feed, unless another contraindication (e.g., street drug abuse) is present. Other drugs (e.g., morphine) are preferable for pain control during breast-feeding. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported. In most samples, the mcg/L concentrations were lower than maternal serum drug concentrations at attritions were lower than average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day, which is approximately 2% to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Although breast-feeding may help mitigate withdrawal symptoms in the neonate, in some cases when methadone maintenance was used during pregnancy, the amount of methadone

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in breast milk may not be enough to fully avoid withdrawal in the infant. Of 8 breast-fed babies born to women maintained on methadone 50 to 105 mg/day, 1 required pharmacotherapy for neonatal abstinence syndrome, whereas 4 of 8 formula-fed babies needed treatment for the event. Advise breast-feeding women taking methadone to monitor the infant for signs of sedation and respiratory depression in infants exposed to methadone through breast milk.

Driving or operating machinery
Patients receiving methadone should be warned about the possibility of sedation occurring during methadone administration and to use caution when driving or operating machinery.

Opiate agonist hypersensitivity
Although true opiate agonist hypersensitivity is rare, patients who have demonstrated a prior hypersensitivity reaction should not receive methadone. It is possible to treat these patients with an opioid agonist from the phencyclidine subclass (fentanyl) or meperidine) or the phenanthrene subclass (codeine, hydromorphone, and oxycodone).

Accidental exposure, opioid-naive patients, potential for overdose or poisoning
All forms of methadone have the potential for overdose or poisoning. Methadone is a long-acting opioid that should only be used as an analgesic in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment. When used for analgesia, methadone should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release, short-acting opioids) are ineffective, not tolerated, or would otherwise be inadequate to provide sufficient pain management. Due to the risk of respiratory depression, use methadone with caution in opioid-naive patients. Patients tolerant to other opioids may be incompletely tolerant to methadone; use caution when converting patients from other opioids to methadone. Special care should be taken to keep it out of the reach of patients for whom it was not prescribed, particularly pediatric patients, as accidental exposure may cause fatal overdose.

Abrupt discontinuation
Abrupt discontinuation of methadone therapy can result in withdrawal symptoms, which may not be seen for days after the last dose in patients on chronic therapy. Gradually taper patients off methadone to avoid a withdrawal reaction. Avoid use of partial agonists (e.g., buprenorphine), mixed agonist/antagonists (e.g., nalbuphine), or pure antagonists (e.g., naloxone) in patients physically dependent on opioids, as an acute withdrawal syndrome may precipitate. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and on the administered dose of the opioid antagonist. If treatment of respiratory depression in an individual physically dependent on opioids is necessary, administer the opioid antagonist with extreme care; titrate the antagonist dose by using smaller than usual doses. In addition, the use of partial agonists or mixed agonist/antagonists in patients who have received or are receiving opioid agonist analgesia should be avoided as these medications may reduce the analgesic effects of methadone.

MAOI therapy
Methadone should be avoided in patients treated with monoamine oxidase inhibitor therapy (MAOI therapy), due to the potential risk for serotonin syndrome. The use of methadone is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. with MAOI therapy. Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of methadone with many types of serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), serotonin-receptor agonists "triptans", S-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAOIs - those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue methadone and other serotonergic agents if serotonin syndrome is suspected and institute appropriate medical treatment.

Intravenous administration
Methadone oral concentrate solution is for oral administration only; do not give via intravenous administration.

Requires an experienced clinician
Methadone therapy requires an experienced clinician when used for the treatment of opioid addiction in detoxification or maintenance programs. Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). An exception may be made for the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of their stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

Infertility, reproductive risk
Chronic opioid use may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes that may manifest as hypogonadism (gonadal suppression) and pose a reproductive risk. Although the exact causal role of opioids in the clinical manifestations of hypogonadism is unknown, patients could experience libido decrease, impotence, amenorrhea, or infertility. It is not known whether the effects on fertility are reversible. Monitor patients for symptoms of opioid-induced endocrinopathy. Patients presenting with signs or symptoms of androgen deficiency should undergo laboratory evaluation.

ADVERSE REACTIONS

Severe
pulmonary edema / Early / Incidence not known
respiratory arrest / Rapid / Incidence not known
apnea / Delayed / Incidence not known
seizures / Delayed / Incidence not known
oliguria / Early / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known
SIADH / Delayed / Incidence not known
ventricular fibrillation / Early / Incidence not known
cardiomyopathy / Delayed / Incidence not known
bradycardia / Rapid / Incidence not known
ventricular tachycardia / Early / Incidence not known
heart failure / Delayed / Incidence not known

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torsade de pointes / Rapid / Incidence not known
neonatal abstinence syndrome / Early / Incidence not known
bone fractures / Delayed / Incidence not known
serotonin syndrome / Delayed / Incidence not known
pancreatitis / Delayed / Incidence not known
biliary obstruction / Delayed / Incidence not known

Moderate
psychological dependence / Delayed / 10.0
tolerance / Delayed / Incidence not known
respiratory depression / Rapid / Incidence not known
hypoventilation / Rapid / Incidence not known
dyspnea / Early / Incidence not known
dysphoria / Early / Incidence not known
confusion / Early / Incidence not known
euphoria / Early / Incidence not known
hallucinations / Early / Incidence not known
glossitis / Early / Incidence not known
constipation / Delayed / Incidence not known
blurred vision / Early / Incidence not known
urinary retention / Early / Incidence not known
edema / Delayed / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known
infertility / Delayed / Incidence not known
hypogonadism / Delayed / Incidence not known
hypokalemia / Delayed / Incidence not known
adrenocortical insufficiency / Delayed / Incidence not known
hypertension / Early / Incidence not known
sinus tachycardia / Rapid / Incidence not known
palpitations / Early / Incidence not known
orthostatic hypotension / Delayed / Incidence not known
percentage vasodilatation / Rapid / Incidence not known
QT prolongation / Rapid / Incidence not known
withdrawal / Early / Incidence not known
physiological dependence / Delayed / Incidence not known
hyperthyroidism / Delayed / Incidence not known
osteoporosis / Delayed / Incidence not known
hyperamylasemia / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known

Mild
agitation / Early / Incidence not known
flushing / Rapid / Incidence not known
fatigue / Delayed / Incidence not known
weakness / Early / Incidence not known
anxiety / Delayed / Incidence not known
asthenia / Delayed / Incidence not known
dizziness / Early / Incidence not known
restlessness / Early / Incidence not known
headache / Early / Incidence not known
insomnia / Early / Incidence not known
anorexia / Delayed / Incidence not known
vomiting / Early / Incidence not known
nausea / Early / Incidence not known
abdominal pain / Early / Incidence not known
miosis / Early / Incidence not known
xerostomia / Early / Incidence not known
urticaria / Rapid / Incidence not known
rash (unspecified) / Early / Incidence not known
injection site reaction / Rapid / Incidence not known
pruritus / Rapid / Incidence not known
amenorrhea / Delayed / Incidence not known
libido decrease / Delayed / Incidence not known
weight gain / Delayed / Incidence not known
gonadal suppression / Delayed / Incidence not known
diaphoresis / Early / Incidence not known
syncpe / Early / Incidence not known

DRUG INTERACTIONS

Abacavir: (Moderate) In a study of 11 adult HIV-infected subjects receiving methadone maintenance therapy (40 to 90 mg/day) and abacavir 600 mg twice daily (twice the current recommended dose), methadone clearance increased by 22% (6% to 42%). While this interaction will not require dosage adjustment in the majority of patients, a small number of patients may require increased doses of methadone. In addition, a significant increase in abacavir Cmax (34%) and increase in Tmax (67%) were noted, but no changes in overall abacavir clearance or half-life were reported. The clinical significance regarding abacavir therapy is not known.

Abacavir; Dolutegravir; Lamivudine: (Moderate) In a study of 11 adult HIV-infected subjects receiving methadone maintenance therapy (40 to 90 mg/day) and abacavir 600 mg twice daily (twice the current recommended dose), methadone clearance increased by 22% (6% to 42%). While this interaction will not require dosage adjustment in the majority of patients, a small number of patients may require increased doses of methadone. In
addition, a significant decrease in abacavir Cmax (34%) and increase in Tmax (67%) were noted, but no changes in overall abacavir clearance or half-life were reported. The clinical significance regarding abacavir therapy is not known. (Moderate) Methadone increases exposure to zidovudine, ZDV. Patients should be monitored for zidovudine toxicity during concurrent methadone treatment; however, the manufacturer of zidovudine states that routine dosage adjustment of zidovudine is not required during coadministration of methadone. Patients who receive both methadone and zidovudine may experience withdrawal and attribute the symptoms characteristic of withdrawal to methadone, due to zidovudine. However, it is more likely patients are actually experiencing zidovudine side effects due to increased levels since zidovudine has no effect on methadone metabolism.

**Acetaminophen; Butalbital; Caffeine; Codeine:** (Major) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Caffeine; Dihydrocodeine:** (Major) Concomitant use of methadone with another CNS depressant, like dihydrocodeine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenytoin:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Codiene:** (Major) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Diphenhydramine:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Hydrocodone:** (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression, and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Oxycodeone:** (Major) Concomitant use of methadone with another CNS depressant, such as oxycodone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Acetaminophen; Pentazocine:** (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as methadone. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and sedative effects. The additive or antagonist effects are dependent upon the dose of the opiate agonist used; antagonist effects are more common at lower doses of the opiate agonist.

**Acetaminophen; Propoxyphene:** (Moderate) Propoxyphene is a weak mu-opiate receptor agonist. As other opiate agonists bind to mu-opiate receptors, concurrent use of an opiate agonist with propoxyphene is not desirable. Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on narcotics. The choice of one mu-opiate receptor agonist needs to be made to avoid duplicate therapy...
and possible adverse effects. Concomitant use of methadone with propanolol can lead to additive respiratory depression, hypotension, profound sedation, or coma. Propanolol in combination with other CNS depressants is a major cause of death-related death. Fatalities within the first hour of combination are not uncommon. Extraventricular use of any CNS-depressant drug and propanolol should be done with extreme caution and a careful assessment of treatment risks versus benefits. The concurrent use of methadone in patients taking a propanolol, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used in reduced dosages if used concurrently with a CNS depressant; also consider using a lower dose of CNS depressant. Monitor patients for sedation and respiratory depression.

Acetaminophen: (Moderate) Concomitant use of acetaminophen with methadone is associated with an increased risk of liver toxicity. The use of acetaminophen with methadone should be avoided in patients with a history of liver disease or alcohol abuse.

Acetylsalicylic Acid: (Moderate) Aspirin is a CYP2C9 inhibitor and may increase the plasma concentrations of methadone. Use with caution in patients taking high doses of methadone.

Acyclovir: (Moderate) Acyclovir is a CYP3A4 inhibitor and may increase the plasma concentrations of methadone. Use with caution in patients taking high doses of methadone.

Acrivastine; Pseudoephedrine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Albisopel: (Moderate) Patients taking medications that decrease GI motility may be at greater risk for serious complications from albisopel, like constipation, via a pharmacodynamic interaction. Constipation is the most frequently reported adverse effect with albisopel. Aloe, if used with drugs such as opiate agonists, may seriously worsen constipation, leading to events such as GI obstruction/impaclion or paralytic ileus.

Alprazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Alvimopan: (Moderate) Patients should not take alvimopan if they have received therapeutic doses of opiate agonists for more than seven consecutive days immediately before initiation of alvimopan therapy. Patients recently exposed to opioids are expected to be more sensitive to the effects of mu-opioid receptor antagonists and may experience adverse effects localized to the gastrointestinal tract such as abdominal pain, nausea, vomiting, and diarrhea.

Amide local anesthetics: (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the central nervous system. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Amiloride: (Moderate) Diuretics can cause electrolyte disturbances such as hyponagmea and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also opiate agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.

Amorpholone; Hydrochlorothiazide, HCTZ: (Moderate) Diuretics can cause electrolyte disturbances such as hyponagmea and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also opiate agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.

Amtriptiline: (Major) The need to coadminister methadone with amitriptyline should be done with extreme caution and a careful assessment of treatment risks versus benefits. At high doses, methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses averaging approximately 400 mg/day in adult patients. Amidarone, a Class III antiarrhythmic agent, is associated with a well-established risk of QT prolongation and TdP. Although the frequency of TdP is less with amidarone than with other Class III agents, amidarone is still associated with a risk of TdP. Due to the extremely long half-life of amidarone, a drug interaction is possible for days to weeks after discontinuation of amidarone. In addition, methadone is a substrate for CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes, such as amidarone, may result in increased serum concentrations of methadone.

Amtriptiline: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as tricyclic antidepressants should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during the initiation of the second drug therapy and after dosages (increases) of either agent. In addition, concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.
Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine.

Amtriptiline; Chloridiazepoxide: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate agonists in patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a benzodiazipine, reduced dosages are recommended; in opioid-naïve adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient who is not taking an opiate agonist, use a lower initial dose of the benzodiazepine and closely follow and the dosage of methadone may need to be increased. Observe the patient for symptoms of methadone withdrawal or other signs of methadone toxicity. If methadone is used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine.

Ammonium Chloride: (Minor) As methadone is a weak base, the renal elimination of methadone is increased by urine acidification. Thus acidifying agents may lower the serum methadone concentration. The limited amounts of circulating methadone that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent. Several studies have demonstrated that methadone is cleared faster from the body with an acidic urinary pH as compared with a more basic pH.

Amoxapine: (Moderate) Opiate agonists such as methadone should be used cautiously with amoxapine due to the potential for additive CNS depressant effects and possible respiratory depression or hypotension. In addition, because amoxapine demonstrates clinically significant antimuscarinic activity, concurrent use with opiate agonists may obstruct intestinal motility or bladder function. Prior to concurrent use of methadone in patients with a history of CNS depression, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower initial dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Amoxicillin; Clarithromycin; Lansoprazole: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as clarithromycin, should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage adjustments (increases) of either agent. In addition, concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. When used concurrently, assess the level of tolerance to CNS depression, the dosage of methadone, and the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine.

Angrile: (Major) Torresades de points (TdP) and ventricular tachycardia have been reported during post-marketing use of angrile. A cardiovascular examination, including an ECG, should be obtained in all patients prior to initiating anagrelide therapy. Monitor patients during anagrelide therapy for cardiovascular effects and evaluate as necessary. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with anagrelide include methadone.

Anthracyclines: (Major) Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Since methadone can prolong the QT interval, it should be used cautiously with anthracyclines due to the potential for cardiac toxicity. Acute cardiotoxicity caused by anthracyclines can result from the administration of anthracyclines; cumulative, dose-dependent cardiomyopathy may also occur. Acute ECG changes during anthracycline therapy are usually transient and include ST wave changes, QT prolongation, and changes in QTc voltage. Sinus tachycardia is the most common arrhythmia, but other arrhythmias such as supraventricular tachycardia (SVT), ventricular tachycardia, heart block, and premature ventricular contractions (PVCs) have been reported during anthracycline therapy.

Anticholinergics: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when methadone is used concomitantly with an anticholinergic drug. The concomitant use of methadone and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Apoporphine: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering methadone with apoporphine. The need to coadminister these drugs should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involving patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Limited data indicate that QT prolongation is unlikely to be a significant issue for patients receiving dosages within the manufacturer's guidelines; however, large increases (>60 mscre from pre-dose) have occurred in two patients receiving 6 mg doses. Doses <= 6 mg SC are associated with minimal increases in QTc; doses > 6 mg SC do not provide additional clinical benefit and are not recommended. Additionally, apoporphine causes significant somnolence. Concomitant administration of apoporphine and CNS depressants (like methadone) could result in additive depressant effects. Careful monitoring is recommended during combined use of a CNS depressant and apoporphine. A dose reduction of one or both drugs may be warranted.

Aprocyclidine: (Minor) Theoretically, aprocyclidine might potentiate the effects of CNS depressant drugs such as opiate agonists. Although no specific drug interactions were identified with systemic agents and aprocyclidine during clinical trials, aprocyclidine can cause dizziness and somnolence.

Aprepitant, Fosaprepitant: (Major) Use caution if methadone and apreptiant, fosaprepitant are used concurrently, and monitor for an increase in methadone-related adverse effects, including excess sedation, for several days after administration of a multi-day apreptiant regimen. Methadone is a CYP3A4 substrate. Apreptiant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may cause profound plasma concentration changes of methadone. For example, in a CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral apreptiant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or apreptiant oral dose, the inhibitory effect of apreptiant on CYP3A4, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to apreptiant and shares many of the same drug interactions. However, as a
single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction.

Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1, there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important. Limited data suggest that fosaprepitant is a CYP2C9 substrate, tolbutamide is a CYP2C9 inhibitor, and methadone is a CYP2C9 substrate. Administration of a CYP2C9 substrate, tolbutamide, on days 1, 4, 8, and 15 with a 3-day regimen of oral aprepitant (125 mg/80 mg/80 mg) decreased the tolbutamide AUC by 23% on day 4, 28% on day 8, and 15% on day 15. The AUC of tolbutamide was decreased by 8% on day 2, 16% on day 4, 15% on day 8, and 10% on day 15 when given prior to oral administration of aprepitant 40 mg on days 2, 4, 8, and 15. The effects of aprepitant on tolbutamide were not considered significant.

Argeine: (Minor) As methadone is a weak base, the renal elimination of methadone is increased by urine acidification. Thus acidifying agents may lower the serum methadone concentration. The limited amounts of circulating methadone that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent. Several studies have demonstrated that methadone is cleared faster from the body with a lower pH as compared with a more basic pH.

Aripiprazole: (Major) QT prolongation has occurred during therapeutic use of aripiprazole and following overdose. The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Arsenic Trioxide: (Major) If possible, drugs that are known to prolong the QT interval should be discontinued prior to initiating arsenic trioxide therapy. QT prolongation should be expected with the administration of arsenic trioxide. Torsade de pointes (TdP) and complete atrioventricular block have been reported. Drugs with a possible risk for QT prolongation and TdP should be used cautiously with arsenic trioxide include methadone. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Articularum: (Moderate) Caution is advised with the coadministration of arsenic trioxide and methadone as concurrent use may result in increased additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthesia in opioid-naive patients for whom any alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Asaprine: (Major) Asepine has been associated with QT prolongation. According to the manufacturer of asepine, the drug should be avoided in combination with other agents also known to have this effect. Drugs with a possible risk for QT prolongation and torsade de pointes (TdP) that should be avoided in combination with asepine include methadone. In addition, coadministration can cause CNS depression and may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness.

Aspirin, ASA: (Moderate) Caution is advised with the use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) with methadone as concurrent use may result in increased additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Aspirin, ASA; Caffeine; Dihydrocodeine: (Moderate) Concomitant use of methadone with another CNS depressant like dihydrocodeine can lead to additive respiratory depression, hypotension, profound sedation, and coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Aspirin, ASA; Carisoprodol: (Major) Concomitant use of opiate agonists with skeletal muscle relaxants may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with local anesthesia in opioid-naive patients for whom any alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a skeletal muscle relaxant, reduced dosages are recommended; in opioid-naive adults, use an initial methadone dose of 2.5 mg PO every 12 hours. If a skeletal muscle relaxant is prescribed for a patient taking an opiate agonist, use a lower initial dose of the skeletal muscle relaxant and titrate to clinical response. Educate patients about the risks of symptoms of respiratory depression and sedation.

Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Concomitant use of methadone with another CNS depressant like codeine can lead to additive respiratory depression, hypotension, profound sedation, and coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Major) Concomitant use of opiate agonists with skeletal muscle relaxants may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with local anesthesia in opioid-naive patients for whom any alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a skeletal muscle relaxant, reduced dosages are recommended; in opioid-naive adults, use an initial methadone dose of 2.5 mg PO every 12 hours. If a skeletal muscle relaxant is prescribed for a patient taking an opiate agonist, use a lower initial dose of the skeletal muscle relaxant and titrate to clinical response. Educate patients about the risks of symptoms of respiratory depression and sedation.

Aspirin, ASA; Oxycodone: (Major) Concomitant use of methadone with another CNS depressant like oxycodone can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Atanavir: (Moderate) Caution is advised with the coadministration of atanavir and methadone as concurrent use may result in increased concentrations of methadone. Methadone is primarily metabolized by CYP3A4; atanavir is a CYP3A4 inhibitor. No clinically significant drug interaction was observed when atanavir was coadministered with a stable maintenance dose of methadone. However, if coadministered, patients should be regularly monitored for excessive methadone-related side effects, as the theoretical possibility for atanavir to inhibit methadone metabolism does exist.

Cobicistat: (Moderate) Caution is advised with the coadministration of atanavir and methadone as concurrent use may result in increased concentrations of methadone. Methadone is primarily metabolized by CYP3A4; atanavir is a CYP3A4 inhibitor. No clinically significant drug interaction was observed when atanavir was coadministered with a stable maintenance dose of methadone. However, if coadministered, patients should be regularly monitored for excessive methadone-related side effects, as the theoretical possibility for atanavir to inhibit methadone metabolism does exist. (Moderate) The plasma concentrations of methadone may be elevated when administered concurrently with cobicistat.
Methadone Hydrochloride Intensol Oral Concentrate (methadone hydrochloride) dose, ...
Bupivacaine Liposomal: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of opiate agonists.

Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) Concomitant use of methadone with another CNS depressant like brompheniramine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also, consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 

Brompheniramine; Dextromethorphan; Guaifenesin: (Moderate) Concomitant use of methadone with another CNS depressant like brompheniramine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also, consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 

Brompheniramine; Guaifenesin; Hydrocode: (Major) Concomitant use of hydrocode with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocode in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocode at 20 mg of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of methadone with another CNS depressant like brompheniramine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also, consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 

Brompheniramine; Hydrocode: (Moderate) Concomitant use of hydrocode with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocode in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocode at 20 mg of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of methadone with another CNS depressant like brompheniramine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also, consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 

Brompheniramine; Pseudoephedrine: (Moderate) Concomitant use of methadone with another CNS depressant like brompheniramine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also, consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 

Bumetanide: (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, caution coadministration with diuretics is needed.

Bupivacaine Liposomal: (Moderate) The use of these drugs together may be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Bupivacaine: (Moderate) The use of these drugs together may be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Bupivacaine, Lidocaine: (Moderate) The use of these drugs together may be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Buprenorphine: (Major) Buprenorphine has been associated with QT prolongation and has a possible risk of torsade de points (Tdp). Methadone has a possible risk for QT prolongation and Tdp and use with buprenorphine should be avoided if possible. FDA-approved labeling for some buprenorphine products recommend avoiding use with Class 1A and Class III antiarrhythmic medications while other labels recommend avoiding use with Class 1A and Class III antiarrhythmic medications. Buprenorphine has the potential to prolong the QT interval. Buprenorphine is a mixed opioid agonist/antagonist with strong affinity for the mu-receptor that may partially block the effects of full mu-receptor opiate agonists and reduce analgesic effects. In some cases of acute pain, trauma, or during surgical management, opiate-dependent patients receiving buprenorphine maintenance therapy may require concurrent treatment with opiate agonists, such as methadone. In these cases, health care professionals must exercise caution in opiate agonist dose selection, as higher doses of opiate agonist may be required to compete with buprenorphine at the mu-receptor. Management strategies may include adding a short-acting opiate agonist to achieve analgesia in the presence of buprenorphine, discontinuation of buprenorphine and use of an opiate agonist to avoid withdrawal and achieve analgesia, or conversion of buprenorphine to methadone while using additional opiate agonists if needed. Closely monitor patients for CNS or respiratory depression. When buprenorphine is used for analgesia, avoid co-use with opiate agonists. Buprenorphine may cause withdrawal symptoms in patients receiving chronic opiate agonists as well as possibly potentiate CNS, respiratory, and hypotensive effects. The
additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.

Buprenorphine; Naloxone: (Major) Buprenorphine has been associated with QT prolongation and has a possible risk of torsade de pointes (Tdp). Methadone has a possible risk for QT prolongation and Tdp and use with buprenorphine should be avoided if possible. FDA-approved labeling for some buprenorphine products recommend avoiding use with Class 1A and Class III antiarrhythmic medications while other labels recommend avoiding use with any drug that has the potential to prolong the QT interval. Buprenorphine is a mixed opiate agonist/antagonist with strong affinity for the mu-receptor that may partially block opiate agonists and reduce analgesic effects. In some cases of acute pain, trauma, or during surgical management, opiate-dependent patients receiving buprenorphine maintenance therapy may require concurrent treatment with opiate agonists, as methadone. In these cases, health care professionals must exercise caution in opiate agonist dose selection, as higher doses of an opiate agonist may be required to compete with buprenorphine at the mu-receptor. Management strategies may include adding a short-acting opiate agonist to achieve analgesia in the presence of buprenorphine and use of an opiate agonist to avoid withdrawal and achieve analgesia, or conversion of buprenorphine to methadone while using additional opiate agonists if needed. Closely monitor patients for CNS or respiratory depression. When buprenorphine is used for analgesia, avoid co-use with opiate agonists. Buprenorphine may cause withdrawal symptoms in patients receiving chronic opiate agonists as well as possible potentiate CNS, respiratory, and hypotensive effects. The addition of an opiate agonist can enhance or moderate the analgesic effects of buprenorphine. If used concurrently, antagonism of opiate agonists is more common at low to moderate doses of the opiate agonist. (Major) Naloxone can antagonize the therapeutic efficacy of methadone in addition to precipitating withdrawal symptoms in patients who are physically dependent on opiate drugs including methadone. Naloxone should only be administered when clinically significant respiratory or cardiovascular depression are present. If therapy with an naloxone is indicated, repeat doses may be needed due to methadone's prolonged duration of action.

Bupropion: (Moderate) Bupropion is an inhibitor of the CYP2D6 isozyme. Plasma concentrations of opiate agents metabolized by CYP2D6 such as methadone may be increased if bupropion is added. Dosage reductions in these agents may be needed. Conversely, if bupropion therapy is discontinued, doses of these agents may need to be adjusted upward in some patients. Excessive use of opioid agonists (e.g., opiate addiction) is associated with an increased seizure risk; seizures may be more likely to occur during concurrent use of bupropion in these patients since bupropion is associated with a dose-related risk of seizures.

Bupropion; Naltrexone: (Major) When naltrexone is used as adjuvant treatment of opiate or alcohol dependence, use is contraindicated in patients currently receiving opiate agonists. Naltrexone will antagonize the therapeutic benefits of opiate agonists and will induce a withdrawal reaction in patients taking opiate agonists. Monitor for withdrawal symptoms if used concurrently. If there is any question of opioid use in the past 7-10 days and the patient is not experiencing opioid withdrawal symptoms and/or the urine is negative for opioids, a naloxone challenge test needs to be performed. If a patient receives naltrexone, and an opiate agonist is needed for an emergency situation, methadone, an opioid agonist of relatively long duration, may be given i.v. Naltrexone's antagonism of opiate agonists is likely to be driven by patient's tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Drowsiness has been reported during administration of carbacetapentane. An enhanced CNS depressant effect may occur when carbacetapentane is combined with other CNS depressants including morphine.

Carbamazepine: (Moderate) Inducers of CYP3A4 such as carbamazepine may induce the hepatic metabolism of opiate agonists, which may lead to opiate withdrawal or inadequate pain control. This interaction is most significant if the enzyme-inducing agent is added after opiate therapy has begun in patients who are opiate tolerant. Clinicians should be alert to changes in the effect of the opioid agonist. Opiate doses may need to be increased if carbamazepine is added. Conversely, doses may need to be decreased if carbamazepine is discontinued.

Carbetapentane; Chlorpheniramine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Drowsiness has been reported during administration of carbacetapentane. An enhanced CNS depressant effect may occur when carbacetapentane is combined with other CNS depressants including morphine.

Carbetapentane; Phenylephrine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced
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http://www.pdr.net/drug-summary/Methadone-Hydrochloride-Intensol-Oral-Concentrate-m... 1/5/2018
Methadone Hydrochloride Intensol Oral Concentrate (methadone hydrochloride) dose, ...
treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant, including alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of methadone with another CNS depressant like hydrocodone can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Major) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Major) Concomitant use of methadone with another CNS depressant like hydrocodeine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. 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Hydrocodeone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodeone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Chlorpheniramine; Hydrocodeone: (Major) Concomitant use of hydrocodeone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodeone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodeone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodeone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 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Monitor patients for sedation and respiratory depression. Chlorpheniramine; Pseudoephedrine: (Major) Concomitant use of hydrocodeone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodeone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodeone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodeone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. 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Methadone is associated with an increased risk for QT prolongation and torsade de pointes, especially at higher doses (approximately 400 mg/day in adult patients). In addition, methadone is a substrate for CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes may result in increased serum concentrations of methadone. Chlorpromazine is specifically associated with an established risk of QT prolongation and TdP and inhibits CYP2D6. In addition, concomitant use of methadone with another CNS depressant, such as chlorpromazine, can also lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to use of methadone in patients taking a CNS depressant, assess the level of tolerance...
to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clonidine: (Moderate) The need to coadminister methadone with drugs known to prolong the QT interval, such as tricyclic antidepressants should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (200 mg/day) but averaging approximately 400 mg/day in adult patients). Caution should be used when methadone is coadministered with tricyclic antidepressants as this combination may increase the risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have also been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Methadone is considered to be associated with an increased risk for QT prolongation and TdP.

Clonazepam: (Moderate) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

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Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including opiate agonists. Clonidine: (Moderate) At high concentrations, clonidine can increase the activity of CYP2C9. Thus, concurrent use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Clonazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clonazepam: (Moderate) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clonazepam: (Moderate) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clonazepam: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as clozapine, should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have also been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Methadone is considered to be associated with an increased risk for QT prolongation and TdP.
use an initial methadone dose of 2.5 mg every 12 hours. Consider a lower dose of the CNS depressant. In addition, combining clozapine with opiate agonists may lead to additive effects on intestinal motility or bladder function.

**Codeine:** The plasma concentrations of methadone are elevated when administered concurrently with codeine. If codeine is used, the dosage of methadone may need to be increased. Methadone is partially metabolized by CYP2B6, while elvitegravir is a CYP2C9 inducer. (Moderate) The plasma concentrations of methadone may be elevated when administered concurrently with codeine. When initiating methadone in patients currently on a regimen containing codeine and atazanavir or darunavir, use the lowest methadone starting dose and slowly titrate to desired effect. When initiating antiretroviral regimens containing codeine and atazanavir or darunavir to patients on methadone, an adjustment of methadone dose may be needed. Monitoring for adverse effects, such as CNS side effects or respiratory depression, is recommended during coadministration. Methadone is metabolized primarily by the cytochrome P450 isoenzymes CYP2C19, CYP3A4, and CYP2B6, and to a lesser extent, by CYP2C9 and CYP2D6. Methadone also is a substrate of P-glycoprotein (P-gp). Cobicistat is an inhibitor of CYP3A, CYP2D6, and P-gp.

**Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Alafenamide:** (Moderate) Caution is warranted when elvitegravir is administered with methadone as there is a potential for decreased methadone concentrations and the dosage of methadone may need to be increased. Methadone is partially metabolized by CYP2B6, while elvitegravir is a CYP2C9 inducer. (Moderate) The plasma concentrations of methadone may be elevated when administered concurrently with cobicistat. When initiating methadone in patients currently on a regimen containing cobicistat and atazanavir or darunavir, use the lowest methadone starting dose and slowly titrate to desired effect. When initiating antiretroviral regimens containing cobicistat and atazanavir or darunavir to patients on methadone, an adjustment of methadone dose may be needed. Monitoring for adverse effects, such as CNS side effects or respiratory depression, is recommended during coadministration. Methadone is metabolized primarily by the cytochrome P450 isoenzymes CYP2C19, CYP3A4, and CYP2B6, and to a lesser extent, by CYP2C9 and CYP2D6. Methadone also is a substrate of P-glycoprotein (P-gp). Cobicistat is an inhibitor of CYP3A4, CYP2D6, and P-gp.

**Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Disoproxi Fumarate:** (Moderate) Caution is warranted when elvitegravir is administered with methadone as there is a potential for decreased methadone concentrations and the dosage of methadone may need to be increased. Methadone is partially metabolized by CYP2B6, while elvitegravir is a CYP2C9 inducer. (Moderate) The plasma concentrations of methadone may be elevated when administered concurrently with cobicistat. When initiating methadone in patients currently on a regimen containing cobicistat and atazanavir or darunavir, use the lowest methadone starting dose and slowly titrate to desired effect. When initiating antiretroviral regimens containing cobicistat and atazanavir or darunavir to patients on methadone, an adjustment of methadone dose may be needed. Monitoring for adverse effects, such as CNS side effects or respiratory depression, is recommended during coadministration. Methadone is metabolized primarily by the cytochrome P450 isoenzymes CYP2C19, CYP3A4, and CYP2B6, and to a lesser extent, by CYP2C9 and CYP2D6. Methadone also is a substrate of P-glycoprotein (P-gp). Cobicistat is an inhibitor of CYP3A4, CYP2D6, and P-gp.

