



Case Study

Mary Williams: 42 year old female

Past Medical History

- Type 2 diabetes mellitus x 8 years
- Painful diabetic neuropathy x 2 years
- Hypertension
- Chronic low back pain
- Tobacco dependence
- Alcohol dependence (in recovery 10 yrs)
- Obesity

Case Study Mary Williams

Current Medications

- **Metformin** 1000 mg 2x/day
- **Lisinopril** 10 mg 1x/day
- **Hydrochlorothiazide** 12.5 mg 1x/day
- **Aspirin** 81 mg 1x/day

Current Pain Medications

- **Oxycodone/APAP** 5mg/325 mg
1-2 tablets every 4-6 hours
- **Gabapentin** 300 mg 3x/day

3

Case Study Mary Williams

Previous Pain Medications

- **NSAIDs**
Inadequate pain relief and upset stomach
- **Acetaminophen**
Inadequate pain relief
- **Tricyclic antidepressants**
Inadequate pain relief and dry mouth
- **Tramadol**
Inadequate pain relief
- **Acetaminophen with codeine**
Inadequate pain relief

4

Case Study Mary Williams

Social History

- **Receptionist**
Law office 20 hours/week
- **Married**
Husband manages hardware store
- **Children**
Ages 6, 12 and 15 years

5

Case Study Mary Williams

Substance Use History

- **Alcohol dependence**
In recovery for past 10 years
- **Tried marijuana in high school**
- **No recent history of illicit drug use**
- **Smokes tobacco**
1 pack per day for the past 25 years

Family History

- **Family history of substance abuse**
Mother died from complications of alcoholic cirrhosis

6



Assessing Chronic Pain and Opioid Misuse Risk



Learning Objectives: Essential Content 1

- Discuss prevalence of chronic pain in the US
- Discuss prevalence of the use and misuse of opioid analgesics
- Describe the pharmacology, efficacy and safety of opioid analgesics
- Describe the components of a thorough opioid misuse risk assessment for a potential candidate for chronic opioid therapy

Case Study Mary Williams

- Visiting provider for first time
- Previous PCP moved out of state

**Takes 4 to 8
oxycodone/
APAP tablets
per day for
chronic pain**

– Makes it
possible for
her to go to
work

**Best pain
relief 8 tablets
per day**

– Previous PCP
limit of 150
tablets per
month
– Afraid she
would
become
“addicted”

**She hopes to
get enough
medication to
consistently
take 8 tablets
per day**

9

Case Study Mary Williams

- Visiting provider for first time
- Previous PCP moved out of state

**Very careful
not to run
out early**

**Gets anxious
if supply runs
out early in
month**

**Nausea,
vomiting and
diarrhea upon
running out**

**Has enough
medication to
last one week**

**Brought in her
previous
medical
records**

10

Case Study Mary Williams

Pain Assessment

- Severe pain in feet
 - Burning, numbness and tingling
- Trouble sleeping and “depressed” because of her chronic pain
- Pain worse at night
- Due to only taking 3-4 tablets/day because it is end of month

On a scale of 0-10 states pain is “20”



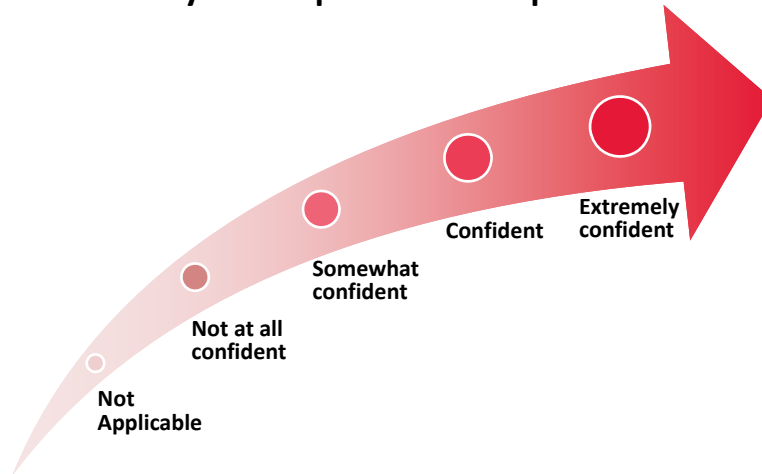
11

Assessing Pain



POLLING QUESTION

How confident are you in your ability to effectively and efficiently assess pain in a new patient?



13

Building Trust

Patient Issues

Patients will assume that
you don't believe their pain complaints



Often demonstrated by
exaggerating pain scores

14

Building Trust

Patient Issues

Some patients with adequate pain relief believe it is not in their best interest to report pain relief



Fear that medication will be reduced



Fear that physician may decrease efforts to diagnose problem

Evers GC, et al. Support Care Cancer. 1997 Nov;5(6):457-60.

15

Building Trust

Provider Issues

- Assume patient fears you think pain is not real or not very severe
- After you take a thorough pain history...

Show empathy for patient experience

Educate patient about need for accurate pain scores to monitor therapy

Validate that you believe pain is real

Discuss factors which worsen pain and limit treatment (i.e. substance abuse, mental health)



Believing a patient's pain complaint does not mean opioids are indicated

16

Pain Assessment

■ Pain scales

- Numeric rating
- Visual analog
- Faces scale

■ Multidimensional instruments

- McGill Pain Questionnaire
 - Brief Pain Inventory (BPI)
 - Pain, Enjoyment, General activity (PEG) scale
- } Impractical for routine use in primary care

Breivik H, et al. Br J Anaesth. 2008 Jul;101(1):17-24.
Krebs EE, et al. J Gen Intern Med. 2009 Jun;24(6):733-8.

