Guidelines on Use of Long-term Opioid Therapy for Chronic Non-cancer Pain

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Acknowledgments


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Purpose

• Understand evidence-based guidelines for risk assessment to guide patient selection for opioids
• Understand evidence-based guidelines for initiation and titration of long-term opioid therapy
• Understand evidence-based guidelines for monitoring of patients on long-term opioid therapy
Chronic noncancer pain is highly prevalent, with substantial burdens.
Opioids are increasingly prescribed for chronic noncancer pain.
Opioids are associated with potential harms, both to patients and to society.
Lack of guidelines based on a rigorous evidence-based process.
Large practice variations.
Prescription drug abuse

- In 2006, nearly 7 million Americans estimated to be abusing prescription drugs.
- Prescription opioids cause more drug overdose deaths than cocaine and heroin combined.
  - Overdose deaths often associated with use of multiple opioids and/or illicit substances.
- Nearly 1 in 10 high school seniors admit to abusing prescription painkillers.
  - About 40% of teens and adults think abusing prescription painkillers is safer than abusing “street” drugs.
- Hydromorphone is the most commonly diverted and abused controlled pharmaceutical in the U.S.
Figure 2. Poisoning deaths involving opioid analgesics, cocaine, and heroin: United States, 1999–2006

NOTES: Drug categories are not mutually exclusive. Deaths involving more than one drug category shown in this figure are counted multiple times. Access data table for Figure 2 at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/Data_Briefs/db022/fig02.xls.

Nonmedical Use of Prescription Pain Relievers in the Past Month, by Age Group: Percentages, 2002 to 2007
# Street value of opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimated street value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycontin</td>
<td>$3-4/mg (40 mg tab =$120-$160)</td>
</tr>
<tr>
<td>Oxycodone/ APAP</td>
<td>$15/tab</td>
</tr>
<tr>
<td>Hydrocodone/ APAP</td>
<td>$6-12/tab</td>
</tr>
<tr>
<td>Codeine/ APAP</td>
<td>$2-4/tab</td>
</tr>
<tr>
<td>Propoxyphene/ APAP</td>
<td>$2-20/tab</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>$15/tab</td>
</tr>
<tr>
<td>Morphine</td>
<td>$1/mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>$1-2/mg</td>
</tr>
</tbody>
</table>
Summary of panel processes and main conclusions

- Multidisciplinary panel, partnership between APS and AAPM
- Series of three face-to-face meetings and multiple telephone conferences
  - Delphi process/GRADE methods
- Approximately 25 recommendations in final guideline
- Consensus reached on 22 recommendations, with one or two dissenting votes in other cases
- Most recommendations based on panel consensus
  - Only 3 recommendations rated as supported by even moderate quality evidence
Definitions

- Chronic pain: Pain that persists beyond normal tissue healing time, which is assumed to be 3 months.
- Noncancer pain: All pain outside of cancer pain and pain at end of life.
- Chronic opioid therapy: Daily or near-daily use of opioids for at least 90 days, often indefinitely.
- Physical dependence: A state of adaptation manifested by a drug class-specific withdrawal syndrome.
- Tolerance: A state of adaptation in which exposure to a drug results in a diminution of opioid effects over time.
Definitions

- Addiction: Behaviors include impaired control over drug use, compulsive use, continued use despite harm, and craving.
- Aberrant drug-related behavior: A behavior outside the boundaries of the agreed upon treatment plan.
- Misuse: Use of a medication other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
- Abuse: Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose such as altering one’s state of consciousness, e.g. getting high.
- Diversion: The intentional transfer of a controlled substance from legitimate distribution and dispensing channels.
1.1 Prior to initiating COT, conduct a history, physical examination and appropriate testing, including an assessment of risk (strong recommendation, low-quality evidence).

1.2 Consider a trial of COT as an option if CNCP is moderate or severe, has an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, low-quality evidence).

