

Clinical Challenges in Prescribing Opioids for Chronic Pain

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American Osteopathic Academy of Addiction Medicine

Supported by:

Center for Substance Abuse Treatment

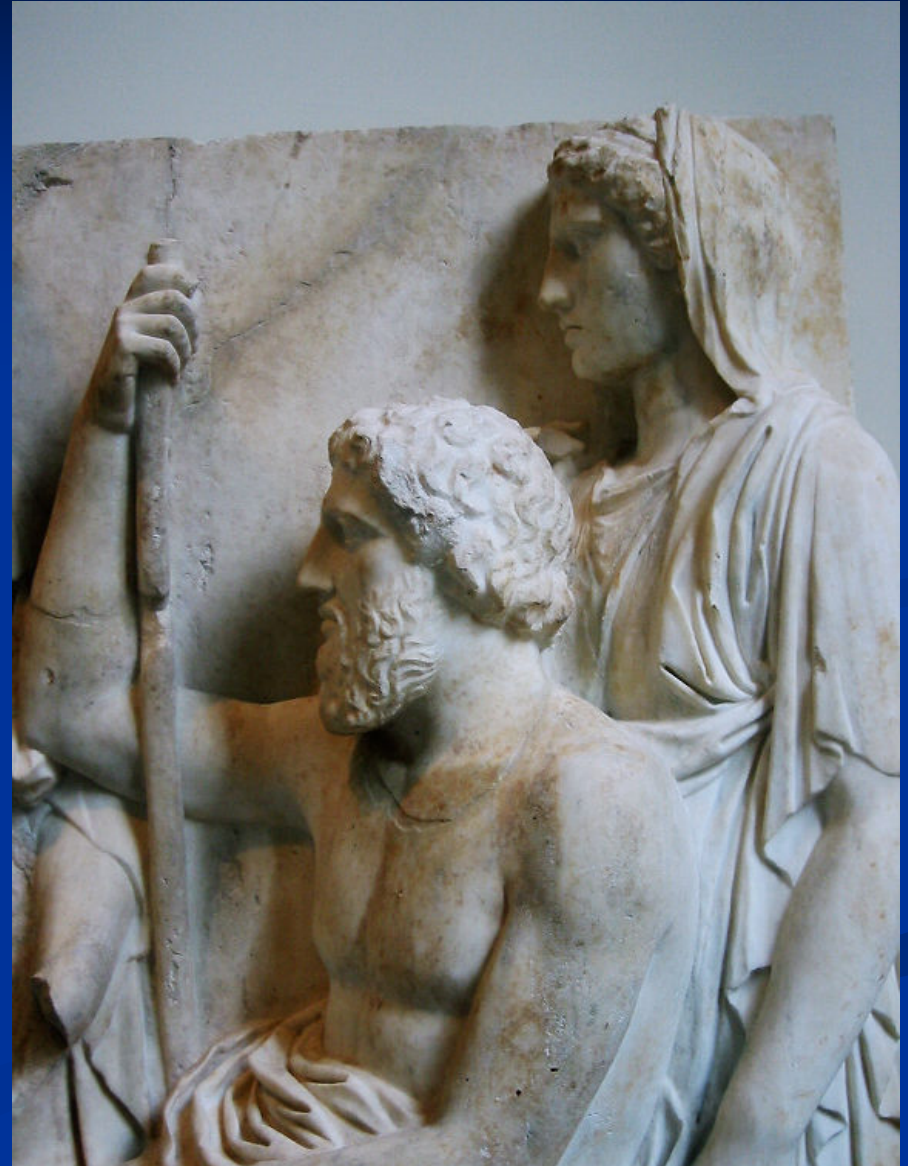
Faculty

- Ted Parran, M.D.
 - Asso. Clinical Director, Departments of Medicine and Family Practice, Case Western Reserve School of Medicine
- Tony Dekker, D.O.
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- John Tanner, D.O.
 - Medical Director , Wekiva Springs Center for Women

There is a long cultural tradition of seeking relief from pain through medication

“to lull all pain and
anger and bring
forgetfulness
of sorrow...”

Homer: The Odyssey



JWF: The Vintage Image Gallery

This course will address the balance between providing optimal pain relief and preventing inappropriate use of opioid analgesics.

Outline of Program

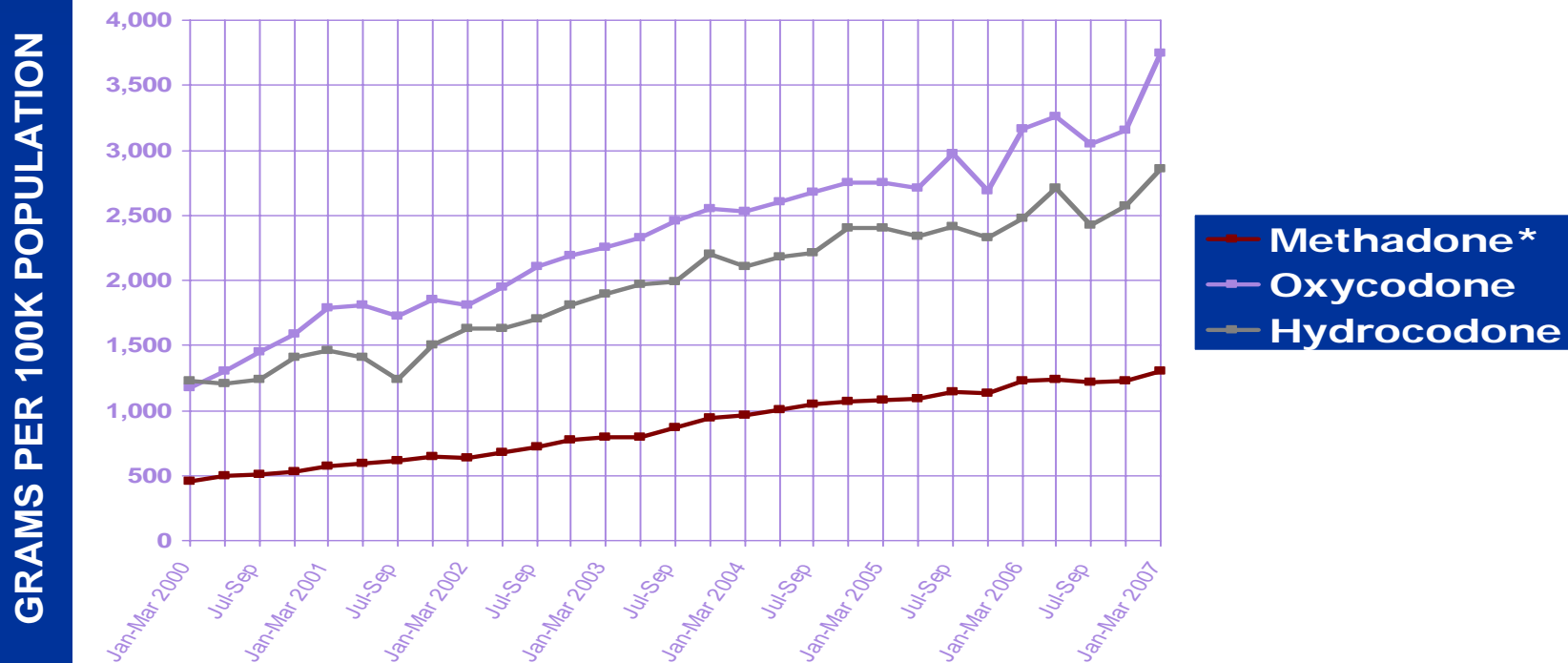
- Welcome and Introduction
- Opioid problem use – A National perspective
- First things first: whether to prescribe an opioid
- General pharmacologic principles about all opioids
- Using methadone safely when prescribing for pain
- Using pearls to avoid pitfalls
- When, why and how to stop prescribing controlled substances
- What are the alternatives to prescribing opioids in the treatment plan for persistent pain:

Opioid Problem Use

A National Perspective

Trend data: Distribution of prescription opioids, U.S., 2000–2007

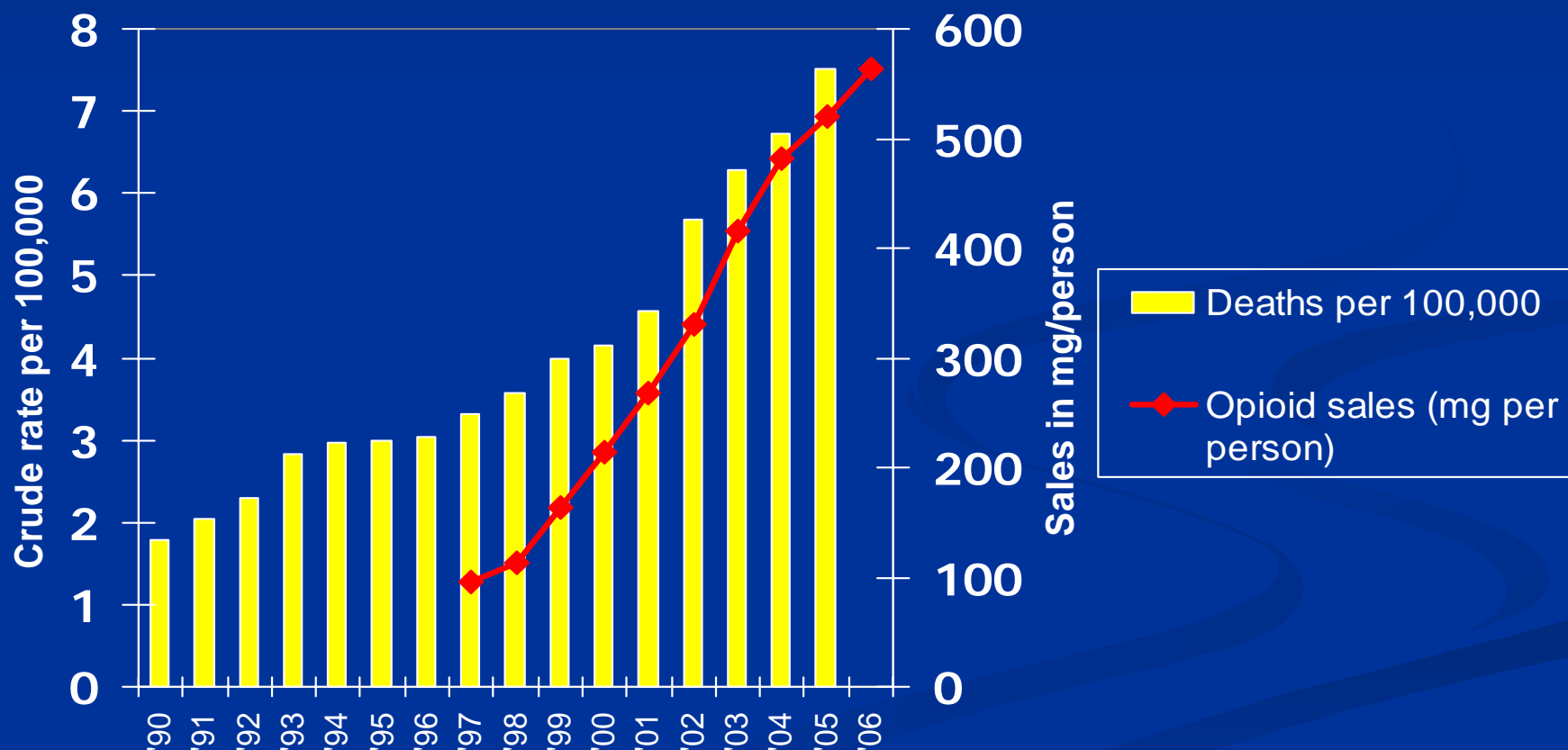
Source: DEA, ARCOS system, 2007



* Includes OTPs

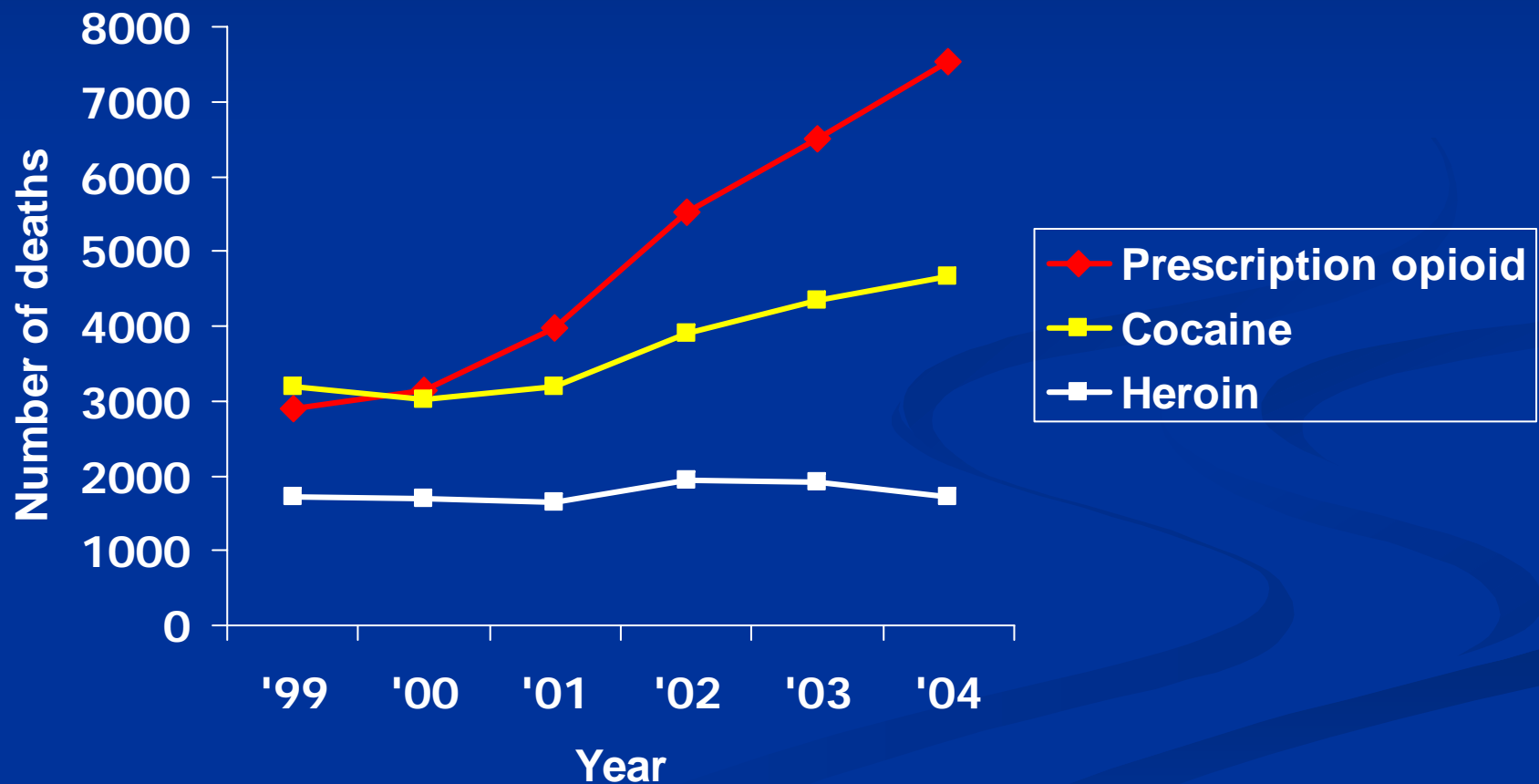
Deaths per 100,000 related to unintentional overdose and annual sales of prescription opioids by year, 1990 - 2006

Source: Paulozzi, CDC, Congressional testimony, 2007



Unintentional drug overdose deaths by specific drug type, U.S., 1999-2004

Source: CDC, National Vital Statistics System, 2006



Toxicity

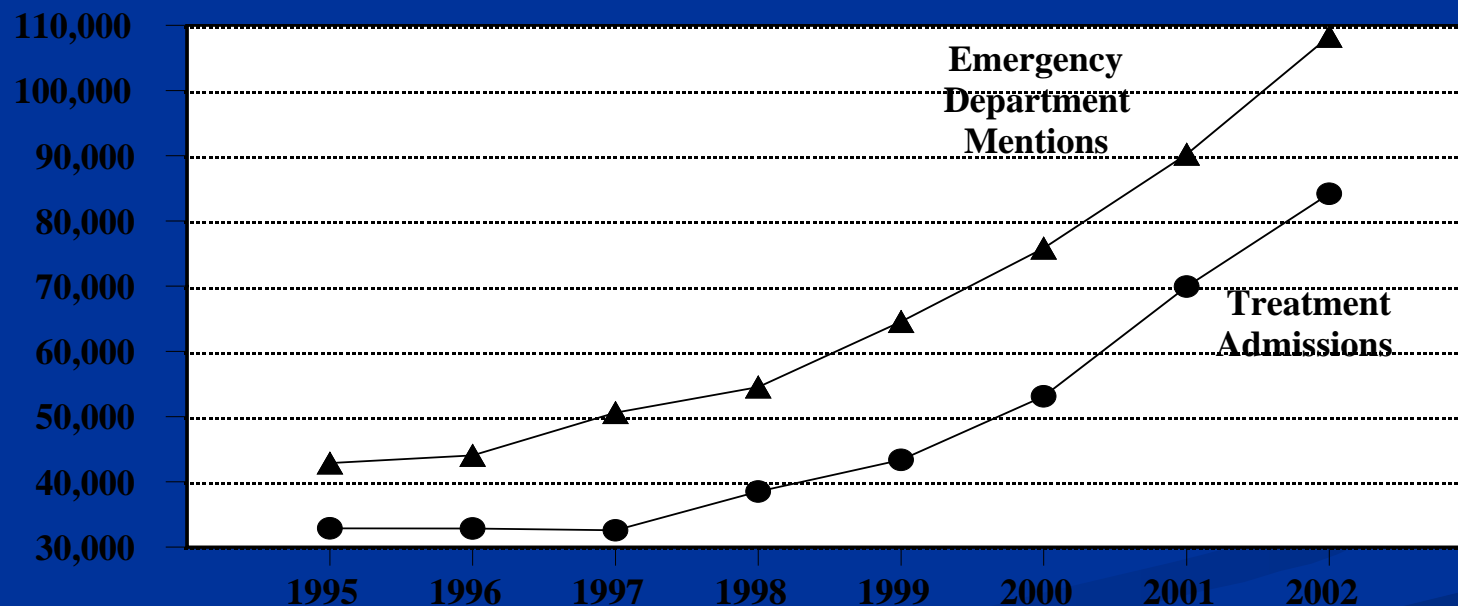
2nd Leading Cause of Accidental Death!

- CDC: 2007

- ATLANTA - Unintentional fatal drug overdoses in the United States nearly doubled from 1999 to 2004, overtaking falls to become the nation's second-leading cause of accidental death, behind automobile crashes, the government reported.