17

Case Study Mary Williams

PEG Scale Assessment

In the past week:

Pain on average?



Pain interfered with **Enjoyment of life?**



Pain interfered with **General activity?**



18

Case Study Mary Williams

Physical

- Normal vital signs
- Weight 220 lbs (BMI 32 = obese)
- No acute distress
- Normal cardiopulmonary exam
- Spine normal alignment, negative straight leg test
- No Achilles tendon reflex bilaterally
- Diabetic foot exam:
 - No lesions/ulcerations
 - Palpable pulses
 - Monofilament testing bilaterally 4/5

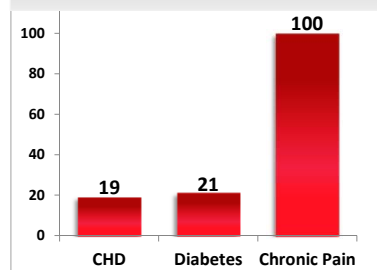
19

Scope of the Problem

100 Million in U.S. with Chronic Pain

- 42% with pain lasting over one year
- 33% report pain as disabling
- 63% have seen primary care physician for help

Prevalence in Millions



\$600 Billion Annual Costs

- Healthcare expenses
- Lost income
- Lost productivity

American Academy of Pain Medicine www.painmed.org
Institute of Medicine. 2011 Relieving Pain in America. Washington D.C.

20

Chronic Pain is Complex

Genetic Predispositions

- Structure and function of the nervous system
- Molecular basis for response to pain and/or analgesia

Environmental Stressor Effects

- Work, home

Social Effects

- Socially determined constructs of pain, suffering and disability
- Beliefs about pain treatment

Apkarian AV, et al. Pain. 2011 Mar;152(3 Suppl):S49-64.
Bennett RM. Mayo Clin Proc. 1999 Apr;74(4):385-98.

21

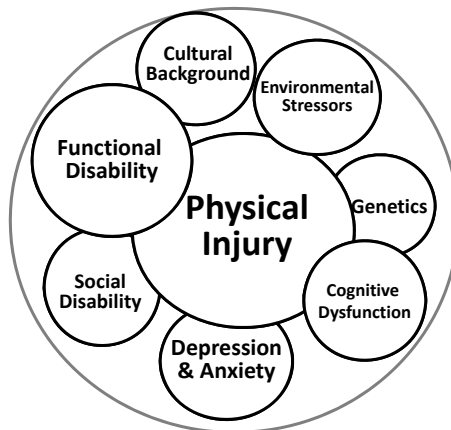
Psychiatric Co-Morbidities

Condition	Incidence Chronic Pain Patients	References
Depression	33 - 54%	Cheatle M, Gallagher R, 2006 Dersh J, et al., 2002
Anxiety Disorders	16.5 - 50%	Knaster P, et al., 2012 Cheatle M, Gallagher R, 2006
Personality Disorders	31 - 81%	Polatin PB, et al. 1992 Fischer-Kern M, et al., 2011
PTSD	49% veterans 2% civilians	Otis, J, et al., 2010 Knaster P, et al., 2012
Substance Use Disorders	15 - 28%	Polatin PB, et al. 1992 Cheatle M, Gallagher R, 2006

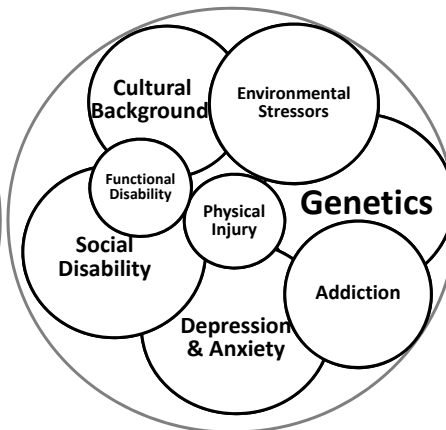
22

Chronic Pain is Complex

Patient "A" Pain 8/10



Patient "B" Pain 8/10



Gatchel RJ. Am Psychol. 2004 Nov;59(8):795-805.

23

Screening for Unhealthy Substance Use

Alcohol

"Do you sometimes drink beer wine or other alcoholic beverages?"

"How many times in the past year have you had 5 (4 for women) or more drinks in a day?"

(+ answer: > 0)

Drugs

"How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?"

(+ answer: > 0)

Smith PC, et al. Gen Intern Med. 2009 Jul;24(7):783-8.
Smith PC, et al. Arch Intern Med. 2010 Jul 12;170(13):1155-60.

24

Screening for Mental Illness

Patient Health Questionnaire (PHQ 2, PHQ 9)

Other psychiatric history – anxiety, PTSD

Suicidal, homicidal

Mental status, competency

25

Screening for Depression

PHQ2

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things

2. Feeling down, depressed, or hopeless

Scoring:

- 0 Not at all
- 1 Several days
- 2 More than half the days
- 3 Nearly every day

■ Interpretation

- Positive if 3 or more points

■ If positive, administer PHQ9

■ Efficacy

- Test Sensitivity: 83%
- Test Specificity: 92%

Kroenke K, Spitzer RL, Williams JB. Med Care. 2003 Nov;41(11):1284-92.