**Codiene; Guaiifenesin:** (Major) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Codiene; Phendelphrine; Promethazine:** (Major) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Codeine:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**COMT inhibitors:** (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants such as COMT inhibitors can lead to additive respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Conivaptan:** (Major) Avoid coadministration of conivaptan, a CYP3A4/P-glycoprotein (P-gp) inhibitor and methadone, a CYP3A4/P-gp substrate. Conivaptan use may result in elevated methadone serum concentrations. According to the manufacturer, concomitant use of conivaptan, a strong CYP3A4 inhibitor, and CYP3A substrates, such as methadone, should be avoided. Coadministration of conivaptan with other CYP3A substrates has resulted in increased mean AUC values (2 to 3 times). Theoretical, similar pharmacokinetic effects could be seen with methadone. Treatment with methadone may be initiated no sooner than 1 week after completion of conivaptan therapy.

**Crizotinib:** (Major) Monitor ECGs for QT prolongation and monitor electrolytes in patients receiving crizotinib concomitantly with methadone; carefully consider the risks versus benefits of coadministration. An interruption of therapy, dose reduction, or discontinuation of therapy may be necessary. Monitor patients taking crizotinib if QT prolongation occurs. Methadone is a substrate of CYP3A4 and can potently inhibit CYP3A4, with an increased risk for QT prolongation and torsade de points (TDP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Crizotinib is a moderate CYP3A4 inhibitor that has been associated with concentration-dependent QT prolongation.
Crofelemer: (Moderate) Pharmacodynamic interactions between crofelemer and opiate agonists are theoretically possible. Crofelemer does not affect GI motility mechanisms, but does have antiarrheal effects. Patients taking medications that can decrease GI motility, such as opiate agonists, may be at greater risk for serious complications from crofelemer, such as constipation with chronic use. Use caution and monitor GI symptoms during coadministration.

Cyclizine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Cyproheptadine: (Major) Concomitant use of opiate agonists with skeletal muscle relaxants may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with skeletal muscle relaxants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a skeletal muscle relaxant, reduced dosages are recommended; in opioid-naive adults, use an initial methadone dose of 2.5 mg PO every 12 hours. If a skeletal muscle relaxant is prescribed for a patient taking an opiate agonist, use a lower initial dose of the skeletal muscle relaxant and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Coadminister methadone with drugs known to prolong the QT interval with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Cyclobenzaprine shares properties similar to the tricyclic antidepressants (TCAs) and to the Class IA antiarrhythmic agents and may prolong the QT interval, particularly in overdose or with higher-dose prescription therapy (elevated serum concentrations).

Cyclophosphamide: (Moderate) Use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 2 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Dalfopristin; Quinupristin: (Moderate) The concurrent administration of methadone and inhibitors of CYP3A4, such as streptogramins (dalfopristin; quinupristin), may result in increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects, proarrhythmias, and torsades de pointes when high doses of methadone are used. Danazol: (Moderate) Danazol is a CYP3A4 inhibitor and can decrease the hepatic metabolism of drugs that are CYP3A4 substrates including methadone.

Dantrolene: (Major) Concomitant use of opiate agonists with skeletal muscle relaxants may cause respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 2 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Darifenacin: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when darifenacin, an anticholinergic drug for overactive bladder, is used with opiate agonists. The concomitant use of these drugs together may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus and decrease increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects, proarrhythmias, and torsades de pointes when high doses of methadone are used. Danazol: (Moderate) Coadministration of danazol with methadone is expected to result in decreased methadone concentrations. Patients should be monitored for opiate abstinence syndrome; an increase in methadone dosage may be considered based on clinical response.

Darunavir: (Moderate) Coadministration of darunavir with methadone is expected to result in decreased methadone concentrations. Patients should be monitored for opiate abstinence syndrome; an increase in methadone dosage may be considered based on clinical response. (Moderate) The plasma concentrations of methadone may be elevated when administered concurrently with co-administered. When initiating methadone in patients currently on a regimen containing co-administered and atazanavir or darunavir, use the lowest methadone starting dose and slowly titrate to desired effect. When initiating antiretroviral regimens containing co-administered and atazanavir or darunavir on patients to methadone, an adjustment of methadone dosage may be needed. Monitoring for adverse effects, such as CNS side effects or respiratory depression, is recommended during coadministration. Methadone is metabolized primarily by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2B6. Methadone also is a substrate inhibitor of CYP3A4, CYP2D6, and P-gp. Co-administered is a CYP3A4 and CYP2D6 inhibitor and may result in increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects and potential for QT prolongation and torsades de pointes when high doses of methadone are used. Dasp contemplating the QT interval and torsades de pointes (TdP), and that the effect may be additive to the QT prolongation risk from methadone. Additionally, due to effects on CYP enzymes responsible for hepatic metabolism, ritonavir may alter the response to various opioid agonists. Administration of methadone and ritonavir has resulted in a 36% decrease in methadone AUC and 38% decrease in methadone Crmax in some reports; increased methadone doses may be required. However, any methadone dose increase should be approached with caution.

Dastatinib: (Major) Due to a possible risk for QT prolongation and torsade de points (TdP), dasatinib and methadone should be used together cautiously. In vitro studies have shown that dasatinib has the potential to prolong cardiac ventricular repolarization (prolong QT interval). The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include dasaretix.

Degarelix: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Degarelix is metabolized primarily by the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP2B6. Methadone also is a substrate of CYP3A4, CYP2D6, and P-gp. Co-administered is a CYP3A4 and CYP2D6 inhibitor and may result in increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects and potential for QT prolongation and torsades de pointes when high doses of methadone are used. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include degarelix.

Delavirdine: (Major) The concurrent administration of methadone and inhibitors of cytochrome P450 3A4, such as delavirdine, may result in increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects and potential for QT prolongation and torsades de points when high doses of methadone are used (e.g., 200 mg/day PO in adult patients). A decrease in methadone doses may be required.

Desfuroate: (Moderate) Concurrent use with opiate agonists can decrease the minimum alveolar concentration (MAC) of desflurane needed to produce anesthesia.

Desloratadine: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as tricyclic antidepressants should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised.
**Deuterobenzamine:** (Major) For patients taking a deuterobenzamine dosage more than 24 mg/day with methadone, assess the QTc interval before and after increasing the dosage of either medication. The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Clinically relevant QTc prolongation may occur with deuterobenzamine. Methadone is considered to be associated with an increased risk for QT prolongation especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Additionally, concomitant use of opiate agonists with deuterobenzamine may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with medications associated with CNS depression, such as deuterobenzamine, to only patients for whom alternative treatment options are inadequate. Reduced dosages of methadone are recommended if methadone is initiated in patients taking medications associated with CNS depression; in opiate-naive adults, an initial methadone dose of 2.5 mg every 12 hours is recommended. If deuterobenzamine is prescribed in a patient taking an opiate agonist, use a lower initial dose of deutetrabenazine.

**Desloratadine:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Dexmedetomidine:** (Moderate) Co-administration of dexmedetomidine with opiate agonists likely lead to an enhancement of CNS depression. Dexpanthenol: (Moderate) Use caution when using dexpanthenol with drugs that decrease gastrointestinal motility, such as opiate agonists, as it may decrease the effectiveness of dexpanthenol.

**Dextromethorphan; Diphenhydramine; Phenytoin:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Dextromethorphan; Promethazine:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Drugs with a potential risk for QT prolongation that should be used cautiously with methadone include promethazine. Additionally, use of methadone with another CNS depressant can lead to additive sedation, respiratory depression, hypotension, or coma. Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; for example, in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Dextromethorphan; Quinidine:** (Severe) Quinidine administration is associated with QT prolongation and torsades de pointes (TdP). Quinidine inhibits CYP2D6 and has QT-prolonging actions; quinidine is contraindicated with other drugs that prolong the QT interval and are metabolized by CYP2D6 as the effects on the QT interval may be increased during concurrent use of these agents. Drugs that prolong the QT and are substrates for CYP2D6 that are contraindicated with quinidine include methadone.

**Diazipam:** (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. If parenteral diazepam is used with an opiate agonist, reduce the opiate agonist dose by at least 1/3. Educate patients about the risks of respiratory depression and sedation.

**Didanosine, ddI:** (Major) Methadone decreases the AUC and Cmax of didanosine, ddI. Methadone may slow absorption, and increase first-pass metabolism of didanosine. Methadone decreased the AUC of didanosine tablets by 60% and the Cmax by 64% suggesting that increased doses of didanosine may be required in patients receiving methadone. Do not coadminister methadone with Videx pediatric powder due to significant decreases in didanosine concentrations. If coadministration of methadone and didanosine is necessary, the extended-release capsules are recommended (Videx EC). Patients should be closely monitored for adequate clinical response when the extended-release capsules are coadministered with methadone, including monitoring for changes in HIV/ RNA viral load.

**Dihydrocodeine; Guaifenesin; Pseudoephedrine:** (Major) Concomitant use of methadone with another CNS depressant like dihydrocodeine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also, consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Diltiazem:** (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Doxepin:** (Moderate) Additive hyponatremic effects may be seen in patients treated with desmopressin and drugs associated with water intoxication, hyponatremia, or SIADH including opiate agonists. Use combination with caution, and monitor patients for signs and symptoms of hyponatremia.

**Drugs that prolong the QT interval:** Quinidine administration is associated with QT prolongation and torsades de pointes (TdP). Quinidine inhibits CYP2D6 and has QT-prolonging actions; quinidine is contraindicated with other drugs that prolong the QT interval and are metabolized by CYP2D6 as the effects on the QT interval may be increased during concurrent use of these agents. Drugs that prolong the QT and are substrates for CYP2D6 that are contraindicated with quinidine include methadone.
depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Diphenhydramine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone with patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Diphenhydramine: Phenylephrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial hydrocodone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Diphenhydramine: Naproxen: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Diphenhydramine: Phenylephrine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Disopyramide: (Major) The need to coadminister methadone with disopyramide should be done with extreme caution and a careful assessment of treatment risks versus benefits. Disopyramide is an antiarrhythmic agent, is associated with a well-established risk of QT prolongation and torsades de pointes (TdP) especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Because of the potential for TdP, use of disopyramide with methadone is contraindicated. Disopyramide, a Class III antiarrhythmic agent, is associated with a well-established risk of QT prolongation and TdP.

Dolasetron: (Major) Due to a possible risk for QT prolongation and torsades de points (TdP), dolasetron and methadone should be used together cautiously. Dolasetron has been associated with a dose-dependent increase in QT, PR, and QRS intervals on an electrocardiogram. Use of dolasetron injection for the prevention of chemotherapy-induced nausea and vomiting is contraindicated because the risk of QT prolongation is higher with the doses required for this indication; when the injection is used at lower doses (i.e., those approved for post-operative nausea and vomiting) or when the oral formulation is used, the risk of QT prolongation is lower and caution is advised. he need to coadminister methadone with dolasetron should be done with extreme caution and a careful assessment of treatment risks versus benefits. Dolasetron is an antiemetic agent, is associated with a well-established risk of QT prolongation and Torsades de Pointes (TdP). Dolasetron is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Supratherapeutic doses of dolasetron (75 to 300 mg/day) have also been associated with prolongation of the QT interval.

Donepezil: (Major) Case reports indicate that QT prolongation and torsade de points (TdP) can occur during donepezil therapy. Donepezil is considered a drug with a known risk of TdP. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring include donepezil and memantine. Donepezil: Memantine: (Major) Case reports indicate that QT prolongation and torsade de points (TdP) can occur during donepezil therapy. Donepezil is considered a drug with a known risk of TdP. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring include donepezil and memantine.

Doxacurium: (Moderate) Concomitant use of methadone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Doxepin: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as tricyclic antidepressants should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Supratherapeutic doses of doxepin (75 to 300 mg/day) have also been associated with prolongation of the QT interval.

Diphenhydramine: Ibuprofen: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Diphenhydramine: Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial hydrocodone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Diphenhydramine: Phenylephrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial hydrocodone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Disopyramide: (Major) Close clinical monitoring is advised with coadministration. Use of these drugs together may cause the plasma concentration of methadone to decrease, thereby resulting in decreased methadone efficacy. No dose adjustments are required when initiating concurrent treatment; however, the maintenance dose of methadone may need to be adjusted in some patients. In addition, due to the potential for QT prolongation and torsade de points (TdP), caution is advised when administering disopyramide with methadone. A careful assessment of treatment risks versus benefits should be conducted prior to coadministration. When initiating concurrent treatment no dose adjustments are required; however, cases of methadone may need to be adjusted during maintenance therapy. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Because of the potential for TdP, use of disopyramide with methadone is contraindicated. Disopyramide, a Class III antiarrhythmic agent, is associated with a well-established risk of QT prolongation and TdP.
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in adult patients). Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially in the initiation of the second concomitant treatment (increases) of either agent. Methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine.

Doxylamine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Dronabinol, THC: (Moderate) Concomitant use of opiate agonists and other CNS depressants such as dronabinol, THC may result in respiratory depression, CNS depression, and/or hypotension. Prior to concurrent use of opiate agonists in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. When concomitant treatment is necessary, reduce the dose of 1 or both drugs. When levophanol is used with dronabinol, reduce the initial levorphanol dose by approximately 50% or more.

Dronedarone: (Severe) The concomitant use of dronedarone and methadone is contraindicated. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that dronedarone inhibits the potassium channel and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been observed in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Droperidol: (Major) Droperidol should be administered with extreme caution to patients receiving other agents that may prolong the QT interval. Droperidol administration is associated with an established risk for QT prolongation and torsades de pointes (TdP). Any drug known to have potential to prolong the QT interval should not be coadministered with droperidol. Drugs with a possible risk for QT prolongation and TdP that should be administered with caution include efavirenz, some HIV protease inhibitors (PIs) such as ritonavir-boosted indinavir and saquinavir, and the antiemetic droperidol. In addition, methadone and eliglustat may result in additive effects on the QT interval and, potentially, increased plasma concentrations of methadone, further increasing the risk of serious adverse events (e.g., respiratory depression, sedation, QT prolongation, cardiac arrhythmias). Methadone-maintenance therapy may experience opiate withdrawal symptoms when efavirenz is added to their HIV-regimen. Methadone-maintenance patients should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Efavirenz: (Major) Coadministration of efavirenz and methadone may increase the risk for QT prolongation and torsade de points (TdP). QT prolongation has been observed with use of efavirenz. Although data are limited, the manufacturer of efavirenz recommends an alternative antiretroviral be considered for patients receiving medications with a known risk for TdP. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, efavirenz induces methadone metabolism via CYP3A4 and is associated with significant decreases in methadone concentrations. Clinical reports suggest that patients who are stabilized on methadone-maintenance therapy may experience opiate withdrawal symptoms when efavirenz is added to their HIV-regimen. Methadone-maintenance patients should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Emtricitabine; Tenofovir: (Major) Coadministration of efavirenz and methadone may increase the risk for QT prolongation and torsade de points (TdP). QT prolongation has been observed with use of efavirenz. Although data are limited, the manufacturer of efavirenz recommends an alternative antiretroviral be considered for patients receiving medications with a known risk for TdP. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, efavirenz induces methadone metabolism via CYP3A4 and is associated with significant decreases in methadone concentrations. Clinical reports suggest that patients who are stabilized on methadone-maintenance therapy may experience opiate withdrawal symptoms when efavirenz is added to their HIV-regimen. Methadone-maintenance patients should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Eliglustat: (Major) Coadministration of methadone and eliglustat may result in increased opioid plasma concentrations and an increased risk for QT prolongation. If coadministration is necessary, use great caution and monitor patients closely at frequent intervals. Consider reducing the dosage of methadone and eliglustat. Eliglustat is a CYP2D6 and P-glycoprotein inhibitor, and is predicted to cause PR, QRS, and/or QT prolongation at significantly elevated plasma concentrations. Although methadone is primarily metabolized by other CYP450 isoenzymes (i.e., CYP3A4, CYP2B6, CYP2C19), it is metabolized to a lesser extent by CYP2D6 and is considered a P-gp substrate. In addition, methadone is independently associated with a risk for QT prolongation and torsade de points (TdP). Coadministration of methadone and eliglustat may result in additive effects on the QT interval, and potentially, increased plasma concentrations of methadone, further increasing the risk of serious adverse events (e.g., respiratory depression, sedation, QT prolongation, cardiac arrhythmias). Methadone-maintenance patients should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Eltorbopag: (Moderate) Eltorbopag is a UDP-glucuronosyltransferase inhibitor. Opiate agonists are a substrate of UDP-glucuronosyltransferases. The presence or effect of drug interaction is not known; however, elevated concentrations of the opiate agonist is possible. Monitor patients for adverse reactions if eltorbopag is administered with an opiate agonist.