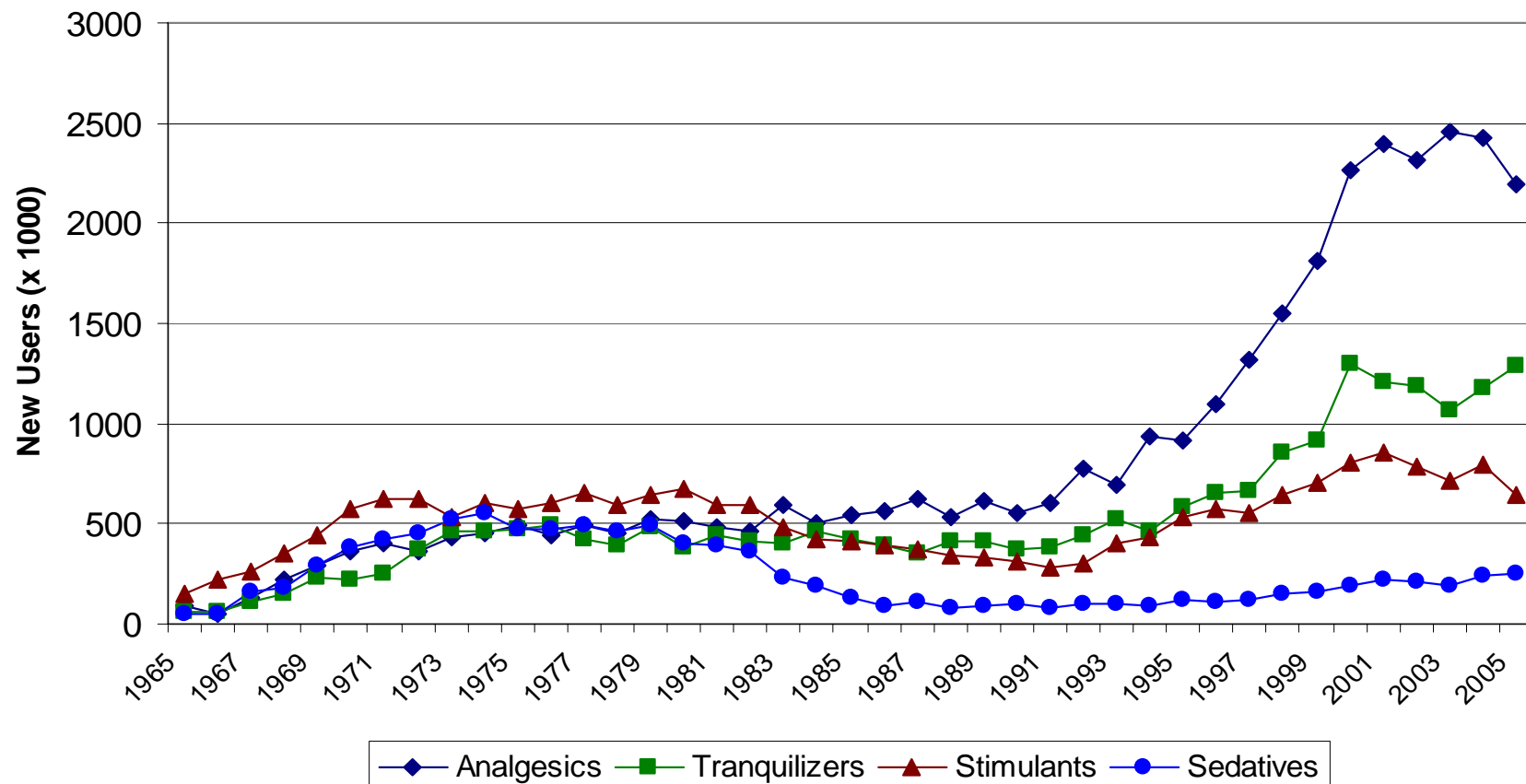
Emergency department mentions and admissions to addiction treatment related to use of prescription opioids, 1995-2002

Source: CDC, National Vital Statistics System, 2006



Non-medical use of opioids is increasing,
particularly among younger age groups...

Exhibit 2: Past Year Initiation of Non-Medical Use of Prescription-type Psychopharmaceuticals, Age 12 or Older: In Thousands, 1965 to 2005¹



Source: SAMHSA, OAS, NSDUH data , July 2007

Teen Rx Drug Abuse Facts

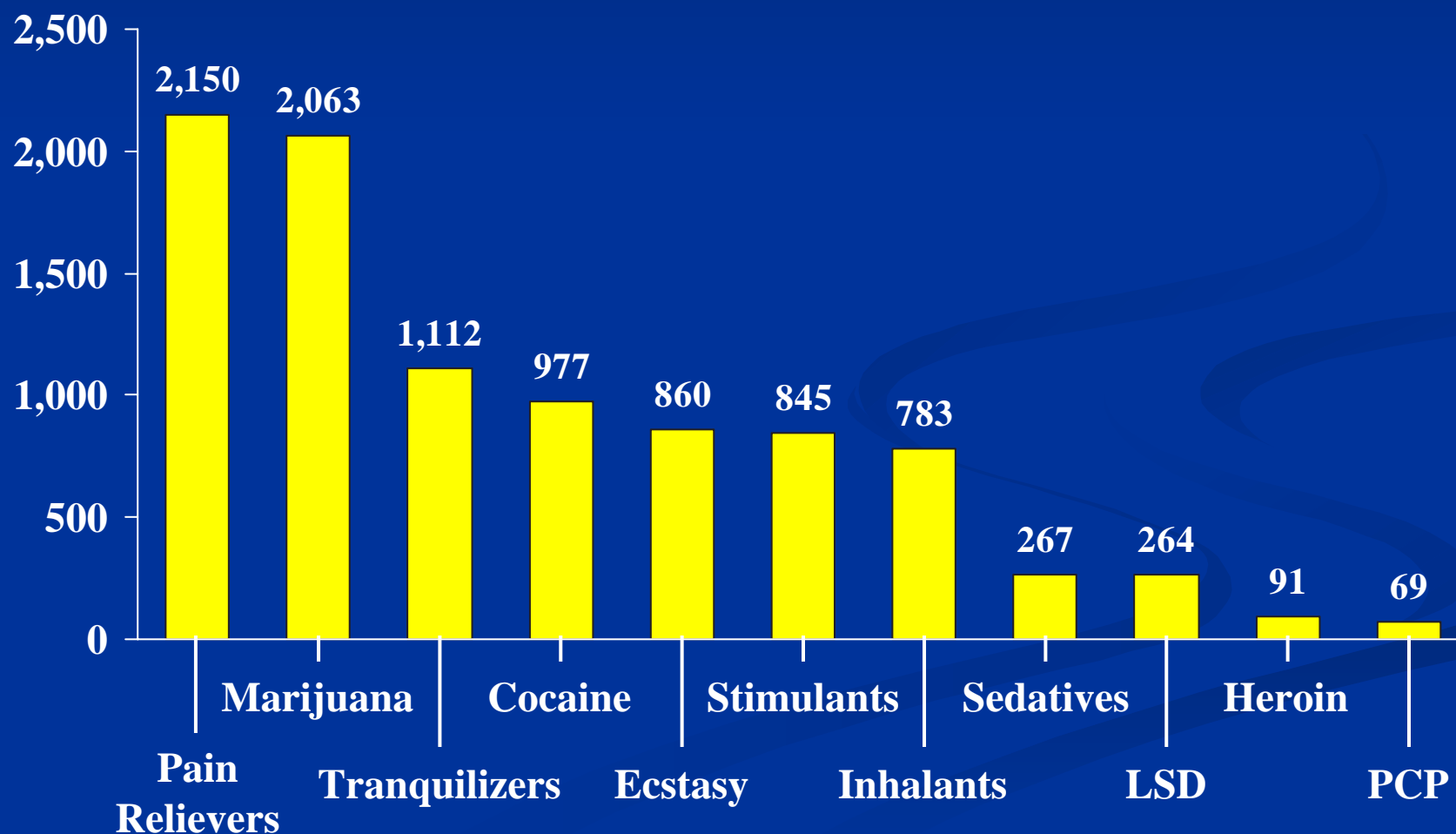
- 1.5 million American kids abuse of prescription drugs.
- Every day 2,700 teens try a prescription drug to get high for the first time.
- Half of teens do not see a great risk in abusing prescription (Rx) or over-the-counter (OTC) drugs.
 - Teens believe that abuse of Rx and OTC medicines is safer than street drugs.
- Over half of teens agree prescription drugs are easier to get than illegal drugs.
 - 1 in 3 teens have a close friend who abuses Rx pain relievers to get high.
- Only 31% of teens “learn a lot about the risk of drugs” from their parents.

Epidemiology

- Overall, youth prescription drug abuse is second largest category of abuse, only behind marijuana
- Past-year use of Oxycontin increased 30 percent between 2002–2007

Past Year Initiates for Specific Illicit Drugs among Persons Aged 12 or Older: 2006

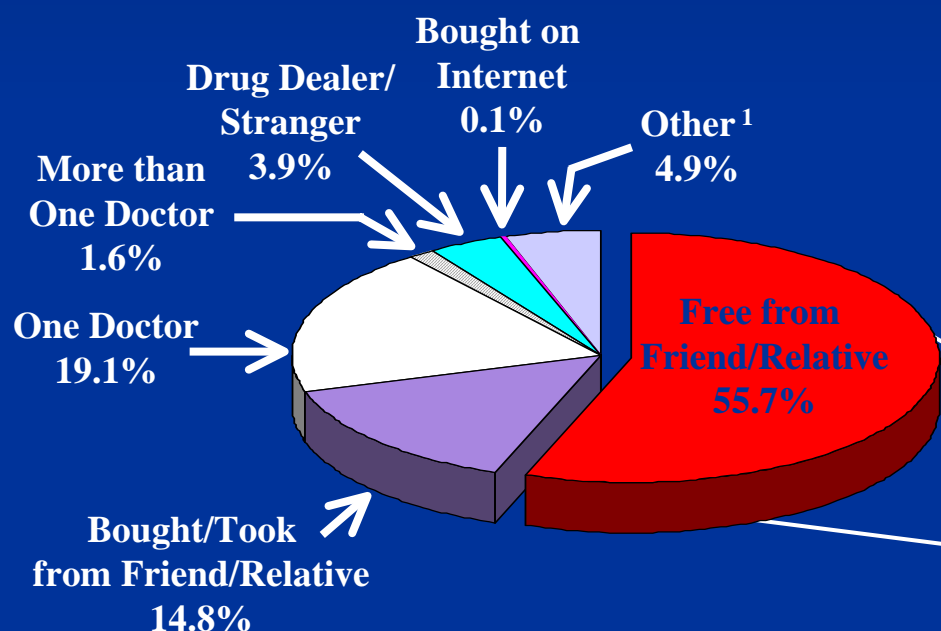
Numbers in Thousands



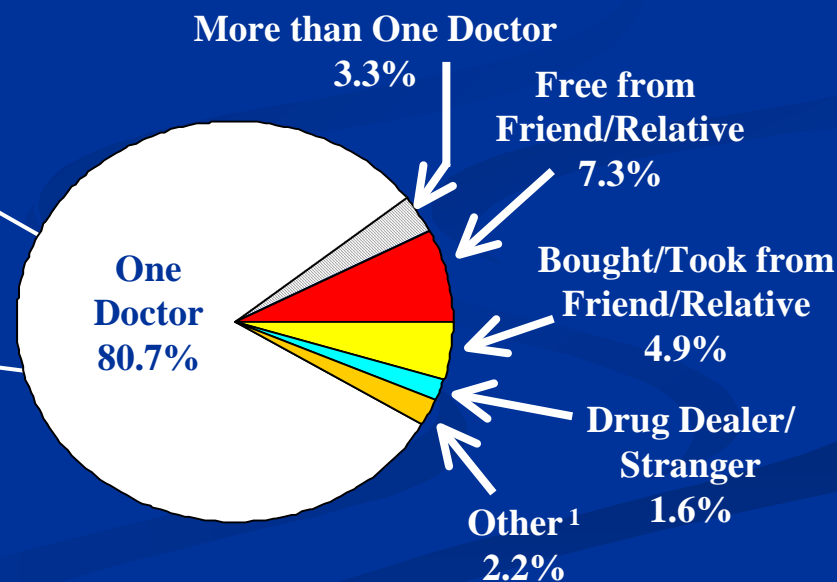
Where Pain Relievers Were Obtained

Most Recent Nonmedical Use among Past Year Users Aged 12 or Older: 2006

Source Where Respondent Obtained



Source Where Friend/Relative Obtained



Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown.

¹ The Other category includes the sources: "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

“Doctors are easy to find and they don’t carry guns”

Medical Economics

- “To stop Rx diversion, the agency (DEA) has hired hundreds of new investigators and expanded its local and state task forces”
- “Quantity alone...may indicated diversion and trigger an investigation”

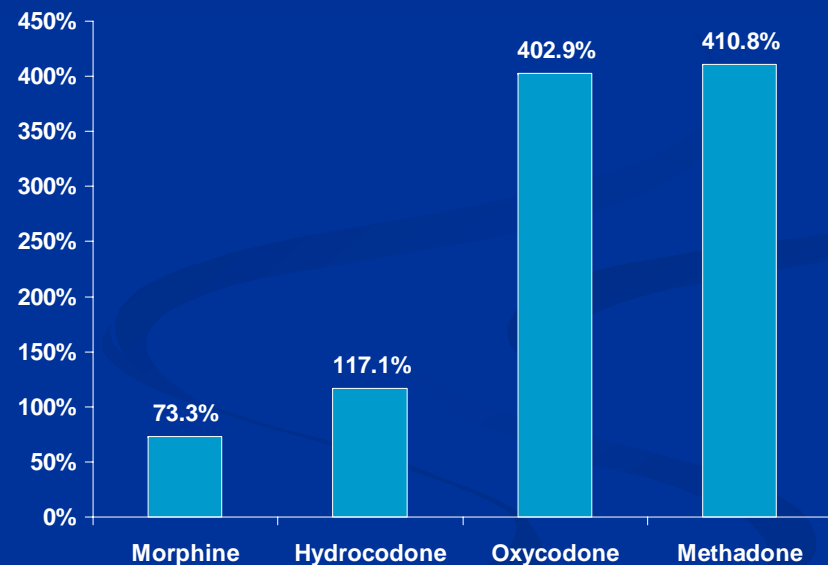


NASPER

National All Schedules Prescription Electronic Reporting Act

- Signed into law by President Bush August 2005
- Point of care reference to all controlled substances prescribed to a given patient
- Each state will implement it's own program
- Treatment tool vs. Law enforcement tool?

Sale of Opioids 1997-2002



Source: 2002 National Survey on Drug Use and Health (NSDUH).

Results from the 2002 National Survey on Drug Use and Health: National Findings. Department of Health and Human Services

Controlled Substance Monitoring

■ Consumer Protection Agency

■ Rx Monitoring Program

- Reduce misuse of prescriptions
- Reduce overdose
- Reduce diversion
- Reduce poly-pharmacy
- Coordinate care

■ Pharmacy linked electronic reporting

■ Physician access

Addiction
Abuse/Dependence

Prescription Drug Misuse

Aberrant Medication Use Behaviors:
A spectrum of patient behaviors
that *may* reflect misuse

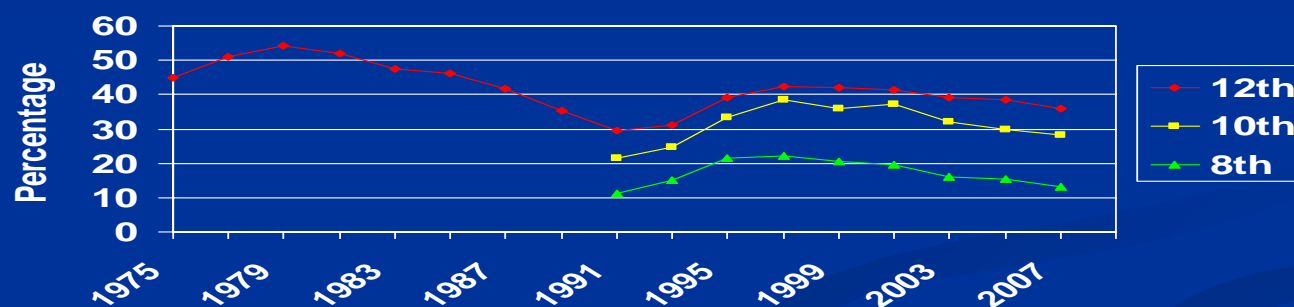
Total Chronic Pain Population

Adapted from Passik. APS Resident Course, 2007

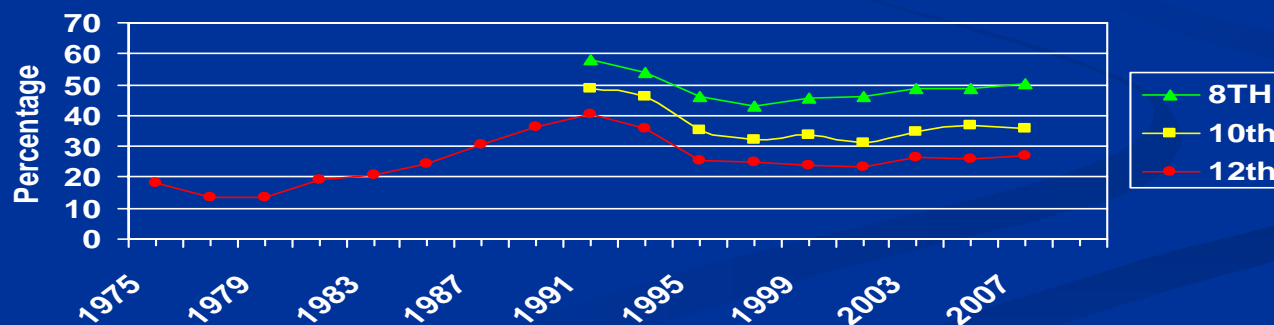
Epidemiology

■ Any Illicit Drug

Long Term Annual Trends in Prevalence



Perceived Risk



Thank you – Stephen A. Wyatt, D.O.
wyattsa@sbcglobal.net

- www.samhsa.gov
- www.ampainsoc.org
- www.jointogether.org
- www.asam.org
- www.aoaam.org
- www.nida.nih.gov

First Things First: Deciding Whether to Prescribe an Opioid

Anthony H. Dekker, D.O., FASAM

Clinical Consultant for Addiction Medicine

Indian Health Service

Phoenix Indian Medical Center

Disclosure

- Disclosure statement here

Chronic Non-Malignant Pain (CNMP)

- Osteoarthritis
- Low back pain
- Myofascial pain
- Fibromyalgia
- Headaches (e.g., migraine, tension-type, cluster)
- “Central pain” (e.g., spinal cord injury, stroke, MS)
- Chronic abdominal pain (e.g., chronic pancreatitis, chronic PUD, IBS)
- Sickle cell disease
- CRPS, Types I and II
- Phantom limb pain
- Peripheral neuropathy
- Neuralgia (e.g., post-herpetic, trigeminal)

Treatment goals in managing CNMP:

- Improve patient functioning
- Identify and eliminate positive reinforcers
- Increase physical activity
- Decrease or eliminate drug use

The goal is NOT pain eradication!

CNMP:

The clinical challenge

- Be aware of the “Heart Sink” patient.
- Remain within your area of expertise.
- Stay grounded in your role.
 - FIRST....Do no harm
 - THEN.....
 - Cure sometimes
 - Comfort always

Non-pharmacologic treatments for CNMP

- ✓ Physical therapy – conditioning
- ✓ Pain Psychology – relaxation / counseling / expectations orientation
- ✓ Massage therapy
- ✓ Spinal manipulation
- ✓ Acupuncture
- ✓ TENS units
- ✓ Nerve blocks
- ✓ Pain management group

Non-opioid medications for CNMP

- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Tricyclics
- Anti-depressants/anxiolytics
- Anti-convulsants
- Muscle relaxants
- Topical preparations—e.g. anesthetics, aromatics
- Others (e.g., tramadol)

Non-opioid medications (cont.)

- **Non-steroidal anti inflammatory drugs (NSAIDs) Inhibit prostaglandin synthesis:**
 - Works on Cyclo-Oxygenase (COX) COX-1 and COX-2
 - ↓ pain-minutes to hours
- **COX-1:**

Aspirin, Ibuprofen, Naproxen, Ketoprofen, Indomethacin, Diclofenac, Piroxicam, Sulindac

Non-opioid medications (cont.)

- **COX-2 Inhibitors:**
 - ↓ gastrointestinal effect
 - Normally not present but induced during inflammation
 - Celecoxib (Celebrex[®]);
 - Rofecoxib (Vioxx[®]); Valdecoxib (Bextra[®])
withdrawn from market due to increased cardiovascular risk

Non-opioid medications (cont.)

- **Antidepressants:**

- ↓ reuptake of serotonin & norepinephrine
- ↑ sleep
- Enhance descending pain-modeling paths
- Tricyclics —amitriptyline (Elavil®)—most studied/most SE's and nortriptyline (Pamelor®)
- SSRIs—not as effective
- SNRI (venlafaxine, Effexor®; duloxetine, Cymbalta®) preliminary evidence of efficacy in neuropathic pain

Non-opioid medications (cont.)

- **Antiepileptic drugs:**
 - ↓ neuronal excitability
 - Exact mechanism is unclear
 - Not due to antiepileptic activity
e.g. phenobarbital is poor analgesic
 - Good for stabbing, shooting, episodic pain from peripheral nerves
 - Gabapentin (Neurontin®)
 - Pregablin (Lyrica®)
 - Carbamazepine (Tegretol®)
 - Topiramate (Topamax®)

Non-opioid medications (cont.)

