Impact of Methadone on prolonged mechanical ventilation in Patients on continuous treatment with Opioids, a randomized trial (IMPACTOR Study)

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STUDY PROTOCOL

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Impact of Methadone on prolonged mechanical ventilation in Patients on continuous treatment with Opioids, a randomized trial (IMPACTOR Study)

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TABLE OF CONTENTS

STUDY PROTOCOL

1. BACKGROUND AND RATIONALE

Our study focus is to identify patients that have been on the ventilator for more than 72 hours receiving fentanyl infusions or its equivalents and enroll them into our study, start them on oral Methadone in order to wean off Fentanyl. Patients on mechanical ventilation are often administered opioids and other sedative medications to control pain, maintain comfort and optimize ventilatory support. The use of effective strategies to help wean patients from continuous infusions of opioids in an ICU setting that do not predispose them to continuous pain or risk of drug withdrawal has been proposed but attaining the above objective remains challenging.

Based on nomenclature used following 2002 American College of Critical Care Medicine sedation consensus guidelines, 72 hours or more on sedation was considered prolonged ICU sedation. [1] There has been very few randomized controlled trials on the best strategy to wean patients from prolonged infusion of opioids beyond 72 hours and there is no national consensus as regards the best strategy. Only a few studies with very small sample sizes have been used to guide current management. [2] During COVID-19 pandemic surge periods Massachusetts General Hospital published strategies for weaning analgesia using oral methadone which most of our ICU physicians are currently using. We do not have evidence of the benefit of this strategy and believe designing a study to assess the benefits will be useful for its continuous use.

1.1. General Introduction

Methadone is an opioid which binds to opioid receptors to produce analgesia and sedation. It is currently in use for treating opioid dependence as well as analgesic for chronic moderate to severe pain

1.2. Rationale and justification for the Study

Variation in sedation practice may lead to undersedation or over sedation. Over sedation is associated with adverse clinical outcomes such as prolonged stay on the ventilator, prolonged ICU length of stay, delirium and increased mortality. [3]
We hypothesize that patients who get oral methadone to help wean off opioids will have shorter ICU length of stay, shorter duration on the ventilator and potentially improved hospital mortality. We hypothesize that we will increase the proportion of patients extubated by day 5.

The use of long-acting opioids by enteral administration to wean mechanically ventilated patients from sedation and analgesia has been well documented by Wanzuita et al. They used 10mg of methadone every six hours enterally while reducing the rate of fentanyl infusion by 20%.

a. Rationale for the Study Purpose

Based on nomenclature used following 2002 American College of Critical Care Medicine sedation consensus guidelines, 72 hours or more on sedation was considered prolonged ICU sedation. [1] There has been very few randomized controlled trials on the best strategy to wean patients from prolonged infusion of opioids beyond 72 hours and there is no national consensus as regards the best strategy. Only a few studies with very small sample sizes have been used to guide current management. [2] A randomized control trial carried out in Brazil introduced the use of Methadone after patients were on ICU sedation for 5 days, compared to Society guidelines, which was two days longer. [4] Current protocols recommend tapering Fentanyl based on a nursing protocolized sedation in which the dose is reduced by 25mcg per hour to bring the patient to a desired RASS (Richmond Agitation Sedation Scale score) set by the physician.

In our study, we seek to identify patients on IMV for over 72 hours and randomize them to those who will receive methadone and those that will get usual care not receiving methadone. We plan to compare any differences in ICU outcomes.

Prior randomized trials introduced the use of methadone after 5 days of ICU sedation which was much longer than the ACCM definition of 3 days on prolonged mechanical ventilation.

b. Rationale for Doses Selected

Patients will be randomized to either Oral Methadone tablets the interventional group or Control group that will receive usual care with IV Fentanyl or hydromorphone per hospital protocols.
Patients on the methadone group will be started on Methadone 5mg, 10mg or 15mg every 8 hours via a feeding tube depending on Fentanyl drip rate (0-100mcg/hr, 100-200mcg/hr or >200mcg/hr) or hydromorphone drip rate (0-1.5mg/hr, 1.5-3mg/hr, or >3mg/hr), Appendix3. The rate of Fentanyl or hydromorphone will be reduced by 25% initially to bring patient to a desired RASS (Richmond Agitation Sedation Scale score) as requested by the physician. While the control group will Not get any medication and will be weaned off opioids as per usual care.

c. Rationale for Study Population

In order to test our hypothesis our population of target needed to be patients admitted to the ICU who have been on mechanical ventilation for more the 72 hours on sedation with opioids. This gives us the opportunity to be able to compare outcomes between those that will receive methadone to those that will not

d. Rationale for Study Design

A randomized control trial gives us the best tool devoid of selection bias as well as controlling for potential confounders.

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

The study hypothesizes that patients who get oral methadone to help wean off opioids will have shorter ICU length of stay, shorter duration on the ventilator and potentially improved hospital mortality. The study hypothesizes that, there will be increase in the proportion of patients extubated by day 5.

2.2. Primary Objectives

To determine the effect of methadone on the duration on mechanical ventilation in critically ill patients receiving more than 72 hours of MV by comparing the number of ventilator free days form enrolment to the time of discharge

2.3. Secondary Objectives

To assess the safety of methadone administration in critically ill patients while in the hospital.

To determine hospital length of stay from the time of enrollment to the time of discharge

2.4. Potential Risks and Benefits:

a. End Points – Efficacy

The study might show the efficacy and potency of methadone in decreasing the length of stay in ICU and duration of mechanically intubation in critically ill patients.

b. End Points – Safety

Adverse events that could be anticipated during the study include signs of opioid withdrawal, elevated liver enzymes, ileus, hypotension and QTC prolongation. Adverse events will be reported in the adverse events registry.

The only two adult studies reported on the use of methadone to wean opioids on mechanical ventilation showed that the much-anticipated risk of QTC prolongation was similar in both patients who received methadone and those that did not receive methadone as shown in the study by Wanzuita et al and Al-Qadheeb et al. [5] Methadone was well tolerated in both studies.

2.5 Outcomes

a. Primary

Proportion of patients on methadone that get extubated by day number 5 from the date of intubation

b. Secondary

Proportion of patients that develop prolonged QTC after administration of methadone. Others will be ICU length of stay, ICU mortality, hospital length of stay and hospital mortality.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled.

All patients admitted to the medical ICU of Memorial Hermann Cypress and to the medical ICU of Memorial Hermann at the Texas medical Center will be screened for eligibility. There will be no restrictions based on the race of subjects. The study will not involve children as the investigators are only credentialed to treat adults aged 18 years and older.

3.2. Criteria for Recruitment

Patient will be screened to confirm they meet study criteria. Consent will be obtained from the legal authorized representative.

3.3. Inclusion Criteria

Patients will be enrolled only if they consented and they meet all of the inclusion criteria listed below.

1. Patients 18 years or older
2. Patients on IMV for more than 72 hours
3. Patients infused Fentanyl or Hydromorphone for more than 72 hours
4. Patients with evidence of reversal of process that caused respiratory failure, adequate oxygenation (PaO2/FIO2>200; Positive end expiratory pressure (PEEP)≤8 and Ph≥7.2
5. Patients hemodynamically stable
6. Patients with a failed single or multiple attempts at spontaneous breathing trials

3.4. Exclusion Criteria

All subjects meeting any of the exclusion criteria at baseline will be excluded from participation.

1. Patients with history of opioid drug abuse
2. Patients receiving schedule II narcotics on a chronic basis for longer than 6 months prior to ICU admission or on other analgesic infusions other than Fentanyl or Hydromorphone
3. Patients with cervical spinal cord injury or neuromuscular disease
4. Patients with end stage liver disease at ICU admission (ie, International normalized ratio ≥2and not taking warfarin and/or a total serum bilirubin ≥1.5 times above normal limits
5. Patients with prolonged QTc interval ≥500
6. Patients with prior history of cardiac conduction defects or sudden death
7. Patients with QTc increase of ≥60 milliseconds above the value of prior EKGs measured during current ICU admission
8. Patients with more than 5 days on IV analgesia
9. Patients intubated for more than 30 days
10. Patients without feeding tubes
11. Patients not receiving enteral feeding
12. Exclusion of patients in a comatose state
13. Exclusion of patients in Status Epilepticus
14. Exclusion of post-operative patients

3.5. Withdrawal Criteria

The study will be discontinued after completion or upon recommendation from Data Safety and Monitoring board DSMB and with help from IRB.

3.6. Subject Replacement

Yes, Subjects who drop out will be replaced.

4.1 Allocation

All patients admitted to the medical ICU will be screened for eligibility. Group assignment will be done using the randomization module of the Research Electronic Data Capture (REDCap) platform. Patients will be randomized in a 1 to 1 ratio, using permuted blocks of 4 or 6, into one of two groups: methadone group and the Non-Methadone group. The randomization will be stratified based on location where patients will be recruited.

4.2 Interventions

Pre-intervention period (1 month)

The objective of this period is to standardize the process to improve familiarity to the investigators. Study procedures will be presented to the nurses by oral presentations, printed material, and by email. The information will include detailed explanation of the process of tapering methadone and weaning patients off opiates as stipulated in the study. It will also elaborate more on the process of managing patients that develop clinical opiate withdrawal symptoms.

Intervention period

Following randomization patients will be assigned to the MG or the NG group. For patients randomized to the MG a “non-formulary medication” order will be placed in the electronic medical record to alert nurses to follow the protocol for patients started on Methadone. For those in the NG group usual hospital protocol of weaning opioids will be followed.
The study is completed for each patient once extubated or discharged from ICU, death, comfort care measures, or after 30 days of participation in the study.
We will collect data regarding participants demographic characteristics, comorbidities, main admission diagnosis, use of mechanical ventilation and vasopressors, ICU and hospital LOS, ICU and hospital mortality. Vital signs, focused general examination, LFTs, with normal ICU standard of care will done. However, EKG will be done at baseline and on day 30 if patient is still on methadone. LFTs are only done at baseline. The duration of use of the medication is not expected to cause an increase in LFTs. The listed labs are the only additional labs other than what is usually ordered for standard care in ICU. The information will be collected by reviewing medical records and will be recorded in electronic form only, using REDCap.

5. STUDY DESIGN

5.1. Summary of Study Design

The study is randomized clinical trial. The duration of the study is 2 years. Patients will be screened to confirm they meet study criteria. Consent will be obtained from the legal authorized representative. Initial demographic data will be obtained using REDCap Database. Patients will be randomized to either Oral Methadone tablets or Non-Methadone group. The control group will receive usual care with IV Fentanyl or hydromorphone per hospital protocols as on appendix 1. Patients on the methadone group will be started on Methadone 5mg, 10mg or 15mg every 8 hours depending on Fentanyl drip rate (0-100mcg/hr, 100-200mcg/hr or >200mcg/hr) or hydromorphone drip rate (0-1.5mg/hr, 1.5-3mg/hr, or >3mg/hr). The rate of Fentanyl or hydromorphone will be reduced by 25% initially. If patients require additional sedation later, this will be administered per usual care and the total amount of additional opioids will be documented and used for analysis as morphine milligram equivalents (MME). Likewise, patients could be weaned more than 25% if they showed signs of tolerance to lesser sedation.