Eluxadoline: (Major) Avoid use of eluxadoline with medications that may cause constipation, such as opiate agonists. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle within the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be exacerbated by the concomitant use of some opiate agonists or may be inhibited by eluxadoline. Although the CYP3A4 inhibitory effects of eluxadoline have not been definitively established, the manufacturer recommends caution when administering eluxadoline concurrently with CYP3A4 substrates that have a narrow therapeutic index, such as fentanyl and alfentanil. Closely monitor for increased side effects if these drugs are administered together. Discontinue use of eluxadoline in patients who develop severe constipation lasting more than 4 days.

Elvitegravir: (Moderate) Caution is warranted when elvitegravir is administered with methadone as there is a potential for decreased methadone concentrations and the dosage of methadone may need to be increased. Methadone is partially metabolized by CYP2C9, while elvitegravir is a CYP2C9 inducer.

Emtricitabine; Rilpivirine; Tenofovir alafenamide: (Major) Close clinical monitoring is advised with coadministration. Use of these drugs together may cause the plasma concentration of methadone to decrease, thereby resulting in decreased methadone efficacy. No dose adjustments are required when initiating concurrent treatment; however, the maintenance dose of methadone may need to be adjusted in some patients. In addition, due to the potential for QT prolongation and torsade de points (TdP), caution is advised when administering rilpivirine with methadone. A careful assessment of treatment risks versus benefits should be conducted prior to coadministration. When initiating methadone, dose adjustments are required; however, the dose of methadone may need to be adjusted during maintenance therapy. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported...
in patients receiving doses commonly used for maintenance treatment of opioid addiction. Suipratherapeutic doses of rilpivirine (75 to 300 mg/day) have also been associated with prolongation of the QT interval. **Etorphine**: (Moderate) Close clinical monitoring is advised with coadministration. Use of these drugs together may cause the plasma concentration of methadone to decrease, thereby resulting in decreased methadone efficacy. No dose adjustments are required; however, the maintenance dose of methadone may need to be adjusted in some patients. In addition, due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering rilpivirine with methadone. A careful assessment of treatment risks versus benefits should be considered prior to coadministration. When initiating concurrent treatment no dose adjustments are required; however, the dose of methadone may need to be adjusted during maintenance therapy. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Suipratherapeutic doses of rilpivirine (75 to 300 mg/day) have also been associated with prolongation of the QT interval. **Enfurane**: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Halogenated anesthetics can prolong the QT interval. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Suipratherapeutic doses of rilpivirine (75 to 300 mg/day) have also been associated with prolongation of the QT interval. **Erythromycin**: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants such as COMT inhibitors can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. **Enalaprilat**: (Major) Monitor for reduced efficacy of methadone and signs of opioid withdrawal if coadministration with enalaprilat is necessary; these effects may be more pronounced and may induce multiple CYP enzyme inhibition. Consider increasing the dose of methadone as needed. If enalaprilat is discontinued, consider a dose reduction of methadone and frequently monitor for signs or respiratory depression and sedation. Methadone is a substrate of CYP2C9, CYP2C19, and CYP3A4; enalaprilat is a strong CYP3A4 inducer, as well as a moderate inducer of both CYP2C9 and CYP2C19. Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. **Estradiol**: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering estradiol with methadone. The need to coadminister these drugs should be done with careful assessment of treatment risks versus benefits. Estradiol is associated with prolongation of the QT interval and TdP. Methadone is also considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses averaging approximately 400 mg/day in adult patients. In addition, methadone is a substrate for CYP3A4 and P-glycoprotein (P-gp), while estradiol is a CYP3A4 and P-gp inhibitor. Concurrent use may result in increased serum concentrations of methadone. **Estramustine**: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering estramustine with methadone. The need to coadminister these drugs should be done with careful assessment of treatment risks versus benefits. Estramustine is associated with prolongation of the QT interval and TdP. Methadone is also considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses averaging approximately 400 mg/day in adult patients. In addition, methadone is a substrate for CYP3A4 and P-glycoprotein (P-gp), while estramustine is a CYP3A4 and P-gp inhibitor. Concurrent use may result in increased serum concentrations of methadone. **Estrone**: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and treatments that are needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. **Estzopiclone**: (Moderate) Concomitant use of methadone with eszopiclone can lead to additive respiratory depression, hypotension, profound sedation, or coma. In addition, the risk of next-day psychomotor impairment is increased during co-administration of eszopiclone and other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of eszopiclone. Monitor patients for sedation and respiratory depression. **Ethinyl Estradiol**: (Moderate) Concomitant use of methadone with ethinyl estradiol can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to prescribing ethinyl estradiol, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages, particularly if the patient is not likely to be compliant with avoiding alcohol. In opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Monitor patients for sedation and respiratory depression.
Ethotoin: (Moderate) Additive CNS depression including respiratory depression, hypotension, profound sedation, or coma may occur with the combined use of the hydantoin (e.g., phenytoin, fosphenytoin, and ethothoin) and methadone. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use of the patient's overall treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced doses if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Methadone is a primary substrate for the CYP3A4 isoenzyme. Serum concentrations of methadone may decrease due to CYP3A4 induction by phenytoin, fosphenytoin, and possibly ethothoin; withdrawal symptoms may occur.

Etomate: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include general anesthetics. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use of the patient's overall treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced doses if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Etravirine: (Moderate) Etravirine dose adjustments are expected when coadministered with etravirine. However, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.

Everolimus: (Moderate) Frequently monitor for respiratory depression and sedation if concurrent use of everolimus is necessary; consider reducing the dose of methadone if clinically appropriate. If everolimus is discontinued, monitor for evidence of opioid withdrawal; consider increasing the methadone dose if needed. Methadone is a CYP3A4 and CYP2D6 substrate; coadministration with weak CYP3A4/2D6 inhibitors like everolimus can increase methadone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of methadone. If everolimus is discontinued, methadone plasma concentrations may decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to methadone.

Ezogabine: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include ezogabine. In addition, due to the CNS effects of ezogabine, an enhanced CNS depressant effect may occur during concurrent use of other centrally-acting medications such as opiate agonists. Patients should be monitored for excessive somnolence during concurrent therapy with these agents.

Fenofibric Acid: (Minor) At therapeutic concentrations, fenofibric acid is a weak inhibitor of CYP2C19 and a mild-to-moderate inhibitor of CYP2C9. Concomitant use of fenofibric acid with CYP2C19 and CYP2C9 substrates, such as methadone, has not been formally studied. Fenofibric acid may theoretically increase plasma concentrations of CYP2C19 and CYP2C9 substrates and could lead to toxicity for drugs that have a narrow therapeutic range. Monitor the therapeutic effect of methadone during coadministration with fenofibric acid.

Fentanyl: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use of the patient's overall treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced doses if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Fesoterodine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when fesoterodine, an anticholinergic drug for overactive bladder, is used with opiate agonists. The combination of these two drugs together may increase the risk of urinary retention, constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Both agents may also cause drowsiness or blurred vision, and patients should use care in driving or performing other hazardous tasks until the effects of the drugs are known.

Fingolimod: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include fingolimod. Fingolimod initiation results in decreased heart rate and may prolong the QT interval. After the first fingolimod dose, overnight monitoring with continuous ECG in a medical facility is advised for patients taking QT prolonging drugs with a known risk of torsades de points (TdP). Fingolimod has not been studied in patients with drugs that prolong the QT interval, but drugs that prolong the QT interval have been associated with cases of TdP in patients with bradycardia.

Flecainide: (Major) Due to the potential for QT prolongation and torsade de points (TdP), caution is advised when administering methadone with flecainide. The need to coadminister these drugs should be done with a careful assessment of treatment risks versus benefits. Methadone is associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Flecainide, a Class IC antiarrhythmic, is also associated with a possible risk for QT prolongation and/or TdP. Flecainide increases the QT interval, but largely due to prolongation of the QRS interval. Although causality for TdP has not been established for flecainide, patients receiving concurrent drugs which have the potential for QT prolongation may have an increased risk of developing proarrhythmias.

Filbanserin: (Moderate) The concomitant use of filbanserin with CNS depressants, such as opiate agonists, may increase the risk of CNS depression (e.g., dizziness, somnolence) compared to the use of filbanserin alone. Patients should avoid activities requiring full alertness (e.g., operating machinery or driving) until at least 6 hours after each dose and until they know how filbanserin affects them.

Fluconazole: (Major) Fluconazole and methadone concomitantly with caution. Both fluconazole and methadone are associated with QT prolongation and TdP, especially at higher doses (> 100 mg/day). Additionally, fluconazole is a moderate inhibitor and methadone is a weak inhibitor of CYP3A4, CYP2C19, and CYP2C9. Therefore, increased concentrations of methadone may occur which may result in prolonged duration of action, increased sedation, respiratory depression, QT prolongation, or other side effect. The manufacturer of fluconazole states dosage adjustments of methadone may be necessary during concomitant therapy with fluconazole.
the R-enantiomer (the active moiety) was increased by the addition of fluoxetine. Patients may experience increases in CNS depressive effects or respiratory depression. Thus, methadone-treated patients receiving fluoxetine should be carefully monitored and dosage adjustments may be warranted.

Fluoxetine: Olanzapine: (Major) Coadministration may increase the risk of serotonin syndrome, QT prolongation, torsade de points (TdP), or opioid-related side effects. QT prolongation and TdP have been reported in patients treated with fluoxetine and the manufacturer recommends caution when using fluoxetine with other drugs that prolong the QT interval. Methadone is associated with an increased risk for QT prolongation and TdP, especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, both fluoxetine and methadone have central serotonergic properties and serotonin syndrome is possible. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome occurs, all serotonergic agents should be discontinued and appropriate medical treatment should be implemented. Lastly, fluoxetine may inhibit the metabolism of methadone via CYP3A4 or CYP2D6. In patients treated with methadone and fluoxetine, the plasma concentration of methadone increased. Interestingly in patients treated with methadone, the R-enantiomer (the active moiety) was increased by the addition of fluoxetine. Patients may experience increases in CNS depressive effects or respiratory depression. Thus, fluoxetine should be carefully monitored and dosage adjustments may be warranted. (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as olanzapine, should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk of QT prolongation and torsade de points (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that fluoxetine inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, fluoxetine may potentiate the CNS-depressant action of methadone. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.

Flurazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Therefore, the use of opiate pain treatment options with benzodiazepines should be avoided. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If fluoxetine is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Fluvanoxamine: (Moderate) Coadministration of fosamprenavir and methadone can decrease plasma levels of methadone. While data suggest that this interaction is not clinically relevant, it would be prudent to monitor patients for methadone-related efficacy and adjust the dose as needed.

Fosarnet: (Moderate) Pain medications that contain opiate agonists may intensify CNS depressive adverse effects seen with fosampanrevir use, such as drowsiness or dizziness. Patients should limit activity until they are aware of how coadministration affects them.

Gefitinib: (Moderate) Caution should be exercised when administering gefitinib with other CYP2D6 substrates, such as methadone; however, CYP2D6 is not the primary route of methadone metabolism. The clinical significance of this interaction is not known.

Gemifloxacin: (Major) The need to coadminister methadone with gemifloxacin should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Gemifloxacin may also prolong the QT interval in some patients, with the maximal change in the QTc interval occurring...
approximately 5 to 10 hours following oral administration. The likelihood of QTc prolongation may increase with increasing dose of gemifloxacin; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher.

**Gemtuzumab Ozogamicin:** (Major) Use gemtuzumab ozogamicin and methadone together with caution due to the potential for additive QT interval prolongation and risk of torsade de points (TdP). If these agents are used together, obtain an ECG and serum electrolytes prior to the start of gemtuzumab and as needed during treatment. Although QT interval prolongation has not been reported with gemtuzumab, it has been reported with other drugs and gemtuzumab has been shown to induce CYP2D6 and QT prolongation and TdP, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

**Goserelin:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies in humans and in vitro, have shown that goserelin, a synthetic luteinizing hormone-releasing hormone agonist, may increase the risk of QTc prolongation and TdP. Methadone is considered to be associated with a moderate risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Therefore, methadone should be used cautiously with drugs having a possible risk for QT prolongation and torsades de points (TdP) such as goserelin.

**Grapefruit Juice:** (Moderate) The concurrent administration of methadone and inhibitors of CYP3A4, such as grapefruit juice, may result in increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects and potential for QT prolongation and torsades de points with high doses of methadone being used.

**Guanafexin; Hydrocodone:** (Major) Concomitant use of hydrocode with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocode in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocode should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocode at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Guanabenz; Hydrocodone:** (Moderate) Concomitant use of hydrocode with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocode in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocode should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocode at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Guanabenz; Methadone:** (Moderate) Concomitant use of methadone with other drugs that have serotonergic properties such as guanabenz. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome is suspected, discontinue granisetron and concurrent serotonergic agents and initiate appropriate medical treatment. In addition, methadone is associated with a risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Therefore, methadone should be used cautiously with drugs having a possible risk for QT prolongation and torsades de points (TdP) such as granisetron.

**Haloperidol:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Haloperidol is a primary substrate for the CYP2D6 isoenzyme. Serum concentrations of methadone may decrease due to CYP2D6 induction by phenytoin, fosphenytoin, and possibly ethotoin; withdrawal symptoms may occur. Also opiate agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.

**Halothane:** (Major) At high doses, methadone is considered to be associated with an increased risk for QT prolongation and torsades de points. This effect may be enhanced if coadminister methadone with halothane. The need to co-administer methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Halothane is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, methadone is a substrate for CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes may result in increased serum concentrations of methadone. Drugs with a possible risk for QT prolongation and TdP include haloperidol. Concomitant use of methadone with another CNS depressant, such as haloperidol, haloperidol, can also lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution in reduced dosages if used concurrently with a CNS depressant; initiate methadone at 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

**Hydantoins:** (Moderate) Additive CNS depression including respiratory depression, hypotension, profound sedation, or coma may occur with the combined use of the hydantoin (e.g., phenytoin, fosphenytoin, and ethosuximide) and methadone. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Methadone is a primary substrate for the CYP3A4 isoenzyme. Serum concentrations of methadone may decrease due to CYP3A4 induction by phenytoin, fosphenytoin, and possibly ethosuximide; withdrawal symptoms may occur.

**Hydrochlorothiazide, HCTZ; Methyldopa:** (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants such as opiate agonists, when administered concomitantly.

**Hydrochlorothiazide, HCTZ; Spironolactone:** (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also opiate agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.

**Hydrochlorothiazide, HCTZ; Spironolactone:** (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also opiate agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.

**Hydrochlorothiazide, HCTZ; Spironolactone:** (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also opiate agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.
Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Hydrocodone; Ibuprofen: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Hydroxyzine; Methadone: (Major) Concomitant use of hydroxyzine with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydroxyzine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Hydroxyzine should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydroxyzine at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Methadone: (Major) Concomitant use of methadone with another CNS depressant, such as oxycodone, can lead to additive respiratory depression, hypotension, profound sedation, coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Hydroxyzine; Methadone; Methyamine; Methyle: (Minor) Hydroxyzine should be used cautiously and with close monitoring with methadone due to the potential for increased risk of QT prolongation and torsades de points (TpD). In vitro studies indicate that hydroxyzine increases the metabolic rate of CYP2D6 isoenzymes. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, concomitant use of methadone with another CNS depressant, such as hydroxyzine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.
of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Iloperidone: (Major) Iloperidone has been associated with QT prolongation; however, torsade de pointes (Tdp) has not been reported. According to the manufacturer, since iloperidone may prolong the QT interval, it should be avoided in combination with other agents also known to have this effect, such as methadone. Methadone is considered to be associated with an increased risk for QT prolongation and Tdp, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with iloperidone as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage adjustments (increases) of either agent. In addition, concomitant use of methadone and iloperidone can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to the concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine.