- **Other drugs:**
 - **Tramadol (Ultram)**
 - Mixed mu opioid agonist & NE/serotonin reuptake inhibitor
 - **Corticosteroids**
 - ↓ inflammation, swelling
 - **Baclofen**
 - GABA receptor agonist
 - Used for spasticity
 - **Ketamine**
 - NMDA antagonist
 - Used in general anesthesia, neuropathic pain
 - Rarely used secondary to side effects

Opioid therapy in CNMP:

*“To prescribe or not to prescribe ...
that is the question!”*

When you are considering prescribing an opioid for CNMP, how do you decide?

- **Indications** – patient-specific and disease-specific
- **Contraindications** – history of or current addictive disease

Indications for opioid therapy

1. Is there a *clear diagnosis*?
2. Is there *documentation* of an adequate work-up?
3. Is there *impairment of function*?
4. Has non-opioid multimodal therapy *failed*?
5. Have *contraindications* been ruled out?

Begin opioid therapy:

Document

Monitor

Avoid poly-pharmacy

Contraindications to opioid therapy

- Allergy to opioid medications ~ *relative*
- Current addiction to opioids ~ *?absolute*
- Past addiction to opioids ~ *?absolute*
- Current /past addiction, opioids never involved ~ *relative; ??absolute if cocaine*
- Severe COPD ~ *relative*

**Pain Patient on
Chronic Opioids**

New Physician

+

Are chronic opioids appropriate?

YES!

Re-document:

Diagnosis
Work-up
Treatment goal
Functional status

Monitor Progress:

Pill counts
Function
Refill flow chart
Occasional urine
toxicology
Adjust medications
Watch for scams

UNSURE

Physical Dependence vs Addiction:

Chemical dependence
screening

Toxicology tests

Pill counts

Monitor for scams

Reassess for
appropriateness

YES!

Discontinue opioids
Instruct patient on
withdrawal symptoms
Tell patient to go to ER
if symptoms emerge

NO

Educate patient
on need to
discontinue opioids

Emergency?

ie: overdoses
selling meds
altering Rx

NO!

3-month self taper
(document in chart)

OK

10-week structured taper

OK

Discontinue opioids at
end of structured taper

How to screen for addiction

- Perform an AUDIT and CAGE.
- Ask family or significant other the f-CAGE.
- Perform one or more toxicology tests.
- Ask prior physicians about use of controlled medications (f-CAGE).
- If history of current or prior addiction, has the patient ever abused opioids?
- Query the Pharmacy Board or PMP

The CAGE and f-CAGE

- **CAGE** =
 - **C**ut down on use?
 - Comments by friends and family about use that have **A**nnoyed you?
 - Embarrassed, bashful or **G**uilty regarding behaviors when using?
 - **E**ye-openers to get started in the mornings?
- **f-CAGE** = Ask the patient's significant other the CAGE questions about the patient's use of alcohol, drugs or medications.

Medical issues in opioid prescribing

- Potential benefits
 - Analgesia
 - Function
 - Quality of life
- Potential risks
 - Toxicity
 - Functional impairment
 - Physical dependence
 - Addiction
 - Hyperalgesia

Are opioids effective for CNMP?

- What do we know?
- What don't we know?

What we don't know about:

- Addiction
- Chronic pain
- Effects of long term opioid analgesia

We can't delay care until we find out!

Review of opioid efficacy

- In short-term studies:
 - Single in vitro studies
 - Oral studies \leq 32 wks
 - Both demonstrate that CNMP can be opioid responsive

Review of opioid efficacy (cont.)

- **In long-term studies:**
 - Usually observational – non randomized / poorly controlled
 - Treatment durations ≤ 6 years.
 - Patients usually attain satisfactory analgesia with moderate non-escalating doses (≤ 195 mg morphine/d), often accompanied by an improvement in function, with minimal risk of addiction.
- The question of whether benefits can be maintained over years rather than months remains unanswered.
 - Ballantyne JC: Southern Med J 2006; 99(11):1245-1255

Conclusions as to opioid efficacy

- Opioids are an essential treatment for some patients with CNMP.
 - They are rarely sufficient
 - They almost never provide total lasting relief
 - They ultimately fail for many
 - They pose some hazards to patients and society
- It is not possible to accurately predict who will be helped – but those with contraindications are at high risk

Conclusions as to opioid efficacy

- A trial (6 mo±) generally is safe
(IF contraindications are ruled out)
- People who expect to take opioids and lie around the house while they get well, won't.
 - Push functional restoration, exercises
 - Make increased drugs contingent on increased activity

Desirable patient characteristics:

- No substance abuse disorder
- Reliable
- History of good medical compliance
- Willing to do their part to recover
- Recognizes that opioids are only a partial solution
- Good support (no substance abusers in the home)

If prescribing opioids:

- Establish treatment goals, such as:
 - Functional improvement
 - Work
 - Play
 - Socialization
 - Affective normalization
 - Pain *reduction* (versus pain *relief*)

Formulate a treatment plan:

- Goals
 - Pain
 - Function
 - What should the person do anatomically?
 - Quality of life
 - Affect?
- Opioids or not
- Other treatment components

Practical suggestions:

- Have realistic expectations (*Appx. A, F*)
- Treat the entire patient
- Select appropriate patients
 - Screen for contraindications! (*Appx. B*)
 - If pain does not result primarily from activity in the nociceptive system, it will not be eliminated by
 - Opioids / Spinal fusion / Epidural steroid injections / Antidepressants / NSAIDs

Opioids – Often necessary, rarely sufficient

- Reconditioning program
- Physiological self-regulation
 - Yoga, biofeedback training, meditation
- TENS
- Adjunctive medications
 - NSAIDs and acetamenophen /
antidepressants / AEDs / topicals

Educate the patient and family

Side effects - Risks - Drug interactions (*Appx. E*)

- Start no new med, even OTC, without discussion

Pregnancy - Danger signs - What opioids can/can't do – Secure storage (*Appx. C*)

- Risks to a teen who abuses / Child who takes inadvertently

Methadone variable T_{1/2}, accumulation

- Keep out of reach first week / administered by friend, family / Never by the bed or recliner

Summary

- Whenever considering long-term prescribing of opioids for CNMP:
 - Stay in your area of expertise
 - When in doubt ... insist on getting help
 - ID *indications* **AND** R/O *contraindications*
 - Initiate prescribing with care / caution
 - Monitor for *improvement / deterioration*
 - IF deterioration, you *must* alter treatment plan

Selecting an Opioid: Pharmacologic Principles

John Tanner, M.D.

Medical Director
Beaches Family Medicine
Neptune Beach, Florida

Opiates & Opioids

Opiates

- Present in opium from seedpod of *Papaver somniferum*
- Morphine, codeine



Highly refined Southwest Asian heroin or Southeast Asian heroin



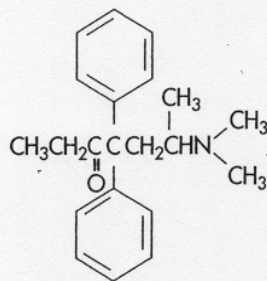
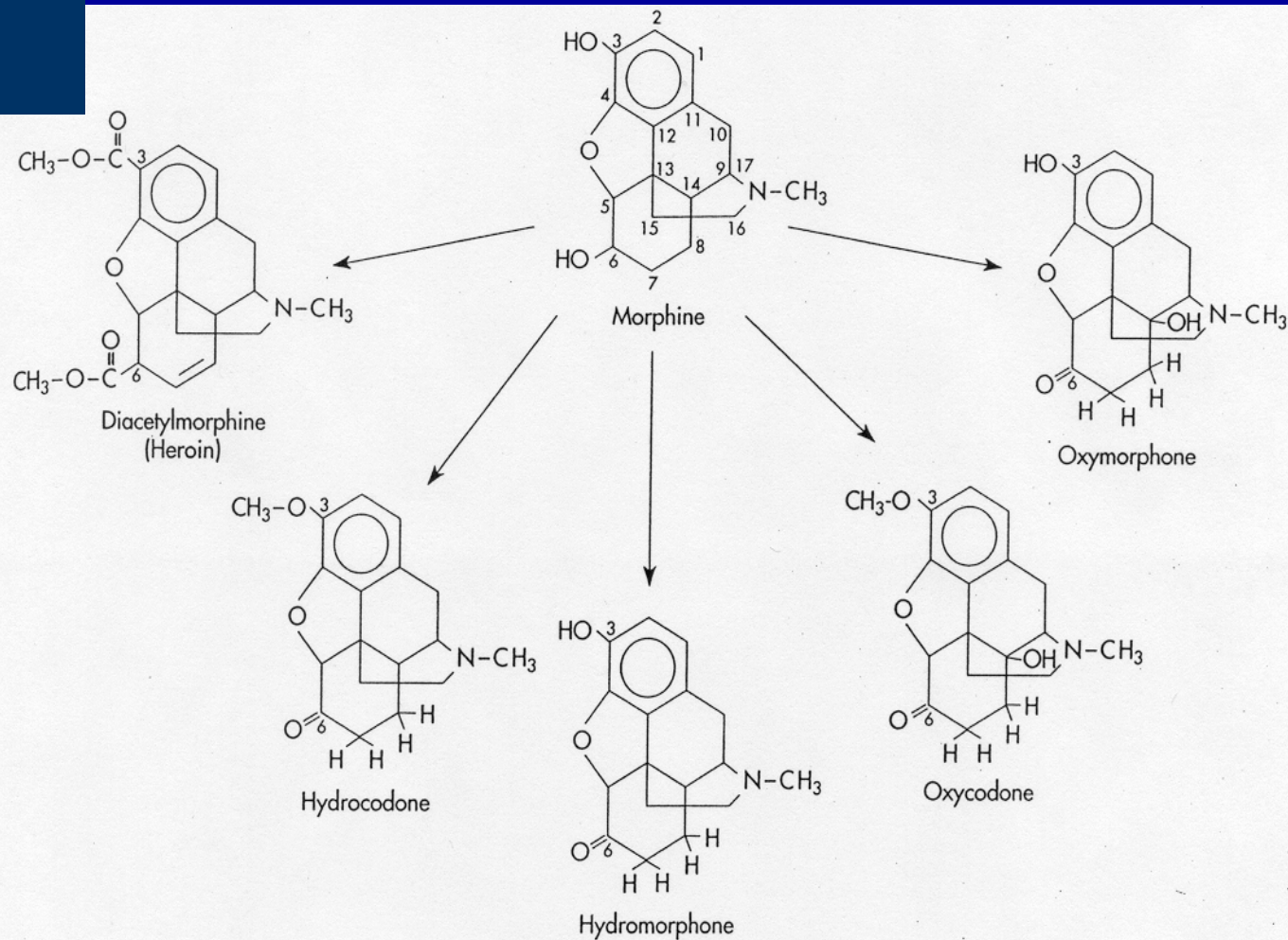
Opioids

- Are manufactured
- Semisynthetics are derived from an opiate
- Synthetics are synthesized to have function similar to natural opiates

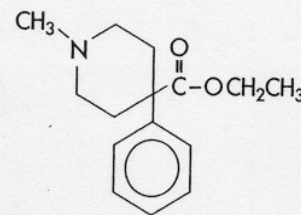
Opioids

Natural (opiates) &
Semisynthetic

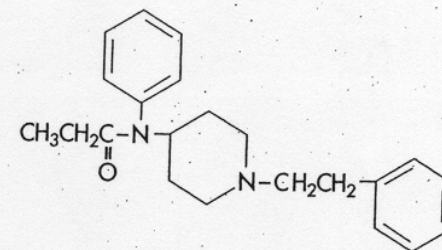
Synthetic



Methadone.

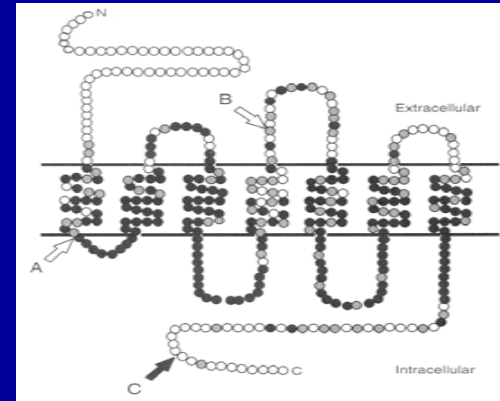


Meperidine.



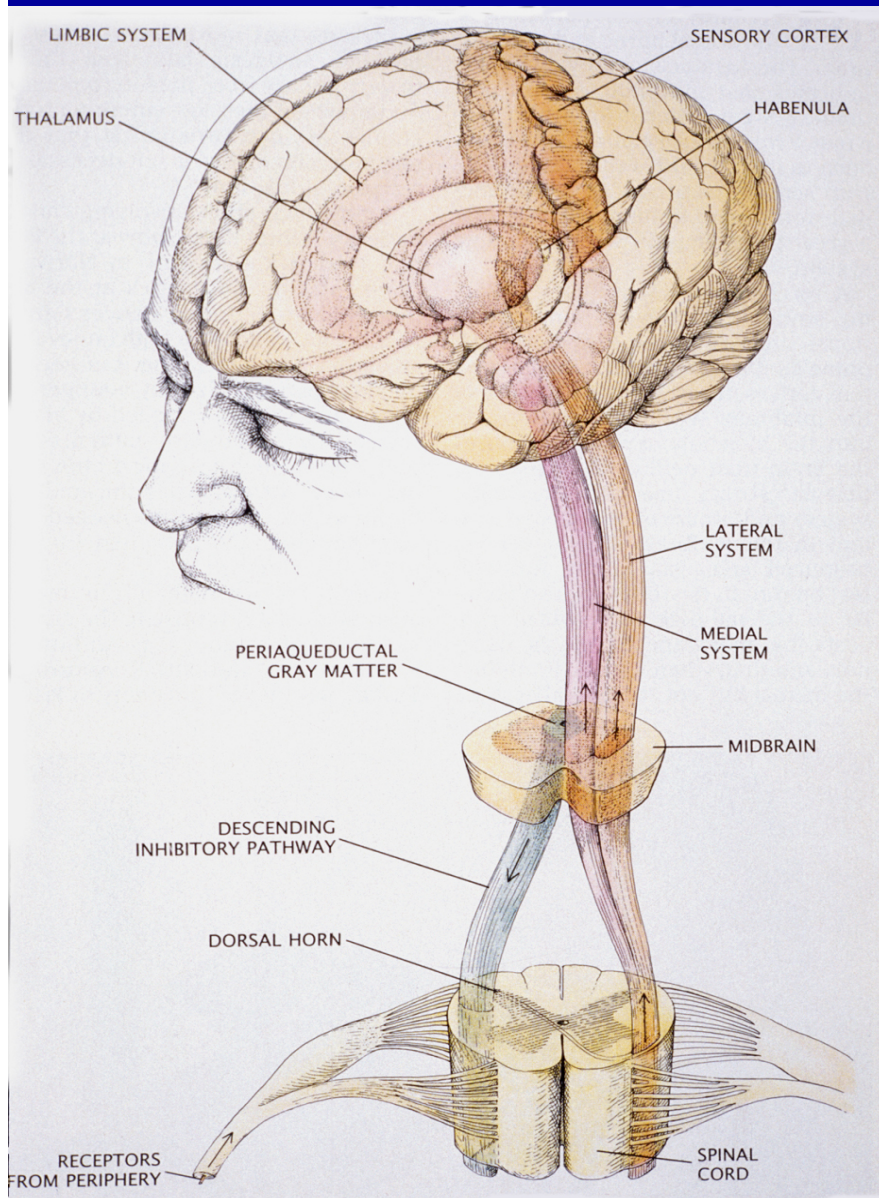
Fentanyl.

Mu Receptor



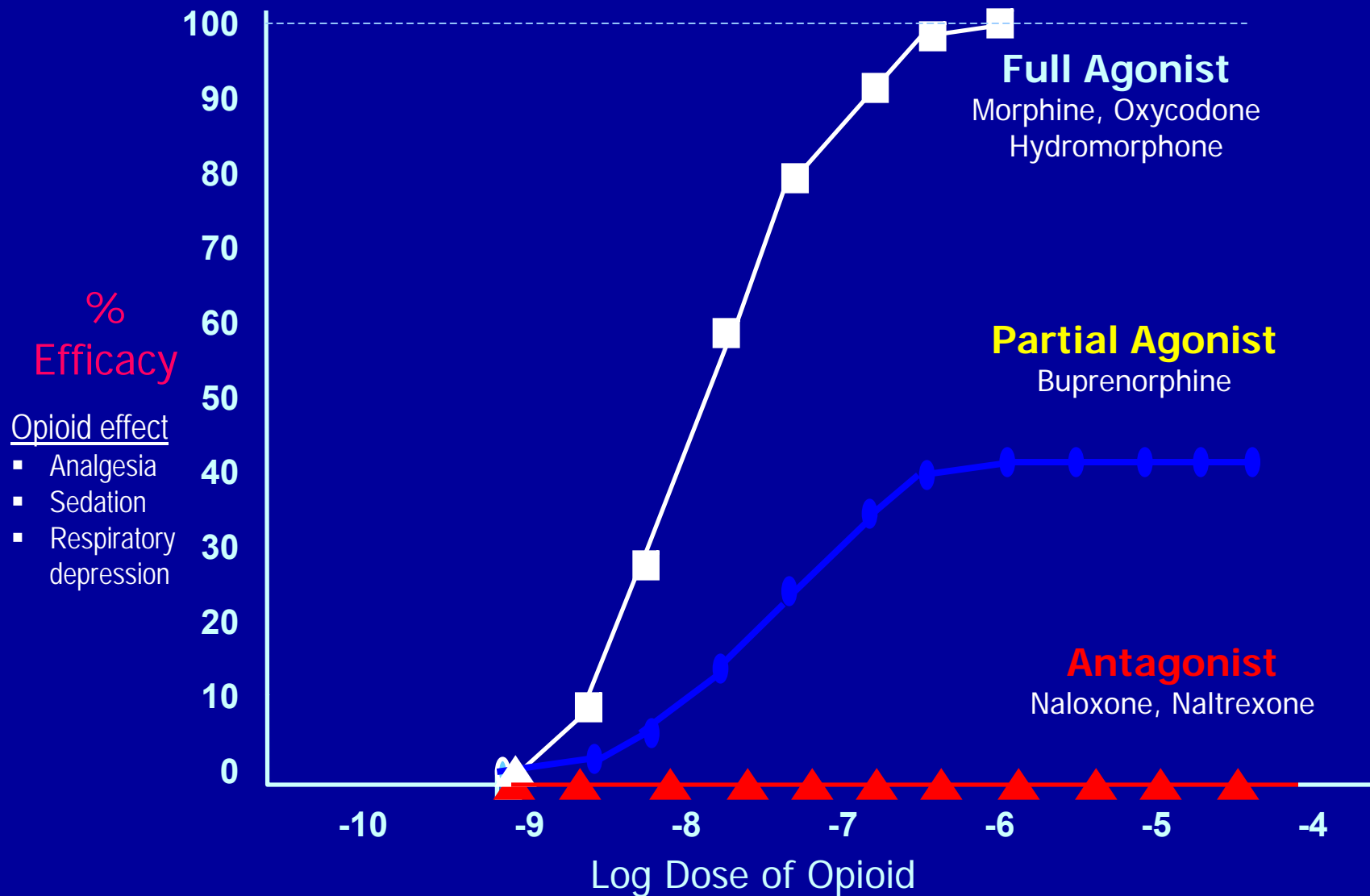
- G protein-coupled receptor family, signal via second messenger (cAMP)
- Found in many sites: pre- and post-synapse in periphery, spinal cord dorsal horn, brain stem, midbrain, thalamus, cortex...
- Mu receptor subtypes
 - Not all patients respond to same opioid in same way
 - Not all pain responds to same opioid in the same way
 - Incomplete cross-tolerance between opioids

Activation of Mu Receptors



- Inhibit activation of nociceptors
- Inhibit cells that release inflammatory mediators
- Inhibit terminals of C-fibers in the spinal cord
- Prevent ascending transmission of pain signal
- Turn on descending inhibitory systems

Opioid Intrinsic Activity



Opioid Responsiveness / Resistance

- **Degree of pain relief with:**
 - Maximum opioid dose
 - In the absence of side effects ie. sedation
- **Not all pain is opioid responsive:**
 - Varies among different types of pain
 - Acute > Chronic
 - Nociceptive > Neuropathic
 - Varies among individuals

Pseudo Opioid-Resistance

- **Some patients with adequate pain relief believe it is not in their best interest to report pain relief**
 - Fear that care would be reduced
 - Fear that physician may decrease efforts to diagnose problem