At Subsequent encounters: Rate of Fentanyl or Hydromorphone drip will be reduced by 25% every 24 hours until the patient is extubated from the ventilator.

Continuous IV opioids for analgesia for patients on mechanical ventilation is routine clinical care and will not be denied to patients. Once patients are extubated oral methadone will be discontinued and patient monitored for any opioid withdrawal symptoms and treated per protocol as shown on appendix 2 based on their clinical opiate withdrawal scale (COWS) appendix 4. For those with a score of less than 25 oral methadone will no longer be required. For those with a COWS score of >25 methadone will be resumed for a short taper of 3 days. The above can be illustrated as on study protocol flow on Appendix 5 and details on methadone taper as on Appendix 2.

6. METHODS AND ASSESSMENTS

Based on the assumptions of successful extubation by day 5 of 50% of patients in the methadone group and 20% of patients in the control group and using a two tailed alpha level of 5%, a power of 80% our sample size calculation comparing proportions of two groups yielded 76. A 5% fallout as correction factor was 4 leaving us with a sample size of 80 patients. Statistical methods will include descriptive statistics and time to event analysis. Baseline characteristics will be reported. Data will be collected on a data collection sheet prior to transfer to REDCAPs database (Appendix 6). We will generate Kaplan-Meier curves and for comparison of hazard between groups we will use Cox regression (Cox proportional hazards model). Patients who die will be censored at time of death. Time of weaning will take into consideration only patients who were permanently disconnected from the ventilator. QTc values will be obtained from patient monitors and documented on data collection tool daily.

Randomization tables will be generated using REDCAPs database by study statistician. At the end of the study recorded information from REDCAPs will be exported to STATA for statistical analysis.

6.1. Randomization and Blinding

Patients will be randomized between two groups, the Methadone group (MG) and the Non-Methadone group (NG). Randomization tables will be generated using REDCap database. Randomization will be stratified by Center of data collection. The investigators evaluating the primary and secondary outcomes will be blinded to the group assignments. The study participants, pharmacists, physicians and nurses taking care of the patients will not be blinded.
Assignment of patients to study groups will be by random allocation by randomization tables. There will be two randomization tables, one for Memorial Hermann Cypress and the other for Memorial Hermann Texas Medical Center. Patients predetermined to receive methadone will receive oral methadone which comes in 5mg tablets. Tablets will be crushed and administered via the feeding tube if patients are still on enteral feeding at the time the medication is administered. Patients predetermined not to receive methadone will continue treatment following usual care per hospital weaning protocols.

6.2. Contraception and Pregnancy Testing

Patients that are pregnant or have a positive pregnancy test or are on oral contraception will not be enroll into the study since they are a vulnerable population screened for eligibility.

6.3. Storage and Drug Accountability

Neither the Pharmacy nor the nursing staff will be accountable for the drugs. Pharmacy will dispense medication as normal physician order for drugs administered. Information on drug administered will be retrieved from patient records.

7. TREATMENT

7.1. Rationale for Selection of Dose

Dose selection will be based on currently approved protocol which is attached as an appendix 2.

7.2. Study Drug Formulations

Drug will be dispensed to patients in form of oral tablets appendix 3.

7.3. Study Drug Administration

Drug to be used is Methadone. Warnings not to use the drug in patients with asthma, GI obstruction, paralytic ileus, renal impairment, hepatic impairment, pregnancy, debilitated patients, QT prolongation, Congestive heart failure, Seizures, alcohol abuse and CNS depression.

7.4. Specific Restrictions / Requirements

Not applicable.

7.5. Blinding

The investigators evaluating the primary and secondary outcomes will be blinded to the group assignments. The study participants, pharmacists, physicians and nurses taking care of the patients will not be blinded.

8. SAFETY MEASUREMENTS

Any adverse events encountered will be documented in the patients' chart once it is noted. These include QTc >500, high grade arrhythmias such as ventricular tachycardia, hypotension and elevated Liver function testing more than 2.5 times the upper limit ofnormal.

8.1. Definitions

Serious adverse events include persistent hypotension, persistently prolonged QTc, ileus, anaphylaxis and death.

8.2. Collecting, Recording and Reporting of Adverse Events

The principal investigator will be responsible for accurate documentation, investigation and follow-up as well as timely reporting of the following:

1- Any adverse event at the study site which in the opinion of the principal investigator is both unexpected and related and places subjects or others at risk of harm
2- Information that indicates a change to the risks or potential benefits of the research
3- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
4- A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB
5- A breach of confidentiality
6- Change in FDA labelling or withdrawal from marketing of a drug, device or biologic used in a research protocol
7- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant
8- Incarceration of a participant in a protocol not approved to enroll prisoners
9- Event that requires prompt reporting to the sponsor
10- Sponsor imposed suspension
11- Complaint by a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
12- Protocol deviation meaning an accidental or unintentional change to IRB approved protocol) that harmed participants or others or that indicates that participants or others may be at increased risk of harm
13- Unanticipated adverse device effect

Nursing staff and physicians will be notified to look out for the above. Any identified adverse event will be reported to the study PI who will discuss and inform the study coordinator about it.

The Principal investigator shall make a judgement about the expectedness of a problem. If the problem is an adverse event, the investigator shall make a judgement about the causality of the adverse event with respect to study intervention. The Principal investigator shall also evaluate whether protocol consent forms are needed.

The Principal investigator shall state whether the problem is expected or unexpected.

For adverse events the Principal Investigator shall evaluate the event and assess causality. He shall reveal evidence or arguments to suggest causal relationship

The Principal Investigator shall report the reportable events described above to CPHS via iRIS as follow: All problems involving local deaths shall be reported immediately, within 24 hours after first knowledge by the investigator. All other problems shall be reported as soon as possible but not later than 7 calendar days after first knowledge by the investigator.

Safety Monitoring Plan

The research team will meet once every 3 months to review adverse events, protocol deviations and other problems encountered. We will work with IRB to create a data and safety monitoring board. A data safety monitoring board will be created and will meet once every quarter to assess study conduct and progress and determine continuity of the study.

9. DATA ANALYSIS

9.1. Data Quality Assurance

After physician or advanced care practitioner entry of information into patient database, research coordinator will verify information for accuracy and correctness. There will be no plans to have ongoing third-party monitoring.

9.2. Data Entry and Storage

Data will be entered electronically on REDCAPs data base. All information will be stored on UTHealth computers.

10. SAMPLE SIZE AND STATISTICAL METHODS

10.1. Determination of Sample Size

Based on the assumptions of successful extubation by day 5 of 50% of patients in the methadone group and 20% of patients in the Non Methadone group and using a two tailed alpha level of 5%, a power of 80% our sample size calculation comparing proportions of two groups yielded 76. A 5% fall out as correction factor was 4 leaving us with a sample size of 80 patients.

10.2. Statistical and Analytical Plans

Methadone when used at appropriate doses is considered safe and is an FDA approved medication. We will not be performing safety analysis. We will perform interim analysis after randomizing up to 50%(40) patients. Categorial variable will be compared using the student Chi-squared test and continuous variables will be compared using the T-test. Interim analysis will be performed by an independent statistician blinded for the treatment allocation. The statistician will report to the data safety and monitoring committee. The DSMB will discuss the results of the interim analysis with the statistician and a steering committee and in a joint meeting will decide on continuation of the trial.

11. ETHICAL CONSIDERATIONS

11.1. Informed Consent

Consent will be obtained from legal authorized representatives while the patient in on mechanical ventilation and will be confirmed by the patient once extubated and sedation weaned in order for the patient to continue in the study. Consent forms and non-electronic data will be stored in protected locked storage in the office of the ICU Director while the research office will keep copies of the regulatory binders. A hospital translation phone will be used for communication with non-English speakers.

11.2. IRB review

Consent forms will be sent to IRB.

11.3. Confidentiality of Data and Patient Records

Patients records that will Include procedures for maintaining subject confidentiality, or any special data security requirements, and record retention will be kept secured.

12. PUBLICATIONS

After Principal investigator or the Co-investigators enter the patients information into the patient database, research coordinator will verify information for accuracy and correctness. There will be no plans to have ongoing third-party monitoring.

13. RETENTION OF TRIAL DOCUMENTS

Records will be stored in ICU Directors office for Memorial Hermann Cypress and Dr. Sami Hossri's office in the Medical school will store documents for Memorial Hermann Texas Medical Center in secured case.

List of Possible Attachments

Reference	
Appendix 1	**ICU Sedation Weaning Protocol**
Appendix 2	**The Massachusetts General sedation weaning strategies**
Appendix 3	**Methadone tablet Packet insert**
Appendix 4	**Clinical Opiate Withdrawal Score**
Appendix 5	**Protocol Flow Diagram**
Appendix 6	**Data Collection Sheet**

REFERENCE

[1] A. Nasa, Impact of Enteral Methadone on the Ability to Wean Off Continuously Infused Opioids in Critically Ill, Mechanically Ventilated Adults: A Case-Control Study, vol. 46, The Annals of Pharmacotherapy, 2012.

[2] J. Jacobi, "Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult," *Critical Care Medicine,* pp. 119-41, 2002.

[3] R. Chang, "COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis," *PloS One,* vol. 16, no. 2, 2021.

[4] R. Wanzuita, "Replacement of Fentanyl infusion by enteral methadone decreases the weaning time from mechanical ventilation: a randomized controlled trial," *Critical Care,* vol. 16, no. R49,2012.

[5] Al-Qadheeb, Nada S, et al. “Impact of Enteral Methadone on the Ability to Wean off Continuously Infused Opioids in Critically Ill, Mechanically Ventilated Adults: A Case-Control Study.” *Annals of Pharmacotherapy*, vol. 46, no. 9, 2012, pp. 1160–1166, doi:10.1345/aph.1r132.

Appendix 1

ICU Sedation Weaning Protocol

Fentanyl 1000microgram in 20mls of Normal saline

Start dose: 50microgram per hour,

Titration: 25microgram per hour every 15minutes, maximum dose: 200microgram per hour

Route: Intravenous

May Rebolus fentanyl 25micrograms IV addition to each infusion increase

Notify the physician when the dose of 200 micrograms per hour is reached.

Hydromorphone 50mg in NS 50ml Titrate Intravenous

50mg, 50ml, Start Dose: 0.2mg/hr.