Indinavir: (Moderate) Caution is advised with the coadministration of indinavir and methadone as concurrent use may result in increased serum concentrations of methadone. Indinavir is a CYP3A4 inhibitor and may decrease the metabolism of methadone, a CYP3A4 substrate. However, administration of indinavir (800 mg every 8 hours) to methadone (200 mg daily) for one week, in subjects on methadone maintenance, resulted in no change in methadone AUC. Based on a comparison to historical data, there was little or no change in indinavir AUC. Patients should be monitored for increased methadone side effects during concurrent use.

Inotuzumab Ozogamicin: (Major) Avoid coadministration of inotuzumab ozogamicin with methadone due to the potential for additive QT prolongation toxicity. Obtain an ECG and serum electrolytes prior to the start of treatment, after treatment initiation, and periodically during treatment. Inotuzumab is considered to be associated with an increased risk for QT prolongation and Tdp, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Isoconozaconium: (Moderate) Concomitant use of isoconozaconium with methadone may result in increased serum concentrations of methadone. Methadone is a substrate of the hepatic isoenzyme CYP3A4; isoconozaconium, the active moiety of isoconozaconium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.

Isoxsuprazole: (Major) Due to the severity of the interaction of meperidine (a related opioid) with monoamine oxidase inhibitors (MAOIs), a sensitivity test for methadone should be performed in patients taking isoconozaconium by administering repeated small incremental doses of methadone over several hours while carefully monitoring the patient's condition and vital signs. Concomitant use of methadone with a MAOI can lead to additive respiratory depression. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant. Respiratory depression, hypotension, and profound sedation or coma may result.

Isoflurane: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de pointes (Tdp), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with isoflurane as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage adjustments (increases) of either agent. In addition, concomitant use of methadone and isoflurane can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to the concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) Concurrent administration of rifampin and methadone is associated with a 33 to 68% decrease in methadone levels due to induction of methadone metabolism by rifampin. When effective alternatives exist, rifampin should not be administered to patients receiving chronic methadone therapy. However, if rifampin treatment is necessary, the methadone dosage will need to be increased to maintain adequate suppression of opiate withdrawal symptoms.

Isoniazid, INH; Rifampin: (Moderate) Concurrent administration of rifampin and methadone is associated with a 33 to 68% decrease in methadone levels due to induction of methadone metabolism by rifampin. When effective alternatives exist, rifampin should not be administered to patients receiving chronic methadone therapy. However, if rifampin treatment is necessary, the methadone dosage will need to be increased to maintain adequate suppression of opiate withdrawal symptoms.

Itraconazole: (Severe) Methadone is contraindicated for use during and for 2 weeks after itraconazole therapy. Serious cardiovascular events, including EKG changes (i.e., QT prolongation) and cardiac arrhythmias, including ventricular arrhythmias and torsades de pointes, cardiac arrest, and/or sudden death have occurred when these drugs were administered together. Methadone is a CYP3A4 substrate; itraconazole is a strong CYP3A4 inhibitor. Use caution if both drugs are administered together. Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage adjustments (increases) of either agent. In addition, concomitant use of methadone and tricyclic antidepressants can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to the concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Ivacaftor: (Moderate) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as methadone. Ivacaftor is an inhibitor of CYP3A, P-glycoprotein (Pgp), and a weak inhibitor of CYP2C9; methadone is metabolized by CYP3A4. CYP2C9, and is a substrate of Pgp. Co-administration of ivacaftor with CYP3A4, CYP2C9, and Pgp substrates, such as methadone may increase methadone exposure leading to increased therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.

Ivabradine: (Moderate) Caution is advised with the coadministration of ivabradine with methadone due to the potential for additive QT prolongation toxicity. Obtain an ECG and serum electrolytes prior to the start of treatment, after treatment initiation, and periodically during treatment. Ivabradine is considered to be associated with an increased risk for QT prolongation and Tdp, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Ketamine: (Severe) Concomitant use of ketamine with methadone is contraindicated due to the risk of serious adverse events, such as QT prolongation, torsade de pointes, and respiratory and/or CNS depression. If coadministration, ketamine may inhibit the CYP3A4 metabolism of methadone, resulting in elevated methadone plasma concentrations. Furthermore, ketamine itself can in prolong the QT interval. Coadministration with methadone can increase the risk for QT prolongation.

Lactulose: (Moderate) Concurrent use of lactulose and methadone can lead to severe constipation and possibly additive CNS depression. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Lamivudine, 3TC; Zidovudine, ZDV: (Moderate) Methadone increases exposure zidovudine, ZDV. Patients should be monitored for zidovudine toxicity. Concomitant methadone treatment; however, routine dose adjustment of zidovudine is not required during coadministration of methadone. Patients who receive both methadone and zidovudine may experience symptoms characteristic of opiate withdrawal and attribute the cause to decreased methadone levels due to zidovudine. However, it is more likely patients are actually experiencing zidovudine side effects due to increased levels since zidovudine has no effect on methadone metabolism. In one pharmacokinetic study (n=8), coadministration of methadone increased the AUC of zidovudine by about 43% (range: 16-54%). It appears methadone inhibits

http://www.pdr.net/drug-summary/Methadone-Hydrochloride-Intensol-Oral-Concentrate-methadone hydrochloride_dose...
zidovudine glucuronidation and, to a lesser extent, decreases zidovudine renal clearance.

**Lapatinib:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, methadone is a substrate for CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes may result in increased serum concentrations of methadone. Drugs with a possible risk for QT prolongation and TdP that inhibit CYP3A4 and P-gp include ketoconazole, clarithromycin, and others. If coadministration is necessary, exercise caution and consider dose reduction of methadone.

**Ledipasvir; Sofosbuvir:** (Moderate) Caution and close monitoring of methadone-associated adverse reactions is advised with concomitant administration of ledipasvir. Methadone is a substrate of the drug transporter P-glycoprotein (P-gp); ledipasvir is a P-gp inhibitor. Taking these drugs together may increase methadone plasma concentrations.

**Lenvatinib:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving lower doses. Methadone is commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with methadone include lenvatinib. QT prolongation was reported in patients with radioactive iodine-refractory differentiated thyroid cancer (RA-raf DTC) in a double-blind, randomized, placebo-controlled clinical trial after receiving lenvatinib daily at the recommended dose; the QT/QTc interval was not prolonged, however, after a single 32 mg dose (1.3 times the recommended daily dose) in healthy subjects.

**Leuprolide:** (Major) Androgen deprivation therapy (e.g., leuprolide) prolongs the QT interval; the risk may be increased with the concurrent use of drugs that may prolong the QT interval. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with leuprolide include methadone.

**Leuprolide; Norethindrone:** (Major) Androgen deprivation therapy (e.g., leuprolide) prolongs the QT interval; the risk may be increased with the concurrent use of drugs that may prolong the QT interval. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with leuprolide include methadone.

**Levobupivacaine:** (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to occasions where alternative treatment options are inadequate, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

**Loratadine:** (Major) Coadministration of loratadine and methadone should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving lower doses. Methadone is commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with loratadine include loperamide.

**Loperamide:** (Major) Coadministration of loperamide and methadone should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with methadone include loperamide. QT prolongation was reported in patients with radioactive iodine-refractory differentiated thyroid cancer (RA-raf DTC) in a double-blind, randomized, placebo-controlled clinical trial after receiving loperamide daily at the recommended dose; the QT/QTc interval was not prolonged, however, after a single 32 mg dose (1.3 times the recommended daily dose) in healthy subjects.

**Lorcainide:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving lower doses. Methadone is commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with methadone include lorcainide. QT prolongation was reported in patients with radioactive iodine-refractory differentiated thyroid cancer (RA-raf DTC) in a double-blind, randomized, placebo-controlled clinical trial after receiving lorcainide daily at the recommended dose; the QT/QTc interval was not prolonged, however, after a single 32 mg dose (1.3 times the recommended daily dose) in healthy subjects.

**Lorazepam:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory
Studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses comparable to those used for maintenance treatment of opioid addiction. Co-administration of a drug that may further increase the risk for QT prolongation and torsades de pointes (TdP). Additive constipation may also be seen with concurrent use of opiate agonists and antidepressants.

Loperamide; Simethicone: (Major) Co-administration of loperamide and methadone should be done with extreme caution and a careful assessment of treatment risks versus benefits. At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, and torsades de pointes (TdP), and cardiac arrest. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses comparable to those used for maintenance treatment of opioid addiction. Co-administration of a drug that may further increase the risk for QT prolongation and torsades de pointes (TdP). Additive constipation may also be seen with concurrent use of opiate agonists and antidepressants.

Loratadine: (Minor) Although loratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness during concurrent use of loratadine with CNS depressants such as opiate agonists.

Loratadine; Pseudoephedrine: (Minor) Although loratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness during concurrent use of loratadine with CNS depressants such as opiate agonists.

Lorazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrently used, it is generally recommended that the lowest effective doses and duration of the treatment be used. Methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naïve adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Lxoxapine: (Moderate) Lxoxapine can potentiate the actions of other CNS depressants such as opiate agonists. Caution should be exercised with simultaneous use of these agents due to potential excessive CNS effects.

Lubiprostone: (Moderate) Non-clinical studies have shown that opioids of the diphenylheptane chemical class (e.g., methadone) dose-dependently reduce the activation of ClC-2 by lubiprostone in the gastrointestinal tract. There is a possibility of a dose-dependent decrease in the efficacy of lubiprostone in patients using diphenpyromethane opioids. Effectiveness in the treatment of opioid-induced constipation in patients taking diphenpyromethane opioids (e.g., methadone) has not been established; patients taking methadone during clinical trials for opioid induced constipation had lower response rates than placebo-treated patients.

Lumacaftor: (Moderate) Theoretically, lumacaftor may increase the side effects of methadone, which is a CYP2C19 and a CYP3A4 substrate. Monitor patients for adverse effects of methadone, such as CNS and respiratory depression. In vitro, therapeutic doses of lumacaftor inhibit the activity of CYP2C19 and CYP3A4 and small systemic concentrations may be noted with topical application, particularly when applied to patients with moderate to severe tinea cruris. No in vivo drug interaction trials were conducted prior to the approval of lumacaftor.

Lumacaftor; Ivaacaftor: (Moderate) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP29 substrates, such as methadone. Ivaacaftor is an inhibitor of CYP3A, P-glycoprotein (Pgp), and a weak inhibitor of CYP2C9; methadone is metabolized by CYP3A4, CYP2C9, and is a substrate of Pgp. Co-administration of ivacaftor with CYP3A, CYP2C9, and Pgp substrates, such as methadone may increase methadone exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined (Major). Lumacaftor; ivacaftor may reduce the efficacy of methadone by decreasing its systemic exposure. If used together, monitor patients closely for loss of methadone efficacy; a methadone dosage adjustment may be required to obtain the desired therapeutic effect. Methadone is a substrate of CYP3A4 (primary), CYP2B6, and CYP2C9. Lucarnia is a strong CYP3A4 inducer; in vitro data also suggest that lumacaftor may induce CYP2B6 and CYP2C19 and induce and/or inhibit CYP2C9. Lumacaftor: (Moderate) Lumacaftor; ivacaftor may reduce the efficacy of methadone by decreasing its systemic exposure. If used together, monitor patients closely for loss of methadone efficacy; a methadone dosage adjustment may be required to obtain the desired therapeutic effect. Methadone is a substrate of CYP3A4 (primary), CYP2B6, CYP2C9, and CYP2C19. Lumacaftor is a strong CYP3A4 inducer; in vitro data also suggest that lumacaftor may induce CYP2B6 and CYP2C9 and induce and/or inhibit CYP2C9. Lansoprazole: (Moderate) Due to the CNS effects of lansoprazole, caution should be used when lansoprazole is given in combination with other centrally acting medications such as opiate agonists.

Magnesium Sulfate: (Minor) Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as opiate agonists. Caution should be exercised when using these agents concurrently.

Maprotiline: (Major) The need to coadminister maprotiline with methadone to prolong the QT interval, such as maprotiline, should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, concomitant use of methadone with another CNS depressant, such as maprotiline, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Consider a lower dose of the CNS depressant.

Meclozine: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include sedating H1-blockers. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Mefloquine: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering mefloquine with methadone. Mefloquine is a CYP3A4 substrate, so co-administration of mefloquine and methadone may increase the risk for QT prolongation and torsades de pointes (TdP). Additive constipation may also be seen with concurrent use of opiate agonists and antidepressants.

Meperidine: (Major) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs.
Methadone Hydrochloride Intensol Oral Concentrate (methadone hydrochloride) dose, ...
Minocycline: (Minor) Injectable minocycline contains magnesium sulfate heptahydrate. Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as opiate agonists. Caution should be exercised when using these agents concurrently.

Mirabegron: (Moderate) Mirabegron is a moderate CYP2D6 inhibitor. Exposure of drugs metabolized by CYP2D6 such as methadone may be increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary.

Mirtazapine: (Major) Co-administration of methadone with drugs known to prolong the QT interval, such as mirtazapine, should be done with extreme caution and a careful assessment of the risk versus benefit. Mirtazapine is associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses (greater than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple doses of methadone, although there are reports in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, coadministration of methadone and other CNS depressants such as mirtazapine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to using methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression, the duration of use, and the patient's overall response to treatment. Assess alcohol or illicit drug use. Reduced dosages of methadone should be used with other CNS depressants. In opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Mitotane: (Use caution) Use of mitotane and methadone are used concomitantly, and monitor for decreased efficacy of methadone and a possible change in dosage requirements. Mitotane is a strong CYP3A4 inducer and methadone is a CYP3A4 substrate; coadministration may result in decreased plasma concentrations of methadone. Concurrent administration of another strong CYP3A4 inducer, rifampin, and methadone is associated with a 33 to 68% decrease in methadone levels due to induction of methadone metabolism by rifampin.

Mivacurium: (Moderate) Concomitant use of mivacurium with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Molindone: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants, such as molindone, can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or molindone is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced depression can potentiate the sedating effects of opioids.

Morphine: (Major) Concomitant use of morphine with methadone can potentiate the effects of both drugs on respiration, blood pressure, and alertness. Profound sedation and coma may also occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. A reduced dosage of morphine and/or methadone is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release capsules; 30 mg or less PO every 24 hours; extended-release capsules). Monitor patients for sedation and respiratory depression.

Morphine; Naltrexone: (Major) Concomitant use of morphine with methadone can potentiate the effects of both drugs on respiration, blood pressure, and alertness. Profound sedation and coma may also occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. A reduced dosage of morphine and/or methadone is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release capsules; 30 mg or less PO every 24 hours; extended-release capsules). Monitor patients for sedation and respiratory depression.

Moxifloxacin: (Major) Concurrent use of methadone and moxifloxacin should be avoided due to an increased risk for QT prolongation and torsade de points (TdP). Moxifloxacin has been associated with prolongation of the QT interval. Additionally, post-marketing surveillance has identified very rare cases of ventricular arrhythmias including TdP, usually in patients with severe underlying proarrhythmic conditions. The likelihood of QT prolongation may increase with increasing concentrations of moxifloxacin, therefore the recommended dose or infusion rate should not be exceeded. Moxifloxacin can also be associated with an increased risk for QT prolongation and TdP (> 200 mg of moxifloxacin every 24 hours but averaging approximately 400 mg/day). Laboratory studies, both in vivo and in vitro, have demonstrated that moxifloxacin inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Nabilone: (Major) Concomitant use of opiate agonists with other central nervous system (CNS) depressants, such as nabilone, can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. A reduced dosage of the opiate and/or methadone is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release capsules; 30 mg or less PO every 24 hours; extended-release capsules). Monitor patients for sedation and respiratory depression.

Mirtazapine: (Major) Co-administration of methadone with mirtazapine can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. A reduced dosage of morphine and/or methadone is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release capsules; 30 mg or less PO every 24 hours; extended-release capsules). Monitor patients for sedation and respiratory depression.

Nalbuphine: (Moderate) Avoid the concomitant use of nalbuphine and opiate agonists, such as methadone. Nalbuphine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Nalbuphine may cause withdrawal symptoms in patients receiving opiate agonists. Nalbuphine will antagonize the therapeutic benefits of opiate agonists and will induce a withdrawal reaction in patients with a naloxone challenge test needs to be performed. If a patient receives nalbuphine, and an opiate agonist is needed for an emergency situation, large doses of opiate agonists may ultimately overwhelm nalbuphine antagonism at opiate receptors. Immediately following administration of exogenous opiate agonists, the opiate plasma concentration may be sufficient to overcome nalbuphine competitive blockade, but the patient may experience deeper and more prolonged respiratory depression and thus, may be in danger of respiratory arrest and circulatory collapse. Non-receptor mediated actions, such as histamine release or bronchoconstriction may occur presumably due to histamine release. A rapidly acting opiate agonist is preferred as the duration of respiratory depression will be shorter. Patients receiving nalbuphine may also experience opiate side effects with low doses of opiate agonists. If the opiate agonist is taken in such a way that high concentrations remain in the body beyond the time nalbuphine exerts its therapeutic effects, serious side effects may occur.