1.3 A benefit-to-harm evaluation should be performed and documented prior to starting COT and on an ongoing basis (strong recommendation, low-quality evidence).
Patient selection and risk stratification

Rationale

- Aberrant drug-related behaviors occur in 0-50% of patients prescribed opioids for chronic non-cancer pain
- Risk stratification pertaining to abuse potential of opioids is a vital (but relatively underdeveloped) skill
  - Strongest predictor is personal or family history of alcohol or drug abuse
  - Risk stratification can help guide the management plan
- Also important to consider likelihood of benefit and adverse effects
- Opioids are not always appropriate
- Tools for risk stratification are available, but require further evaluation
  - SOAPP, ORT
Risk of Addiction or Aberrant Behavior With Opioids

**LOW RISK**
- Short-term exposure to opioids in nonaddicts

**HIGH RISK**
- Long-term exposure to opioids in addicts

Where is your patient?

Porter, 1980; Dunbar, 1996; Passik, 1998

Slide courtesy of Jeffrey Fudin
Population of Prescription Opioid Users Is Heterogeneous

Nonmedical users

Pain patients

SUD = substance use disorder

“Addicted” (SUD)
“Substance abusers”
“Recreational users”
“Self-treaters”
“Adherent”
“Chemical copers”
“Substance abusers”
“Addicted” (SUD)

### Opioid Risk Tool (ORT)

#### Administration
- On initial visit
- Prior to opioid therapy

#### Scoring
- 0-3: low risk (6%)
- 4-7: moderate risk (28%)
- > 8: high risk (> 90%)

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family history of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>□ 1</td>
<td>□ 3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>2. Personal history of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>□ 5</td>
<td>□ 5</td>
</tr>
<tr>
<td>3. Age (mark if between 16-45 yrs)</td>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>4. History of preadolescent sexual abuse</td>
<td>□ 3</td>
<td>□ 0</td>
</tr>
<tr>
<td>5. Psychological disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADO, OCD, bipolar, schizophrenia</td>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>Depression</td>
<td>□ 1</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

**Scoring totals**

## Risk prediction tools

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Number of items and cut-off score</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PLR</th>
<th>NLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOAPP Version 1*</td>
<td>14 (max 67), ≥7</td>
<td>0.91</td>
<td>0.69</td>
<td>2.90</td>
<td>0.13</td>
</tr>
<tr>
<td>SOAPP-R*</td>
<td>24 (max 96), ≥17</td>
<td>0.80</td>
<td>0.68</td>
<td>2.50</td>
<td>0.29</td>
</tr>
<tr>
<td>ORT</td>
<td>10 (max 25), 0-3 (low risk), 4-7 (mod risk), &gt;7 (high risk)</td>
<td>NA</td>
<td>NA</td>
<td>Low risk: 0.08 Mod risk: 0.57 High risk: 14.3</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Derivation study
## Risk prediction tools: application

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Pre-test probability</th>
<th>Post-test probability with positive screen</th>
<th>Post-test probability with negative screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOAPP V1 or SOAPP-R</td>
<td>3%</td>
<td>7-8%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>SOAPP V1 or SOAPP-R</td>
<td>20%</td>
<td>40%</td>
<td>3-7%</td>
</tr>
<tr>
<td>ORT</td>
<td>3%</td>
<td>High risk: 30%</td>
<td>Low risk: 0.2%</td>
</tr>
</tbody>
</table>
Informed consent/chronic pain care plan

Recommendations

2.1 When starting COT, obtain informed consent (strong recommendation, low-quality evidence).

2.2 Consider a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education (weak recommendation, low-quality evidence).
Informed consent/chronic pain care plan

Rationale

• Counsel patient on potential adverse effects, risks associated to abuse potential
  ○ Documentation of discussion of “material risks” required in Oregon

• COT management plans in all patients
  ○ Goals of therapy, how COT will be prescribed and taken, expectations for follow-up and monitoring, alternatives to COT, expectations regarding use of concomitant therapies, and potential indications for tapering or discontinuing COT
  ○ Consider written COT management plan (not required in Oregon)
3.1 Consider the initial treatment with opioids as a therapeutic trial to determine whether COT is appropriate (strong recommendation, low-quality evidence).