Titration: 0.2mg/hr. every 15min,

Maximum Dose: 5mg/hr.

Route: Intravenous

Final Concentration =1mg/ml

Total volume=50ml

Contact the physician if the dose of 5mg/hr. is reached.

Use similar dosing for titrating up or down

Appendix 2 The Massachusetts General sedation weaning strategies

Version 1.0 04/29/2020

MASSACHUSETTS GENERAL HOSPITAL

This document was prepared (in March-May, 2020) by and for MGH medical professionals (a.k.a. clinicians, care givers) and is being made available publicly for informational purposes only, in the context of a public health emergency related to COVID-19 (a.k.a. the coronavirus) and in connection with the state of emergency declared by the Governor of the Commonwealth of Massachusetts and the President of the United States. It is neither an attempt to substitute for the practice of medicine nor as a substitute for the provision of any medical professional services. Furthermore, the content is not meant to be complete, exhaustive, or a substitute for medical professional advice, diagnosis, or treatment. The information herein should be adapted to each specific patient based on the treating medical professional's independent professional judgment and consideration of the patient's needs, the resources available at the location from where the medical professional services are being provided (e.g., healthcare institution, ambulatory clinic, physician's office, etc.), and any other unique circumstances. This information should not be used to replace, substitute for, or overrule a qualified medical professional's judgment.

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Strategies for Weaning Analgesia & Sedation

COVID-19 patients may be managed on high dose sedation and analgesia to allow for ventilator synchrony. The following recommendations should be utilized to develop tapering plans and monitoring closely for signs and symptoms of withdrawal during the weaning period of their recovery.

Criteria for weaning: Use of an analgesic or sedative agent for ≥7 days with P:F >200 & plans for transition to pressure support in the next 24-48 hours

Opioid Weaning

Options include weaning current opioid infusion by 10-30% per day or alternatively, utilize oral/transdermal replacements to help facilitate faster infusion weaning.

Once oral replacement initiated, reduce opioid infusion by 25% per dose to off.

Monitor for S/Sx of Withdrawal:
Abdominal cramps, diarrhea, nausea, and/or vomiting. Lacrimation, diaphoresis, shivering, and piloerection. Mydriasis, hypertension and tachycardia, irritability, insomnia, agitation, restless leg syndrome, tremor
OR
Clinical Opiate Withdrawal Scale
Can be wrenched into vital signs flowsheet.
Goal COWS <25

Methadone Taper
Consider for patients requiring higher opioid infusion doses or expected prolonged wean. Caution w/ hepatic impairment.
Monitor QTc, PO:IV 2:1

Initial Methadone Dose per Opioid Infusion Requirement		
Hydromorphone	**Fentanyl**	**Methadone (PO)**
0-1.5 mg/hr	0-100 mcg/hr	5-10 mg q8h
1.5-3 mg/hr	100-200 mcg/hr	7.5-10 mg q8h
>3 mg/hr	>200 mcg/hr	10-15 mg q8h

Oral Equivalent Taper
Consider if hydromorphone infusion <1.5 mg/hr or fentanyl <150 mcg/min

Initial Total Daily Oral Dose per Opioid Infusion Requirement			
Infusion	**Dose**	**Hydromorphone**	**Oxycodone**
Hydromorphone	0.5-1.5 mg/hr	30-90 mg	80-240 mg
Fentanyl	50-150 mcg/hr	20-60 mg	50-150 mg
Divide Total Daily Dose into q4-6 hour intervals			

Opioid Infusion
Wean by 25% per day. Once at low dose, transition to standing IV at equivalent dose or intermittent bolus dosing (0.5-2mg prn q2-4h)

If continuous infusions are unable to wean off, consider uptitrating initial oral replacement dose. Once infusions are off x24 hours, initiate planned taper by decreasing total daily replacement medication by 10-30% every 24-48 hours (see example).

If S/Sx of Withdrawal or COWS ≥ 25:
Consider use of adjunctive agents (clonidine).
Treat symptoms of withdrawal w/ prn bolus doses (0.5-2mg) IV or PO
Remain at same dose or increase to previous dose until signs/symptoms are well-controlled (COWS <25) for 12-24 hours.
Then restart/continue taper.

Example PO Methadone Taper
Start taper once infusion off x 24 hours

Methadone 10 mg q8h x48 hours
Methadone 7.5 mg q8h x48 hours
Methadone 5 mg q8h x48 hours
Methadone 5 mg q12h x 24-48 hours
Methadone 2.5 mg q12h x24-48 hours

If tapering multiple agents, consider staggering taper on opposite days

Example PO Hydromorphone Taper
Start taper once off infusion x24 hours

Hydromorphone 8 mg q4h x48 hours
Hydromorphone 6 mg q4h x48 hours
Hydromorphone 4 mg q4h x24-48 hours
Hydromorphone 4 mg q6h x24-48 hours
Transition to intermittent dosing

If tapering multiple agents, consider staggering taper on opposite days

Equianalgesic Doses		Metabolism/Elimination	Additional
Hydromorphone	IV: 1.5mg / PO 7.5mg	Hepatic metabolism via glucuronidation to inactive metabolites	Least affected by renal or hepatic impairment
Fentanyl	IV: 100 mcg	Hepatic metabolism via 3A4 to inactive metabolites	Half life increases with obesity and prolonged use
Morphine	IV: 10 mg/PO: 30 mg	Hepatic metabolism to active metabolites which are renally cleared	Avoid in renal dysfunction, may cause histamine release
Oxycodone	PO: 20 mg	Hepatic metabolism to active metabolites which are renally cleared	Use caution in patients with renal and hepatic dysfunction
Doses should be reduced by 33-66% when switching between agents to account for incomplete cross tolerance			

Version 1: 4/29/2020

Appendix 2

Strategies for Weaning Analgesia & Sedation

COVID-19 patients may be managed on high dose sedation and analgesia to allow for ventilator synchrony. The following recommendations should be utilized to develop tapering plans and monitoring closely for signs and symptoms of withdrawal during the weaning period of their recovery.

Criteria for weaning: Use of an analgesic or sedative agent for ≥7 days with P:F >200 & plans for transition to pressure support in the next 24-48 hours

Midazolam Weaning

Options include weaning current midazolam infusion by 10-30% per day or alternatively, utilize oral replacements to help facilitate faster infusion weaning.

Once oral replacement initiated, reduce midazolam infusion by 25% per dose to off.

Monitor for S/Sx of Withdrawal:
Tremors
Anxiety
Perceptual disturbances
Dysphoria
Psychosis
Seizures

Lorazepam
Preferred due to lack of drug-drug interactions, shorter half-life

1) Calculate total daily dose of midazolam
2) Divide total daily dose by 6 for daily lorazepam dose (consider dividing by 3 for difficult to wean patients)
3) Divide total daily lorazepam dose into q4h-q6h regimen
4) Wean midaz infusion by 25% with each lorazepam dose until off

Phenobarbital
Significant DDI with methadone, discuss with pharmacy if both required. Avoid with significant hepatic impairment. Levels for this indication not routinely recommended.

1) Utilize initial bolus dose of 5-10mg/kg Ideal Body Weight
2) Order maintenance dose 1-3mg/kg IBW divided into q8h-q12h dosing
3) Wean midazolam infusion by 25% after the bolus dose and by 25% more with each phenobarbital dose until off

Midazolam Infusion
Wean midazolam infusion by ~25% per day. Once at low dose, consider transition to intermittent bolus dosing

Approximately Equivalent Benzodiazepine Doses
Lorazepam 1 mg: Midazolam 2mg: Diazepam 10 mg

Additional adjustments for half-life & active metabolites, Discuss interchanging of agents w/ Pharmacy

If continuous infusion is unable to wean off, consider uptitrating initial oral replacement dose.

Once infusions are discontinued, decrease total daily replacement medication by 10-30% every 24-48 hours (see example).

If S/Sx of Withdrawal:
Treat acute symptoms of withdrawal w/ prn bolus doses (0.5-2mg IV or PO) Remain at same dose or increase to previous dose until signs/symptoms are well-controlled for 12-24 hours. Then continue taper

Dexmedetomidine
Wean infusion by 25% every 6 hours
Monitor for S/Sx of Withdrawal:
Hypertension
Tachycardia

Initiate Clonidine, uptitrate with each dose to max 0.6mg q8h
If Dexmedetomidine dose < 0.7 mcg/kg/hr:
Start Clonidine: 0.1 mg q8h
If Dexmedetomidine dose >0.7 mcg/kg/hr
Start Clonidine: 0.2-0.3 mg q8h

May consider clonidine patch, however, 72h required for full effect

Example Clonidine Taper
Start taper once infusion off x24 hrs

Clonidine 0.3 mg q8h x 24 hours
Clonidine 0.2 mg q8h x 24 hours
Clonidine 0.1 mg q8h x 24 hours
Clonidine 0.1 mg q12h x 24 hours

Agents for Refractory Agitation		Delirium Management
Quetiapine	25 mg PO q6-12 hours -Increase dose for (+) delirium screen or need for PRN haloperidol -Recommended max 400 mg/day	**Non-pharmacologic Strategies** -Ensure daily SAT -Reorient patient frequently -Early Mobilization -Promote sleep/wake cycles -Timely removal of catheters/restraints -Ensure use of glasses/hearing aids -Minimize noise/stimulation at night
Olanzapine	-2.5-5 mg PO daily -Increase by 2.5-5 mg QD for (+) delirium screen or need for PRN haloperidol (Max: 20 mg/day) -Based on onset (6h), PO/SL should not be used for agitated delirium	
Haloperidol	2.5-5 mg IV q4h prn agitation	
Melatonin	3-5 mg qHS to promote sleep	
Propranolol	10-20 mg PO q8h	
Valproic Acid	Discuss with pharmacy	

Example Lorazepam Taper
(From Midazolam 3 mg/hr)
Start taper once infusion off x 24 hours

Lorazepam 3 mg q6h x24 hours
Lorazepam 2 mg q6h x24 hours
Lorazepam 1 mg q6h x24 hours
Lorazepam 1 mg q8h x 24 hours
Lorazepam 1 mg q12h x12-24 hours

If tapering multiple agents, consider staggering taper on opposite days

Version 1: 4/29/2020

APPENDIX 3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METHADONE HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for METHADONE HYDROCHLORIDE TABLETS.

METHADONE HYDROCHLORIDE tablets, for oral use, CII
Initial U.S. Approval: 1947

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; LIFE-THREATENING QT PROLONGATION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and TREATMENT FOR OPIOID ADDICTION

See full prescribing information for complete boxed warning.