Naproxen: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include nefazodone. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced doses if used concurrently with a CNS depressant; in opioid-naive patients use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Nelfinavir: (Moderate) Nelfinavir decreases methadone concentrations and the dose of methadone may need to be increased. Monitor patient response and titrate the methadone dose as needed.

Nefazodone: (Moderate) The potential for hypotension may be increased when coadministering nesiritide with opiate agonists.

Neuromuscular blockers: (Moderate) Concomitant use of methadone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Nevirapine: (Major) Nevirapine induces the CYP3A4 metabolism of methadone, resulting in decreased methadone AUC by 46% after 3 weeks. Clinically, patients who are stabilized on methadone-maintenance therapy may experience narcotic withdrawal symptoms within 7 days of begin...
nevirapine therapy. Methadone-maintained patients should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly. In one series of patients, an average 45% increase in the methadone dose was required to prevent withdrawal symptoms in patients also receiving nevirapine.

Nicardipine: (Moderate) Nicardipine, a CYP3A4 inhibitor can theoretically inhibit hepatic metabolism of some opiate agonists, CYP3A4 substrates, such as methadone.

Nitrofurantoin: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses averaging approximately 400 mg/day. In addition, methadone is a substrate for CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes may result in increased serum concentrations of methadone. Drugs with a possible risk for QT prolongation and TdP that inhibit CYP3A4, CYP2D6, and P-gp that should be used cautiously with methadone include nitrofurantoin, nitroglycerin, and quinolones.

Nicardipine: (Moderate) Nicardipine, a CYP3A4 inhibitor can theoretically inhibit hepatic metabolism of some opiate agonists, CYP3A4 substrates, such as methadone.

Nitrofurantoin: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as tricyclic antidepressants should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for cardiac effects and sudden death in patients. If concurrent treatment with tricyclic antidepressants is clinically warranted, careful observation of the patient is required, especially during initiation of the second therapy and after dosage adjustments (increases) of either agent. In addition, concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use, patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine.

Ondansetron: (Major) Both ondansetron and methadone may cause QT prolongation, although the relationship of the QT prolongation to co-administration is not established as many of these patients had underlying cardiac disease. Also, ondansetron may decrease the analesic effect of methadone or morphine. If a loss or decrease in pain control occurs with concomitant therapy, consider discontinuing the ondansetron. In a case report, a patient with chondrosarcoma who was receiving chronic methadone experienced a loss of pain control after starting somatostatin as part of a chemotherapy regimen. The patient required increased doses of methadone and was subsequently switched to morphine, intravenous then spinal administration, with no pain relief. After discontinuing the somatostatin, the patient's pain decreased and myosis and sedation occurred for the first time.

Oxitrazepate: (Major) Due to an increased risk for QT prolongation and torsade de points (TdP), caution is advised when administering methadone with oxitrazepate. Methadone is associated with QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine. Additionally, post-marketing surveillance for oxitrazepate has identified very rare cases of TdP.

Olanzapine: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as olanzapine, should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, concomitant use of methadone with another CNS depressant, such as olanzapine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use, patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Omronat: (Major) Methadone may potentiate the analgesic properties of methadone. Methadone is a substrate for CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes may result in increased serum concentrations of methadone. Drugs with a possible risk for QT prolongation and TdP that inhibit CYP2D6 and P-gp that should be used cautiously with methadone include olanzapine, and quinolones.

Osimertinib: (Moderate) Osimertinib may result in QT prolongation and the effect may be additive to the QT prolongation risk from methadone. Alternatively, due to effects on CYP enzymes responsible for hepatic metabolism, ritonavir may alter the response to various opioid agonists. Administration of methadone and ritonavir has resulted in a 36% decrease in methadone AUC and 38% decrease in methadone Cmax in some reports; increased methadone doses may be required. However, any methadone dose increase should be approached with caution. Osimertinib: (Major) The need to coadminister methadone with osimertinib as a CYP3A4 and P-gp inhibitor, may result in QT prolongation and torsade de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, concomitant use of methadone with another CNS depressant, such as olanzapine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use, patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Oxaliplatin: (Major) The need to coadminister methadone with oxaliplatin should be done with extreme caution and a careful assessment of treatment risks versus benefits. Monitor electrolytes and ECGs for QT prolongation if coadministration of methadone with oxaliplatin is necessary; correct electrolyte abnormalities prior to administration of oxaliplatin. QT prolongation and ventricular arrhythmias including fatal torsade de points (TdP) have been reported with oxaliplatin use in post-marketing experience. Methadone is also considered to be associated with an increased risk of hypotension and chemical pain in patients receiving oxaliplatin. Methadone is also considered to be associated with an increased risk of QT prolongation and torsade de points (TdP) if used concurrently with oxaliplatin.
for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Methadone should be used with caution in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Oxazepam: (Major) Concomitant use of methodone with another CNS depressant, such as oxazepam, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naïve adults, use an initial dose of methadone 2.5 mg every 12 hours. Also, consider a lower dose of the CNS depressant; use an initial dose of oxazepam at one-third to one-half the usual dosage. Monitor patients for sedation and respiratory depression.

Oxymorphone: (Moderate) Concomitant use of methodone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Oxazepam: (Moderate) Closely monitor for an increase in methodone-related adverse reactions (e.g., sedation, respiratory depression) if coadministration with oxazepam is necessary. Consider a methodone dose reduction until stable drug effects are achieved. The addition of oxazepam, a weak time-dependent inhibitor of CYP3A, and methodone, a sensitive CYP3A4 substrate, may increase methodone serum concentrations and prolong opioid adverse effects. Fatal respiratory depression may occur, especially if a CYP3A4 inhibitor is added to a stable dose of methodone. If oxazepam is discontinued, monitor for signs of opioid withdrawal.

Pazopanib: (Major) Pazopanib has been associated with QT prolongation; however, torsade de points (TdP) has not been reported. According to the manufacturer, since pazopanib may prolong the QT interval, it should be avoided in combination with other agents also known to have this effect, such as methodone. However, if coadministration is considered necessary by the practitioner, and the patient has known risk factors for cardiac arrhythmia, then close monitoring is essential. QT prolongation is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, methadone is a substrate for CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of these enzymes, such as paroxetine, may result in increased serum concentrations of methadone. Pentazocine: (Moderate) Concomitant use of methodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Panobinostat: (Major) QT prolongation has been reported with panobinostat therapy in patients with myeloma in a clinical trial; use of panobinostat with other agents that prolong the QT interval is not recommended. Obtain an electrocardiogram at baseline and periodically during treatment. Hold panobinostat if the QT interval increases to >= 480 milliseconds during therapy and permanently discontinue if QT prolongation does not resolve. Drugs with a possible risk for QT prolongation and torsade de points that should be used cautiously and with close monitoring with panobinostat include methodone.

Papaverine: (Moderate) Papaverine is a benzylisoquinoline alkaloid of opium and may have synergistic effects with opiate agonists. Concurrent use of papaverine with potent CNS depressants could lead to enhanced central opioid agonist effects.

Paroxetine: (Moderate) Coadministration may increase the risk of serotonin syndrome or methodone-related adverse effects. Both paroxetine and methodone have central serotonergic properties and serotonin syndrome is possible. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome occurs, all serotonergic agents should be discontinued and appropriate medical treatment should be implemented. Paroxetine may inhibit the metabolism of methodone via potent CYP3A4 inhibition. Patients may experience increases in CNS depressant effects or respiratory depression. Thus, methodone-treated patients receiving paroxetine should be carefully monitored and dosage adjustments may be warranted.

Passireotide: (Major) The need to coadminister methodone with passireotide should be done with extreme caution and a careful assessment of treatment risks versus benefits, as coadministration may have additive effects on the prolongation of the QT interval. At high doses, methodone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses averaging approximately 400 mg/day.

Peginterferon Alfa-2b: (Major) The administration of weekly peginterferon alfa-2b 1.5 mcg/kg to patients on methadone treatment may be associated with increases in methadone AUC. After 4 weeks of peginterferon alfa-2b, a mean increase of 16% in methadone AUC occurred; 2 of the 18 patients experienced an approximate doubling in methadone AUC. All patients were on stable methadone maintenance therapy of at least 40 mg daily. The methadone dose may need to be reduced in patients who also take peginterferon alfa-2b. As too much methadone can be fatal, use with peginterferon alfa-2b should be with extreme caution. If the drugs are used together, carefully monitor patients for an increased narcotic effect.

Pegvisomant: (Moderate) In clinical trials, patients taking opiate agonists often required higher serum pegvisomant concentrations to achieve appropriate suppression compared with patients not receiving opiate agonists. The mechanism of this interaction is unknown.

Pentamidine: (Major) Pentamidine has been associated with QT prolongation. Methadone may inhibit cardiac potassium channels and may prolong the QT interval. The need to coadminister methadone or pentamidine with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Pentazocine: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as methadone. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. (Major) Naloxone can antagonize the therapeutic efficacy of methadone in addition to
precipitating withdrawal symptoms in patients who are physically dependent on opiate drugs including methadone. Naloxone should only be administered when clinically significant respiratory or cardiovascular depression are present. If therapy with a naloxone is indicated, repeat doses may be necessary due to methadone's prolonged duration of action.

Perampanel: (Moderate) Co-administration of perampanel with CNS depressants, including ethanol, may increase CNS depression. The combination of perampanel (particularly at high doses) with ethanol has led to decreased mental alertness and ability to perform complex tasks (such as driving), as well as increased levels of anger, confusion, and depression; similar reactions should be expected with concomitant use of other CNS depressants, such as opiate agonists.

Perphenazine: (Minor) Perphenazine should be used cautiously and with close monitoring with methadone. Perphenazine, a phenothiazine, is associated with a possible risk for QT prolongation. The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, methadone is a substrate for CYP2D6. Concurrent use of methadone with inhibitors of this enzyme, such as certain antidepressants, may result in increased serum concentrations of methadone Phenothiazines can also potentiate the CNS-depressant action of methadone. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.

Pimavanserin: (Major) Due to the severity of the interaction of meperidine (a related opioid) with monoamine oxidase inhibitors (MAOIs), a sensitivity test should be performed in patients taking phenoxybenzamine or methadone. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Desipramine blood concentrations have increased with concomitant methadone therapy. Monitor patients for adverse effects of desipramine. (Minor) Perphenazine should be used cautiously and with close monitoring with methadone. Perphenazine, a phenothiazine, is associated with a possible risk for QT prolongation. The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). In addition, methadone is a substrate for CYP2D6. Concurrent use of methadone with inhibitors of this enzyme, such as certain antidepressants, may result in increased serum concentrations of methadone Phenothiazines can also potentiate the CNS-depressant action of methadone. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.

Pimozide: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Drugs with a potential for QT prolongation that should be used cautiously with methadone include pimozide. Additionally, use of methadone with another CNS depressant can cause sedation, respiratory depression, hypotension, and profound drowsiness. The use of methadone with pimozide, a dopamine antagonist, may potentiate orthostatic hypotension when given concomitantly with spironolactone. Potassium-sparing diuretics: (Minor) As methadone is a weak base, the renal elimination of methadone is increased by urine acidification. Thus acidifying agents may lower the serum methadone concentration. The limited amounts of circulating methadone that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent. Several studies have demonstrated that methadone is cleared faster from the body with an acidic urinary pH as compared with a more basic pH.

Pimavanserin: (Major) Pimavanserin may cause QT prolongation and should generally be avoided in patients receiving other medications known to prolong the QT interval, such as methadone. Pimavanserin is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP) especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone. Monitor patients for sedation and respiratory depression. Methadone is a primary substrate for the CYP3A4 isoenzyme. Serum concentrations of methadone may decrease due to CYP3A4 induction by phenytoin, fosphenytoin, and possibly ethotoin; withdrawal symptoms may occur.

Phenelzine: (Moderate) Additive CNS depression including respiratory depression, hypotension, profound sedation, or coma may occur with the combined use of the hydantoin (e.g., phenytoin, fosphenytoin, and ethotoin) and methadone. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; for example, in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Phenytoin: (Moderate) Additive CNS depression including respiratory depression, hypotension, profound sedation, or coma may occur with the combined use of methadone and phenytoin or fosphenytoin. Methadone is cleared faster from the body with an acidic urinary pH as compared with a more basic pH.

Pimozide: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Drugs with a potential for QT prolongation that should be used cautiously with methadone include pimozide. Additionally, use of methadone with another CNS depressant can cause sedation, respiratory depression, hypotension, and profound drowsiness. The use of methadone with pimozide, a dopamine antagonist, may potentiate orthostatic hypotension when given concomitantly with spironolactone. Potassium-sparing diuretics: (Minor) As methadone is a weak base, the renal elimination of methadone is increased by urine acidification. Thus acidifying agents may lower the serum methadone concentration. The limited amounts of circulating methadone that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent. Several studies have demonstrated that methadone is cleared faster from the body with an acidic urinary pH as compared with a more basic pH.

Potassium Phosphate; Sodium Phosphate: (Minor) As methadone is a weak base, the renal elimination of methadone is increased by urine acidification. Thus acidifying agents may lower the serum methadone concentration. The limited amounts of circulating methadone that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent. Several studies have demonstrated that methadone is cleared faster from the body with an acidic urinary pH as compared with a more basic pH.

Potassium-sparing diuretics: (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, caution coadministration with diuretics is needed. Also opiates agonists may increase orthostatic hypotension when given concomitantly with spironolactone.

Pramipexole: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma; examples include pramipexole. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-
naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Propoxyphene: (Major) Pramoxine slows gastric emptying and the rate of nutrient delivery to the small intestine. Medications with the potential to slow GI motility, such as opiate agonists, should be used with caution, if at all, with pramoxine until more data are available from the manufacturer. Monitor blood glucose.

Pregabalin: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants can potentiate the effects of the opiate agonist and lead to additive respiratory depression, sedation, or coma. Examples of CNS depressants include pregabalin. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced CNS depression can exacerbate the sedating effects of opioids.

Prlione: (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate agonists with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

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Quinidine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If methadone is initiated in a patient taking a benzodiazepine, reduced dosages are recommended; in opioid-naive adults, use an initial dose of methadone 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Quazepam: (Major) Concomitant use of quetiapine and methadone should be avoided due to an increased risk for QT prolongation and torsade de points (Tdp). The need to coadminister these drugs should be done with extreme caution and a careful assessment of treatment risks versus benefits. Limited data, including some case reports, suggest that quetiapine may be associated with a significant prolongation of the QTc interval in rare instances. Methadone is also considered to be associated with an increased risk for QT prolongation and TDP, especially at higher doses. Additionally, concomitant use of methadone with an additional drug has been shown to increase the risk of QT prolongation and TDP. Caution is advised when administering quetiapine with other drugs that are associated with an increased risk for QT prolongation and TDP. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant.

Quinine: (Contraindicated) Quinine is contraindicated with quinidine include methadone.

Quinidine: (Severe) Quinidine administration is associated with QT prolongation and torsades de pointes (TdP). Quinidine inhibits CYP2D6 and has QT-prolonging actions; quinidine is contraindicated with other drugs that prolong the QT interval and are metabolized by CYP2D6 as the effects on the QT interval may be increased during concurrent use of these agents. Drugs that prolong the QT and are substrates for CYP2D6 that are contraindicated with quinidine include methadone.

Quinine: (Major) Concurrent use of quinine and methadone should be avoided due to an increased risk for QT prolongation and torsade de points (TdP). Quinidine has been associated with prolongation of the QT interval and rare cases of TdP. Methadone is also considered to be associated with an increased risk for QT prolongation and TDP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. These effects may involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, concentrations of methadone may be increased with concomitant use of quinidine. Methadone is a CYP3A4 and CYP2D6 substrate and quinidine is a CYP3A4/CYP2D6 inhibitor.

Ranolazine: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. At high doses, methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses averaging approximately 400 mg/day. In addition, methadone is a substrate for CYP2D6 and P-glycoprotein (P-gp). Concurrent use of methadone with inhibitors of those enzymes may result in increased serum concentrations of methadone. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include ranolazine.