3.2 Opioid selection, initial dosing, and titration should be individualized according to the patient’s health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms (strong recommendation, low-quality evidence).
Initiation and titration of opioids

Rationale

- Initial course of treatment should be viewed as a short-term, therapeutic trial
  - The decision to proceed (or continue) with COT should be a conscious one
  - Do not continue COT in patients who are not benefitting
- Start at low doses and titrate cautiously
- Insufficient evidence to recommend short-vs. long-acting opioids, round-the-clock versus PRN
  - Potential benefits of long-acting, round-the-clock dosing include more stable pain control and less potential for addiction
  - Potential harms of long-acting, round-the-clock opioids include development of hyperalgesia, tolerance, endocrinologic adverse effects
"Purdue ... acknowledged that it illegally marketed and promoted OxyContin by falsely claiming that OxyContin was less addictive, less subject to abuse and diversion, and less likely to cause withdrawal symptoms than other pain medications - all in an effort to maximize its profits"

Methadone

Recommendation

4.1 Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously, by clinicians familiar with its use and risks (strong recommendation, moderate-quality evidence).
“Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat”

What prompted this warning?

http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124346.htm
Figure 2. Age-specific methadone-related death rates: 1999–2005

Deaths per 100,000 population (log scale)

SOURCE: CDC/NCHS, data from the National Vital Statistics System.
Methadone

Rationale

• Increased methadone deaths nationwide
• Half-life 15 to 60 hours, up to 120 hours
  ○ 60 hour half-life=12 days to steady-state
  ○ Prolongation of QT intervals, sudden death
  ○ Start at 2.5 mg q8 hrs, increase slowly
• Little evidence on use of methadone for CNCP
  ○ One poorly designed trial
  ○ A new VA cohort study found methadone associated with lower mortality risk compared to morphine (Krebs EE et al. Pain 2011; doi:10.1016/j.pain.2011.03.023)
• Equianalgesic doses of methadone relative to other opioids vary
  ○ Even in patients on high doses of other opioids, start methadone at no higher than 30 to 40 mg/day
### Morphine to methadone conversion

<table>
<thead>
<tr>
<th>24 hour total oral morphine</th>
<th>Oral morphine to methadone conversion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg</td>
<td>2:1</td>
</tr>
<tr>
<td>31-99 mg</td>
<td>4:1</td>
</tr>
<tr>
<td>100-299 mg</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>500-999 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>20:1</td>
</tr>
</tbody>
</table>

5.1 Assess patients periodically and as warranted by changing circumstances. (strong recommendation, low-quality evidence).
Monitoring

Rationale

- All patients on COT should be monitored
- Optimal monitoring intervals uncertain
  - 3 to 6 months in low-risk, up to weekly in high-risk
- Monitoring should assess multiple domains (4 A’s)
  - Pain severity (analgesia), functional ability (ADLs), adverse events, aberrant drug-related behaviors
- Patient self-report may not be reliable
  - Urine drug screens, pill counts, family members, prescriptions drug monitoring programs
5.2 In high-risk patients, periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care (strong recommendation, low-quality evidence).

5.3 In patients not at high risk, consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care (weak recommendation, low-quality evidence).
Status of State Prescription Drug Monitoring Programs (PDMPs)

© 2009 Research is current as of June 30, 2009. In order to ensure that the information contained herein is as current as possible, research is conducted using both nationwide legal database software and individual state legislative websites. Please contact Sarah Kelsey at 703-836-6100, ext. 119 or at skelsey@namsdl.org with any additional updates or information that may be relevant to this document.


1Washington has temporarily suspended its PMP operations due to budgetary constraints.
2Legislation has been proposed in Wisconsin that, if passed, would establish a PDMP.
Urine drug tests

Rationale

• Urine drug tests can be difficult to interpret
  ○ Diagnostic accuracy for abuse/addiction not well studied
  ○ Need to understand metabolic pathways of different opioids
  ○ Differential diagnosis for abnormal results includes poorly controlled pain, drug abuse, diversion
  ○ Potential for false reassurance
  ○ No evidence that urine drug testing improves patient outcomes, and potential for harms
  ○ Test prior to starting opioids and periodically
    ○ Testing interval can be longer in lower-risk patients
Internet Search for “Clean Urine”