- **Methadone hydrochloride tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors and conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect. Monitor closely, especially upon initiation or following a dose increase. (5.3)**
- **Accidental ingestion of methadone hydrochloride tablets, especially by children, can result in fatal overdose of methadone. (5.3)**
- **QT interval prolongation and serious arrhythmia (*torsades de pointes*) have occurred during treatment with methadone. Closely monitor patients with risk factors for development of prolonged QT interval, a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction. (5.4)**
- **Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of use of methadone hydrochloride tablets during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. The balance between the risks of NOWS and the benefits of maternal methadone hydrochloride tablets use may differ based on the risks associated with the mother's underlying condition, pain, or addiction. Advise the patient of the risk of NOWS so that appropriate planning for management of the neonate can occur. (5.5)**
- **Concomitant use with CYP3A4, 2B6, 2C19, 2C9 or 2D6 inhibitors or discontinuation of concomitantly used CYP3A4 2B6, 2C19, or 2C9 inducers can result in a fatal overdose of methadone. (5.6, 7)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. (5.7, 7)**
- **Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by certified opioid treatment programs as stipulated in 42 CFR 8.12. (1, 2.1)**

----------INDICATIONS AND USAGE----------

Methadone hydrochloride tablets are an opioid agonist indicated for the:

1. Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
   Limitations of Use
   - Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioids, reserve methadone hydrochloride tablets for use in patients for 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.
   - Methadone hydrochloride tablets are not indicated as an as-needed (prn) analgesic.
2. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
3. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services. (1)
   Limitations of Use
   Methadone products used for the treatment of opioid addiction in detoxification or maintenance programs are subject to the conditions for distribution and use required under 42 CFR 8.12. (2.1)

----------DOSAGE AND ADMINISTRATION----------

- Consider prescribing naloxone based on the patient's risk factors for overdose (2.3, 5.1, 5.3, 5,7).

Management of Pain

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.4)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.4)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.4)
- For opioid-naïve patients, initiate methadone hydrochloride tablets treatment with 2.5 mg every 8 to 12 hours. (2.4)
- To convert to methadone hydrochloride tablets from another opioid, use available conversion factors to obtain estimated dose. (2.4)
- Titrate slowly with dose increases no more frequent than every 3 to 5 days. (2.5)
- Do not abruptly discontinue methadone hydrochloride tablets in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.6, 5.15)

Initiation of Detoxification and Maintenance Treatment

- A single dose of 20 to 30 mg may be sufficient to suppress withdrawal syndrome. (2.7)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg and 10 mg (3)

----------CONTRAINDICATIONS----------

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to methadone (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.8)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue methadone hydrochloride tablets if serotonin syndrome is suspected. (5.9)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use in patients with circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of methadone hydrochloride tablets in patients with impaired consciousness or coma. (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions are: lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt at 1-800-778-7898 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Antiretroviral Agents: May result in decreased efficacy or, in certain cases, increased toxicity. (7)
- Potentially Arrhythmogenic Agents: Pharmacodynamic interactions may occur. Monitor patients closely for cardiac conduction changes. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with methadone hydrochloride tablets because they may reduce analgesic effect of methadone hydrochloride tablets or precipitate withdrawal symptoms. (5.15, 7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of methadone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Monitor breastfed infants for increased drowsiness and breathing difficulties. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; LIFE-THREATENING QT PROLONGATION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and TREATMENT FOR OPIOID ADDICTION

Addiction, Abuse, and Misuse

Methadone hydrochloride tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing methadone hydrochloride tablets, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of methadone hydrochloride tablets. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period. Monitor for respiratory depression, especially during initiation of methadone hydrochloride tablets or following a dose increase *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of methadone hydrochloride tablets, especially by children, can result in a fatal overdose of methadone *[see Warnings and Precautions (5.3)]*.

Life-Threatening QT Prolongation

QT interval prolongation and serious arrhythmia (*torsades de pointes*) have occurred during treatment with methadone. 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. Closely monitor patients with risk factors for development of prolonged QT interval, a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction for changes in cardiac rhythm during initiation and titration of methadone hydrochloride tablets *[see Warnings and Precautions (5.4)]*.

Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of use of methadone hydrochloride tablets during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. The balance between the risks of NOWS and the benefits of maternal methadone hydrochloride tablets use may differ based on the risks associated with the mother's underlying condition, pain, or addiction. Advise the patient of the risk of NOWS so that appropriate planning for management of the neonate can occur *[see Warnings and Precautions (5.5)]*.

Cytochrome P450 Interaction

The concomitant use of methadone hydrochloride tablets with all cytochrome P450 3A4, 2B6, 2C19, 2C9 or 2D6 inhibitors may result in an increase in methadone plasma concentrations, which could cause potentially fatal respiratory depression. In addition, discontinuation of concomitantly used cytochrome P450 3A4 2B6, 2C19, or 2C9 inducers may also result in an increase in methadone plasma concentration. Follow patients closely for respiratory depression and sedation, and consider dosage reduction with any changes of concomitant medications that can result in an increase in methadone levels *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of methadone hydrochloride tablets and benzodiazepines or other CNS depressants for use in patients for whom alternatives to benzodiazepines or other CNS depressants are inadequate.**
- **Limit dosages and durations to the minimum required for patients being treated for pain.**
- **Follow patients for signs and symptoms of respiratory depression and sedation. If the patient is visibly sedated, evaluate the cause of sedation, and consider delaying or omitting the daily methadone dose.**

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

1 INDICATIONS AND USAGE

Methadone hydrochloride tablets are indicated for the:

1. Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

   Limitations of Use
   - Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioids *[see Warnings and Precautions (5.1)]*, reserve methadone hydrochloride tablets for use in patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
   - Methadone hydrochloride tablets are not indicated as an as-needed (prn) analgesic.
2. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
3. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

   Limitations of Use

   Methadone products used for the treatment of opioid addiction in detoxification or maintenance programs are subject to the conditions for distribution and use required under 42 CFR 8.12 *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

Code of Federal Regulations, Title 42, Sec 8: Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.
- During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

2.2 Important General Information

- The peak respiratory depressant effect of methadone occurs later and persists longer than its peak therapeutic effect.
- A high degree of opioid tolerance does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.
- With repeated dosing, methadone is retained in the liver and then slowly released, prolonging the duration of potential toxicity.
- Methadone has a narrow therapeutic index, especially when combined with other drugs.

2.3 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with methadone hydrochloride tablets *[see Warnings and Precautions (5.1, 5.3, 5.7), Overdosage (10)]*.

For Patients Being Treated for Pain
Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient.

For Patients Being Treated for Opioid Addiction
Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose.

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with methadone hydrochloride tablets itself.

Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone *[see Warnings and Precautions (5.3), Patient Counseling Information (17)]*.

Inform patients and caregivers of their options for obtaining naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Patient Counseling Information (17)]*.

2.4 Methadone Hydrochloride Tablets for Management of Pain

Important Dosage and Administration Information
Methadone hydrochloride tablets should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Consider the following important factors that differentiate methadone from other opioid analgesics:

- There is high interpatient variability in absorption, metabolism, and relative analgesic potency of methadone. Population-based equianalgesic conversion ratios between methadone and other opioids are not accurate when applied to individuals.
- The duration of analgesic action of methadone is 4 to 8 hours (based on single-dose studies) but the plasma elimination half-life is 8 to 59 hours.
- With repeated dosing, the potency of methadone increases due to systemic accumulation.
- Steady-state plasma concentrations and full analgesic effects are not attained until at least 3 to 5 days on a dose, and may take longer in some patients.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with methadone hydrochloride tablets and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

Use of Methadone Hydrochloride Tablets as the First Opioid Analgesic
Initiate treatment with methadone hydrochloride tablets with 2.5 mg orally every 8 to 12 hours.

Conversion from Other Oral Opioids to Methadone Hydrochloride Tablets
Discontinue all other around-the-clock opioid drugs when methadone hydrochloride tablets therapy is initiated. Deaths have occurred in opioid-tolerant patients during conversion to methadone.

The potency of methadone relative to other opioid analgesics is nonlinear and increases with increasing dose. Table 1 provides an estimated conversion factor for use when converting patients from another opioid to methadone. Because of the high inter-patient variability in absorption, metabolism, and relative potency, it is critical to avoid overestimating the methadone dose which can lead to fatal respiratory depression. It is safer to underestimate a patient's 24-hour methadone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour methadone dosage and manage an adverse reaction due to an overdose.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** another oral opioid analgesic **to** methadone hydrochloride tablets.

- The table **cannot** be used to convert **from** methadone hydrochloride tablets **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

Table 1: Conversion Factors to Methadone Hydrochloride Tablets

Total Daily Baseline **Oral Morphine Equivalent Dose**	Estimated Daily **Oral Methadone Requirement as Percent of Total Daily Morphine Equivalent Dose**
< 100 mg	20% to 30%
100 to 300 mg	10% to 20%
300 to 600 mg	8% to 12%
600 mg to 1,000 mg	5% to 10%
> 1,000 mg	< 5%

To calculate the estimated methadone hydrochloride tablets dose using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid, convert it to a Morphine Equivalent Dose according to specific conversion factor for that specific opioid, then multiply the Morphine Equivalent Dose by the corresponding percentage in the above table to calculate the approximate oral methadone daily dose. Divide the total daily methadone dose derived from the table above to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).
- For patients on a regimen of more than one opioid, calculate the approximate oral methadone dose for each opioid and sum the totals to obtain the approximate total methadone daily dose. Divide the total daily methadone dose derived from the table above to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Always round the dose down, if necessary, to the appropriate methadone hydrochloride tablets strength(s) available.

Example conversion from a single opioid to methadone hydrochloride tablets:

Step 1:
Sum the total daily dose of the opioid (in this case, Morphine Extended Release Tablets 50 mg twice daily)

50 mg Morphine Extended Release Tablets 2 times daily = 100 mg total daily dose of Morphine

Step 2:
Calculate the approximate equivalent dose of methadone hydrochloride tablets based on the total daily dose of Morphine using Table 1.

100 mg total daily dose of Morphine x 15% (10% to 20% per Table 1) = 15 mg methadone hydrochloride tablets daily

Step 3:
Calculate the approximate starting dose of methadone hydrochloride tablets to be given every 12 hours. Round down, if necessary, to the appropriate methadone hydrochloride tablets strengths available.

15 mg daily / 2 = 7.5 mg methadone hydrochloride tablets every 12 hours
Then 7.5 mg is rounded down to 5 mg methadone hydrochloride tablets every 12 hours

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to methadone hydrochloride tablets.

Conversion from Parenteral Methadone to Methadone Hydrochloride Tablets
Use a conversion ratio of 1:2 mg for parenteral to oral methadone (e.g., 5 mg parenteral methadone to 10 mg oral methadone).

2.5 Titration and Maintenance of Therapy for Pain

Individually titrate methadone hydrochloride tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving methadone hydrochloride tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of methadone hydrochloride tablets, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the methadone hydrochloride tablets dosage.