Rapacuronium: (Moderate) Concomitant use of methadone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Rasagiline: (Severe) Concurrent use of rasagiline and methadone is contraindicated. A serious reaction characterized by coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse, and death may occur if rasagiline and propoxyphene are used together. At least 14 days should elapse between rasagiline discontinuation and propoxyphene initiation.

Regadenoson: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include regadenoson.

Remifentanil: (Moderate) Concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Ribociclib: (Moderate) Avoid coadministration of ribociclib with methadone due to an increased risk for QT prolongation and torsade de points (TdP). Systemic exposure of methadone may also be increased resulting in an increase in methadone-related adverse reactions including respiratory depression and sedation. Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner. Methadone has also been associated with an increased risk of QT prolongation and TDP, especially at higher doses (> 200 mg per day but averaging approximately 400 mg per day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Concomitant use may increase the risk for QT prolongation. Ribociclib is also a moderate CYP3A4 inhibitor and methadone is a CYP3A4 substrate.

Rilpivirine: (Moderate) Rilpivirine administration is associated with QT prolongation and torsades de pointes (TdP). Systemic exposure of methadone may also be increased resulting in an increase in methadone-related adverse reactions including respiratory depression and sedation. Rilpivirine has been shown to prolong the QT interval in a concentration-dependent manner. Methadone has also been associated with an increased risk of QT prolongation and TDP, especially at higher doses (> 200 mg per day but averaging approximately 400 mg per day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Concomitant use may increase the risk for QT prolongation. Ribociclib is also a moderate CYP3A4 inhibitor and methadone is a CYP3A4 substrate.

Rifapentine: (Major) Rifapentine is an inducer of CYP3A4 metabolism. If coadministered with rifapentine, serum concentrations of methadone may be decreased because of CYP enzyme induction and an increased methadone dose may be needed. Induction of methadone metabolism may take several days to become effective. This interaction is most significant if rifapentine is added after methadone therapy has begun. Additionally, methadone doses may need to be decreased if rifapentine is discontinued.

Rilpivirine: (Major) Close clinical monitoring is advised with coadministration. Use of these drugs together may cause the plasma concentration of methadone to decrease, thereby resulting in decreased methadone efficacy. No dose adjustments are required when initiating concurrent treatment; however, ongoing maintenance dose of methadone may need to be adjusted in some patients. In addition, due to the potential for QT prolongation some torsade de points (TdP), caution is advised when administering rilpivirine with methadone. A careful assessment of treatment risks versus benefits should be conducted prior to coadministration. When initiating concurrent treatment no dose adjustments are required; however, the dose of methadone may need to be adjusted during maintenance therapy. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both
in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have also been associated with prolongation of the QT interval.

**Risperidone:** (Major) Methadone has a known risk of QT prolongation and torsade de points (Tdp) and a careful assessment of risks versus benefits should be performed before coadministration with drugs having a possible risk of QT prolongation and Tdp such as risperidone. Methadone is primarily metabolized with an increased risk for QT prolongation and Tdp (i.e., 400 mg/day in adults). Concomitant use of CNS depressants, such as risperidone and methadone, can lead to additive CNS depression, hypotension, or coma. Prior to the use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, the patient's overall response to treatment, and the patient's use of alcohol or illicit drugs. In opioid-naive adults, initiate methadone at a dose of 2.5 mg every 12 hours in patients taking other CNS depressant medications. Consider using a lower dose of the CNS depressant.

**Ritonavir:** (Major) Ritonavir may result in QT prolongation and the effect may be additive to the QT prolongation risk from methadone. Additionally, due to effects on CYP enzymes responsible for hepatic metabolism, ritonavir may alter the response to various opioid agonists. Administration of methadone and ritonavir has resulted in a 36% decrease in methadone AUC and 38% decrease in methadone Cmax in some reports; increased methadone doses may be required. However, any methadone dose increase should be approached with caution.

**Rocuronium:** (Moderate) Concomitant use of methadone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

**Rolapitant:** (Major) Use caution if methadone and rolapitant are used concurrently, and monitor for methadone-related adverse effects. Methadone is a substrate of CYP2D6 and P-glycoprotein (P-gp), where an increase in exposure may significantly increase adverse effects; rolapitant is an inhibitor of CYP2D6 and P-gp. The inhibitory effect of rolapitant on CYP2D6 lasts for at least 7 days, and may last longer after single dose administration. The Cmax and AUC of another CYP2D6 substrate, dextromethorphan, were increased by 120% and 160%, respectively, on day 1 of methadone administration. The Cmax and AUC of another CYP2D6 substrate, dextromethorphan, were increased by 120% and 160%, respectively, on day 1 with rolapitant, and by 180% and 230%, respectively, on day 8 after rolapitant administration.

**Ropivacaine:** (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

**Safinamide:** (Severe) Safinamide is contraindicated for use with methadone due to the risk of serotonin syndrome. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. At least 14 days should elapse between the discontinuation of safinamide and the initiation of methadone.

**Sapropterin:** (Moderate) Caution is advised with the concomitant use of sapropterin and methadone as coadministration may result in increased systemic exposure of methadone. Methadone is a substrate for the drug transporter P-glycoprotein (P-gp); in vitro data show that sapropterin may inhibit P-gp. If these drugs are used together, closely monitor for increased side effects of methadone.

**Selegiline:** (Major) Concurrent use of methadone and selegiline boosted with ritonavir should be avoided if possible due to the risk of life-threatening cardiac arrhythmias such as torsade de points (Tdp). If no alternative therapy is acceptable, perform a baseline ECG prior to initiation of concomitant therapy and follow recommended ECG monitoring. Selegiline boosted with ritonavir causes dose-dependent QT and PR prolongation. Methadone may also prolong the QT interval. Administering methadone (60 to 120 mg daily) in combination with selegiline/ritonavir (1000/100 mg twice daily) has resulted in a decrease in both methadone and saquinavir serum concentrations. Monitor patients carefully and adjust the methadone dose if necessary.

**Sertraline:** (Severe) Concurrent use of methadone and sertraline is contraindicated. Although at low doses sertraline is selective for MAO type B, in doses above 30-40 mg/day, this selectivity is lost. Severe reactions such as excitation, sweating, rigidity, hyperpyrexia, severe respiratory depression, coma, and peripheral vascular collapse, possibly resulting in death, can occur. At least 2 weeks should elapse between stopping sertraline and starting methadone.

**Serpentline:** (Major) Coadministration should be avoided if possible due to the potential risk of serotonin syndrome. QT prolongation or torsade de points (Tdp) or opioid-related side effects. There have been postmarketing reports of QT prolongation and Tdp during treatment with sertraline and the manufacturer of sertraline recommends avoiding concurrent use with drugs known to prolong the QTc interval. The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is associated with an increased risk for QT prolongation and Tdp, especially at higher doses (greater than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, both sertraline and methadone have central serotonergic properties and serotonin syndrome is possible. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome occurs, all serotonergic agents should be discontinued and appropriate medical treatment should be implemented. Lastly, sertraline is a CYP2D6 inhibitor and methadone is partially metabolized by CYP2D6, which may increase the risk of CNS depressive effects, respiratory depression, QT prolongation, or other adverse effects.

**Sevoflurane:** (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Halogenated anesthetics can prolong the QT interval. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (Tdp), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

**Short-acting beta-agonists:** (Minor) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de points (Tdp), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

**Other drugs:** Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with methadone include the beta-blockers. Beta-blockers may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or
Sildenafil: (Moderate) Prolonged erections have been reported in two patients taking sildenafil with dihydrocodeine. Although more data are needed to confirm this, caution should be exercised when prescribing opioid agonists and sildenafil concomitantly.

Simepreiv: (Moderate) Simepreiv, a P-glycoprotein (P-gp) inhibitor and a mild intestinal CYP3A4 inhibitor, may increase the side effects of methadone, which is a P-gp and CYP3A4 substrate. Monitor patients for adverse effects of methadone, such as CNS and respiratory depression.

Sodium Benzoate; Sodium Phenylacetate: (Minor) As methadone is a weak base, the renal elimination of methadone is increased by urine acidification and by certain acidic agents that can stimulate the secretion of acidic urine. The limited amounts of methadone that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent. Several studies have demonstrated that methadone is cleared faster from the body with an acidic urinary pH as compared with a more basic pH.

Sodium Oxinate: (Major) Additive CNS depressant effects may be possible when sodium oxinate is used concurrently with opioid agonists.

Soltal: (Major) The need to coadminister methadone with sotalol should be done with extreme caution and a careful assessment of treatment risks versus benefits. Sotalol administration is associated with QT prolongation and torsade de pointes (Tdp). Proarrhythmic events should be anticipated after initiation and after each upward dosage adjustment. Methadone is considered to be associated with an increased risk for QT prolongation and Tdp, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone. Although cases have been reported in patients receiving doses comparable to the usual therapeutic dosages of methadone, all cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Sparfloxacin: (Severe) At high doses, methadone is considered to be associated with an increased risk for QT prolongation and torsade de pointes. This effect may be enhanced if coadministered with sparfloxacin. The need to co-administer methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits.

Spironolactone: (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also opioid agonists may potentiate orthostatic hypotension when given concomitantly with spironolactone.

St. John's Wort, Hypericum perforatum: (Major) The concomitant use of methadone and St. John's Wort may result in decreased efficacy and withdrawal symptoms in patients physically dependent on methadone. If St. John's Wort is discontinued in patients receiving methadone, effects of methadone may be increased or prolonged potentially resulting in serious respiratory depression, sedation, and death. If concomitant use is necessary, consider increasing the methadone dose until stable drug effects are achieved and monitor for signs of withdrawal. If St. John's Wort is discontinued in patients receiving methadone, consider monitoring the patient closely for respiratory depression and sedation. Methadone is a substrate of CYP3A4, CYP2B6, CYP2C19, and CYP2C9; St. John's Work induces these hepatic isoenzymes. In addition, there is a risk of serotonin syndrome when methadone is used concomitantly with serotonergic agents such as St. John's Wort. Onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later. If serotonin syndrome is suspected, discontinue the serotonergic agents and treat as per standards of care.

Stavudine, d4T: (Minor) Methadone decreases the bioavailability stavudine, d4T by slowing its absorption and increasing its first-pass metabolism. As a result, stavudine's AUC and Cmax are decreased by 18% and 39%, respectively; however, these effects are probably not clinically significant.

Stimulants: (Moderate) The concurrent administration of methadone and inhibitors of CYP3A4, such as stimulants (dextroamphetamine, amphetamine), may result in increased concentrations of methadone through competitive inhibition of methadone metabolism and lead to toxicity including CNS adverse effects and potential for QT prolongation and torsade de pointes when high doses of methadone are used.

Sucralfate: (Major) Concomitant use of methadone with other CNS depressants, such as neumocellular blockers, can potentiate the effects of methadone on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Solifenacin: (Moderate) Concomitant use of methadone with another O1 antagonist or CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; also consider using a lower dose of methadone if the patient is at risk for respiratory depression.

Sodium Oxybate: (Minor) As methadone inhibits cardiac potassium channels and prolongs the QT interval, caution is advised when administering sodium oxybate with opiate agonists. Other CNS depressant drugs may have cumulative effects when administered concurrently and they should be used cautiously with suvorexant. A reduction in dose of the CNS depressant may be needed in some cases.

Tacrolimus: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as tacrolimus, should be done with extreme caution and a careful assessment of treatment risks versus benefits. When coadministering tacrolimus with other substrates of CYP3A4, especially those that also have the potential to prolong the QT interval, such as methadone, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Consider obtaining electrocardiograms (ECGs) and monitoring electrolytes (potassium, magnesium, and calcium) periodically during treatment in at-risk patients. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de pointes (TdP), especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Many cases involve patients being treated for pain with large, multiple daily doses of methadone. Although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction, tacrolimus may also prolong the QT interval and has been reported to cause TdP.

Tamoxifen: (Major) Caution is advised with the concomitant use of tamoxifen with methadone due to an increased risk of QT prolongation and torsade de pointes (Tdp). Tamoxifen has been reported to prolong the QT interval, usually in overdose or with high doses. Rare case reports of TdP prolongation have also been described when tamoxifen is used at lower doses. Methadone is considered to be associated with an increased risk for QT prolongation and Tdp, especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.
Tapentadol: (Moderate) Additive CNS depressive effects are expected if tapentadol is used in conjunction with other CNS depressants, including other opioid agonists. Severe hypotension, profound sedation, coma, or respiratory depression may occur. Prior to concurrent use of tapentadol in patients known to be CNS depressant, assess the level of tolerance that has developed, the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If an opiate agonist is used concurrently with tapentadol, a reduced dosage of tapentadol and/or the opiate agonist is recommended. If the extended-release tapentadol tablets are used concurrently with a CNS depressant, it is recommended to use an initial tapentadol dose of 50 mg PO every 12 hours. Monitor patients for sedation and respiratory depression.

Tolazolid: (Moderate) Use telazolid and methadone concurrently with caution and careful monitoring. The concomitant administration of methadone, a weak serotonin re-uptake inhibitor (SRI), and monoamine oxidase inhibitors (MAOIs), as well as telazolid, may increase the risk of serious adverse events, such as serotonin syndrome. If concurrent use of methadone and a MAO is required, a sensitivity test should be performed by administering repeated small incremental doses of methadone over several hours while carefully monitoring the patient's condition and vital signs. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression.

Telaprevir: (Moderate) Close clinical monitoring is advised when administering methadone with telaprevir due to the potential for decreased methadone efficacy. When initiating concurrent treatment with methadone and telaprevir, no dose adjustments are required; however, the dose of methadone may need to be adjusted during maintenance therapy. If methadone dose adjustments are made, they should be re-adjusted upon completion of telaprevir treatment.

Telavancin: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering telavancin with methadone. The need to coadminister these drugs should be done with careful assessment of treatment risks versus benefits. Telavancin has been associated with QT prolongation. Methadone is considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Telithromycins: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering telithromycin with methadone. The need to coadminister these drugs should be done with a careful assessment of treatment risks versus benefits. Telithromycin is associated with QT prolongation and TdP. Methadone is also considered to be associated with an increased risk for QT prolongation and TdP, especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Additionally, telithromycin is a long inhibitor of CYP3A4 and may affect the metabolism of methadone. Concurrent use may result in increased serum concentrations of methadone.

Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and methadone is necessary, as the systemic exposure of methadone may be decreased resulting in reduced efficacy in patients physically dependent on methadone. If these drugs are used together, monitor patients for suboptimal efficacy of methadone or for signs or symptoms of opioid withdrawal; consider increasing the dose of methadone if necessary. If telotristat ethyl is discontinued, methadone exposure may increase; monitor patients for respiratory depression and sedation and consider a methadone dose reduction. Methadone is partially metabolized by CYP3A4. The mean Cmax and mean AUC of the more sensitive CYP3A4 substrates were decreased by 46% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.

Temozolomide: (Moderate) Use caution if coadministration of temozolomide with methadone is necessary, and monitor for an increase in methadone-related adverse reactions. Temozolomide is a P-glycoprotein (P-gp) inhibitor in vitro. Methadone is a primarily a CYP3A4 substrate, but is also a P-gp substrate. Pharmacokinetic data are not available for concomitant use of temozolomide with P-gp substrates, but exposure to methadone may increase.

Terbinafine: (Moderate) Coadministration of methadone and terbinafine may result in increased methadone concentrations. Systemic terbinafine inhibits hepatic isoenzyme CYP2D6, and thus may inhibit the clearance of drugs metabolized by this isoenzyme.

Tetranabenzine: (Major) Tetranabenzine causes a small increase in the corrected QT interval (QTc). The manufacturer recommends avoiding concurrent use of tetranabenzine with other drugs known to prolong QTc such as methadone. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In addition, concurrent use of methadone and tetranabenzine should generally be avoided since the risk of adverse effects such as drowsiness, sedation, dizziness, or orthostatic hypotension may be increased.

Thalidomide: (Major) Avoid the concomitant use of thalidomide with opiate agonists; antihistamines; antipsychotics; anxiolytics, sedatives, and hypnotics; and other central nervous system depressants due to the potential for additive sedative effects.

Thiazide diuretics: (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. In addition, opiate agonists may potentiate orthostatic hypotension when used concurrently with diuretics.