26

Case Study Mary Williams

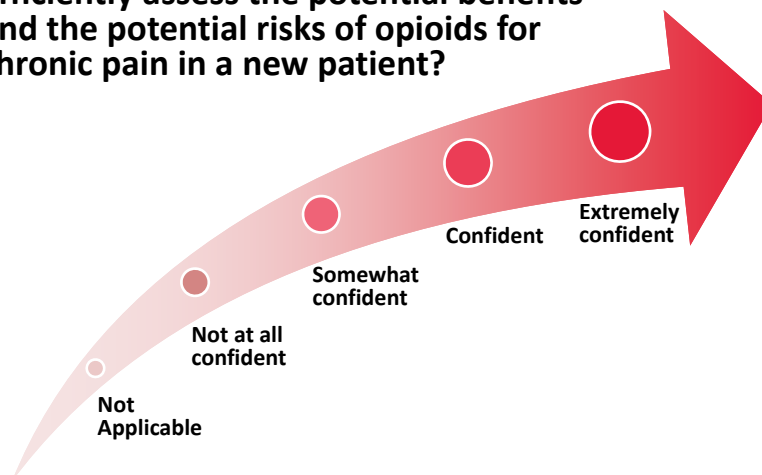
Screening Results

- Screened negative for unhealthy substance use and depression

27

POLLING QUESTION

How confident are you in your ability to efficiently assess the potential benefits and the potential risks of opioids for chronic pain in a new patient?



28

Opioid Pharmacology



Case Study Mary Williams

When are opioids indicated?

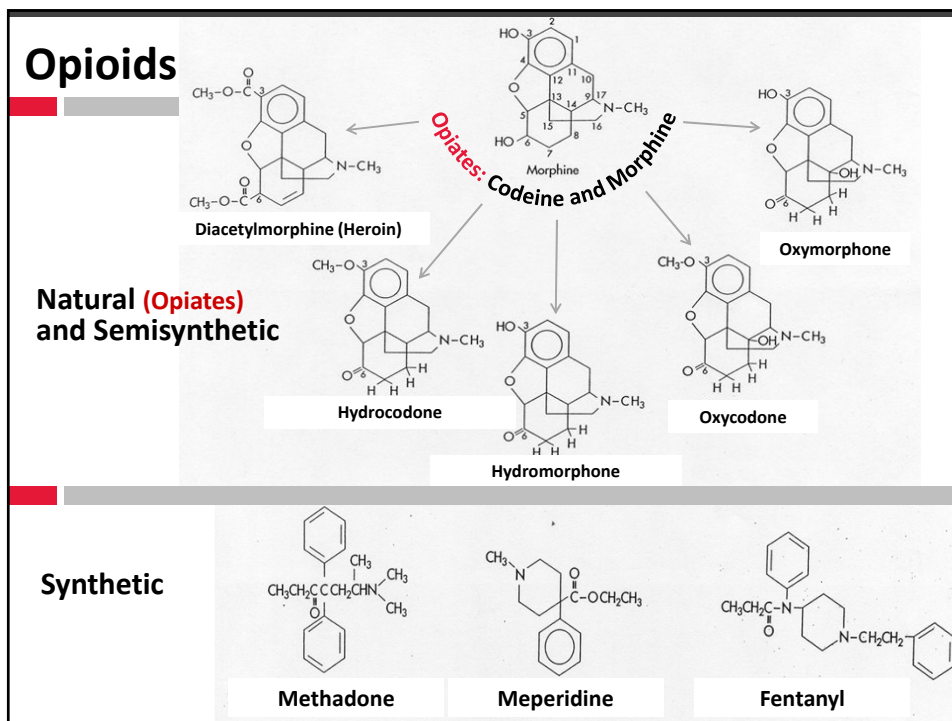
YES Pain is moderate to severe

YES Pain has significant impact on function

YES Pain has significant impact on quality of life

YES Non-opioid pharmacotherapy has failed

NOT KNOWN If already on opioids, is there documented benefit



Not All Opioids are the Same

Opioid Chemical Classes

Phenathrenes <i>prototypical opioids</i>	Morphine, Codeine, Hydromorphone, Hydrocodone, Oxycodone, Buprenorphine
Benzomorphans	Pentazocine
Phenylpiperidines	Fentanyl
Diphenylheptanes	Methadone

Trescot AM, et al. Pain Physician 2008;11:S133-53.

32

Activation of Mu-Opioid Receptors

Opioid Pharmacodynamics

- Turn on descending inhibitory systems in the midbrain
- Prevent ascending transmission of pain signal
- Inhibit terminals of C-fibers in the spinal cord
- Inhibit activation of peripheral nociceptors

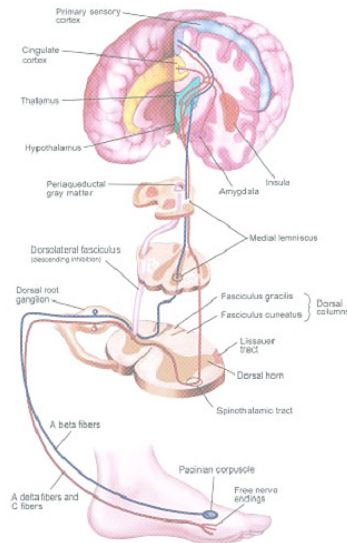


Image source: www.mayo.edu/proceedings
McCleane G, Smith HS. Med Clin North Am. 2007 Mar;91(2):177-97.

33

How Good are Opioids for Chronic Pain?