Opioid Efficacy in Chronic Pain

- Most literature surveys & uncontrolled case series
- RCTs are short duration <4 months with small sample sizes <300 pts
- Mostly pharmaceutical company sponsored
- Pain relief modest
 - Some statistically significant, others trend towards benefit
 - One meta-analysis decrease of 14 points on 100 point scale
- Limited or no functional improvement

Balantyne JC, Mao J. NEJM 2003

Martell BA et al. Ann Intern Med 2007; Eisenberg E et al. JAMA. 2005

Number Needed to Treat *(NNT)

** to obtain one patient with 50% pain relief*

	Post Herpetic Neuralgia
Tricyclic Antidepressants	2.3
Oxycodone	2.5
Gabapentin	3.2
Capsaicin	5.3

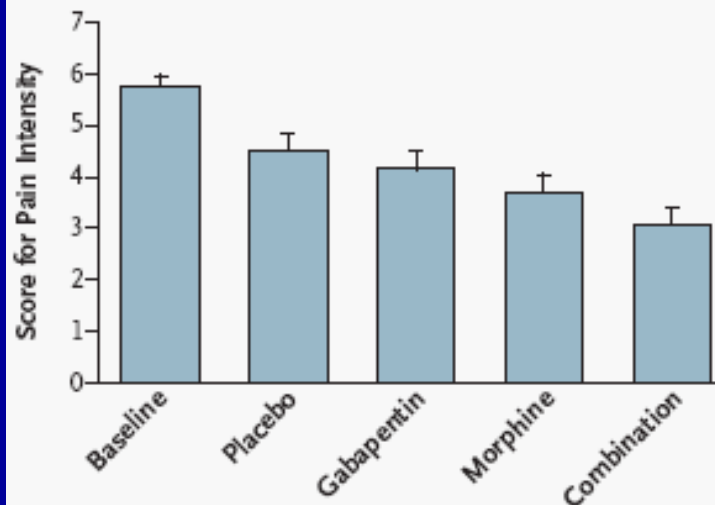
Multimodal Analgesia

ORIGINAL ARTICLE

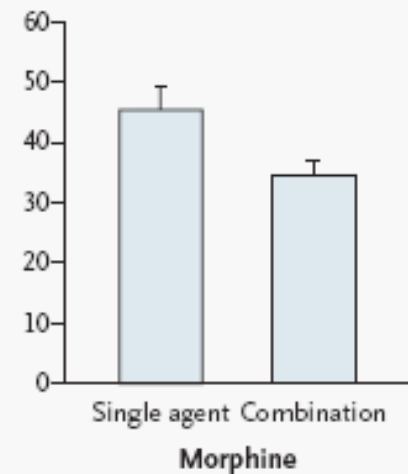
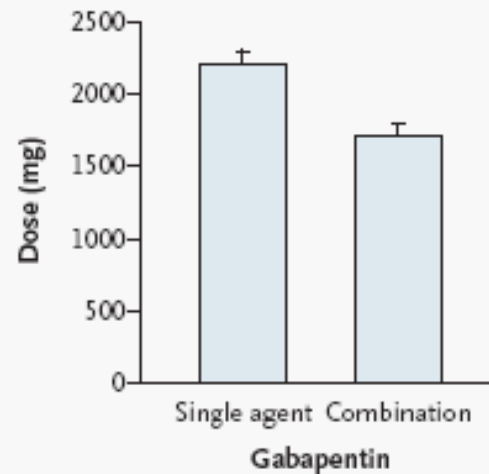
Morphine, Gabapentin, or Their Combination for Neuropathic Pain

Ian Gilron, M.D., Joan M. Bailey, R.N., M.Ed., Dongsheng Tu, Ph.D.,
Ronald R. Holden, Ph.D., Donald F. Weaver, M.D., Ph.D.,
and Robyn L. Houlden, M.D.

B Mean Daily Pain



C Maximal Tolerated Dose



Opiophobia

- Overestimate potency and duration of action
- Fear of being scammed
- Often prescribed with too small a dose and too long a dosing interval
- Exaggerated fear of addiction risk

Opioid Side Effects

- **Side effects are common:**
 - Nausea and vomiting
 - Sedation, respiratory depression
 - Constipation and urinary retention
 - Sweating, insomnia, decreased sexual function
 - Cognitive impairment and psychomotor dysfunction
 - Opioid-induced delirium

Opioid Allergies

- Opioids release histamine from mast cells
 - Pruritis, urticaria may not mean allergy
- Allergies, when they occur, tend to be to entire chemical families:
 - *Diphenylheptanes*: methadone, propoxyphene
 - *Phenylpiperidines*: meperidine, fentanyl
 - *Phenanthrenes*: codeine, hydromorphone, morphine, oxycodone, hydrocodone
- Rashes more likely from inactive additives

Opioid Safety

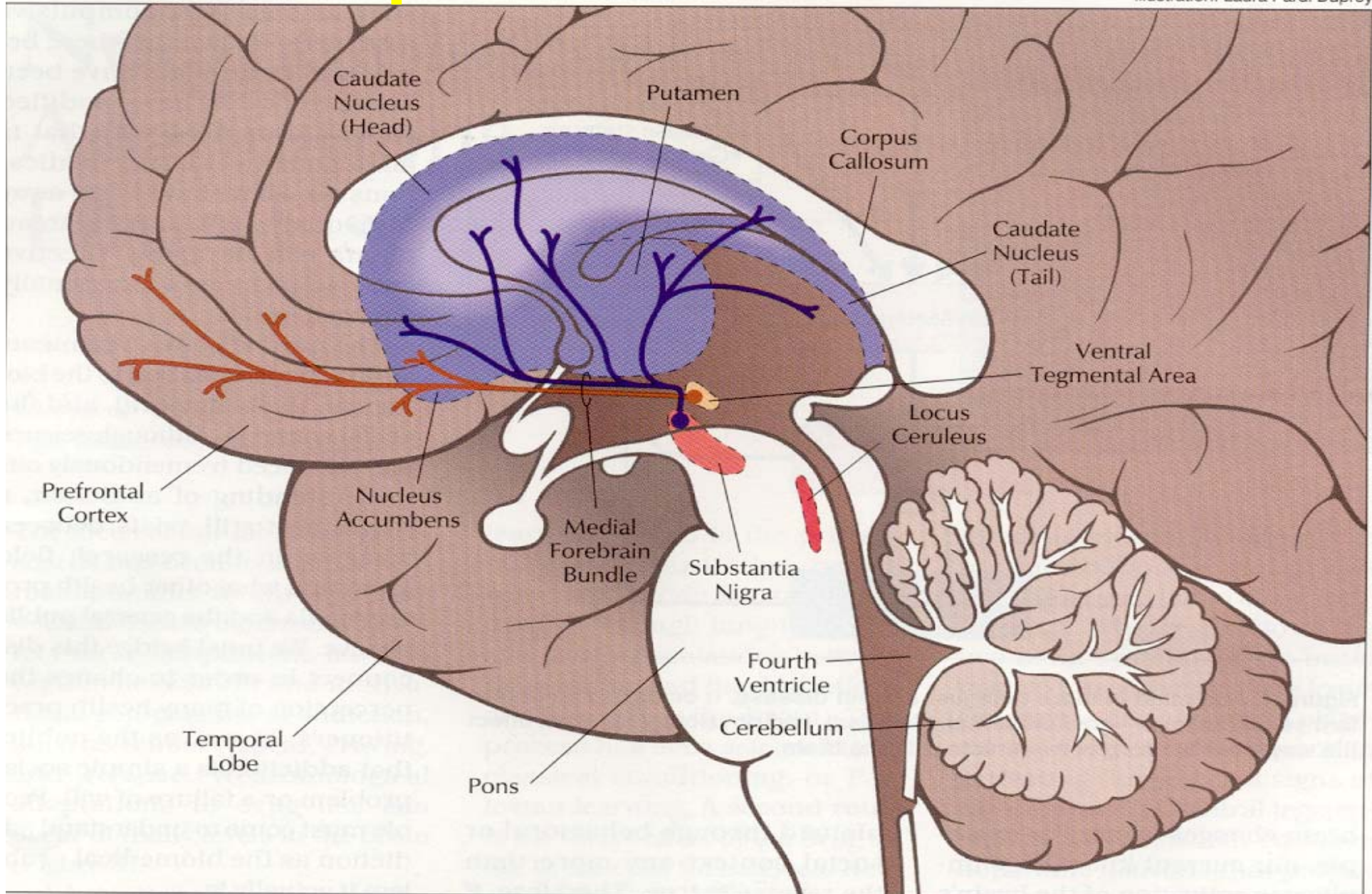
- Organ toxicity is rare
 - Hypothalamic-pituitary-adrenal axis - ↓ cortisol
 - Hypothalamic-pituitary-gonadal axis - ↑ prolactin ↓ LH, FSH, testosterone, estrogen, progesterone
- Overdose esp. when combined w/ other sedatives
- Worsening pain? Withdrawal or hyperalgesia
- Risk of addiction (opioid dependence)?
- Societal toxicity - diversion and trafficking

Ballantyne & Mao: NEJM 2003

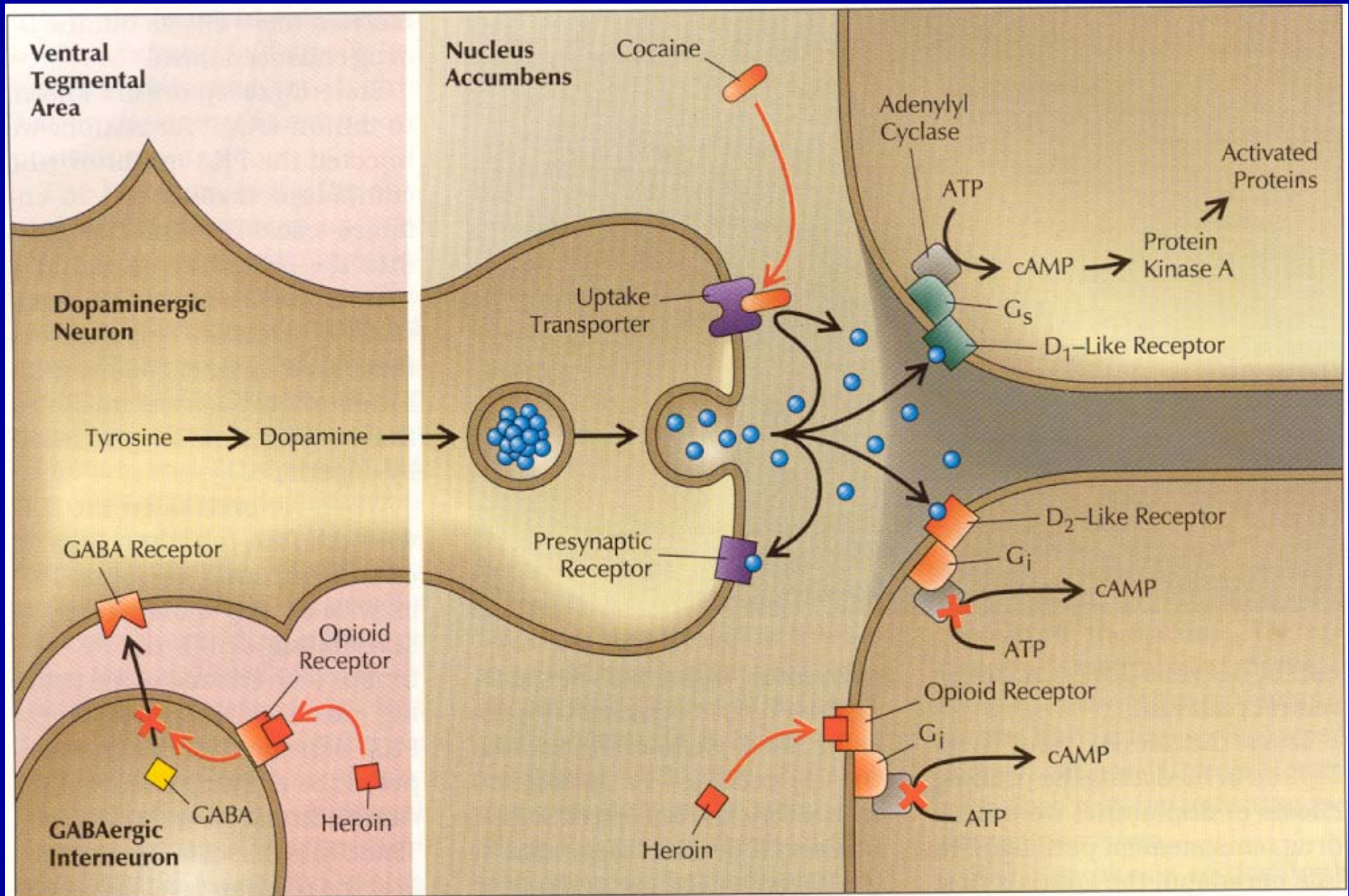
Rahim RT et al. J Neuroimmunol. 2002; Abs R et al. J Clin Endocrinol Metab 2000

Opioids and the Brain

Illustration: Laura Pardi Duprey



The Reward Pathway (VTA→NAc→PFC)



Pain alters opioid responses

- Significantly less opioid reward or euphoria
- Less morphine analgesic tolerance in pain assays
- Less morphine physical withdrawal symptoms
- Patients on morphine with successful nerve block will develop respiratory and CNS depression

Can opioids worsen pain?

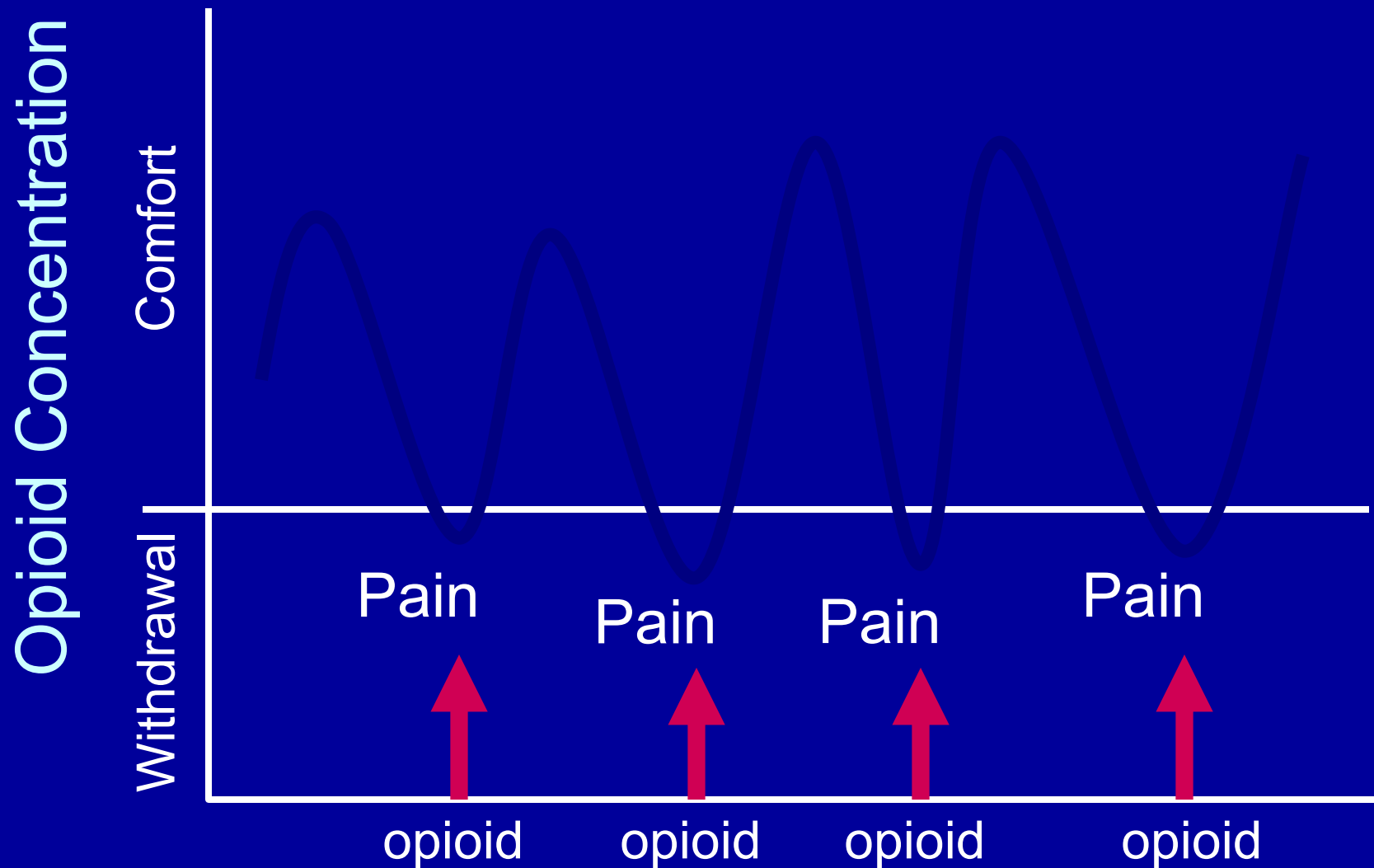
- In animal studies,¹ chronic opioid administration results in increased pain sensitivity versus placebo
- Methadone maintenance patients² with enhanced pain sensitivity versus controls
- ? Release of peptides “anti-opioids”, increase levels of dynorphin
- ? Neuroadaptation to chronic opioids

Li X et al. Brain Res Mol Brain Res 2001

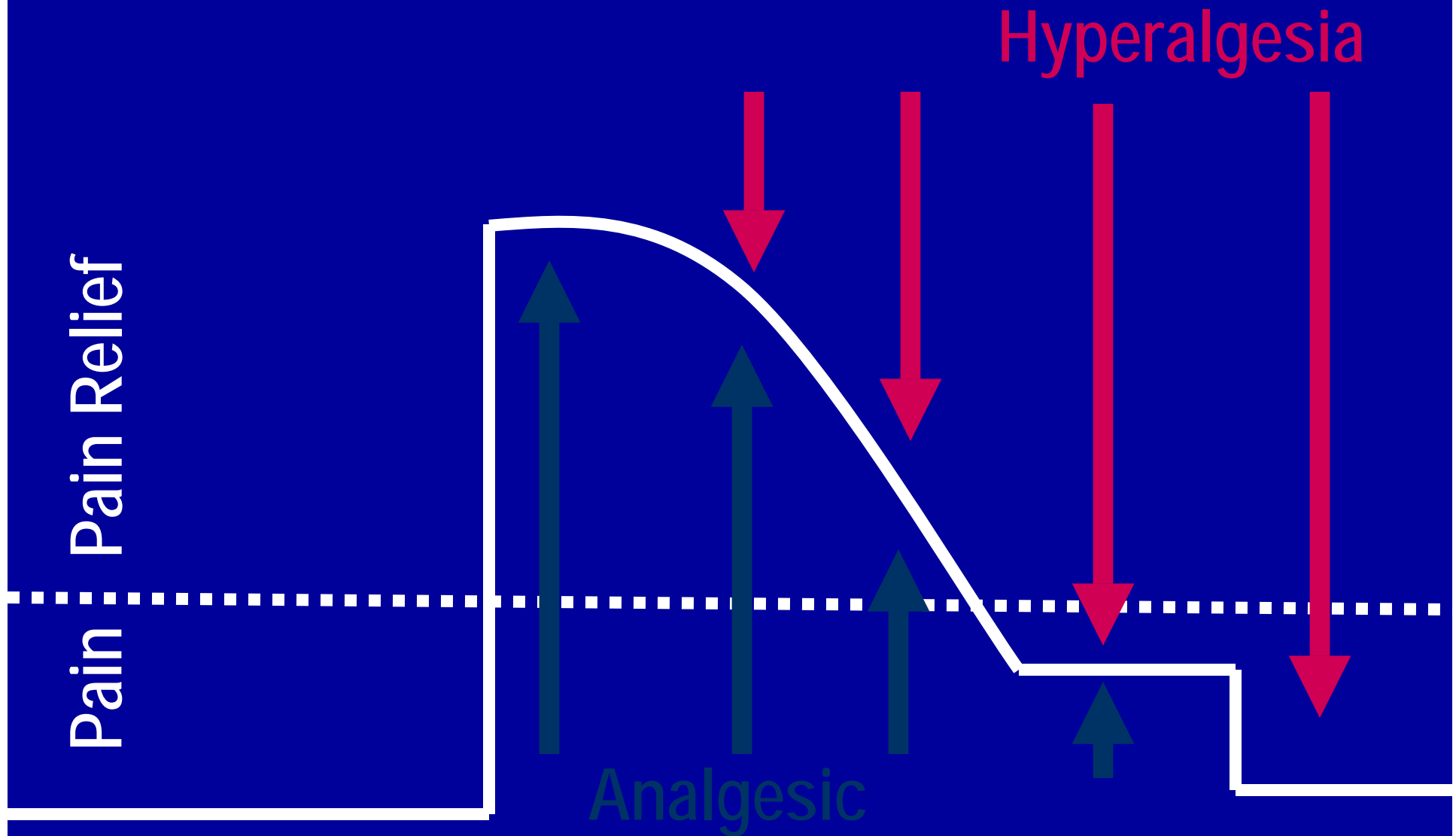
Doverly M et al. Pain 2001

Angst MS, Clark JD. Anesthesiology 2006

Withdrawal-mediated pain



Opioid-induced hyperalgesia



Adapted from Compton P. AMERSA 2002

Choosing an opioid

- Strong vs weak (ceiling effect)
- Duration and onset of action
 - “Rate hypothesis” - fast on, fast off – most addicting
- Patient’s prior experience
 - *Mu* polymorphisms – differences in opioid responsiveness
- Route of administration
- Side effects and cost
- There are **NO** abuse-resistant opioids or opioid formulations!!