1. You're Clean Provides drug testing and detox products designed to help people prepare for and pass a urine or hair drug test. Find out about the company's guarantee.
   www.youreclean.com
2. pass a drug test urine Drug testing products and information to help you pass urine and hair follicle drug test.
   www.cleartest.com
   or hair - ClearTest
3. You're Clean Drug testing, Drug test, Pass a urine drug test, pass a hair drug test, Info for helping people pass the urine drug test & hair drug test. Protect your rights. Don't be a victim of drug testing. Use our proven drug
   www.youreclean.com/index2facts.html: drug testing solutions Pass a urine drug test & hair test
4. pass a drug test Be Negative pass testing Clean pass a drug test. "BeNegative.Com" Drug Testing Solutions "Be Negative" can provide you with products to help you pass a drug test. You can pass a hair follicle drug test, blood or urine test. We carry detox products and hair cleaners at low prices.
   www.benegative.com
5. Terminader Gold 60 Clean Detox Urine Drug Testing terminader gold 60 clean detox urine testing drink
   www.webspawner.com/users/Terminader
6. anti drug testing products - for urine and hair follicle drug tests Drug testing products and information to help you pass hair follicle and urine drug tests.
   www.cleartest.com/products
7. Drug Testing Marijuana - Self Test Drug Kits Unbiased providers of drug and alcohol self / home test kits for people who want to test themselves for marijuana and other drugs.
   www.drugtestingmarijuana.com
8. Always Test Clean Sells capsules, drinks, and shampoos designed to remove the toxins that cause positive results on urine, hair, or blood drug tests. Find out how each product works.
   www.alwaystestclean.com
   www.passdrugtesting.com
    www.passyourdrugtesting.com/hair-drug-testing-urine-drug-testing.htm
    www.passdrugtesting.com/urine_drug_test.html
12. Drug Testing Products - Marijuana Information - Home Test Kits Drug testing kits, products and
   "Clean Urine" slide courtesy of Jeffrey Fudin

American Pain Society
www.passdrugtest.com/blood_drug_test_information.html

www.PassDrugTest.com
Help to pass a drug test. Pass urine drug test. Pass blood drug test. Pass saliva drug test. Pass hair drug test. We also have do it yourself drug test kits. For drug test information and list of toxins that cause false positive see Drug Test Q&Aower left.
Order Today Receive Shipment Tomorrow 77-345-5555

Carbo Cleansing Shake
Pass Urine Drug Test.
Pass Blood Drug Test.
Pass Saliva Drug Test.

Slide courtesy of Jeffrey Fudin
I heard from Dr. Grow that dog urine (of all things) can be substituted, and will pass the test! However, I don't know how age, gender, pH, or creatinine test would result. Someone was able to use dog urine for several months to pass the test. This subsection assumes you have a clean dog. I know my dog's urine wouldn't pass; he eats more weed than humans do. It would make more sense to use human urine, but dog urine provides a workable substitution in an emergency.
The Clean Whiz Kit
(http://www.cleanwhiz.com/cleankit.html)

Slide courtesy of Jeffrey Fudin
Chart of common opiate metabolites

- Heroin
  - 6-acetylmorphine
    - Morphine containing drugs and poppy seeds
      - Morphine
        - Hydromorphone
          - Codeine
            - Hydrocodone
              - Oxycodone
                - Oxymorphone
              - Fentanyl
            - Methadone
<table>
<thead>
<tr>
<th>Agent taken by patient</th>
<th>Codeine</th>
<th>Morphine</th>
<th>Hydrocodone</th>
<th>Hydromorphone</th>
<th>Oxycodone</th>
<th>Oxymorphone</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>*</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>*</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>-</td>
<td>*</td>
<td>*</td>
<td>+</td>
<td>-</td>
<td>**</td>
<td>-</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>-</td>
<td>-</td>
<td>**</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>**</td>
<td>*</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Methadone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Heroin</td>
<td>*</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+/- = possible with high doses of parent drug
* = highly unlikely but reverse metabolism possible
** = theoretically possible, but does not normally occur
# Interpretation of urine drug tests