Because of individual variability in the pharmacokinetic profile (i.e., terminal half-life ($T_{1/2}$) from 8 to 59 hours in different studies *[see Clinical Pharmacology (12.3)]*, titrate methadone hydrochloride tablets slowly, with dose increases no more frequent than every 3 to 5 days. However, because of this high variability, some patients may require substantially longer periods between dose increases (up to 12 days). Monitor patients closely for the development of potentially life-threatening adverse reactions (e.g., CNS and respiratory depression).

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced and/or the dosing interval adjusted (i.e., every 8 hours or every 12 hours). Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.6 Safe Reduction or Discontinuation of Methadone Hydrochloride Tablets for Pain

Do not abruptly discontinue methadone hydrochloride tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking methadone hydrochloride tablets, there are a variety of factors that should be considered, including the dose of methadone hydrochloride tablets the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and followup plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on methadone hydrochloride tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed

with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.15), Drug Abuse and Dependence (9.3)]*.

2.7 Induction/Initial Dosing for Detoxification and Maintenance Treatment of Opioid Addiction

For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

Administer the initial methadone dose under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. An initial single dose of 20 to 30 mg of methadone hydrochloride tablets will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg.

To make same-day dosing adjustments, have the patient wait 2 to 4 hours for further evaluation, when peak levels have been reached. Provide an additional 5 to 10 mg of methadone hydrochloride tablets if withdrawal symptoms have not been suppressed or if symptoms reappear.

The total daily dose of methadone hydrochloride tablets on the first day of treatment should not ordinarily exceed 40 mg. Adjust the dose over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). When adjusting the dose, keep in mind that methadone levels will accumulate over the first several days of dosing; deaths have occurred in early treatment due to the cumulative effects. Instruct patients that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Use lower initial doses for patients whose tolerance is expected to be low at treatment entry. Any patient who has not taken opioids for more than 5 days may no longer be tolerant. Do not determine initial doses based on previous treatment episodes or dollars spent per day on illicit drug use.

During the induction phase of methadone maintenance treatment, patients are being withdrawn from opioids and may have opioid withdrawal symptoms. Monitor patients for signs and symptoms of opioid withdrawal including: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilling alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss and consider dose adjustment as indicated.

Short-Term Detoxification
For a brief course of stabilization followed by a period of medically supervised withdrawal, titrate the patient to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. After 2 to 3 days of stabilization, gradually decrease the dose of methadone hydrochloride tablets. Decrease the dose of methadone hydrochloride tablets on a daily basis or at 2-day intervals, keeping the amount of methadone hydrochloride tablets sufficient to keep withdrawal symptoms at a tolerable level. Hospitalized patients may tolerate a daily reduction of 20% of the total daily dose. Ambulatory patients may need a slower schedule.

2.8 Titration and Maintenance Treatment of Opioid Dependence

Titrate patients in maintenance treatment to a dose that prevents opioid withdrawal symptoms for 24 hours, reduces drug hunger or craving, and blocks or attenuates the euphoric effects of self-administered opioids, ensuring that the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day. During prolonged administration of methadone, monitor patients for persistent constipation and manage accordingly.

2.9 Medically Supervised Withdrawal After a Period of Maintenance Treatment for Opioid Addiction

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. Dose reductions should generally be less than 10% of the established tolerance or maintenance dose, and 10- to 14-day intervals should elapse between dose reductions. Apprise patients of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

2.10 Risk of Relapse in Patients on Methadone Maintenance Treatment of Opioid Addiction

Abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms *[see Drug Abuse and Dependence (9.3)]*. Opioid withdrawal symptoms have been associated with an increased risk of relapse to illicit drug use in susceptible patients.

2.11 Considerations for Management of Acute Pain During Methadone Maintenance Treatment

Patients in methadone maintenance treatment for opioid dependence who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. When opioids are required for management of acute pain in methadone maintenance patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients due to the opioid tolerance induced by methadone.

2.12 Dosage Adjustment During Pregnancy

Methadone clearance may be increased during pregnancy. During pregnancy, a woman's methadone dose may need to be increased or the dosing interval decreased *[see Use in Specific Populations (8.1)]*.

3 DOSAGE FORMS AND STRENGTHS

5 mg Tablets: white to off-white, modified rectangle shaped convex tablets and are debossed with a score between "57" and "55" on one side and M on the other side.

10 mg Tablets: white to off-white, modified rectangle shaped convex tablets and are debossed with a score between "57" and "71" on one side and M on the other side.

4 CONTRAINDICATIONS

Methadone hydrochloride tablets are contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*.

- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*.
- Hypersensitivity (e.g., anaphylaxis) to methadone *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Methadone hydrochloride tablets contain methadone, a Schedule II controlled substance. As an opioid, methadone hydrochloride tablets expose users to the risks of addiction, abuse, and misuse. As long-acting opioids such as methadone hydrochloride tablets have pharmacological effects over an extended period of time, there is a greater risk for overdose and death *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed methadone hydrochloride tablets. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing methadone hydrochloride tablets, and monitor all patients receiving methadone hydrochloride tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as methadone hydrochloride tablets, but use in such patients necessitates intensive counseling about the risks and proper use of methadone hydrochloride tablets along with the intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.3), Warnings and Precautions (5.3)]*.

Abuse or misuse of methadone hydrochloride tablets by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the methadone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing methadone hydrochloride tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.

- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of methadone, even when used as recommended. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of methadone hydrochloride tablets, the risk is greatest during the initiation of therapy or following a dosage increase. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period. Monitor patients closely for respiratory depression when initiating therapy with methadone hydrochloride tablets and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of methadone hydrochloride tablets are essential *[see Dosage and Administration (2.4, 2.5)]*. Overestimating the methadone hydrochloride tablets dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of methadone hydrochloride tablets, especially by children, can result in respiratory depression and death due to an overdose of methadone.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with methadone hydrochloride tablets.

For Patients Being Treated for Pain

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient.

For Patients Being Treated for Opioid Addiction

Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose.

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with methadone hydrochloride tablets itself *[see Overdosage (10)]*.

Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

Inform patients and caregivers of their options for obtaining naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and, if naloxone is prescribed, how to treat with naloxone. Emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)]*.

5.4 Life-Threatening QT Prolongation

Cases of QT interval prolongation and serious arrhythmia (*torsades de pointes*) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 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. In most patients on the lower doses typically used for maintenance, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients. The effects of methadone on the QT interval have been confirmed in *in vivo* laboratory studies, and methadone has been shown to inhibit cardiac potassium channels in *in vitro* studies.

Closely monitor patients with risk factors for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia), a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone.

Evaluate patients developing QT prolongation while on methadone treatment for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs that might cause electrolyte abnormalities, and drugs that might act as inhibitors of methadone metabolism.

Only initiate methadone hydrochloride tablets therapy for pain in patients for whom the anticipated benefit outweighs the risk of QT prolongation and development of dysrhythmias that have been reported with high doses of methadone.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied.

5.5 Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Advise the patient of the risk of NOWS so that appropriate planning for management of the neonate can occur. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly *[see Specific Populations (8.1)]*.

The balance between the risks of NOWS and the benefits of maternal methadone hydrochloride tablets use may differ based on the risks associated with the mother's underlying condition, pain or addiction, and the risks of the alternative treatments.

- For management of pain, prescribers should discuss all available treatment options with females of reproductive potential, including non-opioid and non-pharmacologic options.
- Untreated opioid addiction often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. NOWS can result from *in utero* exposure to opioids regardless of the source. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

5.6 Risks of Concomitant Use of Cytochrome P450 3A4, 2B6, 2C19, 2C9, or 2D6 Inhibitors or Discontinuation of P450 3A4, 2B6, 2C19, or 2C9 Inducers

Concomitant use of methadone hydrochloride tablets with CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors, may increase plasma concentrations of methadone, prolong opioid adverse reactions, and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dosage of methadone hydrochloride tablets is achieved. Similarly, discontinuation of concomitant CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers in methadone hydrochloride tablets-treated patients may increase methadone plasma concentrations resulting in fatal respiratory depression. Consider dosage reduction of methadone hydrochloride tablets when using concomitant CYP3A4, CYP2B6, CYP2C19, CYP2C9 or CYP2D6 inhibitors or discontinuing CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers in methadone-treated patients, and follow patients closely at frequent intervals for signs and symptoms of respiratory depression and sedation *[see Drug Interactions (7)]*.

Addition of CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuation of CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors in patients treated with methadone hydrochloride tablets may decrease methadone plasma concentrations, reducing efficacy and may lead to opioid withdrawal symptoms in patients physically dependent on methadone. When using methadone hydrochloride tablets with CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuing CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors, follow patients for signs or symptoms of opioid withdrawal and consider increasing the methadone hydrochloride tablets dosage as needed *[see Drug Interactions (7)]*.

5.7 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of methadone hydrochloride tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol).

For Patients Being Treated for Pain
Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid *analgesics [see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.3), Warnings and Precautions (5.3)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when methadone hydrochloride tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

For Patients Being Treated for Opioid Addiction
Concomitant use of methadone and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.

As a routine part of orientation to methadone treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, or alcohol.

Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at admission to methadone treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of methadone as a strategy to address benzodiazepine use in methadone-treated patients. However, if a patient is sedated at the time of methadone dosing, ensure that a medically-trained healthcare provider evaluates the cause of sedation, and delays or omits the methadone dose if appropriate.

Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.

For patients in methadone treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's methadone treatment and coordinate care to minimize the risks associated with concomitant use.

If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in methadone treatment for opioid use disorder *[see Warnings and Precautions (5.3)]*.

In addition, take measures to confirm that patients are taking the medications prescribed and not diverting or supplementing with illicit drugs. Toxicology screening should test for prescribed and illicit benzodiazepines *[see Drug Interactions (7)]*.

5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of methadone hydrochloride tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.3), Warnings and Precautions (5.3)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when methadone hydrochloride tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

For Patients Being Treated for Opioid Addiction
Concomitant use of methadone and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.

As a routine part of orientation to methadone treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, or alcohol.

Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at admission to methadone treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of methadone as a strategy to address benzodiazepine use in methadone-treated patients. However, if a patient is sedated at the time of methadone dosing, ensure that a medically-trained healthcare provider evaluates the cause of sedation, and delays or omits the methadone dose if appropriate.

Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.

For patients in methadone treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's methadone treatment and coordinate care to minimize the risks associated with concomitant use.

If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in methadone treatment for opioid use disorder *[see Warnings and Precautions (5.3)]*.

In addition, take measures to confirm that patients are taking the medications prescribed and not diverting or supplementing with illicit drugs. Toxicology screening should test for prescribed and illicit benzodiazepines *[see Drug Interactions (7)]*.