Choosing an Opioid

Short-acting

- Hydrocodone
- Hydromorphone
- Morphine
- Oxycodone

Long-acting

- Slow-release delivery system
 - Transdermal fentanyl
 - Extended release morphine
 - Extended release oxycodone
- Intrinsic pharmacokinetic property
 - Methadone

Opioid Rotation

- Switch to another opioid as means of restoring analgesic efficacy or limiting adverse effects
- Based on large intra-individual variation in response to different opioids
- Different variants of mu-opioid receptors
- Based on surveys and anecdotal evidence
- Use equianalgesic table to calculate dose of new opioid
 - Determine clinically relevant starting point
 - Decrease equianalgesic dose by 25-50%

Opioid conversion chart

ANALGESIC	ORAL	PARENTERAL
Morphine	30	10
Codeine	200	120
Hydromorphone	7.5	2
Oxycodone	20	-
Hydrocodone	30	-
Methadone	20	10
Fentanyl	100-200 mcg [TM] 50 mcg [TD]	100 mcg
Meperidine	300	100
Propoxyphene	65-130	-
Tramadol	100-150	-

adapted from © Copyright 2008 American College of Physicians

Equianalgesic tables

- Derived from relative potency ratios using single-dose analgesic studies
- Subjects with limited opioid exposure
- Do not reflect clinical realities of chronic opioid administration
- Therefore dose ratios are guidelines to be used cautiously

Morphine - The gold standard

- Effective po, sublingual, rectal, vaginal, topical, intrathecal, intra-articular
- Several dose forms, routes of administration
- Kinetics vary with route
- Sedating
- Strong GI effects
- Inexpensive (IR)
- M-6-glucuronide – active, accumulates in renal failure
 - Analgesic, respiratory depressant

M-3-G accumulates in some products

Codeine

- IM / po = 2 / 3
- Onset in 30 minutes, peak 60 minutes, duration 3-6 hrs
- Mild to moderate pain
- Hepatic and renal elimination
- Prodrug – 10% transformed to morphine
 - Nonfunctional cytochrome P450-2D6: 7-10% of Caucasians
 - Can't convert it, get side effects but no analgesia
 - Eckhardt K et al: Pain 1998

Hydrocodone

Trade name: Lortab, Vicodin, Vicoprofen

- OA: 15-30 min, PE: 30-60 min, DOA: 4-8 hrs
- Mild to moderate pain
- Hepatic and renal elimination
- Crosses placenta and in breast milk

**What's special about
methadone?**

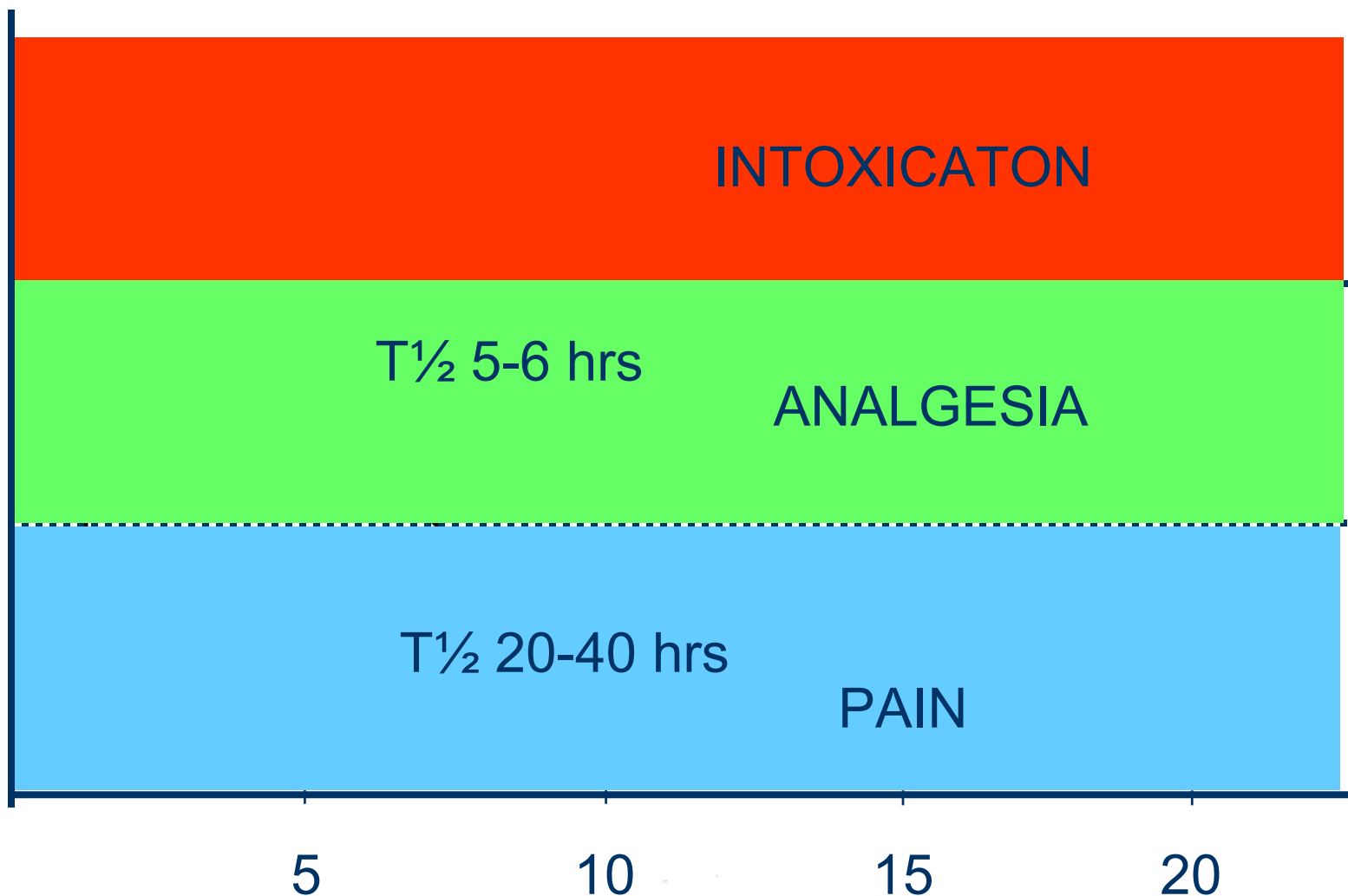
Kinetics

- Good (> 80%) oral absorption
- Rapid and extensive distribution phase
 - 2-3 hours.
- Primarily metabolized by CP450 - 3A4
 - Expression varies up to 30-fold
- To a lesser extent by 2D6, 1A2
 - genetic polymorphism exists
 - *ranges from poor to very rapid metabolism*

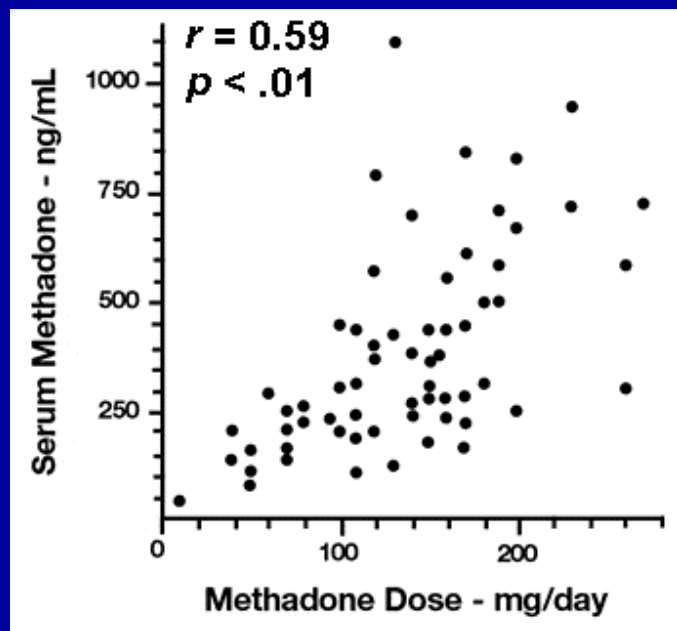
Kinetics (cont.)

- **Large inter-individual variations in pharmacology**
 - influenced by absorption, variable metabolism and protein binding, urinary pH, concomitant medications, diet, physical condition, patient age or pregnancy, vitamins

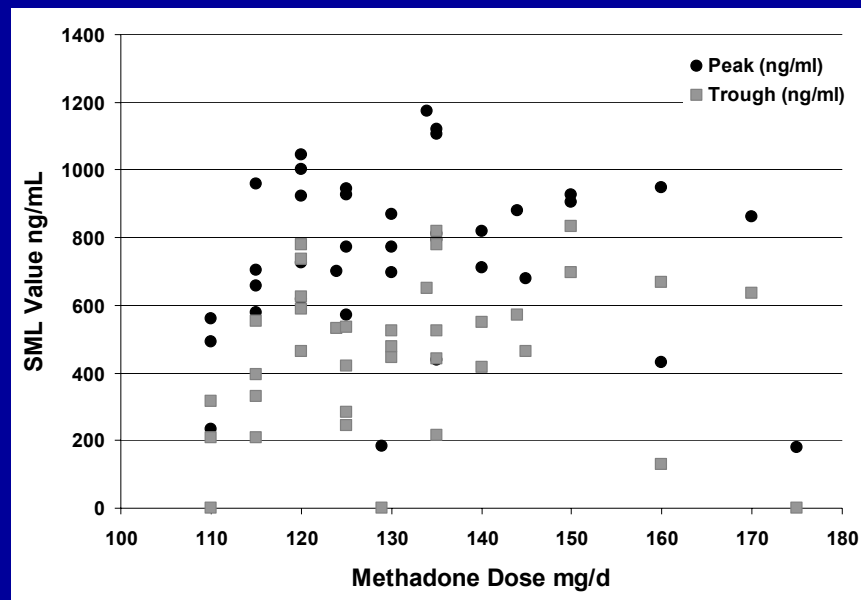
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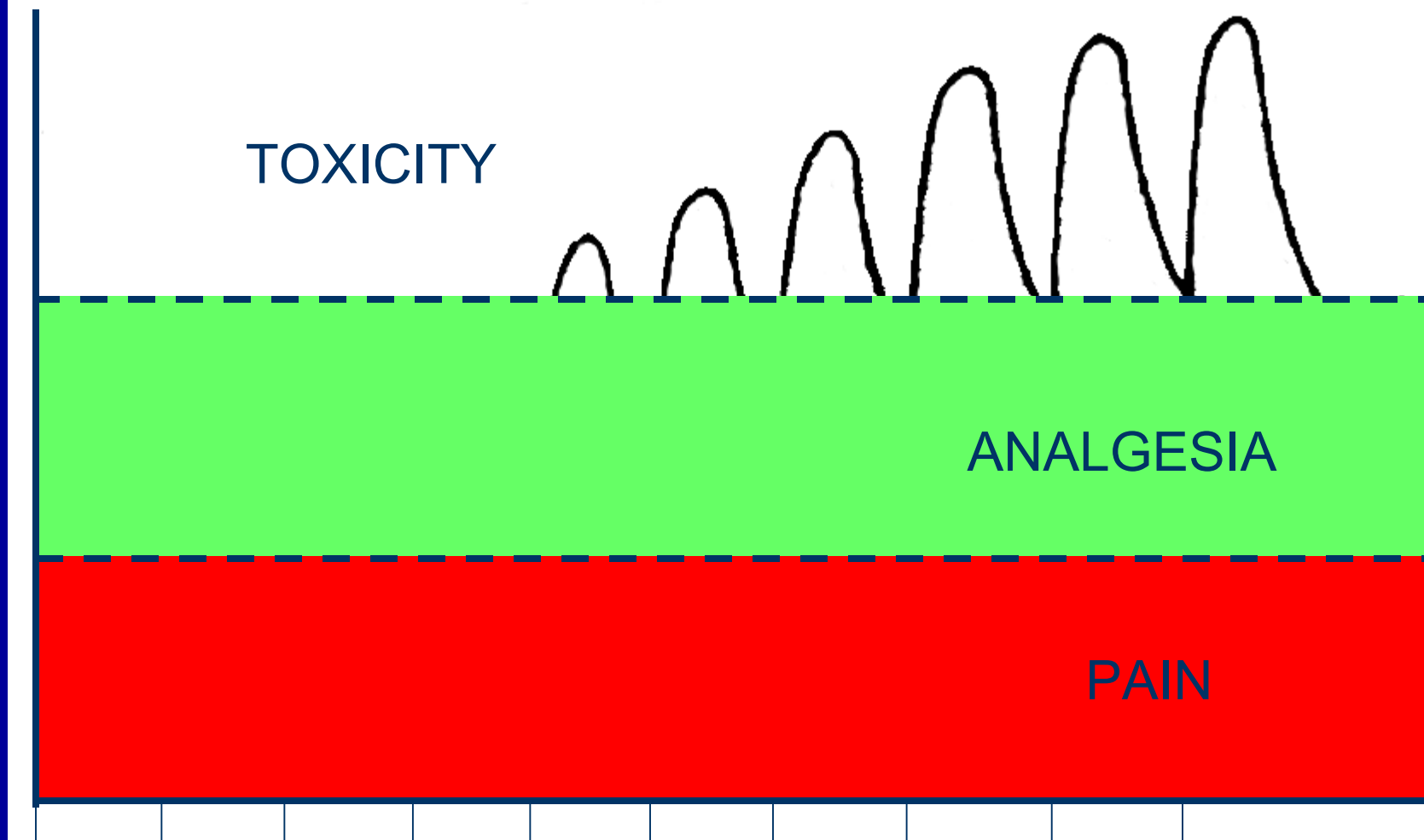


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 - *Alcohol / benzodiazepines / barbiturates*
- CYP450 active drug effect
 - Addition of *inhibitor* or discontinuation of *inducer* can lead to drug accumulation

Fixed methadone dose interval



Dose intervals

Nilsson MI, et al. Acta anaesth. scand 1982, Suppl 74

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- IQ unchanged
- Reaction time unchanged
- Sustained attention – no consistent change
- Perceptual motor function, driving simulators – no significant change
- Driving
 - No increase in violations
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More about methadone

- The number of methadone-related deaths in the U.S. increased from 790 in 1999 to 2,993 in 2003
- Methadone has been linked to a recent increase in mortality in pain patients.
- Methadone can accumulate to harmful serum levels during the first few days of treatment for addiction or pain.
- Some methadone conversion tables are
 - *at least problematic;*
 - *some are incorrect (recommending too high initial methadone doses)*

Methadone's idiosyncrasies:

Beneficial ones

1. NMDA receptor antagonist
 - Less tolerance, dose escalation
 - Better rx of neuropathic pain/central sensitization?
2. Less euphoria? (po)
3. 5HT, NE uptake inhibition
4. No neurotoxic metabolites
 - Unlike morphine, propoxyphene, meperidine
5. Low cost

More about methadone

- Methadone kills in one of three ways:
 - ***Single overdose***
i.e., accidental ingestion; over estimation of tolerance, abuse-type bingeing
 - ***Accumulated toxicity***
i.e., too rapid induction / titration
 - ***Drug-drug interactions***
i.e., addition or subtraction of certain drugs

Prescribing methadone

- **“Start low, go slow” is a good rule of thumb**
- **Find a model that works for you**
- **Watch for respiratory depression**
- **Do not fear the drug; use good medical / nursing / pharmacy practice principles**

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- Calculate total daily dose of MS.
- Calculate methadone daily equivalent –
using a reasonable model
- Stop the current opioid
- Start methadone, dividing into Q8h doses
- Breakthrough dose is 5% of total daily dose
QID prn – or low dose short T1/2 opioid.
- Adjust dose only q 7 – 14 days

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Problematic ones

1. Long, variable, unpredictable half-life
 - 13 – 100+ hrs
 - Half life doesn't predict analgesia
2. Numerous interactions
3. QTc prolongation, risk of torsade de points
4. Variable, not fully predictable relative potency

Drug interactions with methadone

- *PDR* lists 73 interactions, some of which are groups.
- Antiretrovirals have multiple and variable interactions – check before use (***Appx. E***).
- CNS depressants have additive effect:
 - Opioids, anesthetics, sedatives, ethanol
 - Cause respiratory depression, hypotension, profound sedation, coma.
- Potential serotonin syndrome with SSRIs, tramadol
- Grapefruit inhibits methadone metabolism
- Smoking induces CYP1A2, and ↓ methadone levels

Interactions with methadone (cont.)

Levels *decreased* by 3A4 inducers:

- Self – induces its own metabolism
 - 3.5 fold increase in total clearance between 1st dose & steady state
- Anticonvulsants
 - Phenytoin, carbamazepine, phenobarbital
- Antiretrovirals
 - Amprenavir, efavirenz, lopinavir, nelfinavir, nevirapine, ritonavir, zidovudine
- Other: Rifampin, chronic alcohol

Interactions with methadone (cont.)