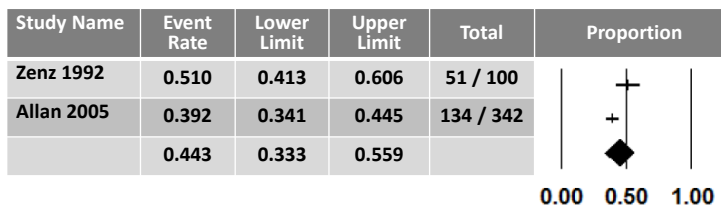
- Most literature: surveys and uncontrolled case series
- RCTs are short duration <8 months with small samples <300 patients
- Mostly pharmaceutical company sponsored
- Outcomes
 - Better analgesia with opioids vs. placebo
 - Pain relief modest
 - Mixed reports on function
 - Addiction not assessed

Ballantyne JC, Mao J. N Engl J Med. 2003 Nov 13;349(20):1943-53.
Kelso E, et al. Pain. 2004 Dec;112(3):372-80.
Eisenberg E, McNicol ED, Carr DB. JAMA. 2005 Jun 22;293(24):3043-52.
Furlan AD, et al. CMAJ. 2006 May 23;174(11):1589-94.
Noble M, et al. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006605.

34

Opioid Efficacy in Chronic Pain

- Proportion of patients with at least 50% pain relief
- Oral opioids
- N = 442
- Follow-up 7.5 months (mean) to 13 months (1² 77.3%)



44.3% of participants had at least 50% pain relief

Noble M et al. Cochrane Systematic Reviews 2010

35

Variable Response to Opioids



Not all **patients** respond to the same opioid in the same way



Not all **pain** responds to the same opioid in the same way

36

Variable Response to Opioids

Mu-opioid Receptor

- G protein-coupled receptor family, signal via second messenger (cAMP)
- >100 polymorphisms in the human MOR gene
- Mu-opioid receptor subtypes

Smith HS. Pain Physician. 2008 Mar-Apr;11(2):237-48.

37

Variable Response to Opioids

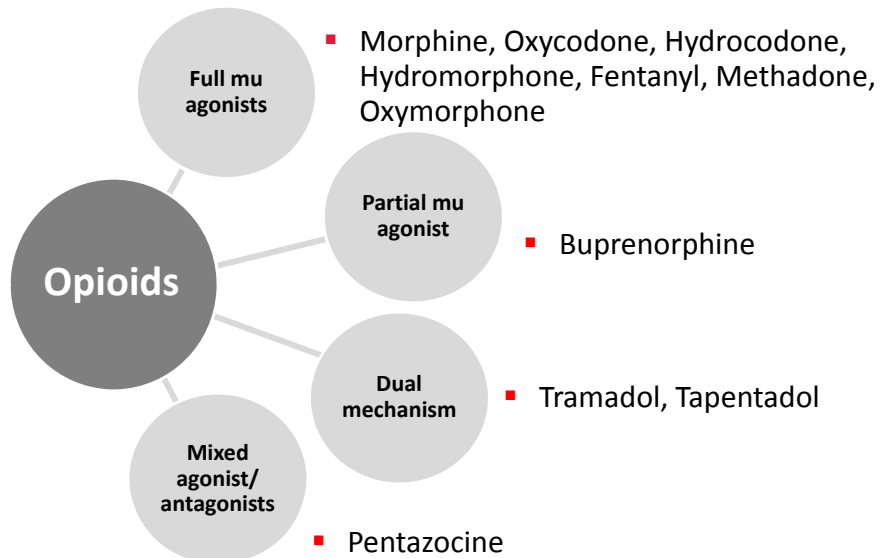
Opioid Pharmacokinetics

- Opioid metabolism differs by individual opioid and by individual patient
- Most opioids are metabolized by the cytochrome P450 (CYP) system
 - Codeine may be ineffective in ~10% of Caucasians due to genetic polymorphisms in CYP2D6
- Trial of several opioids may be needed to find acceptable balance between analgesia and tolerability

Smith HS. Mayo Clin Proc. 2009 Jul;84(7):613-24.

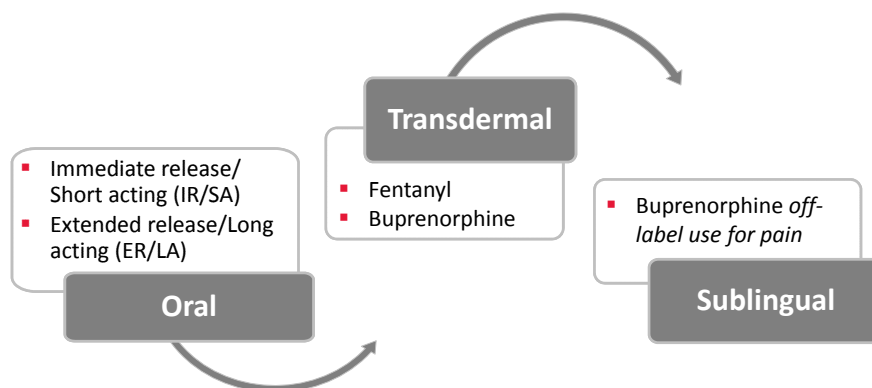
38

Opioid Choices with Examples



39

Opioid Formulations and Routes



40

Transdermal Preparations

- Fentanyl and Buprenorphine
- Convenient dosing
 - Fentanyl every 72 hours
 - Buprenorphine every 7 days
- Slow onset and delayed offset
- Requires predictable blood flow and adequate subcutaneous fat
- Absorption is altered with fever, broken skin, edema
- Some with metal foil backing and not compatible with MRI

41

Opioid Choice

Immediate Release (IR/SA)

- Morphine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol

- Codeine

Extended Release / Long-acting (ER/LA)