<table>
<thead>
<tr>
<th></th>
<th>Expected result</th>
<th>Unexpected result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine drug test</td>
<td>Prescribed medication, appropriate use</td>
<td>Use of non-prescribed medications</td>
</tr>
<tr>
<td>is positive</td>
<td>Metabolite of prescribed medication</td>
<td>Use of illicit drugs</td>
</tr>
<tr>
<td></td>
<td>Prescribed medication, inappropriate use</td>
<td>Use of previously prescribed medications (hoarding)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-reaction (food, OTC, herbal products)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contamination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laboratory error</td>
</tr>
<tr>
<td>Urine drug test</td>
<td>Drug screen doesn’t pick up the drug in question</td>
<td>Diversion</td>
</tr>
<tr>
<td>is negative</td>
<td>Patient appropriately not taking opioid</td>
<td>Outside time frame for positive test</td>
</tr>
<tr>
<td></td>
<td>Test performed prior to initiation of opioids</td>
<td>Fast metabolizer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laboratory processing error</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extreme dilution of urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malabsorption?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hoarding/binging</td>
</tr>
</tbody>
</table>
Monitoring Instruments

- **COMM**: 17 item instrument, cut-off score $\geq 10$ (max 68)
  - Sensitivity 0.74, specificity 0.73
  - PLR 2.77, NLR 0.35
  - Derivation study

- **PADT**: Useful for assessing and documenting the 4 A’s; not designed as an instrument for identifying presence of aberrant behaviors

- No evidence on effects of using different monitoring instruments (or different methods of monitoring) on patient outcomes
6.1 Consider COT for high-risk patients only if able to implement more frequent and stringent monitoring parameters. In such situations, strongly consider consultation with a mental health or addiction specialist (strong recommendation, low-quality evidence).

6.2 Evaluate patients engaging in aberrant drug-related behaviors for appropriateness of COT or need for restructuring of therapy, referral for assistance in management, or discontinuation of COT (strong recommendation, low-quality evidence).
High-risk patients are more vulnerable to opioid abuse, misuse, addiction.

Clinician must be able to implement additional measures to manage these risks:
- More frequent monitoring
- Limited prescription fills
- Consultation with addiction specialists and mental health professionals
- Opioid-deterrent formulations undergoing FDA approval process, clinical effectiveness is yet to be established.
BAYER Pharmaceutical Products
HEROIN-HYDROCHLORIDE
is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, $4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

The Cheapest Specific for the Relief of Coughs
(In bronchitis, phthisis, whooping cough, etc., etc.)

WRITE FOR LITERATURE TO
FARBENFABRIKEN OF ELBERFELD COMPANY
SELLING AGENTS
P. O. Box 2160 40 Stone Street, NEW YORK
Aberrant drug-related behaviors must be evaluated

- Behaviors vary in seriousness
- Need to judge seriousness, the cause or causes, likelihood of recurrence, and clinical context
  - Predictors of high likelihood of future aberrant behaviors include 3 or more episodes of aberrant behaviors and sense of “losing control”
  - Serious behaviors include diversion, injecting oral drugs
- Responses range from patient education and enhanced monitoring to referral to addiction specialist and discontinuation of therapy
7.1 When repeated opioid dose escalations occur, evaluate potential causes and re-assess benefits relative to harms (strong recommendation, low-quality evidence).

7.2 In patients who require relatively high doses of COT, evaluate for unique opioid-related toxicities, changes in health status, and adherence to the COT treatment plan on an ongoing basis, and consider more frequent follow-up visits (strong recommendation, low-quality evidence).
• No theoretical ceiling with opioids
  ○ But, little evidence to guide prescribing at higher doses
  ○ Patients who do not respond to lower doses of opioids often do not respond to higher doses
  ○ Additional risks (hyperalgesia, endocrine), unclear benefit, and can be a marker for abuse, addiction, or diversion
  ○ Higher doses may be associated with higher risk
• Panel defined >200 mg/day of morphine (or equivalent) as “higher dose”
  ○ Based on doses evaluated in trials and observed in cohorts
  ○ Re-assess patients and consider more frequent or intense monitoring
  ○ Consider tapering off medication if not achieving therapeutic goals
  ○ Need trials comparing dose escalations beyond certain thresholds and alternative management strategies
3 large observational studies published in 2010/2011 evaluated association between opioid dose and risk of overdose or death