Levels *increased* by 3A4 inhibitors:

- Psychotropics
 - Diazepam, fluvoxamine, fluoxetine, sertraline
- Antimicrobials
 - Erythromycin, ciprofloxacin, azole antifungals, clarithromycin, protease inhibitors,
- Others
 - diclofenac, doxycycline, nicardipine, propofol, quinidine, and verapamil, nifedipine, cimetidine, acute alcohol

Antidepressants

- TCAs are metabolized mostly by 2D6
 - Desipramine levels increase
 - Amitriptyline increases α -1-acid glycoprotein, decreases methadone clearance
 - increases methadone via α 1 acid glycoprotein
- 1A2 inhibited: fluvoxamine, paroxetine, sertraline, fluoxetine
- 2D6 inhibited: paroxetine, fluoxetine
- 3A4 inhibited: fluvoxamine, paroxetine, sertraline, fluoxetine
 -
- SSRIs boost methadone levels in rapid metabolizers
 - have produced respiratory arrest when added to methadone
- Venlafaxine has least potential for drug interaction

Methadone and 2D6

- **Methadone may increase levels of 2D6 substrates**
 - amphetamines, some β -blockers, dextromethorphan, fluoxetine, lidocaine, mirtazapine, paroxetine, risperidone, thioridazine, tricyclics, and venlafaxine
- **Methadone can decrease efficacy of prodrugs**
 - codeine, hydrocodone, oxycodone, tramadol

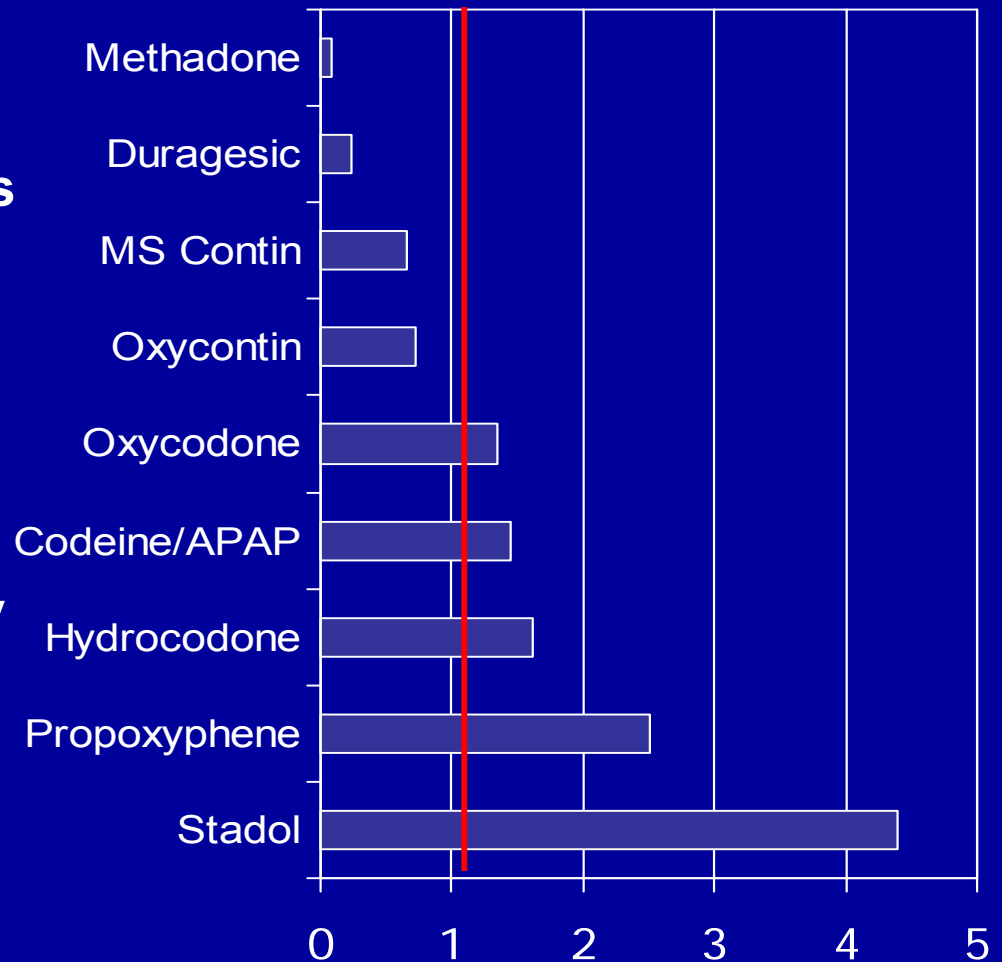
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- **RCT**

- N=40, advanced cancer
- methadone vs morphine
- Doses of both drugs were minimized and titrated to acceptable analgesia with minimal adverse effects.
- Pain control and side effects were similar
- Opioid escalation was significantly less with methadone
- More stable analgesia over time was seen in patients treated with methadone.
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Methadone's relative abuse potential

- 3-year retrospective
- Free-standing pain clinic
- Patients discharged for opioid misuse vs. 200 random patients receiving opioid therapy
 - Multisourcing
 - toxicology discrepancies
 - repeated escalation , etc.
- “Relative misuse potential”
 - Drug frequency in the discharged patients/frequency in active patients
- **Problem:**
 - True misuse potential would require prospective study with random assignment



NMDA antagonism

- The d isomer of methadone is an NMDA receptor antagonist
- Analgesic tolerance (tail-flick) after 5 days of morphine was completely blocked by coadministration of d-methadone.
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- Methadone blocks cardiac HERG K⁺ currents
- Risk of Torsades de Pointes
- Case series n=17
 - 82% (14/17) had known risk factors for arrhythmias
 - hypokalemia, concomitant drugs that prolong QT
- Prospective study
 - n= 132 heroin addicts
 - ECG at baseline and 2 months
 - QTc mean increase = 10.8 ms
 - Greatest: men, higher doses (110 to 150 mg)
 - No QTc increase > 40 ms
generally accepted threshold for an increase that should prompt clinical concern

Conclusions: Methadone

1. Methadone must be started very cautiously due to kinetics, lethality
2. The most important part of COAT is close monitoring for beneficial / harmful outcomes
3. Outcomes are improved with use of adjuvants
4. The physician has an obligation to protect society from diversion, when possible
5. Simple questionnaires can facilitate patient monitoring while improving physician efficiency

Selecting a specific opioid

- Long T1/2 / slow-release products are generally interchangeable (except methadone)

Selecting a specific opioid

Methadone has unique advantages . . .

- Duration of action
- Slow development of tolerance to analgesia
- Cost

. . . and disadvantages

- Interactions
- Unpredictable kinetics
- Different $T_{1/2}$ for pain v. respiratory depression
- Cardiac toxicity

What's special about methadone?

Anthony Dekker, DO
Chief Clinical Consultant in Addiction
Medicine and Chronic Pain
Indian Health Service

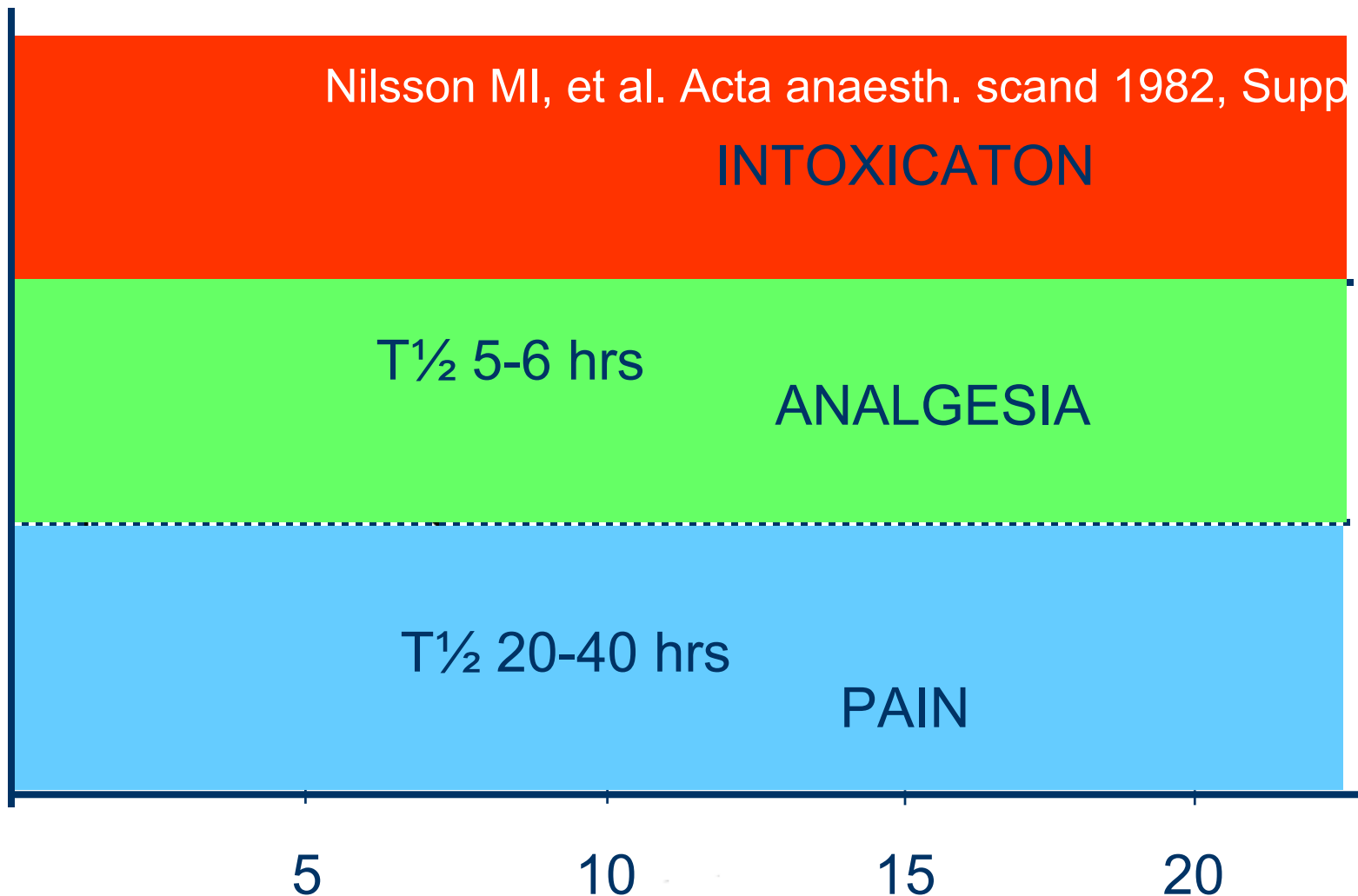
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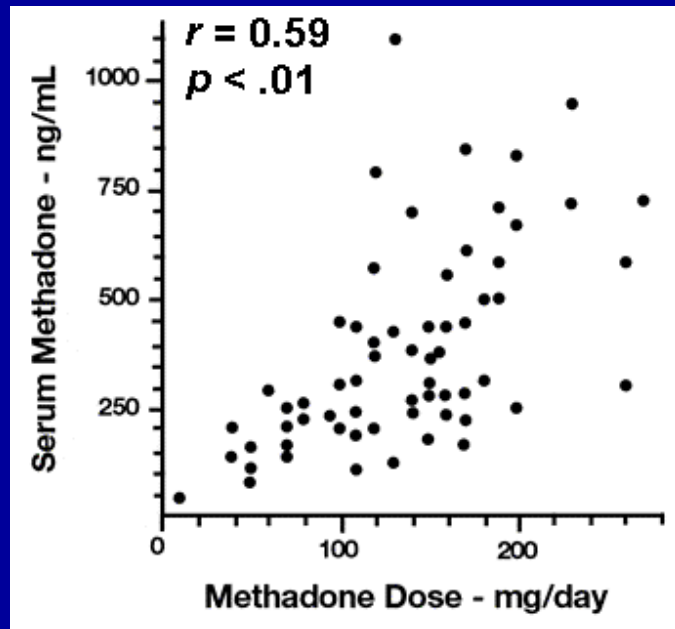
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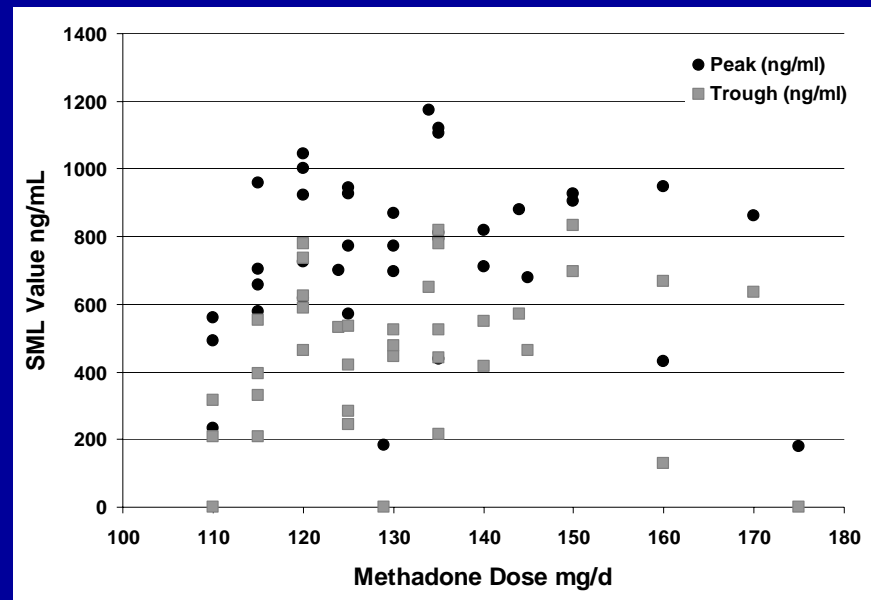
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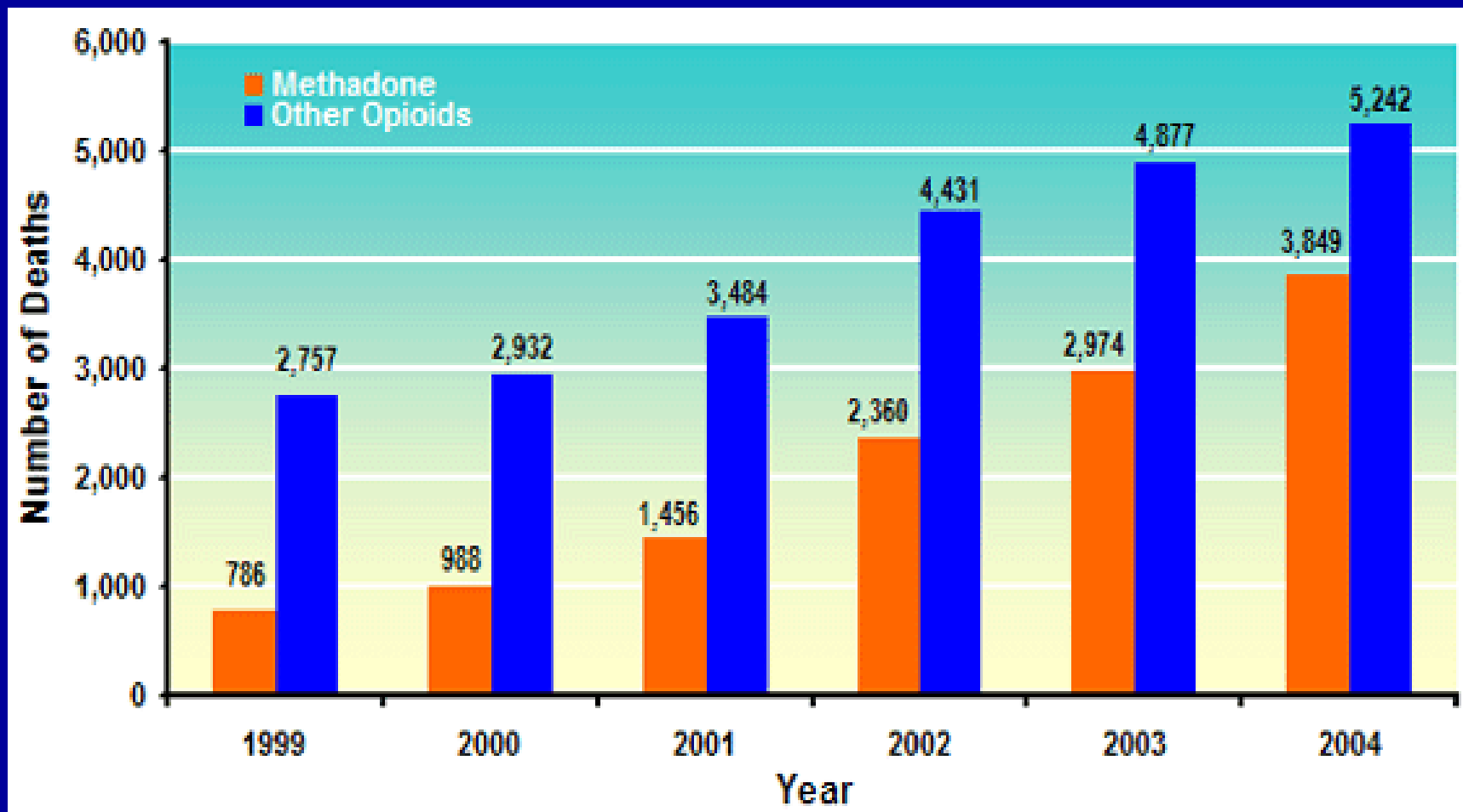


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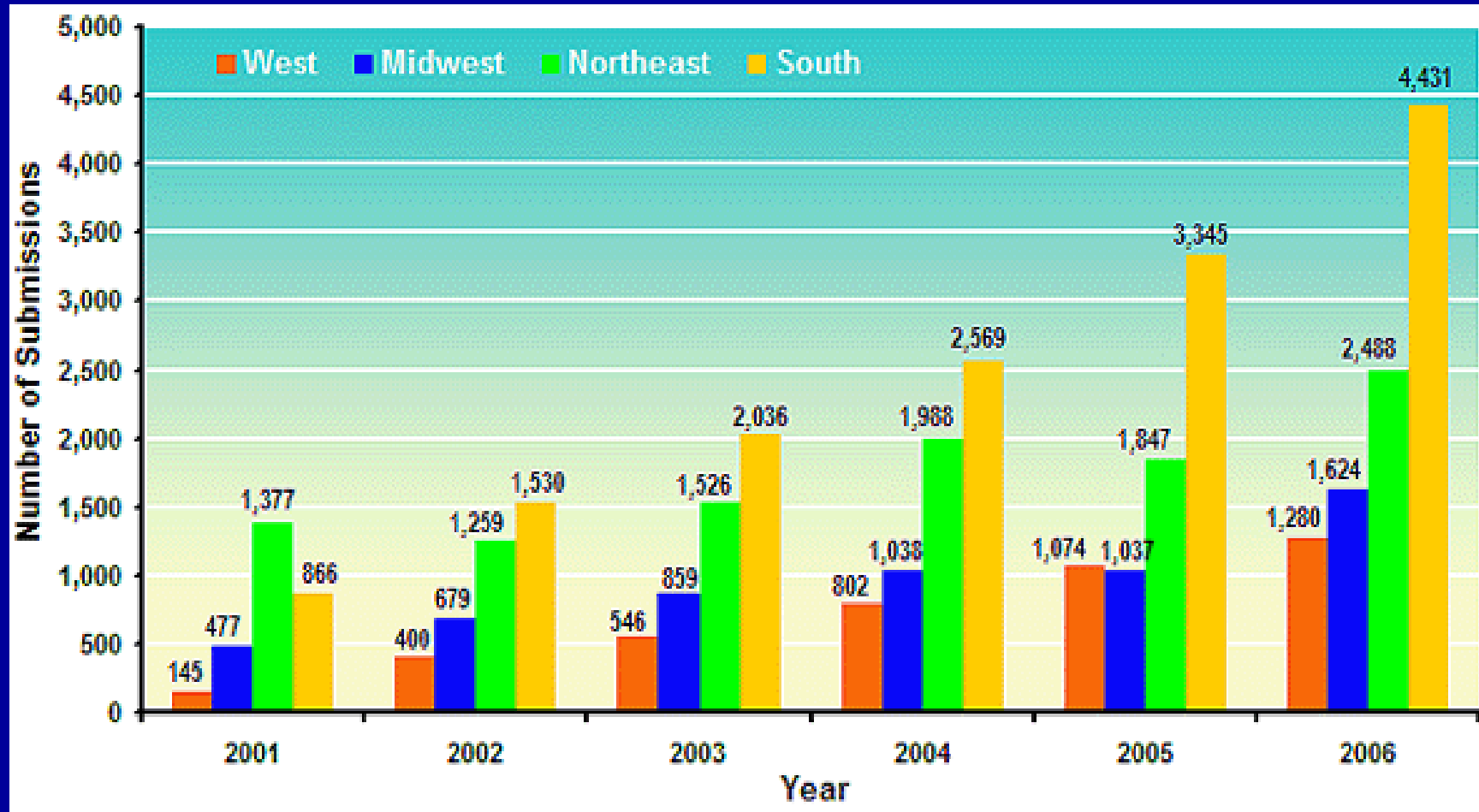
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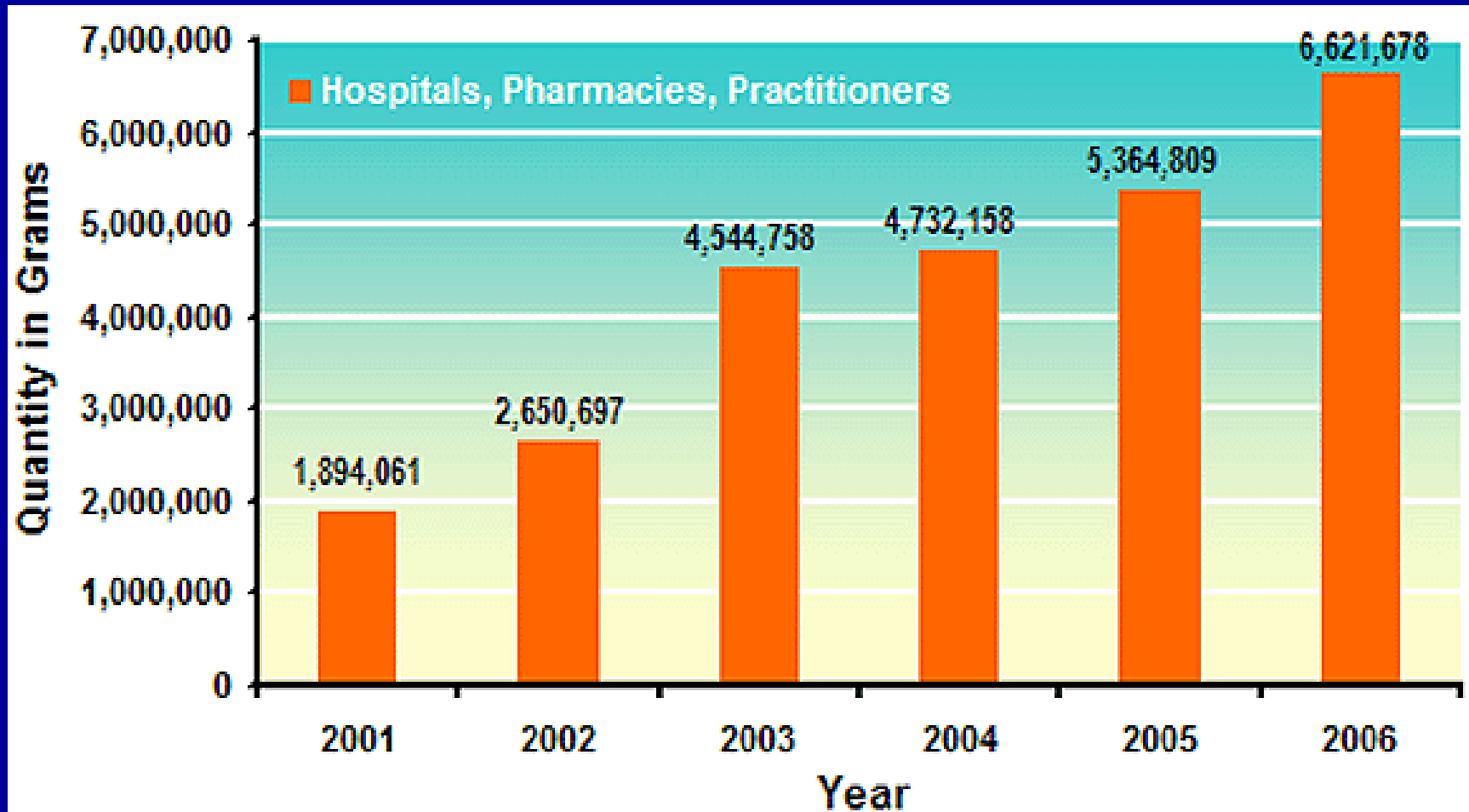
Methadone and other Opioid Deaths