- Morphine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol

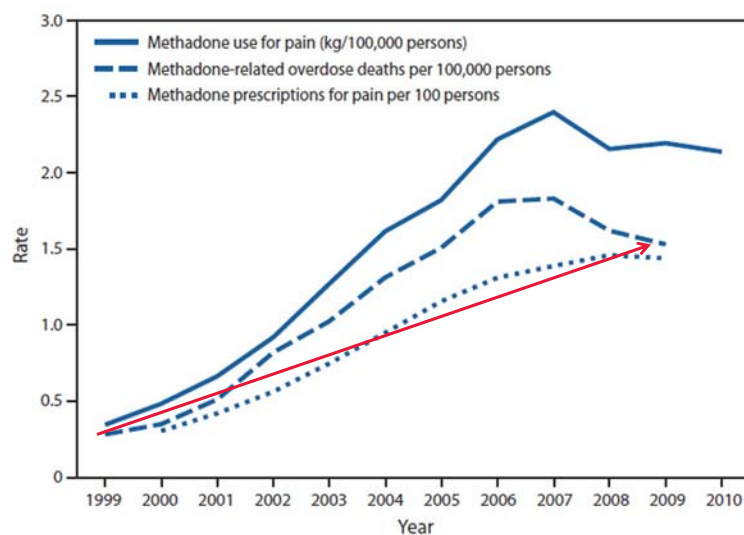
- Methadone
- Fentanyl transdermal
- Buprenorphine transdermal

42

Selected Opioids With Unique Properties



Methadone is Different



CDC, Morbidity and Mortality Weekly Report (MMWR) July 6, 2012 / 61(26):493-497.

44

Methadone is Different

The problem...

- Long, variable, unpredictable half-life
 - Analgesia 6-8 hours
 - Serum $t_{1/2}$ 20-100 hours
- QTc prolongation, risk of torsade de points

Some possible advantages...

- Mu-opioid agonist, NMDA receptor antagonist
 - Potentially less tolerance, better efficacy in neuropathic pain
- No active metabolites
- Inexpensive, small dosage units (5mg tablets)

Fredheim OM, et al. Acta Anaesthesiol Scand. 2008 Aug;52(7):879-89.

45

Dual Mechanism Opioids

Tramadol

- Mu-opioid agonist and NE and serotonin reuptake inhibitor
- Seizure risk
- Physical dependence
- Not scheduled as controlled substance BUT has addiction potential

Tapentadol

- Mu-opioid agonist and NE reuptake inhibitor
- Seizure risk
- Physical dependence
- Schedule II controlled substance with addiction potential

Medical Letter April 2010

46

Resources on Specific Opioids

Providers

e.g., dosing, specific product risks, limitations for use in patients with gastrointestinal problems such as inability to swallow, feeding tubes or malabsorption issues

- dailymed.nlm.nih.gov/dailymed
- accessdata.fda.gov/scripts/cder/drugsatfda/
- Package inserts on ER/LA website
- Adverse events to be reported to FDA
fda.gov/Drugs/InformationOnDrugs/ucm135151.htm

Patients

e.g., side effects, drug-drug interactions including CNS depressants, safe disposal

- Materials:
er-la-opioidrems.com/lwgUI/rems/products.action
- Medication guide given at the pharmacy

47

Opioid Risks



Issues Preventing Opioid Prescribing

Issues	Prevalence
Potential for patients to become addicted	89%
Potential for patients to sell or divert	75%
Opioid side effects	53%
Regulatory/law enforcement monitoring	40%
Hassle and time required to track/refill	28%

Upshur CC, Luckmann RS, Savageau JA. J Gen Intern Med. 2006 Jun;21(6):652-5.

49

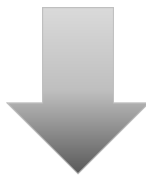
Opioid Tolerance and Physical Dependence

Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure



Tolerance:

- Increased dosage needed to produce specific effect
 - Develops readily for CNS and respiratory depression
 - Less so for constipation
 - Unclear about analgesia

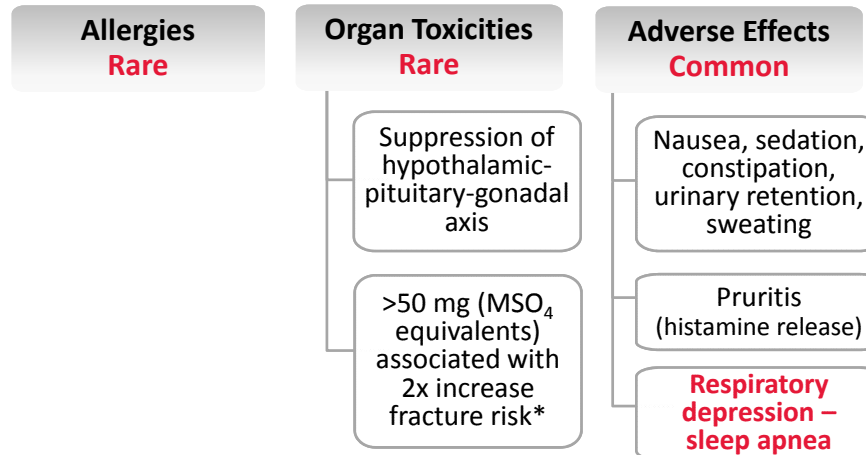


Physical Dependence:

- Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction

50

Opioid Safety and Risks



Benyamin R, et al. Pain Physician. 2008 Mar;11(2 Suppl):S105-20.
*Saunders KW, et al. J Gen Intern Med. 2010 Apr;25(4):310-15.