5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of methadone hydrochloride tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease
Methadone hydrochloride tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of methadone hydrochloride tablets *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients
Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating methadone hydrochloride tablets and when methadone hydrochloride tablets are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3, 5.7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of methadone hydrochloride tablets with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This 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 hydrochloride tablets if serotonin syndrome is suspected.

5.10 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.11 Severe Hypotension

Methadone hydrochloride tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of methadone hydrochloride tablets. In patients with circulatory shock, methadone hydrochloride tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of methadone hydrochloride tablets in patients with circulatory shock.

5.12 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) methadone hydrochloride tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with methadone hydrochloride tablets.

Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of methadone hydrochloride tablets in patients with impaired consciousness or coma.

5.13 Risks of Use in Patients with Gastrointestinal Conditions

Methadone hydrochloride tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The methadone in methadone hydrochloride tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.14 Increased Risk of Seizures in Patients with Seizure Disorders

The methadone in methadone hydrochloride tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during methadone hydrochloride tablets therapy.

5.15 Withdrawal

Do not abruptly discontinue methadone hydrochloride tablets in a patient physically dependent on opioids. When discontinuing methadone hydrochloride tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of methadone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.6), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist, including methadone hydrochloride tablets. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

5.16 Risks Driving and Operating Machinery

Methadone hydrochloride tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of methadone hydrochloride tablets and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.17 Laboratory Test Interactions

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

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- QT Prolongation *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.9)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*

The following adverse reactions associated with the use of methadone were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following:

Body as a Whole: asthenia (weakness), edema, headache

Cardiovascular: arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, *torsades de pointes*, ventricular fibrillation, ventricular tachycardia

Central Nervous System: agitation, confusion, disorientation, dysphoria, euphoria, insomnia, hallucinations, seizures, visual disturbances, congenital oculomotor disorders (nystagmus, strabismus)

Endocrine: hypogonadism, decreased testosterone

Gastrointestinal: abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic: reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic: hypoglycemia, hypokalemia, hypomagnesemia, weight gain

Renal: antidiuretic effect, urinary retention or hesitancy

Reproductive: amenorrhea, reduced libido and/or potency, reduced ejaculate volume, reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology

Respiratory: pulmonary edema, respiratory depression

Skin and Subcutaneous Tissue: pruritus, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Hypersensitivity: Anaphylaxis has been reported with ingredients contained in methadone hydrochloride tablets.

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- QT Prolongation *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.9)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*

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Renal: antidiuretic effect, urinary retention or hesitancy

Reproductive: amenorrhea, reduced libido and/or potency, reduced ejaculate volume, reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology

Respiratory: pulmonary edema, respiratory depression

Skin and Subcutaneous Tissue: pruritus, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Hypersensitivity: Anaphylaxis has been reported with ingredients contained in methadone hydrochloride tablets.

Serotonin Syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Androgen Deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Inhibitors of CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6	
Clinical Impact:	Methadone undergoes hepatic N-demethylation by several cytochrome P450 (CYP) isoforms, including CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6. The concomitant use of methadone hydrochloride tablets and CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors can increase the plasma concentration of methadone, resulting in increased or prolonged opioid effects, and may result in a fatal overdose, particularly when an inhibitor is added after a stable dose of methadone hydrochloride tablets is achieved. These effects may be more pronounced with concomitant use of drugs that inhibit more than one of the CYP enzymes listed above. After stopping a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor, as the effects of the inhibitor decline, the methadone plasma concentration can decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or withdrawal symptoms in patients physically dependent on methadone.
Intervention:	If concomitant use is necessary, consider dosage reduction of methadone hydrochloride tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor is discontinued, follow patients for signs of opioid withdrawal and consider increasing the methadone hydrochloride tablets dosage until stable drug effects are achieved.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), fluconazole, fluvoxamine, some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine)
Inducers of CYP3A4, CYP2B6, CYP2C19, or CYP2C9	
Clinical Impact:	The concomitant use of methadone hydrochloride tablets and CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers can decrease the plasma concentration of methadone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of withdrawal symptoms in patients physically dependent on methadone. These effects could be more pronounced with concomitant use of drugs that can induce multiple CYP enzymes. After stopping a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer, as the effects of the inducer decline, the methadone plasma concentration can increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, sedation, or death.
Intervention:	If concomitant use is necessary, consider increasing the methadone hydrochloride tablets dosage until stable drug effects are achieved. Monitor for

	signs of opioid withdrawal. If a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer is discontinued, consider methadone hydrochloride tablets dosage reduction and monitor for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin, St. John's Wort, Phenobarbital
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	*For Patients Being Treated for Pain* Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.7)]*. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Warnings and Precautions (5.1, 5.3, 5.7)]*. *For Patients Being Treated for Opioid Addiction* Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in treatment for opioid use disorder *[see Warnings and Precautions (5.1, 5.3, 5.7)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Potentially Arrhythmogenic Agents	
Clinical Impact:	Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents or drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia).
Intervention:	Monitor patients closely for cardiac conduction changes.
Examples:	Drugs known to have potential to prolong QT interval: Class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. Drugs capable of inducing electrolyte disturbances: Diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.9)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue methadone hydrochloride tablets if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3

	receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.9)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	The use of methadone hydrochloride tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of methadone hydrochloride tablets and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact:	Methadone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of methadone hydrochloride tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Warnings and Precautions (5.3, 5.7)]*.
Examples:	Cyclobenzaprine, metaxalone.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when methadone hydrochloride tablets are used concomitantly with anticholinergic drugs.

Paradoxical Effects of Antiretroviral Agents on Methadone Hydrochloride Tablets
Concurrent use of certain antiretroviral agents with CYP3A4 inhibitory activity, alone and in combination, such as abacavir, amprenavir, darunavir+ritonavir, efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, lopinavir+ritonavir, saquinavir+ritonavir, and tipranavir+ritonavir, has resulted in increased clearance or decreased plasma levels of methadone. This may result in reduced efficacy of methadone hydrochloride tablets and could precipitate a withdrawal syndrome. Monitor methadone-maintained patients receiving any of these antiretroviral therapies closely for evidence of withdrawal effects and adjust the methadone dose accordingly.

Effects of Methadone Hydrochloride Tablets on Antiretroviral Agents
Didanosine and Stavudine: Experimental evidence demonstrated that methadone decreased the area under the concentration-time curve (AUC) and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine: Experimental evidence demonstrated that methadone increased the AUC of zidovudine, which could result in toxic effects.

Effects of Methadone Hydrochloride Tablets on Antidepressants
Desipramine: Blood levels of desipramine have increased with concurrent methadone administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The majority of available data from clinical trials, observational studies, case series, and case reports on methadone use in pregnancy do not indicate an increased risk of major malformations specifically due to methadone.

Pregnant women involved in methadone maintenance programs have been reported to have improved prenatal care leading to reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors, including maternal use of illicit drugs, nutrition, infection and psychosocial circumstances, complicate the interpretation of investigations of the children of women who take methadone during pregnancy. Information is limited regarding dose and duration of methadone use during pregnancy, and most maternal exposure in these studies appears to occur after the first trimester of pregnancy (*see Data*).

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.6)]*.

In published animal reproduction studies, methadone administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) in the hamster at doses 2 times the human daily oral dose of 120 mg/day on a mg/m^2 basis (HDD) and in mice at doses equivalent to the HDD. Administration of methadone to pregnant animals during organogenesis and through lactation resulted decreased litter size, increased pup mortality, decreased pup body weights, developmental delays, and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD. Administration of methadone to male rodents prior to mating with untreated females resulted in increased neonatal mortality and significant differences in behavioral tests in the offspring at exposures comparable to and less than the HDD (*see Data*). Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and Embryo-Fetal Risk: Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

Dosage Adjustment During Pregnancy: Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with methadone hydrochloride tablets. Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery *[see Dosage and Administration (2.9) and Clinical Pharmacology (12.3)]*. Withdrawal signs and symptoms should be closely monitored and the dose adjusted as necessary.

Fetal/Neonatal Adverse Reactions: Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with methadone hydrochloride tablets.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.6)]*.

Labor or Delivery: Opioid-dependent women on methadone maintenance therapy may require additional analgesia during labor.

Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data
Human Data: The majority of available data from clinical trials, observational studies, case series, and case reports on methadone use in pregnancy do not indicate an increased risk of major malformations specifically due to methadone. Findings regarding specific major malformations, decreased fetal growth, premature birth and Sudden Infant Death Syndrome have been inconsistent. Children prenatally exposed to methadone have been reported to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests and visual abnormalities.

In a multicenter, double-blind, randomized, controlled trial [Maternal Opioid Treatment: Human Experimental Research (MOTHER)] designed primarily to assess neonatal opioid withdrawal effects, opioid-dependent pregnant women were randomized to buprenorphine (n=86) or methadone (n=89) treatment, with enrollment at an average gestational age of 18.7 weeks in both groups. A total of 28 of the 86 women in the buprenorphine group (33%) and 16 of the 89 women in the methadone group (18%) discontinued treatment before the end of pregnancy.

Among women who remained in treatment until delivery, there was no difference between methadone-treated and buprenorphine-treated groups in the number of neonates requiring NOWS treatment or in the peak severity of NOWS. Buprenorphine-exposed neonates required less morphine (mean total dose, 1.1 mg vs. 10.4 mg), had shorter hospital stays (10.0 days vs. 17.5 days), and shorter duration of treatment for NOWS (4.1 days vs. 9.9 days) compared to the methadone-exposed group. There were no differences between groups in other primary outcomes (neonatal head circumference), or secondary outcomes (weight and length at birth, preterm birth, gestational age at delivery, and 1-minute and 5-minute Apgar scores), or in the rates of maternal or neonatal adverse events. The outcomes among mothers who discontinued treatment before delivery and may have relapsed to illicit opioid use are not known. Because of the imbalance in discontinuation rates between the methadone and buprenorphine groups, the study findings are difficult to interpret.

Animal Data: Formal reproductive and developmental toxicology studies for methadone have not been conducted. Exposure margins for the following published study reports are based on a human daily dose (HDD) of 120 mg methadone using a body surface area comparison.