Forensic Methadone Lab Requests

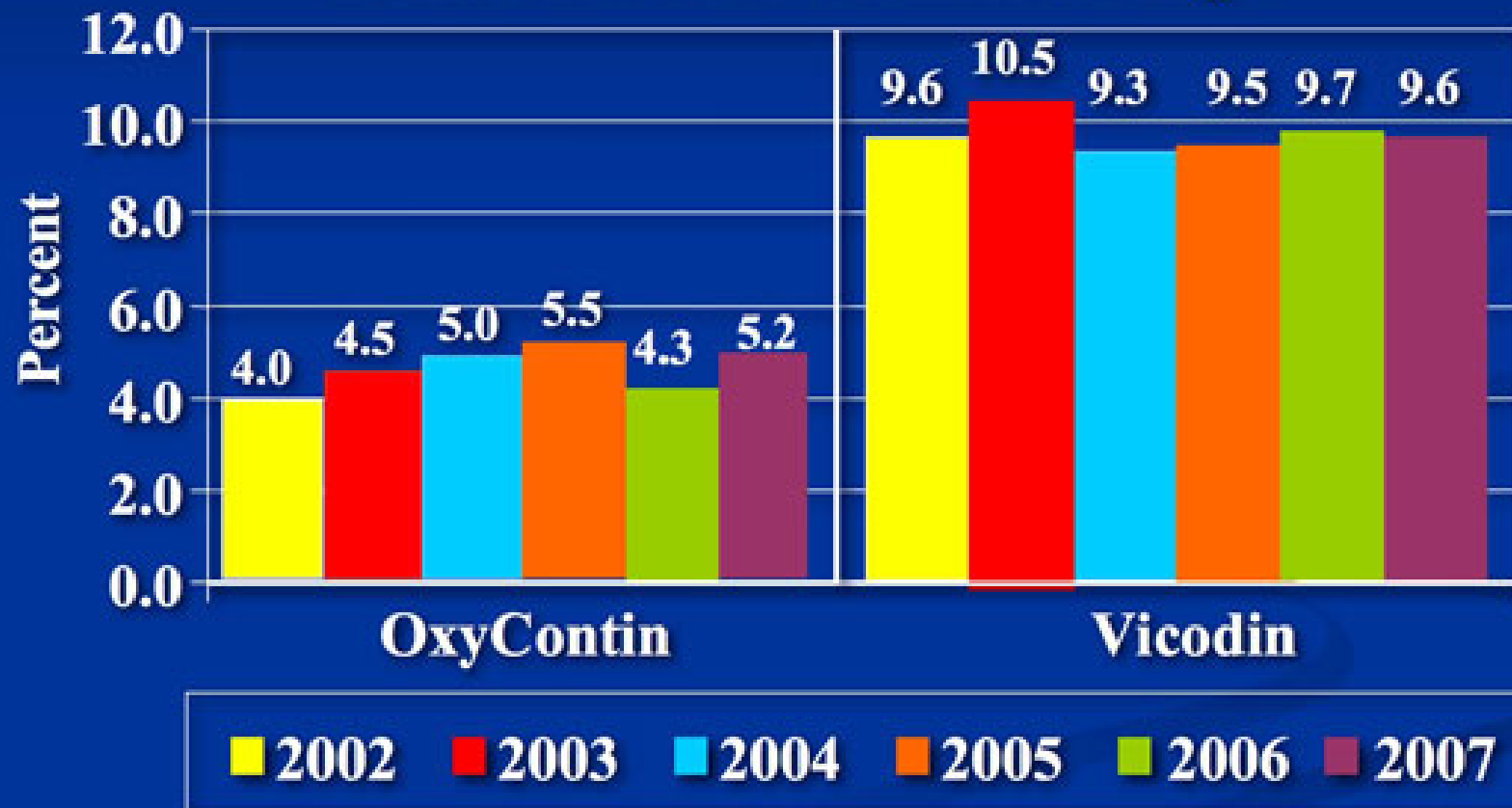


Legitimate Use of Methadone



Issues of Concern

Percent of 12th Graders Reporting Nonmedical Use of OxyContin and Vicodin in the Past Year Remained High

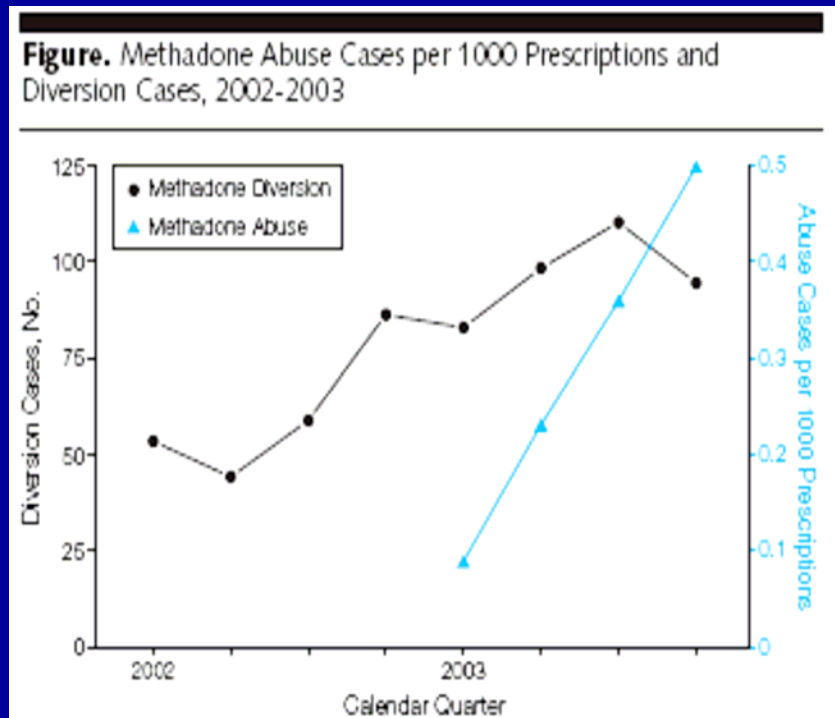


No year-to-year differences are statistically significant.

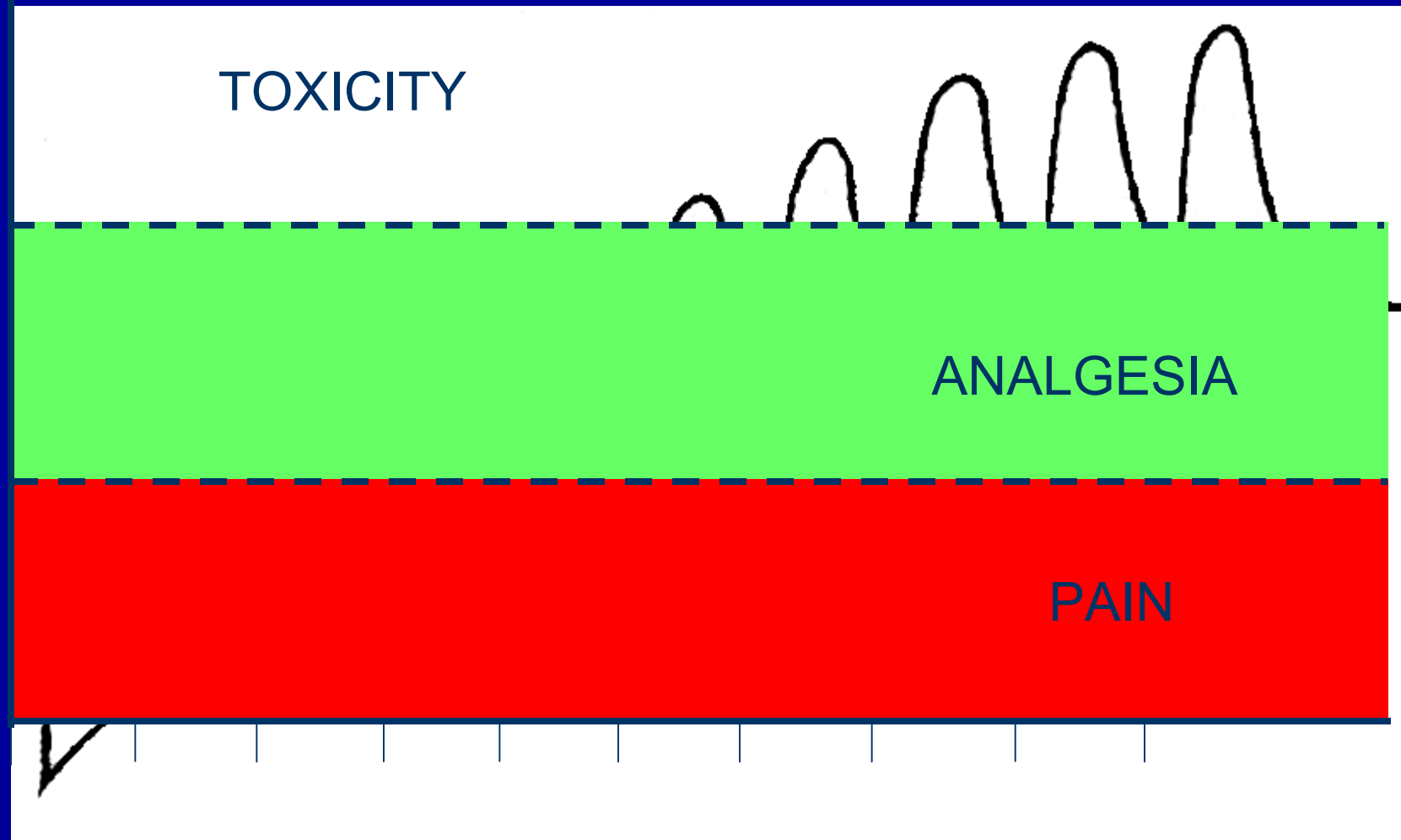
FDA Methadone Warning

FDA ALERT [11/2006]: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias

FDA has reviewed reports of death and life-threatening side effects such as slowed or stopped breathing, and dangerous changes in heart beat in patients receiving methadone. These serious side effects may occur because methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements. Methadone has specific toxic effects on the heart (QT prolongation and Torsades de Pointes). Physicians prescribing methadone should be familiar with methadone's toxicities and unique pharmacologic properties. Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect even in patients who are opioid-tolerant. Physicians should closely monitor patients when converting them from other opioids and changing the methadone dose, and thoroughly instruct patients how to take methadone. Healthcare professionals should tell patients to take no more methadone than has been prescribed without first talking to their physician.



Fixed methadone dose interval



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- Reaction time unchanged
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- Perceptual motor function, driving simulators – no significant change
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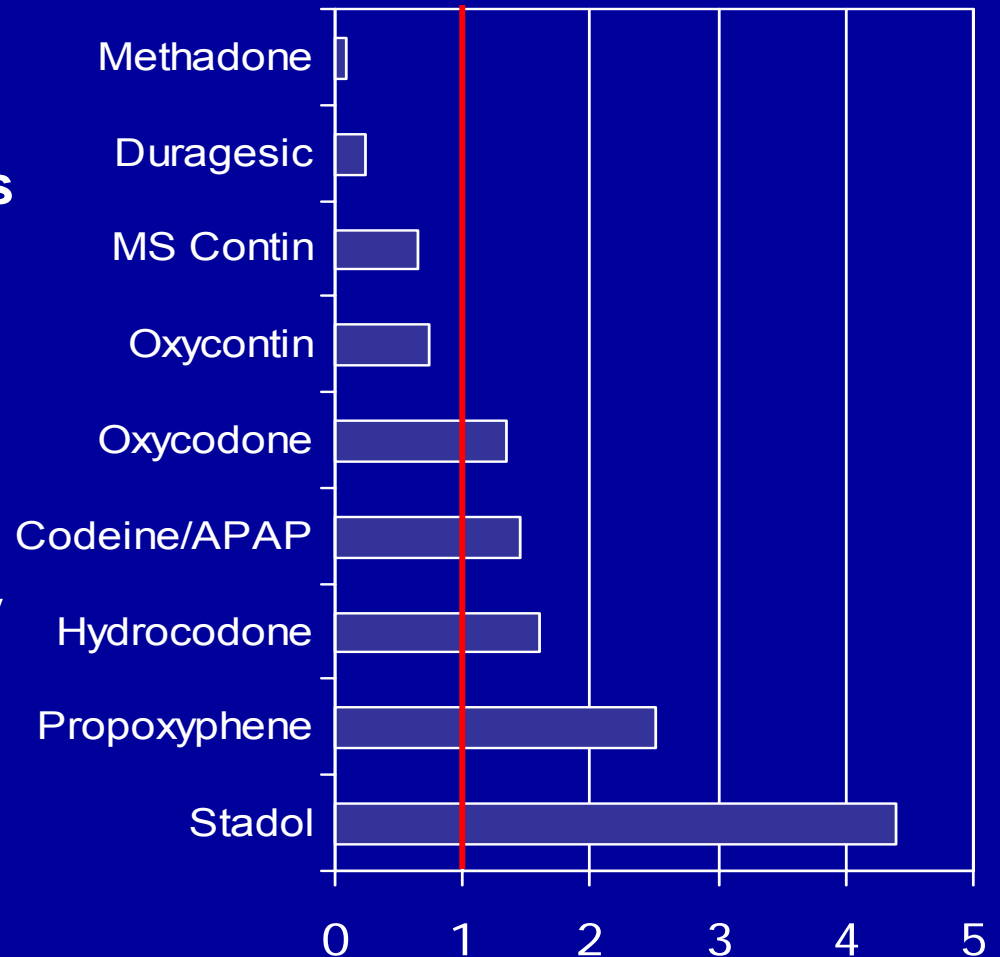
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QTc prolongation

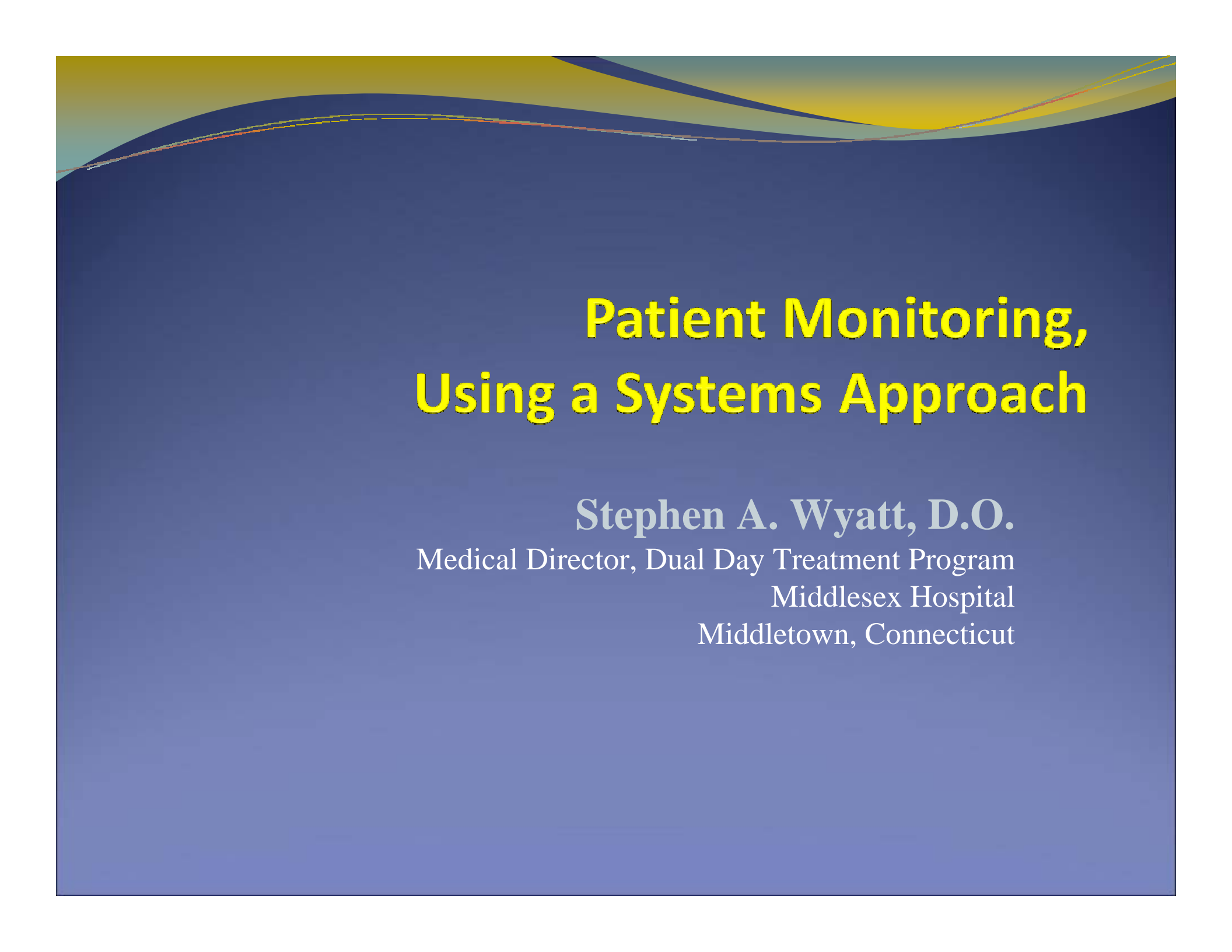
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5. Simple questionnaires can facilitate patient monitoring while improving physician efficiency

Selecting a specific opioid

- Long T_{1/2} / slow-release products are generally interchangeable (except methadone)



Patient Monitoring, Using a Systems Approach

Stephen A. Wyatt, D.O.

Medical Director, Dual Day Treatment Program
Middlesex Hospital
Middletown, Connecticut

Monitoring:

Regularly assess the 4 A's:

- Analgesia
- Activity / function
- Adverse effects
- Aberrant behaviors

**Pain Patient on
Chronic Opioids**

+

New Physician

Are chronic opioids appropriate?

YES!

Re-document:

Diagnosis
Work-up
Treatment goal
Functional status

Monitor Progress:

Pill counts
Function
Refill flow chart
Occasional urine
toxicology
Adjust medications
Watch for scams

UNSURE

Physical Dependence vs Addiction:

Chemical dependence
screening

Toxicology tests

Pill counts

Monitor for scams

Reassess for
appropriateness

YES!