51

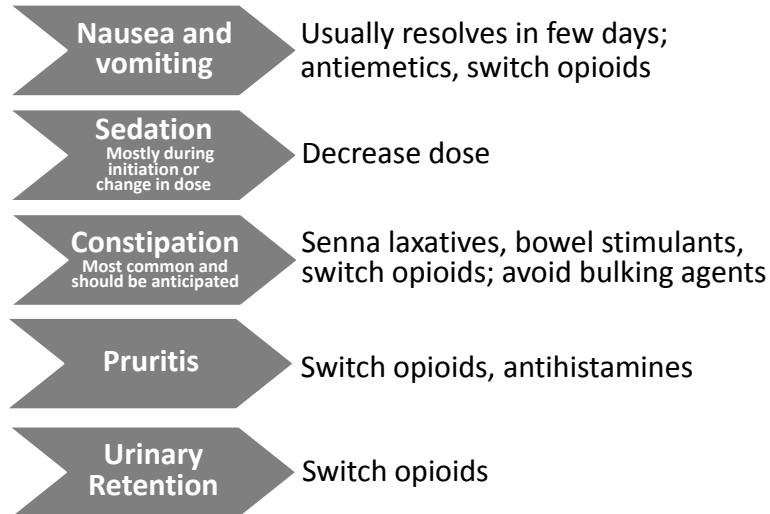
Respiratory Depression

- Depression of the medullary respiratory center
- Decreased tidal volume and minute ventilation
- Right-shifted CO₂ response
- Hypercapnea, hypoxia and decreased oxygen saturation
- Various agonist-type opioids do appear to differ in potential for ventilatory depression in humans
- Immediately life threatening
- The key to remember is that sedation occurs before respiratory depression therefore it is a warning sign that the patient is overmedicated

Dahan A, et al. Anesthesiology. 2010 Jan;112(1):226-38.

52

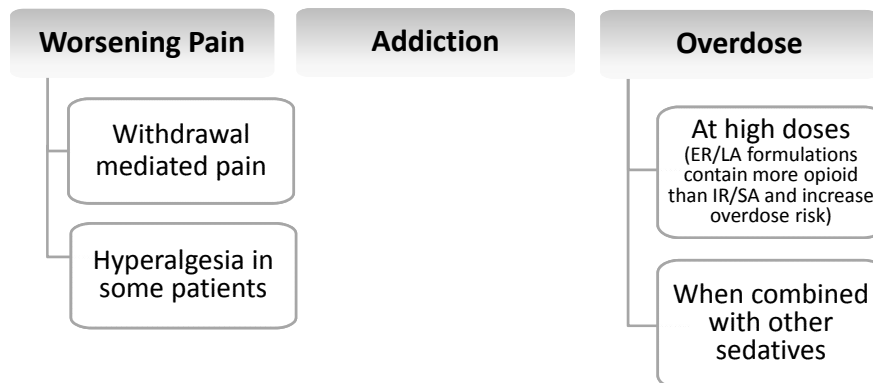
Managing Opioid Adverse Effects



Benyamin R, et al. Pain Physician. 2008 Mar;11(2 Suppl):S105-20.

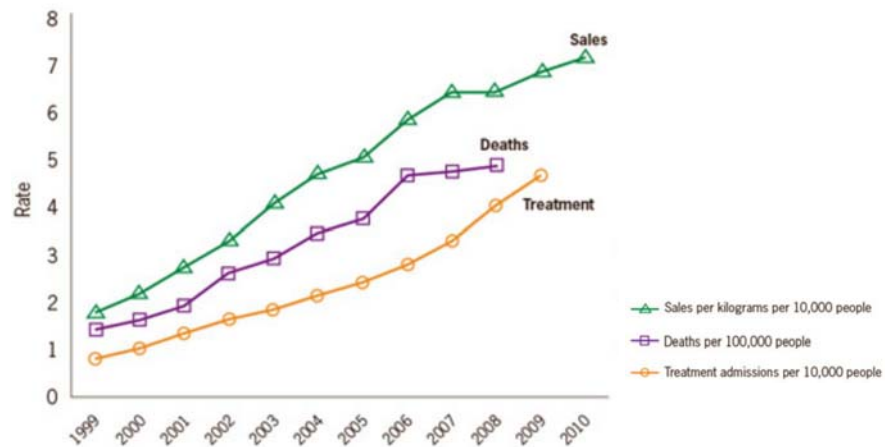
53

Opioid Safety and Risks



54

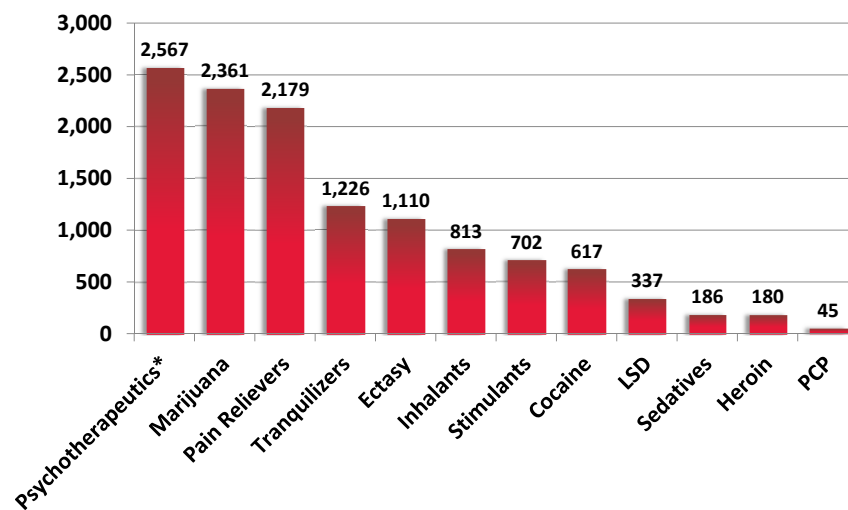
Opioid Sales, Deaths and Substance Abuse Treatment Admissions



National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009.