Thioridazine: (Severe) Because of the potential for torsades de pointes (TdP), concurrent use of methadone and thioridazine is contraindicated. Thioridazine is associated with a well-established risk of QT prolongation and torsades de pointes (TdP) and is considered contraindicated for use along with agents that, when combined with a phenothiazine, may prolong the QT interval and increase the risk of TdP, and/or cause orthostatic hypotension. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Thiothixene: (Moderate) Use caution if coadministration of thiothixene with methadone is necessary, and monitor for an increase in methadone-related adverse reactions. Thiothixene is a P-glycoprotein (P-gp) inhibitor in vitro. Methadone is a primarily a CYP3A4 substrate, but is also a P-gp substrate. Pharmacokinetic data are not available for concomitant use of thiothixene with P-gp substrates, but exposure to methadone may increase.

Tianzianide: (Moderate) Use caution if coadministration of tianzianide with methadone is necessary, and monitor for an increase in methadone-related adverse reactions. Tianzianide is a P-glycoprotein (P-gp) inhibitor in vitro. Methadone is a primarily a CYP3A4 substrate, but is also a P-gp substrate. Pharmacokinetic data are not available for concomitant use of tianzianide with P-gp substrates, but exposure to methadone may increase.
Tolcapone: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants such as COMT inhibitors can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of both agents, assess the level of tolerance to CNS depression that has developed, the duration of use and the patient’s overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Tolterodine: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Torsades de pointes has been associated with dose-dependent prolongation of the QT interval, especially in poor CYP2D6 metabolizers. Additionally, monitor patients for signs of urinary retention or reduced gastric motility when methadone is used concomitantly with an anticholinergic drug, such as tolterodine. The concomitant use of methadone and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Ileus increases the tone and decreases the progress of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Toremfine: (Major) The need to coadminister methadone with drugs known to prolong the QT interval should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with methadone include toremfene. Toremfene has been shown to prolong the QTc interval in a dose- and concentration-related manner.

Torsemide: (Moderate) Diuretics can cause electrolyte disturbances such as hypomagnesemia and hypokalemia, which may prolong the QT interval. As methadone may also prolong the QT interval, cautious coadministration with diuretics is needed. Also, torsemide can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced torsemide dose is recommended.

Tramadol: (Major) Due to the risk of serotonin syndrome and the potential for QT prolongation and torsade de pointes (TdP), concurrent use of tramadol and other serotonergic medications, such as fentanyl, should be avoided if possible. Tramadol can prolong the QT/QTC interval at therapeutic doses. In addition, there are post-marketing reports of torsade de pointes (TdP). Methadone is considered to be associated with an increased risk for QT prolongation and torsades de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Several studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. If concomitant use is clinically warranted, patients should be informed of the increased risk of QT prolongation and serotonin syndrome, particularly during treatment initiation and during dose increases. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Treatment with tramadol and any concomitant serotonergic agents should be discontinued immediately if signs and symptoms of serotonin syndrome occur, and supportive symptomatic treatment should be initiated. In addition, CNS depressants such as opiate agonists should be used cautiously in patients receiving tramadone because of additive CNS-depressant effects, including respiratory depression, hypotension, and death.

Triacyclic antidepressants: (Major) The need to coadminister methadone with drugs known to prolong the QT interval, such as tricyclic antidepressants, should be done with extreme caution and a careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsade de pointes (TdP), especially at higher doses (> 200 mg/day but averaging approximately 400 mg/day in adult patients). Caution is also advised when methadone is coadministered with tricyclic antidepressants as this combination may increase the potential for serotonin syndrome development. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage adjustments (increases) of either agent. In addition, concomitant use of methadone with another CNS depressant can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with extreme caution and in reduced dosages if used concurrently with a CNS depressant; also consider a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression.

Tramadol: (Moderate) The concurrent use of tramadol and other serotonergic drugs, such as trimethobenzamide with other medications that cause CNS depression, like opiate agonists, may potentiate the effects of either tramethobenzamide or the opiate agonist.
Methadone is a long-acting, partial agonist opioid used for the maintenance treatment of opioid addiction. It is available in various formulations, including Methadone Hydrochloride Intensol Oral Concentrate.

### Methadone Hydrochloride Intensol Oral Concentrate
Methadone is indicated for the management of opioid dependence. It is a highly effective treatment for opioid addiction and is commonly used in opioid maintenance therapy.

#### Drug Interactions

**Vorinostat:**
Vorinostat is a histone deacetylase inhibitor used in the treatment of Hodgkin's lymphoma and cutaneous T-cell lymphoma. It can prolong the QT interval in a concentration-dependent manner. TdP and sudden death have been reported in patients receiving vorinostat; therefore, caution should be used when vorinostat is coadministered with methadone.

**Vincristine Liposomal:**
Vincristine is a microtubule stabilizer used in the treatment of various cancers. It is known to prolong the QT interval and can cause QT prolongation and torsades de pointes.

**Vilazodone:**
Vilazodone is an antidepressant used in the treatment of major depressive disorder. It is a serotonin-norepinephrine reuptake inhibitor (SNRI) and can prolong the QT interval.

**Vigabatrin:**
Vigabatrin is an antiepileptic drug used in the treatment of certain types of epilepsy. It can cause QT prolongation and torsades de pointes, especially at high doses.

**Verapamil:**
Verapamil is a calcium channel blocker used to treat hypertension, angina, and other cardiovascular conditions. It can increase the risk of QT prolongation and torsades de pointes, especially at high doses.

**Voriconazole:**
Voriconazole is an antifungal drug used in the treatment of invasive fungal infections. It can increase the risk of QT prolongation and torsades de pointes, especially at high doses.

**Vasopressin (Antidiuretic Hormone):**
Vasopressin is a hormone that regulates urine output and blood pressure. It can cause QT prolongation and torsades de pointes, especially at high doses.

**Vicerein (Opiate Analgesic):**
Vicerein is an opioid used for pain management. It can cause QT prolongation and torsades de pointes, especially at high doses.

**Varenicline (Cholinergic Acetylcholine Receptor):**
Varenicline is a medication used to help people stop smoking. It can cause QT prolongation and torsades de pointes, especially at high doses.

**Vardenafil (Phosphodiesterase 5 Inhibitor):**
Vardenafil is a medication used to treat erectile dysfunction and pulmonary arterial hypertension. It can cause QT prolongation and torsades de pointes, especially at high doses.

**Valerian (Herb):**
Valerian is a herbal supplement used for various conditions, including anxiety and sleep disturbances. It can cause QT prolongation and torsades de pointes, especially at high doses.

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careful assessment of treatment risks versus benefits. Methadone is considered to be associated with an increased risk for QT prolongation and torsades de points (TdP), especially at higher doses (>200 mg/day but averaging approximately 400 mg/day in adult patients). Laboratory studies, both in vitro and in vivo, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Most cases involve patients being treated for pain with multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Viorinostat therapy is associated with a risk of QT prolongation and should be used cautiously with methadone.

Zafirlukast (Moderate) The concurrent administration of methadone and inhibitors of cytochrome P450 3A4, such as zafirlukast, may result in increased concentrations of methadone. Inhibition of methadone metabolism can lead to toxicity including CNS adverse effects and potential for QT prolongation and torsades de points when high doses of methadone are used.

Zaleplon (Moderate) Concomitant use of methadone with zaleplon can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of zaleplon.

Ziconotide (Severe) According to the manufacturer, ziconotide is contraindicated with any drugs that list QT prolongation as a pharmacodynamic effect when this effect has been described within contraindications or boxed warnings of the official labeling for such drugs. Ziconotide has been associated with a possible risk for QT prolongation and torsades de points (TdP). Clinical trial data indicate that ziconotide causes QT prolongation. In one study, ziconotide increased the QT interval 10 msec more than placebo at the maximum recommended dosage. Comparative data with other antipsychotics have shown that the mean QTc interval prolongation occurring with ziconotide exceeds that of haloperidol, quetiapine, olanzapine, and risperidone, but is less than that which occurs with thioridazine. Given the potential for QT prolongation, ziconotide is contraindicated for use with drugs that are known to cause QT prolongation with potential for torsades de points including methadone.

Zolpidem (Moderate) Concomitant use of methadone with zolpidem can lead to additive respiratory depression, hypotension, profound sedation, or coma. In addition, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of zolpidem and other CNS depressants than with zolpidem alone. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient’s overall response to treatment. Consider the patient’s use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of zolpidem. For Intermezzo brand of sublingual zolpidem tablets, reduce the dose to 1.75 mg/night. Monitor patients for sedation and respiratory depression.

Zonisamide (Minor) Zonisamide is a weak inhibitor of P-glycoprotein (P-gp), and methadone is a substrate of P-gp. There is theoretical potential for zonisamide to affect the pharmacokinetics of drugs that are P-gp substrates. Use caution when starting or stopping zonisamide or changing the zonisamide dosage in patients also receiving drugs which are P-gp substrates.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies with methadone in pregnant women. Use methadone for severe pain during pregnancy only if the potential benefit justifies the potential risk to the fetus. Medical withdrawal of pregnant, opioid-dependent women from methadone is not recommended. When methadone is used during pregnancy as part of a supervised, therapeutically necessary regimen, it is unlikely to pose substantial teratogenic risk. Women undergoing methadone maintenance programs may have reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality compared to women using heroin as an illicit drug. Untreated or under-treated withdrawal in pregnancy is associated with adverse obstetrical outcomes and risk of continued or relapsing illicit opioid use. Consider these risks in pregnant women treated with methadone for maintenance treatment of opioid addiction. No increased risk of miscarriage in the second trimester or premature delivery in the third trimester was noted by a retrospective review of data from 101 opioid-dependent women. Benefits of methadone therapy during pregnancy include assisting women staying free of heroin or other drugs, increasing prenatal care, decreasing the possibility of fetal death, and reducing the risk of maternal and fetal hepatitis infections. Neonates born to narcotic-addicted women treated with methadone during pregnancy have been found to have decreased fetal growth with reduced birth weight, head circumference, or length, or head circumference. The growth deficit does not appear to persist into later childhood. Children born to mothers who received methadone during pregnancy demonstrate mild but persistent performance deficits on psychometric and behavioral tests and may have an increased risk of visual development anomalies. Administration of methadone to pregnant animals during organogenesis through lactation resulted in decreased litter size, increased pup mortality, decreased pup body weights, developmental delays, and long-term neurochemical changes in the brain which correlate with altered behavioral responses at exposures comparable to and less than the human daily dose of 120 mg. Methadone clearance may be increased during pregnancy. The methadone dose or interval may need to be increased as the pregnancy progresses due to changes in plasma volume and renal blood flow; due to an increased metabolism of methadone during pregnancy, close monitoring of pregnant women is recommended. Methadone is not recommended for analgesia during labor and obstetric delivery due to its prolonged duration of action and potential for respiratory depression in the newborn. Women maintained on methadone require appropriate obstetric pain management, as methadone maintenance does not provide analgesia. Narcotics with mixed agonist/antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal. Prolonged maternal use of opioids, such as methadone, during pregnancy may result in neonatal opioid withdrawal syndrome (NOWS). This syndrome can be life-threatening. Severe symptoms may require pharmacologic therapy managed by clinicians familiar with neonatal opioid withdrawal. Monitor the neonate for withdrawal symptoms including irritability, hyperactivity, abnormal sleep pattern, high-pitched crying, tremor, vomiting, diarrhea, and failure to gain weight. Onset, duration, and severity of opioid withdrawal may vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination by the newborn.

MECHANISM OF ACTION

Methadone is a potent µ-opioid receptor agonist. Opiate receptors include μ (mu), kappa (kappa), and delta (delta), which have been reclassified by an International Union of Pharmacology subcommittee as OP1 (delta), OP2 (kappa), and OP3 (µ). These receptors are coupled with G-protein (guanine-nucleotide-binding protein) receptors and function as modulators, both positive and negative, of synaptic transmission via G-proteins that activate or inhibit intracellular enzymes. Opioid-G-protein (G-protein) systems include adenyl cyclase-cyclic adenosine monophosphate (cAMP) and phospholipase C (PLC)-inositol 1,4,5 triphosphate (Ins[1,4,5]P3-Ca2+). The optical isomers of methadone differ in their binding affinities for opiate receptors. The R-isomer of methadone has a higher affinity for µ1 and µ2 receptors than S-methadone or the racemate. It appears that R-methadone has a receptor binding pattern similar to morphine and S-methadone does not contribute to the opioid effects of the racemic methadone.
isomers and the racemate have low affinities for delta and kappa receptors. Methadone is considered a weak serotonin re-uptake inhibitor and has been implicated in serotonin syndrome toxicity reactions.

Opiates do not alter the pain threshold of afferent nerve endings to noxious stimuli, nor do they affect the conductance of impulses along peripheral nerves. Analgesia is mediated through changes in the perception of pain at the spinal cord (µ2-, delta-, kappa-receptors) and higher levels in the CNS (µ1- and kappa3 receptors). There is no ceiling effect of analgesia for opiates. The emotional response to pain is also altered. Opiates close N-type voltage-operated calcium channels (kappa-receptor agonist) and open calcium-dependent inwardly rectifying potassium channels (µ and delta receptor agonist) resulting in hyperpolarization and reduced neuronal excitability. Binding of the opiate stimulates the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the G-protein complex. Binding of GTP leads to a release of the G-protein subunit, which acts on the effector system. In this case of opioid-induced analgesia, the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane. Thus, opiate modulates the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and norepinephrine. Opiates also modulate the endocrine and immune systems. Opiates inhibit the release of vasopressin, somatostatin, insulin and glucagon.

Clinically, stimulation of µ-receptors produces analgesia, euphoria, respiratory depression, miosis, decreased gastrointestinal motility, and physical dependence. Methadone has a blunted euphoric effect due to its long duration of action and slow onset of action. The decreased euphoric effects of methadone make it unattractive as a drug of abuse and an appropriate agent for the management of opiate dependence. During addiction, the functioning of the opiate receptor is altered due to repeated opiate exposure. Methadone treatment normalizes neurologic and endocrine process. Methadone suppresses opiate craving and produces a blockade of the euphoria induced by morphine-like opiate agonists. Miosis is produced by an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve. Respiratory depression is caused by direct action of opiate agonists on respiratory centers in the brain stem. Opiate agonists increase smooth muscle tone in the antral portion of the stomach, the small intestine (especially the duodenum), the large intestine, and the sphincters. Opiate agonists also decrease secretions from the stomach, pancreas, and biliary tract. The combination of effects of opiate agonists on the GI tract results in constipation and delayed digestion. Urinary smooth muscle tone is also increased by opiate agonists. The tone of the bladder detrusor muscle, ureters, and vesical sphincter is increased, which sometimes causes urinary retention.

Several other clinical effects occur with opiate agonists including cough suppression, hypotension, and nausea/vomiting. The antitusive effects of opiate agonists are mediated through direct action on receptors in the cough center of the medulla. Cough suppression can occur at lower doses than those required to produce analgesia. Hypotension is possibly due to an increase in histamine release and/or depression of the vasomotor center in the medulla. Induction of nausea and vomiting possibly occurs from direct stimulation of the vestibular system and/or the chemoreceptor trigger zone.

PHARMACOKINETICS

Methadone may be administered orally, intravenously, subcutaneously, or intramuscularly. It undergoes a distribution phase with a half-life of 2 to 3 hours. Methadone is 85% to 90% bound to alpha-1-acid-glycoprotein. Disease states, such as cancer, and other medications that affect the serum concentrations of alpha-1-acid-glycoprotein may alter patient response. Methadone is widely distributed into tissues due to its basic and lipophilic properties, and is secreted into breast milk. Concentrations in amniotic fluid and cord plasma are proportional to maternal plasma concentrations. Due to slow release from tissue binding sites, prolonged serum concentrations and cumulative effects occur. Steady-state plasma concentrations and full analgesic effects are usually not obtained until days 3 to 5 of dosing. The peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects, especially during the early dosing period. Depressant effects after overdosage can persist for 36 to 48 hours.

Methadone undergoes N-demethylation in the liver by CYP450 microsomal isoenzymes CYP3A4 (primary), CYP2B6, and CYP2C19 to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP); CYP2C9 and CYP2D6 are involved to a lesser degree. With chronic dosing, methadone is a substrate for P-glycoprotein. The transport of methadone across the gut wall may be increased in the presence of P-glycoprotein inhibitors. Action occurs within 30 to 60 minutes of oral dose administration. Methadone also undergoes first-pass metabolism in the GI tract where methadone is a substrate for P-glycoprotein. The transport of methadone across the gut wall may be increased in the presence of P-glycoprotein inhibitors.

Absorption after intramuscular administration of methadone has not been well characterized but appears to be unpredictable.

Absorption after subcutaneous administration of methadone has not been well characterized but appears to be unpredictable.

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