In a published study in pregnant hamsters, a single subcutaneous dose of methadone ranging from 31 mg/kg (2 times the HDD) to 185 mg/kg on Gestation Day 8 resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting neural tube defects including exencephaly, cranioschisis, and "various other lesions." The majority of the doses tested also resulted in maternal death. In a study in pregnant JBT/Jd mice, a single subcutaneous dose of 22 to 24 mg/kg methadone (approximately equivalent to the HDD) administered on Gestation Day 9 produced exencephaly in 11% of the embryos. In another study in pregnant mice, subcutaneous doses up to 28 mg/kg/day methadone (equivalent to the HDD) administered from Gestation Day 6 to 15 resulted in no malformations, but there were increased postimplantation loss and decreased live fetuses at 10 mg/kg/day or greater (0.4 times the HDD) and decreased ossification and fetal body weight at

20 mg/kg/day or greater (0.8 times the HDD). In a second study of pregnant mice dosed with subcutaneous doses up to 28 mg/kg/day methadone from Gestation Day 6 to 15, there was decreased pup viability, delayed onset of development of negative phototaxis and eye opening, increased righting reflexes at 5 mg/kg/day or greater (0.2 times the HDD), and decreased number of live pups at birth and decreased pup weight gain at 20 mg/kg/day or greater (0.8 times the HDD).

No effects were reported in a study of pregnant rats and rabbits at oral doses up to 40 mg/kg (3 and 6 times, respectively, the HDD) administered from Gestation Days 6 to 15 and 6 to 18, respectively.

When pregnant rats were treated with intraperitoneal doses of 2.5, 5, or 7.5 mg/kg methadone from one week prior to mating, through gestation until the end of lactation period, 5 mg/kg or greater (0.4 times the HDD) methadone resulted in decreases in litter size and live pups born and 7.5 mg/kg (0.6 times the HDD) resulted in decreased birth weights. Furthermore, decreased pup viability and pup body weight gain at 2.5 mg/kg or greater (0.2 times the HDD) were noted during the preweaning period.

Additional animal data demonstrate evidence for neurochemical changes in the brains of offspring from methadone-treated pregnant rats, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems at doses below the HDD. Other animal studies have reported that prenatal and/or postnatal exposure to opioids including methadone alters neuronal development and behavior in the offspring including alterations in learning ability, motor activity, thermal regulation, nociceptive responses, and sensitivity to drugs at doses below the HDD. Treatment of pregnant rats subcutaneously with 5 mg/kg methadone from Gestation Day 14 to 19 (0.4 times the HDD) reduced fetal blood testosterone and androstenedione in males.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone at doses comparable to and less than the HDD for 1 to 12 days before and/or during mating (with more pronounced effects in the first 4 days). In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Examination of uterine contents of methadone-naïve female mice bred to methadone-treated male mice (once a day for three consecutive days) indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states at 1 mg/kg/day or greater (0.04 times the HDD). Chromosome analysis revealed a dose-dependent increase in the frequency of chromosomal abnormalities at 1 mg/kg/day or greater.

Studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

8.2 Lactation

Risk Summary

Based on two small clinical studies, methadone was present in low levels in human milk, but the exposed infants in these studies did not show adverse reactions. Based on an 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. There have been rare case reports of sedation and respiratory depression in infants exposed to methadone through breast milk (*see Data*). Monitor infants exposed to methadone hydrochloride tablets through breast milk for excess sedation and respiratory

depression. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for methadone and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Data
In a study of ten breastfeeding women maintained on oral methadone doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk were reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose.

In a study of twelve breastfeeding women maintained on oral methadone doses of 20 to 80 mg/day, methadone concentrations from 39 to 232 mcg/L in milk were reported. Based on an 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.

8.3 Females and Males of Reproductive Potential

Infertility
The effect of methadone hydrochloride tablets on fertility is unknown. Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6), Clinical Pharmacology (12.2), Nonclinical Pharmacology (13.1)]*. Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported.

In published animal studies, methadone produces a significant regression of sex accessory organs and testes of male mice and rats and administration of methadone to pregnant rats reduced fetal blood testosterone and androstenedione in male offspring *[see Nonclinical Toxicology (13)]*.

8.4 Pediatric Use

The safety, effectiveness, and pharmacokinetics of methadone in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

Elderly patients (aged 65 years or older) may have increased sensitivity to methadone. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of methadone hydrochloride tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)]*.

Methadone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways; therefore, patients with liver impairment may be at risk of increased systemic exposure to methadone after multiple dosing. Start these patients on lower doses and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression.

8.7 Renal Impairment

Methadone pharmacokinetics have 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 central nervous system depression.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methadone hydrochloride tablets contain methadone, a Schedule II controlled substance.

9.2 Abuse

Methadone hydrochloride tablets contain methadone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. Methadone hydrochloride tablets can be abused and are subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

All patients treated with opioids for pain management require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Methadone hydrochloride tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment and selection of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Methadone Hydrochloride Tablets
Abuse of methadone hydrochloride tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone and alcohol or other substances. Methadone hydrochloride tablets are for oral use only and must not be injected. With intravenous abuse the inactive ingredients in methadone hydrochloride tablets can result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue methadone hydrochloride tablets in a patient physically dependent on opioids. Rapid tapering of methadone hydrochloride tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing methadone hydrochloride tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of methadone hydrochloride tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.6), Warnings (5.15)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.5)]*.

10 OVERDOSAGE

Clinical Presentation
Acute overdosage with methadone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal-muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Methadone overdosage is associated with rhabdomyolysis. Seek medical attention, especially if abuse/misuse results in prolonged immobilization. Acute toxic leukoencephalopathy has been reported after methadone overdose, often weeks after apparent recovery from the initial intoxication. Hearing loss has been reported after methadone overdose, in some cases permanent.

Treatment of Overdose
In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

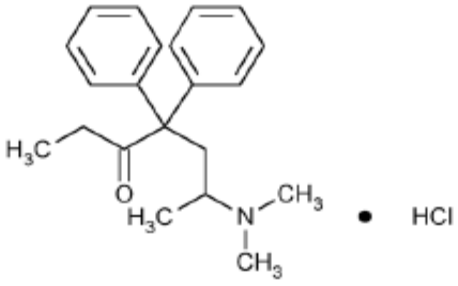
Because the duration of reversal would be expected to be less than the duration of action of methadone in methadone hydrochloride tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to opioid antagonists is suboptimal or not sustained, administer additional antagonist as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-hepatanone hydrochloride. Methadone hydrochloride USP is a white powder. Its molecular formula is $C_{21}H_{27}NO{\cdot}HCl$ and it has a molecular weight of 345.91. Methadone hydrochloride has a melting point of 235°C, and a pKa of 8.25 in water at 20°C. Its octanol/water partition coefficient at pH 7.4 is 117. A solution (1:100) in water has a pH between 4.5 and 6.5.

It has the following structural formula:



$C_{21}H_{27}NO \cdot HCl$ **MW = 345.91**

Methadone Hydrochloride Tablets are available for oral administration containing either 5 mg or 10 mg of methadone hydrochloride USP. Each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose and silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methadone hydrochloride is a mu-agonist; a synthetic opioid with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone withdrawal syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown.

12.2 Pharmacodynamics

Effects on the Central Nervous System
Methadone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Methadone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Some NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Methadone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Methadone produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System
Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of methadone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.2, 2.5)]*.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing methadone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.2, 2.4, 2.5)]*.

12.3 Pharmacokinetics

Absorption
Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1,255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution
Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to α1-acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Elimination
Metabolism: Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine. Methadone appears to be a substrate for P-glycoprotein but its pharmacokinetics do not appear to be significantly altered in case of P-glycoprotein polymorphism or inhibition.

Excretion: The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life ($T_{1/2}$) was highly variable and ranged between 8 to 59 hours in different studies. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Also, since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Drug Interaction Studies
Cytochrome P450 Interactions: Methadone undergoes hepatic N-demethylation by cytochrome P450 (CYP) isoforms, principally CYP3A4, CYP2B6, CYP2C19, CYP2C9 and CYP2D6. Co-administration of methadone with CYP inducers may result in more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to CYP induction activity *[see Drug Interactions (7)]*.

Cytochrome P450 Inducers: The following drug interactions were reported following co-administration of methadone with known inducers of cytochrome P450 enzymes:

Rifampin: In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin: In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg twice daily initially for 1 day followed by 300 mg daily for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

St. John's Wort, Phenobarbital, Carbamazepine: Administration of methadone with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 Inhibitors:

Voriconazole: Voriconazole can inhibit the activity of CYP3A4, CYP2C9, and CYP2C19. Repeat dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the peak plasma concentration (C_{max}) and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg daily). The C_{max} and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during co-administration. Dose reduction of methadone may be needed *[see Drug Interactions (7)]*.

Antiretroviral Drugs: Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to CYP induction activity.

Abacavir, Amprenavir, Darunavir+Ritonavir, Efavirenz, Nelfinavir, Nevirapine, Ritonavir, Telaprevir, Lopinavir+Ritonavir, Saquinavir+Ritonavir, Tipranavir+Ritonavir Combination: Co-administration of these antiretroviral agents resulted in increased clearance or decreased plasma levels of methadone *[see Drug Interactions (7)]*.

Didanosine and Stavudine: Methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered *[see Drug Interactions (7)]*.

Zidovudine: Methadone increased the AUC of zidovudine which could result in toxic effects *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (HDD). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times the HDD. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times the HDD. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis
There are several published reports on the potential genetic toxicity of methadone. Methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E. coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays. In contrast, methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures.

Impairment of Fertility
Published animal studies show that methadone treatment of males can alter reproductive function. Methadone produces decreased sexual activity (mating) of male rats at 10 mg/kg/day (corresponding to 0.3 times the human daily oral dose of 120 mg/day based on body surface area). Methadone also produces a significant regression of sex accessory organs and testes of male mice and rats at 0.2 and 0.8 times the HDD, respectively. Methadone treatment of pregnant rats from Gestation Day 14 to 19 reduced fetal blood testosterone and androstenedione in males. Decreased serum levels of testosterone were observed in male rats that were treated with methadone (1.3 to 3.3 mg/kg/day for 14 days, corresponding to 0.1 to 0.3 times the HDD) or 10 to 15 mg/kg/day for 10 days (0.8 to 1.2 times the HDD).

16 HOW SUPPLIED/STORAGE AND HANDLING

Methadone Hydrochloride Tablets USP 5 mg are white to off-white, modified rectangle shaped convex tablets, one side debossed with a score between "57" and "55"; M on the other side.

Bottles of 100 .....NDC 0406-5755-01
Unit Dose (10 x 10).....NDC 0406-5755-62

Methadone Hydrochloride Tablets USP 10 mg are white to off-white, modified rectangle shaped convex tablets, one side debossed with a score between "57" and "71"; M on the other side.

Bottles of 100 .....NDC 0406-5771-01
Unit Dose (10 x 10).....NDC 0406-5771-62

Store at 20° to 25°C (68° to 77°F), with excursions permitted between 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

Store methadone hydrochloride tablets securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Storage and Disposal
Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store methadone hydrochloride tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving methadone hydrochloride tablets unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused methadone hydrochloride tablets should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse
Inform patients that the use of methadone hydrochloride tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share methadone hydrochloride tablets with others and to take steps to protect methadone hydrochloride tablets from theft or misuse.