- Cohort study (n=9940, 51 opioid overdoses, 6 fatal)
  - Risk of opioid overdose (vs. 1 to <20 mg/day)
    - >=100 mg/d: HR 8.9 (4.0-20)
    - 50-<100 mg/d: HR 3.7 (1.5-9.5)
    - 20-<50 mg/d: HR 1.4 (0.57-3.6)

- Case-control study (VA, 750 cases)
  - Risk of opioid overdose-related death (vs. 1 to <20 mg/day)
    - >=100 mg/d: HR 7.2 (4.8-11)
    - 50-<100 mg/d: HR 4.6 (3.2-6.7)
    - 20-<50 mg/d: HR 1.9 (1.3-2.7)

- Nested case-control study (Ontario, 498 cases)
  - Risk of opioid-related mortality (vs. 1 to <20 mg/day)
    - >=200 mg/d: OR 2.9 (1.8-4.6)
    - 100-199 mg/d: OR 2.0 (1.3-3.2)
    - 50-99 mg/d: OR 1.9 (1.3-2.8)
    - 20-49 mg/d: OR 1.3 (0.94-1.8)

7.3 Consider opioid rotation when patients for intolerable adverse effects or inadequate benefit despite dose increases (weak recommendation, low-quality evidence).

7.4 Taper or wean patients off of COT when they engage in intractable aberrant drug-related behaviors or drug abuse/diversion, experience no progress towards meeting therapeutic goals, or experience intolerable adverse effects (strong recommendation, low-quality evidence).
• Opioid rotation
  ○ Theory of incomplete cross-tolerance
  ○ Patients may respond to different opioids with greater pain relief or fewer adverse effects
  ○ Little evidence on benefits of opioid rotation and mixed results
  ○ Caution when switching from one opioid to another (particularly with methadone)
8.1 Anticipate, identify and treat common opioid-associated adverse effects (strong recommendation, moderate-quality evidence).
Opioid-related adverse effects

**Rationale**

- Consider routine bowel regimen
- No good evidence on prevention/management of sedation, nausea, pruritus, mycolonus
- Hypogonadism observed in several cross-sectional studies
  - Cause and effect not established
  - Clinical relevance of “subclinical” hypogonadism unknown
  - Optimal methods of monitoring and effects of treatment unknown
  - Ask patients about symptoms of hypogonadism and test if they are present
9.1 Routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies (strong recommendation, moderate-quality evidence).
Chronic pain is often a complex biopsychosocial condition

- Opioids alone do not address psychosocial contributors to chronic pain
- In patients with impaired function, psychological issues, or co-morbidities, COT is likely to be most effective as part of a multimodal treatment program
- Consider cognitive-behavioral therapy, functional restoration, interdisciplinary therapy
10.1 Counsel patients on COT about transient or lasting cognitive impairment that may effect driving and work safety (strong recommendation, low-quality evidence).
Driving and work safety

Rationale

- Opioids may cause somnolence, incoordination, clouded mentation, or slower reflexes
- Clinicians should counsel patients not to drive or perform dangerous activities when impaired
  - Impairment more likely when starting therapy, when increasing doses, and when using other drugs with psychoactive effects
  - No evidence that patients on opioids should be restricted from driving in the absence of signs of impairment
  - State laws vary on reporting requirements
• **Risk Evaluation and Mitigation Strategies**
  - FDA Amendments Act of 2007 gave FDA authority to require REMS from manufacturers to help insure benefits exceed risks
    - Elements include medication guides, patient/provider education, timetable for assessment, metrics for assessment
    - Proposed for schedule II, long-acting or extended-release opioids
    - Proposal rejected by FDA advisory committee July 2010, no accepted proposal yet
      - Mandatory versus voluntary education
      - Call to include pharmacists in requirements
      - Call for registries
      - Call to extend REMS requirements to all opioids