55

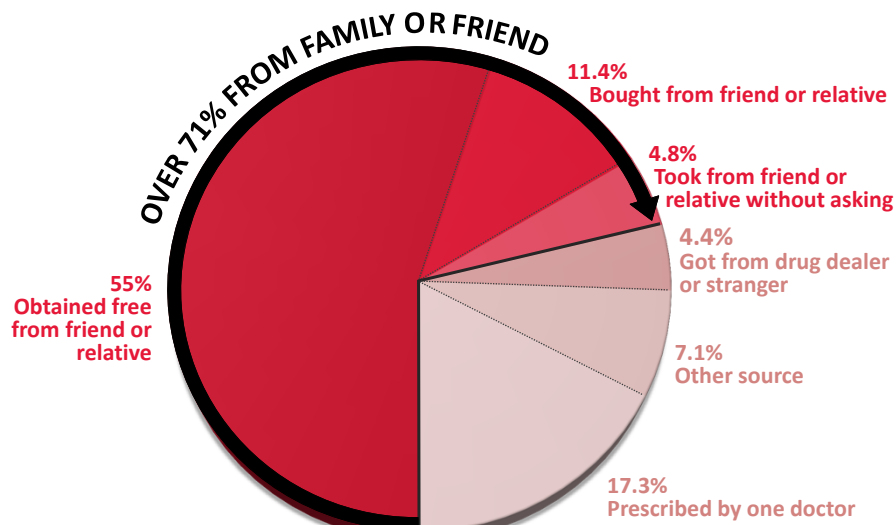
New Users: Specific Illicit Drugs



* Includes pain relievers, tranquilizers, stimulants, and sedatives
SAMSHA, 2009 National Survey on Drug Use and Health (September 2010).

56

Where Pain Relievers Were Obtained



2010 National Survey on Drug Use and Health: SAMHSA, Office of Applied Studies; 2011

57

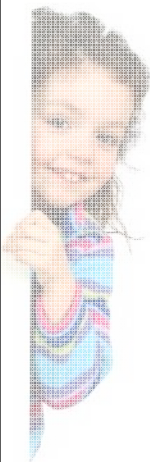
Collateral Opioid Risk

■ Risks

- Young children ingestion and overdose
- Adolescents experimentation leading to overdose and addiction

■ Mitigating risk

- Safe storage and disposal
- Educate family members
- Have poison control number handy
- Intranasal naloxone distribution (if available)



Opioid Addiction Risk

- True incidence and prevalence of addiction in chronic pain populations prescribed opioids is unknown due to different criteria used to define addiction in different studies
- The range in prevalence reported is 0-50%
- The most commonly cited range is 4-26%

Højsted J, Sjøgren P. Eur J Pain. 2007 Jul;11(5):490-518.
Fishbain DA et al. Pain Med. 2008 May-Jun;9(4):444-459
Sehgal N et al. Pain Physician. 2012; 15:ES67-ES92

59

Opioid Misuse Risk

Known Risk Factors

Good Predictors for Prescription Opioid Misuse

- Young age (less than 45 years)
- Personal history of substance abuse
 - Illicit, prescription, alcohol, nicotine
- Family history of substance abuse
- Legal history
 - DUI, incarceration
- Mental health problems
- History of sexual abuse

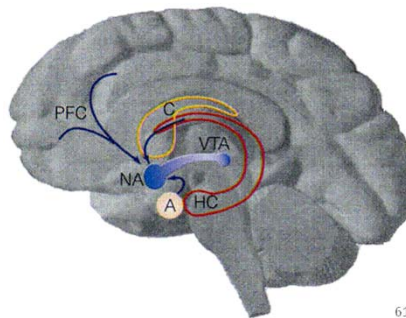
Akbik H, et al. J Pain Symptom Manage. 2006 Sep;32(3):287-93.
Ives J, et al. BMC Health Serv Res. 2006 Apr 4;6:46.
Liebschutz JM, et al. J Pain. 2010 Nov;11(11):1047-55.
Michna E, et al. J Pain Symptom Manage. 2004 Sep;28(3):250-8.
Reid MC, et al. J Gen Intern Med. 2002 Mar;17(3):173-9.

60

Why Patients Become Addicted to Opioids

Opioids activate mu-opioid receptors in midbrain “reward pathway” causing euphoria

- Dopaminergic system that is very reinforcing
- Most rewarding are fast onset (IR/SA) opioids
- ER/LA should be less rewarding if taken as prescribed but are very rewarding if adulterated (e.g., crushed, chewed)

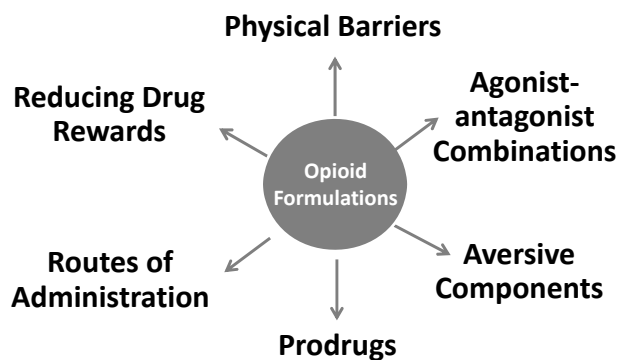


Kosten TR, George TP. Sci Pract Perspect. 2002 Jul;1(1):13-20.

61

Abuse Deterrent/Resistant Formulations

In Development



Currently there are NO PROVEN abuse deterrent/resistant opioids or formulations

Passik SD. Mayo Clin Proc. 2009 Jul;84(7):593-601.
Stanos SP, et al. Mayo Clin Proc. 2012 Jul;87(7):683-94.

