Clinical Guidelines for Opioid Use in Chronic Noncancer Pain

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Conflict of Interest Disclosure

- Dr. Chou has received research funding from the Agency for Healthcare Research and Quality and the Drug Effectiveness Review Project, and has received honoraria from the American Pain Foundation
Purpose

• Explain methods used to develop APS/AAPM guidelines on use of opioids for chronic pain
• Understand the APS/AAPM recommendations for use of chronic opioid therapy for chronic noncancer pain
• Understand new research that may affect recommendations on use of long-term opioid therapy
Background

- 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
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, but evidence gaps clearly delineated
  - Only 3 recommendations viewed as supported by even moderate quality evidence
GRADE approach: Strong/Weak Recommendations

Recommendations

- **Strong recommendation**—indicates a judgment that most well informed people would make
- **Weak recommendation**—indicates a judgment that a majority of well informed people would make, but a substantial minority would not
  - More finely balanced benefits to harms, costs, or burdens
  - Weaker evidence
  - Decisions likely to be highly influenced by patient preferences/values
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.
Patient Selection And Risk Stratification

Recommendations

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
  - Aberrant behaviors vary in seriousness
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?

~45%

Porter, 1980; Dunbar, 1996; Passik, 1998

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

Nonmedical users

Pain patients

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

SUD = substance use disorder

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%)

Mark each box that applies

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family history of substance abuse</td>
<td></td>
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</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)
Initiation and Titration of Opioids

Recommendations

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
  - Practice of long-acting, round-the-clock dosing based on cancer guidelines and expert opinion, potential benefits not proven
  - Potential harms of long-acting, round-the-clock opioids include development of hyperalgesia, tolerance, endocrinologic adverse effects
Purdue Settles Oxycontin Charge For $600M

"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“


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).
FDA Public Health Advisory, November 2006

“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

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

- Increased methadone deaths nationwide
- Half-life 15 to 60 hours, up to 120 hours
  - 60 hour half-life=12 days to steady-state
  - Increased methadone-related deaths
  - 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;152:1789-1795)
- 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>

Monitoring

Recommendations

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

• 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, also progress towards achieving therapeutic goals
• 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)

The operation of Nebraska's Prescription Monitoring Program is currently being facilitated through the state's Health Information initiative. Participation by patients, physicians, and other health care providers is voluntary.


This information was compiled using legal databases, state agency websites and direct communications with state PDMP representatives.
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
  ◦ Routine, universal testing versus individualized testing
    ◦ Individualized testing likely to miss some patients, but balanced against higher yield and reduced costs
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.htmlan: 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
12. Drug Testing Products - Marijuana Information - Home Test Kits Drug testing kits, products and

Slide courtesy of Jeffrey Fudin
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
Where To Get Clean Urine

http://www.csun.edu/~hbcsc096/dt/ftbc.html/node114.html

- Urine From A Donor
- Powdered Urine
- Making Your Own Powdered Urine
- Dog Urine

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.

Slide courtesy of Jeffrey Fudin

http://www.csun.edu/~hbcsc096/dt/ftbc.html/node114.html
The Clean Whiz Kit
(http://www.cleanwhiz.com/cleankanit.html)

Slide courtesy of Jeffrey Fudin
Chart of Common Opiate Metabolites

- Heroin
  - 6-acetylmorphine
    - Morphine
      - Hydromorphone
        - Morphine containing drugs and poppy seeds
      - 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>
</table>
| **Urine drug test is positive** | Prescribed medication, appropriate use  
Metabolite of prescribed medication  
Prescribed medication, inappropriate use | Use of non-prescribed medications  
Use of illicit drugs  
Use of previously prescribed medications (hoarding)  
Cross-reaction (food, OTC, herbal products)  
Contamination  
Laboratory error |
| **Urine drug test is negative** | Drug screen doesn’t pick up the drug in question  
Patient appropriately not taking opioid  
Test performed prior to initiation of opioids | Diversion  
Outside time frame for positive test  
Fast metabolizer  
Laboratory processing error  
Extreme dilution of urine  
Malabsorption?  
Hoarding/binging |
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

- 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
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
Evaluation of Aberrant Drug-related Behaviors

- 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).
## Dose Escalations

### Rationale

- No theoretical ceiling with opioids
  - But, little evidence to guide prescribing at higher doses
  - Additional risks (hyperlgesia, 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
  - Other guidelines use lower threshold for high dose
  - Need trials comparing dose escalations beyond certain thresholds and alternative management strategies
Dose Escalations

- 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)

Opioid Rotation and Discontinuation Of Opioid Therapy

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

Rationale

• 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)
Opioid-related Adverse Effects

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
Use of psychotherapeutic co-interventions

9.1 Routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies (strong recommendation, moderate-quality evidence).
## Use of Psychotherapeutic Co-interventions

**Rationale**

- 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 ensure 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
  • **Approved by FDA July 2012**
    • Voluntary prescriber continuing education (not required for DEA licensure) for which financial support by manufacturers is mandatory
    • Patient education document for prescribers to go over with the patient
    • Medication Guide (MedGuide) for pharmacists to dispense with the medication
    • Knowledge assessment and independent third-party audits of the continuing education content
    • Expected to be available March 2013
Please Click the Link Below to Access the Post Test

Upon completion of the Post Test:

- You will receive an email detailing correct answers, explanations and references for each question.
- You will be directed to a module evaluation, upon completion of which you will be emailed your module Certificate of Completion.

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