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting methadone hydrochloride tablets or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.3)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose
Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with methadone hydrochloride tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.3), Warnings and Precautions (5.3)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:
- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Accidental Ingestion
Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*.

Symptoms of Arrhythmia
Instruct patients to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, near syncope, or syncope) when taking methadone *[see Warnings and Precautions (5.4)]*.

Interactions with Benzodiazepines and Other CNS Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if methadone hydrochloride tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and

to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.9), Drug Interactions (7)]*.

MAOI Interaction
Inform patients to avoid taking methadone hydrochloride tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking methadone hydrochloride tablets *[see Warnings and Precautions (5.9), Drug Interactions (7)]*.

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.10)]*.

Important Administration Instructions
Instruct patients how to properly take methadone hydrochloride tablets, including the following:

- Use methadone hydrochloride tablets exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) *[see Dosage and Administration (2), Warnings and Precautions (5.3)]*.

Important Discontinuation Instructions
In order to avoid developing withdrawal symptoms, instruct patients not to discontinue methadone hydrochloride tablets without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.6)]*.

Hypotension
Inform patients that methadone hydrochloride tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.11)]*.

Anaphylaxis
Inform patients that anaphylaxis has been reported with ingredients contained in methadone hydrochloride tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy
Neonatal Opioid Withdrawal Syndrome: Advise women that if they are pregnant while being treated with methadone hydrochloride tablets, the baby may have signs of withdrawal at birth and that withdrawal is treatable *[see Warnings and Precautions (5.5), Specific Populations (8.1)]*.

Embryo-Fetal Toxicity: Inform female patients of reproductive potential that methadone hydrochloride tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise women who are breastfeeding to monitor the infant for increased sleepiness (more than usual), difficulty breathing or limpness. Instruct nursing mothers using methadone hydrochloride tablets to watch for signs of methadone toxicity in their infants, which include increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's healthcare provider immediately if they notice these signs. If they cannot reach the healthcare provider right away, instruct them to take the baby to the emergency room or call 911 (or local emergency services) *[see Use in Specific Populations (8.2)]*.

Infertility
Advise patients that chronic use of opioids, such as methadone hydrochloride tablets, may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery
Inform patients that methadone hydrochloride tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.16)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

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Mallinckrodt™ Pharmaceuticals

An electronic copy of this medication guide can be obtained from www.mallinckrodt.com/Medguide/L20M28.pdf or by calling 1-800-778-7898 for alternate delivery options.

Medication Guide

Methadone Hydrochloride Tablets USP, CII
(METH a done HYE droe KLOR ide)
Rx only

Methadone hydrochloride tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse than can lead to death.
- Not for use to treat pain that is not around-the-clock.
- Also used to manage drug addiction.

Important information about methadone hydrochloride tablets:

- **Get emergency help or call 911 right away if you take too much methadone hydrochloride tablets (overdose).** When you first start taking methadone hydrochloride tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for emergency treatment of opioid overdose.
- Taking methadone hydrochloride tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your methadone hydrochloride tablets. They could die from taking it. Selling or giving away methadone hydrochloride tablets is against the law.
- Store methadone hydrochloride tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take methadone hydrochloride tablets if you have:

- Severe asthma, trouble breathing, or other lung problems.
- A bowel blockage or have narrowing of the stomach or intestines.

Before taking methadone hydrochloride tablets, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- heart rhythm problems (Long QT syndrome)
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

Tell your healthcare provider if you are:

- **Pregnant or plan to become pregnant.** If you take methadone hydrochloride tablets while pregnant, your baby may have symptoms of opioid withdrawal or respiratory depression at birth. Talk to your doctor if you are pregnant or plan to become pregnant.
- **Breastfeeding.** Methadone passes into breast milk and may harm your baby.
- Living in a household where there are small children or someone who has abused street or prescription drugs.
- Taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking methadone hydrochloride tablets with certain other medicines may cause serious side effects.

When taking methadone hydrochloride tablets:

- Do not change your dose. Take methadone hydrochloride tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Do not take more than your prescribed dose in 24 hours. If you take methadone hydrochloride tablets for pain and miss a dose, take methadone hydrochloride tablets as soon as possible and then take your next dose 8 or 12 hours later as directed by your healthcare provider. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.
- If you take methadone hydrochloride tablets for opioid addiction and miss a dose, take your next dose the following day as scheduled. Do not take extra doses. Taking more than the prescribed dose may cause you to overdose because methadone hydrochloride tablets build up in your body over time.
- Do not crush, dissolve, snort or inject methadone hydrochloride tablets because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking methadone hydrochloride tablets without talking to your healthcare provider.**
- Dispose of expired, unwanted, or unused methadone hydrochloride tablets by promptly flushing down the toilet, if a drug takeback option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking methadone hydrochloride tablets DO NOT:

- Drive or operate heavy machinery, until you know how methadone hydrochloride tablets affect you. Methadone hydrochloride tablets can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with methadone hydrochloride tablets may cause you to overdose and die.

The possible side effects of methadone hydrochloride tablets are:

- Constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away if you have:

- Trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, lightheadedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of methadone hydrochloride tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

For more information, please call 1-800-778-7898.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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FULL PRESCRIBING INFORMATION

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2018

*Sections or subsections omitted from the full prescribing information are not listed.

Appendix 4

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

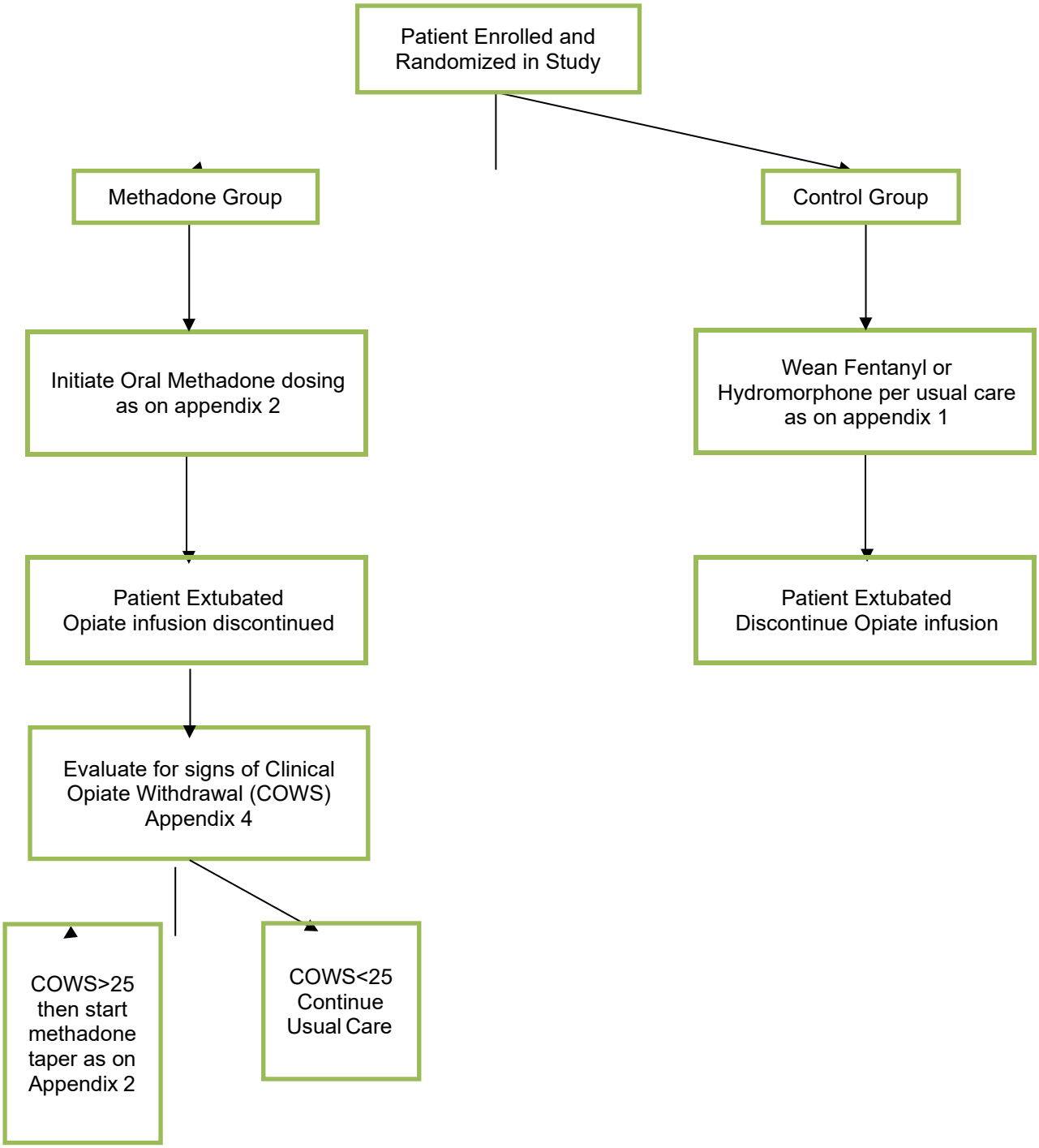
This version may be copied and used clinically.

Journal of Psychoactive Drugs Volume 35 (2), April - June 2003

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

Appendix 5

Protocol Flow



Appendix 6

Data Collection Tool

Patient Identification Code (MRN):

Baseline Characteristics		
Age (years)		
Sex		
Race		
Weight (Kg)		
Duration on ventilator at time of randomization (Hours)		
Cause of Lung injury	Pneumonia = 1	
	Aspiration = 2	
	Non-Pulmonary Sepsis = 3	
	COPD Exacerbation = 4	
	Other Causes = 5	
Assessments and Measurements		
APACHE II Score		
Total SOFA Score		
Tidal Volume ml/kg of predicted body weight		
Peep at time of enrollment (cm H2O)		
PaO2: FIO2 ratio (mmHg)		
FiO2 at time of enrollment		
Duration on mechanical ventilation before start of weaning(hours)		
Last recorded Ph prior to enrollment		
Duration in ICU stay after enrollment (Hours)		
Mean QTc while on Methadone		
Clinical Opiate Withdrawal Scale (COWS) after extubation		
Adverse Event		
Medication Parameters		
Fentanyl Initial Dose (mcg/hour)		
Fentanyl accumulated dose(mcg)		
Days on Fentanyl before start of weaning		
Hydromorphone initial Dose (mg/hour)		
Hydromorphone accumulated dose(mg)		
Days on Hydromorphone before start of weaning		
Dexmedetomidine accumulated dose(mcg)		
Midazolam accumulated dose(mg)		
Propofol accumulated dose (mg)		
Ketamine accumulated dose (mg)		