62

Drug-Drug Interactions

Profiles Vary Among Different Opioids and Opioid Formulations

Central nervous system depressants (alcohol, sedatives, hypnotics, tricyclic antidepressants)

- Can have potentiating effect on sedation and respiratory depression caused by opioids

Some ER/LA opioid formulations

- May rapidly release opioid (dose dump) when exposed to alcohol
- Some drug levels may increase without dose dumping when exposed to alcohol

Diuretics

- Opioids can reduce efficacy by inducing release of antidiuretic hormone (ADH)

Some Opioids (methadone, buprenorphine)

- Can prolong the QTc interval

Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes

- Can result in higher or lower than expected blood levels of some opioids

FDA Blueprint: www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf

63

Important Resource: DailyMed



**Daily
Med**
Current
Medication
Information

<http://dailymed.nlm.nih.gov/dailymed>

- Updated medication content and labeling
 - Search and download
- Reformatted drug labeling easier to read
- National Library of Medicine (NLM) provides as a public service; does not accept advertisements

64

Risk in Elderly

- Drug-drug interactions
- Drug-disease interactions
 - CHF, chronic liver and renal disease
 - Dementia
- Decline in therapeutic index
- Age-related predisposition to adverse drug effects
- Start low and go slow

American Geriatrics Society Panel. J Am Geriatr Soc. 2009 Aug;57(8):1331-46.



Risk Assessment



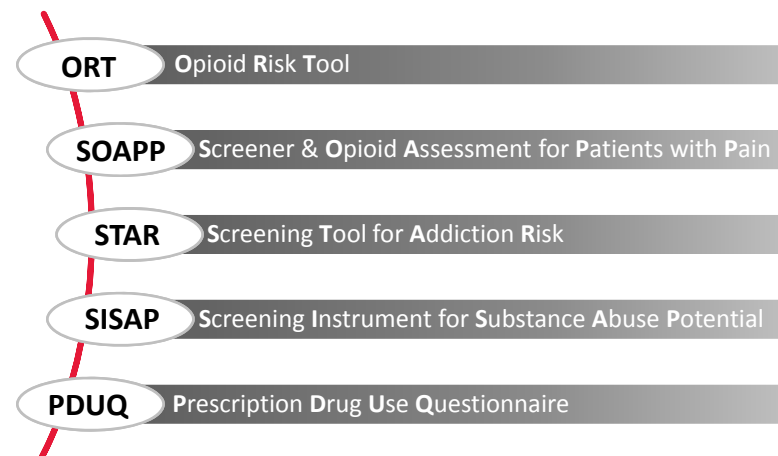
Assess for Opioid Misuse Risk

Prior to Prescribing

- Validated questionnaire
- Urine drug testing
- Check state prescription drug monitoring program data (if available)
- Review old medical records
- Talk to previous provider (if possible)

67

Validated Questionnaires



**No “Gold Standard”
All lack rigorous testing**

Moore TM, et al. Pain Med. 2009 Nov;10(8):1426-33.

68

Case Study Mary Williams

Opioid Risk Tool Score

	Female	Male
Family history of substance abuse		
Alcohol	☒ 1	☐ 3
Illegal drugs	☐ 2	☐ 3
Prescription drugs	☐ 4	☐ 4
Personal history of substance abuse		
Alcohol	☒ 3	☐ 3
Illegal drugs	☐ 4	☐ 4
Prescription drugs	☐ 5	☐ 5
Age between 16-45 years	☒ 1	☐ 1
History of preadolescent sexual abuse	☐ 3	☐ 0
Psychological disease		
ADHD, OCD, bipolar, schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1

SCORING

0-3 Low Risk

4-7 Moderate Risk

>8 High Risk

Webster LR, Webster RM. Pain Med. 2005 Nov-Dec;6(6):432-42.

69

Opioid Misuse Risk Stratification

How should it be used?

Discuss level of concern with patient

- “Despite being in recovery from alcoholism, you are at higher risk for developing problems with the opioid pain medication.”

Level of monitoring that should be implemented

- Frequency of visits, urine drug testing, etc.
- High risk patients may need to agree to random call-backs

Need for pain and/or addiction consultant

- If available

Some patients may be too risky for opioids analgesics

- e.g., patient with recent opioid addiction

70

Prescription Drug Monitoring Programs

**Clinical tool
that supports
safe
prescribing
and
dispensing**

**May help
prevent or
stop harm
from drug
diversion,
misuse and
abuse**

**Specifics vary
from state to
state**

Can provide:

- Patient's prescription history for Schedule II–V
- Solicited reports online; real time or delay of days to weeks
- Unsolicited reports on patients with “questionable activity”

Perrone J, Nelson LS. N Engl J Med. 2012 Jun 21;366(25):2341-3.

71

Case Study Mary Williams

Next Steps

- Patient agrees to return in one week
- Provider has time to check records and Prescription Drug Monitoring Program (PDMP)
- Patient has left a Urine Drug Test (UDT)

72

Summary Points: Essential Content 1

Opioids:

- Can be beneficial for some
- Can be harmful for some
- Side effects are common but can be managed
- Carry significant risk including overdose and addiction
- Misuse risk can be assessed using systematic approach which includes validated risk assessment questionnaires

73

Case Study Mary Williams

Review of Medical Records

- Progress notes, medication lists are reconciled
- Radiology reports
 - Lumbar degenerative joint disease
 - Mild spinal stenosis
- No evidence of misuse of her opioid prescriptions
- Lack of adequate documentation about pain and functional benefits in her old record

74

Questions for Next Visit

Initiating Opioid Therapy Safely

Clinician Concerns:

- Should I change her opioid prescription?
- Should I change the opioid dose?
- What about any other adjuvant medications or therapies?
- What sort of treatment plan should I develop?



75