Discontinue opioids
Instruct patient on
withdrawal symptoms
OBOT Buprenorphine
Tell patient to go to ER
if symptoms emerge

NO

Educate patient
on need to
discontinue opioids

Emergency?

ie: overdoses
selling meds
altering Rx

NO!

3-month self taper
(document in chart)

OK

10-week structured taper

OK

Discontinue opioids at
end of structured taper

Why monitor in clinical practice?

- To determine whether your intervention / treatment plan is producing improvement.
- To adjust the treatment plan for:
 - Patient variability
 - Increased / maximized efficacy
- To identify side effects / toxicity
- To stop or substantially change the treatment if it is producing harm

Prescribing Practices Warranting Board Scrutiny

- Issuing prescriptions for large amounts of controlled substances and/or in excess of prescribed dosage
- Failing to keep accurate records
- Failing to evaluate/monitor patients
- Prescribing to drug-dependent persons without adequate consultation/evaluation and monitoring

Areas and elements of patient care that require documentation

- History and physical evaluation
- The diagnosis and the clinical indication for prescribing opioids (*Appx. A*)
- The patient's informed consent and agreement for treatment (*Appx. D*)
- Monitoring / periodic review (*Appx. G*)
- Consultation and referrals

From Table 4 in Nicholson B, Passki SD, *Management of Chronic Noncancer Pain in the Primary Care Setting* South Med J. 2007
<http://www.medscape.com/viewarticle/565076>

Patient monitoring, using a systems approach

Use a flow chart to monitor patient progress (*Appx. G*):

- Assessment of function / pain assessment
- Medication(s) / Dose / Refills
- Toxicology test results (quarterly/random)
- Corroboration phone calls re: function / (quarterly)
- Info from your state's Pharmacy Board web-site query (twice yearly), NASPER
- Referral / Study / Test follow through
- Etc.

Monitor when initiating opioid treatment for CNMP

- Identify a clear diagnosis.
- Document an adequate work-up.
- Ensure that non-opioid therapy failed or is not appropriate (tx. rationale).
- Identify anticipated outcome (tx. goal).
- Use an Informed Consent Form (*Appx. D*)
- ? Consult a physician with expertise in the part of the body / organ system involved

Monitor for side effects

Short-term

- CNS: euphoria, anxiety, miosis, sedation
- Respiratory: respiratory depression & overdose
- CV: hypotension, edema
- GI: anorexia, vomiting

Long-term

- Sleep disturbance including OSA
- Decreased testosterone, libido
- QTc prolongation
- Constipation
- Urinary retention
- Sweating
- Depression and other psychiatric co-morbidities

Monitor for use of other drugs

Make access to opioids contingent on abstinence from illicit drugs / alcohol:

- Non-negotiable requirement for most
- Avoid arguments re “medical marijuana”

If the patient is *unwilling or unable* to relinquish use of non-prescribed drugs:

- the pain problem most likely does not warrant chronic opioid therapy

If the patient is *unable* to relinquish use of non-prescribed drugs:

-- addiction treatment is indicated and pain treatment is jeopardized

Use of urine toxicology in monitoring

Urine should contain the prescribed drug/s:

- If not, the patient may be diverting or providing a fake sample to cover other substances, make sure you know what your UDS is capable of detecting

Urine should be free of non-prescribed substances:

- If the patient is unable to relinquish alcohol / recreational drugs in order to receive treatment, either treatment is not very important or the other drugs are overly important, and addiction assessment/RX is needed. (*Heit & Gourlay, Appx. B*)

Urine toxicology in monitoring (cont.)

Test for what you're seeking:

- Immunoassays typically miss synthetics, semi-synthetics – SO ASK FOR THEM!
- GC/MS detects these but \$\$\$
- May need to specify compounds sought (e.g. methadone)

Use “therapeutic drug monitoring” codes:

- e.g., treat the test clinically like a Digoxin or aminophylline level.

Urine toxicology in monitoring (cont.)

Testing should be random

Testing should be routine AND “for cause”:

- Open to biases (e.g., disproportionate testing of minorities),
- Misses 50% of those using unprescribed or illicit drugs.
 - Katz NP. American Academy of Pain Medicine 2001

Excellent review of UDT available in online monograph:

- Gourlay D et al. 2002. (http://www.alaskaafp.org/urine_test.htm, accessed April 8, 2006)

Monitor for outcomes

- Analgesia – pain level – 0 -10 but subjective
- Affect – Beck Depression Inventory, Zung, Ham-D
- Activity level – Pain Disability Index, Oswestry
- Adverse effects – cognition, alertness, depression
- Aberrant behaviors – multisourcing, lost drugs

If not effective,



Summary: Monitoring strategy when prescribing chronic opioids

- Document functional improvement.
- Titrate opioids to improved function.
- Monitor medications (pill counts).
- Avoid non-planned escalation / early fills.
- Monitor for scams (informed consent form)
- Use toxicology tests (Q3-6months).
- Document, document, document!

Identifying and Addressing Aberrant Medication Use Behaviors

John Tanner, D.O.

Medical Director
Beaches Family Medicine
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Terminology

- Appropriate use
- Inappropriate use or misuse
- Physical dependence
- Abuse
- Drug-seeking behavior
- Aberrant medication use behavior

Appropriate use

- Use of medication as prescribed.
- Use only for the condition indicated.
- Use only for the duration needed.

Most meds are **not** abused: Estimates of addiction within setting of chronic pain management: 3 to 19% (higher in training settings).

Weaver M and Schnoll S, J Addiction Medicine, 2007

Inappropriate use or misuse

- **Use of a medication for a reason other than that for which it was prescribed or in doses or frequencies other than prescribed.**
- **Misuse is unintentional secondary to:**
 - Ignorance
 - Confusion
 - Cognitive impairment
 - Visual impairment
- **Misuse is related to poor judgment in an attempt to gain relief: “pseudo-addiction”**

Inappropriate use or misuse:

“Chemical coping”

- **Using medication prescribed for one indication to treat other emotional or situational conditions or issues.**
- **Coping with:**
 - Insomnia
 - Mood: depression/lability/anger/anxiety
 - Situational stressors
 - Lack of energy/motivation

Weaver W and Schnoll S, J Addict Med, 2007

Physical dependence

- Withdrawal syndrome when the drug is withdrawn acutely.
- May or may not be associated with increasing doses and increasing tolerance to the drug.
- May or may not be associated with abuse of the drug.

Abuse

- Use of a medication outside the normally accepted standard for that drug.
- Recurrent problems in multiple life areas.
- Continued use in spite of negative consequences.
- Preoccupation with the drug, drug seeking behavior, loss of control of use.
- Tolerance or physical dependence may or may not be present.

Adapted from DSM IV, APA, 1994

Aberrant behaviors that are less indicative of abuse

- Aggressive complaining about dose
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Acquisition of similar drugs from other medical sources
- Unsanctioned dose escalation 1-2 times
- Unapproved use of the drug to treat other symptoms
- Reporting psychic effects not intended by the clinician

Passik and Weinreb. 2002

Aberrant behaviors that are *more indicative of abuse*

- Selling prescription drugs
- Forgery of prescriptions
- Stealing another person's meds
- Injecting / snorting oral preparations/ tampering with sustained-release preparations
- Obtaining from non-medical sources
- Concurrent abuse of related illicit drugs
- Multiple unsanctioned dose escalations
- Recurring prescription losses

Drug-seeking behavior

- Pattern of calling for refills after hours.
- Prescriptions from multiple providers.
- Frequent visits to the Emergency Room
- Strong preference for specific drug
("allergic to everything but...")
- Repeatedly needing early refills.

What the clinician hears:

Excuses:

- “I lost the prescription. I left it on the plane”
- “It was stolen out of my car/purse/bedroom.”
- “The dog ate the prescription.”
- “I spilled the bottle in the toilet.”

Fears / complaints:

- “That dose doesn’t work anymore. I used a few of my mom’s”
- “I can’t sleep without it. I need it for my nerves”
- “I can’t get through the day without it.”

Limits of the term “drug-seeking”

- Non-specific and potentially stigmatizing
- Important as a “red flag” requiring further assessment
- Assess for:
 - Pseudo-addiction: inadequate management
 - Tolerance / hyperanalgesia
 - Chemical coping
 - Characterologic or emotional issues
 - Abuse / dependence
 - Diversion / illegal activity

Aberrant medication use

Be prepared to intervene for:

- Inappropriate use or misuse
- Pseudoaddiction
- Chemical coping
- Physical dependence
- Abuse or addiction
 - If the patient responds to intervention
 - If the patient is unwilling / unable to comply
- Diversion

Intervening for unintentional misuse

- Clarify/restate the therapeutic instructions.
- Explore the patient's concerns or difficulties.
- Identify and problem-solve complicating factors (simplify regimen, avoid look alike drugs, use "brown bag").
- Explain any medication changes.
- Involve family members / caregivers.

Intervening for pseudo-addiction

- **Reassess medication management:**
 - adjustment of controlled drug therapy
 - adjunctive, lower risk medication
 - non-medication modalities
- **Referral/consultation:**
 - pain management
 - psych management
 - behavioral therapy
- **Restate or reframe therapeutic agreement and
continue to monitor**

Intervening for chemical coping

- **Explore alternative strategies (medication and/or behavioral) for symptoms being self-medicated (sleep, “stress”, energy)**
- **Refer for psychological evaluation: psychiatric or psychotherapeutic**
- **Refer for substance abuse evaluation**

Intervening for chemical coping (cont.)

- **Refer for behavioral intervention: make part of the therapeutic agreement:**

Cognitive Behavioral Therapy (CBT)
Dialectical Behavioral Therapy (DBT)
Trauma Processing Therapy

Intervening when abuse is suspected

- Express your behavior-specific concerns
- Ask further questions about drug use (how much, how often, increasing doses, need to supplement, symptoms of withdrawal)
- Ask about other drug or alcohol abuse
- Use urine drug screening and/or pill counts
- Include family members if available
- Look for a pattern: “rough guide”

Intervening when abuse is confirmed

Express your specific concerns in terms of the patient's well-being:

“I know that you have a problem with pain...but I believe you also have a problem with how you are using your medication. These are the things I've noticed that worry me....”

“Do you agree that this is a problem for you?”

Weigh the risks of continuing therapy with opioids or other controlled drugs.

Intervening when abuse is confirmed (cont.)

Restructure the treatment agreement:

- Closer monitoring
- More tightly managed prescriptions
- Urine drug screening
- Pill counts

Require a referral for addiction evaluation and treatment

Consider the need for inpatient treatment

If the patient is opioid-dependent, consider a referral for substitution or agonist treatment

Intervening when abuse is confirmed (cont.)

Restructure the treatment agreement:

- Closer monitoring
- More tightly managed prescriptions
- Urine drug screening
- Pill counts

Require a referral for addiction evaluation and treatment

Consider the need for inpatient treatment

If the patient is opioid-dependent, consider a referral for substitution or agonist treatment

Intervening when abuse is confirmed (cont.)

“I will continue to work with you to help with your pain,
but we have to get you help for your drug abuse
problem as well.”

“Will you follow through with seeing this consultant?”

Intervening when abuse is confirmed (cont.)

“If you do not follow through with this referral and the consultant’s recommendations, it will no longer be safe for me to prescribe this controlled medication.

In the meantime, we will have to manage your use of this medicine much more closely. ”

Intervening when the patient is unwilling or unable to comply

- Express your concern in terms of patient's well-being
- State that the particular medication is no longer safe or indicated and you will not continue to prescribe it (arrange taper or referral)
- Explore other therapeutic options
- Assess for withdrawal risk
- Refer for specialized addiction treatment

When and How to Stop Prescribing Opioids and Manage the Patient with a Different Approach

Anthony Dekker, D.O.

Clinical Consultant for Addiction Medicine

Indian Health Service

Phoenix Indian Medical Center

**Pain Patient on
Chronic Opioids**

+

New Physician

Are chronic opioids appropriate?

YES!

Re-document:

Diagnosis
Work-up
Treatment goal
Functional status

Monitor Progress:

Pill counts
Function
Refill flow chart
Occasional urine
toxicology
Adjust medications
Watch for scams

UNSURE

Physical Dependence vs Addiction:

Chemical dependence
screening

Toxicology tests

Pill counts

Monitor for scams

Reassess for
appropriateness

YES!

Discontinue opioids
Instruct patient on
withdrawal symptoms
Tell patient to go to ER
if symptoms emerge

NO

Educate patient
on need to
discontinue opioids

Emergency?

ie: overdoses
selling meds
altering Rx

NO!

3-month self taper
(document in chart)

OK

10-week structured taper

OK

Discontinue opioids at
end of structured taper

Non-emergency contraindications to continued opioid prescribing

1. Note in chart the reason for discontinuing opioids, non-emergency situation, outline of taper, end date for prescribing.
2. Have patient read and initial the note.
3. Prescribe 10% fewer opioid analgesics each week (*Appx. J*)
4. Reassess on week #8:
 - If going well, continue.
 - If not going well, plan detoxification
5. ***At Week 10:*** Stop prescribing and educate patient about withdrawal symptoms. Urge the patient to go to the ER if withdrawal appears and admit for detoxification.

Emergency contraindications to continued opioid prescribing

- 1. Altering a prescription = *Felony***
- 2. Selling prescription drugs = *Drug dealing***
- 3. Accidental/intentional overdose = *Death***
- 4. Threatening staff = *Extortion***
- 5. Too many scams = *Out of control***

Emergency contraindications to continued opioid prescribing

What is a physician to do?

- Identify the contraindicated behavior.
- State that prescribing is inappropriate.
- Educate the patient about withdrawal symptoms.
- Instruct the patient about what to do if in withdrawal.
- Offer care without a prescription, and/or a referral.

Possible Interventions

- **Weaning or tapering (avoid the term “detoxifying”)**
- **Referral for substance abuse treatment while tapering**
- **Substitution or agonist therapy with methadone or buprenorphine**

Legalities

- Only specifically licensed programs / physicians can treat addiction
- Any physician licensed to prescribe controlled substances is licensed to taper them when they are no longer needed or effective
 - Heit HA, Covington EC, Good PM, Pain Medicine 2004;5(3):303
- ***Note: PDR recommendations support this stance.***

Three phases of weaning

- **Establish a baseline**
 - Opioids
 - Sedatives
- **Dose reduction**
 - There are numerous ways to do it
 - None is demonstrably superior
 - Excellent summary: Fishbain DA et al., *Annals of Clinical Psychiatry*, 5:53-65, 1993)
 - Sedatives
- **Treatment of protracted / post-acute withdrawal**

Opioid withdrawal

Hours after use	Grade	Symptoms / Signs
4-6	0	Anxiety, Drug Craving
	1	Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia
	2	Dilated pupils, Gooseflesh, Muscle twitching & shaking, Muscle & Joint aches, Loss of appetite
6	3	Nausea, extreme restlessness, elevated blood pressure, Heart rate > 100, Fever
8-12	4	Vomiting / dehydration, Diarrhea, Abdominal cramps, Curled-up body position
12-72		

Symptoms of opioid withdrawal

- Dilated pupils, rhinorrhea (runny nose)
- Tachycardia, hypertension
- Nausea, vomiting, diarrhea, abdominal cramps
- Goose bumps, sweats, muscle/bone/joint aches.
- Insomnia, anxiety, headache

Medications for opioid withdrawal

- **Alpha-2 agonist: Clonidine**
 - 0.1 mg prn if systolic BP \geq 120
 - Consider transdermal
- **Sedation / tranquilization**
 - Trazodone
 - Doxepin
 - AEDs given for pain also reduce the anxiety component
 - Others
- **Loperamide (Imodium)**
- **Anti-emetics**

Opioid options

- All pure mu agonists are effective
- All are legal (under Federal law)
 - Including methadone and buprenorphine
- Kinetics and costs are probably the main issues
 - Longer $T_{1/2}$ – fewer troughs and peaks
- 24-hour morphine is a personal favorite
 - No need to carry / dose opioids through the day
 - No accumulation
 - 2 - 3 hours after dose it is apparent whether too much / too little

Adjuvant drugs for opioid withdrawal

- Alpha-2 agonists
 - Clonidine
 - 0.1 mg prn if systolic BP \geq 120
 - Transdermal difficult to titrate
 - Tizanidine
 - Pinelli A et al., Drug Alcohol Depend 1998
 - Lofexidine (UK)
 - Guanfacine (Tenex)
 - Cochrane Database of Systematic Reviews. 3, 2003

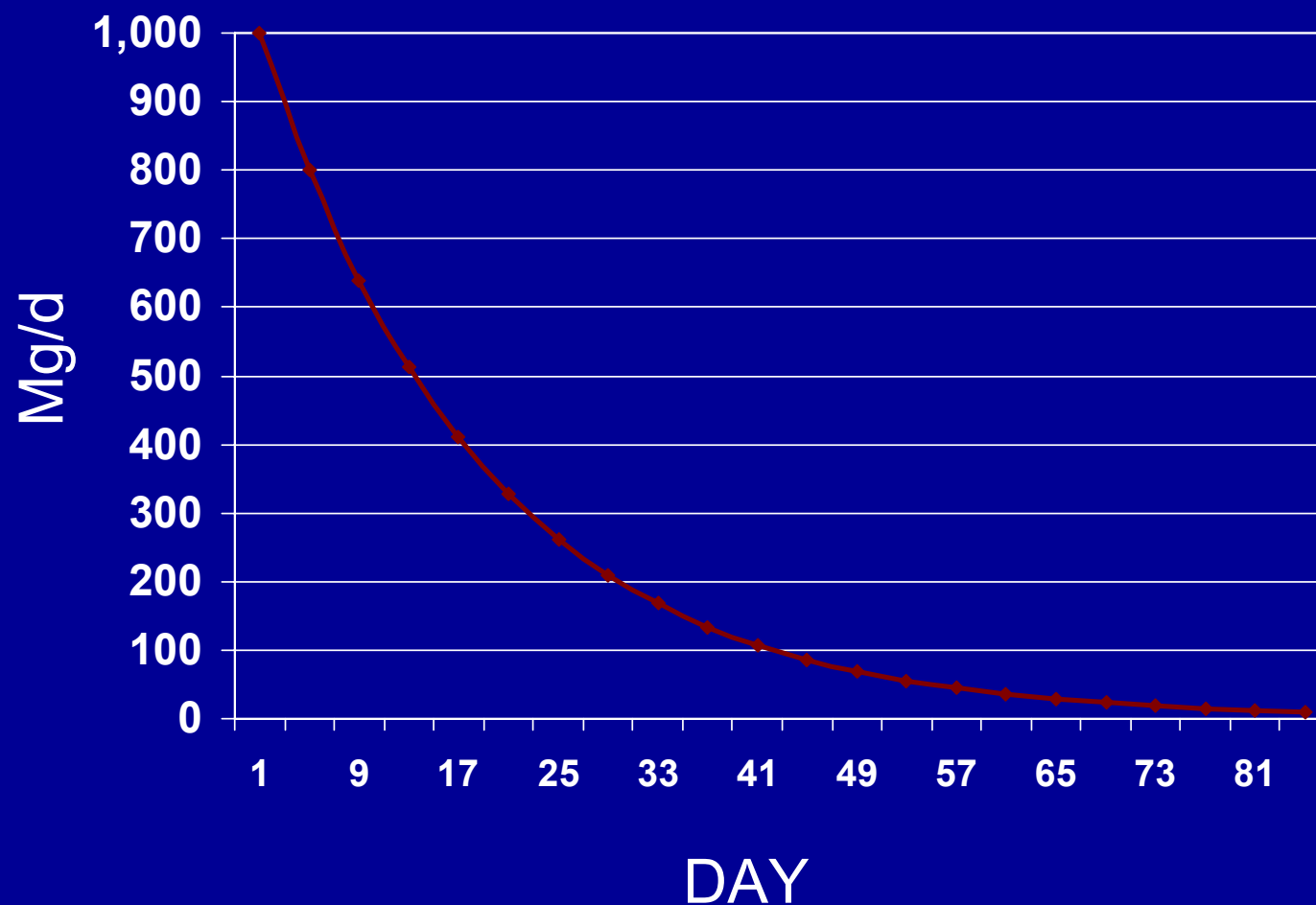
Adjuvant drugs for opioid withdrawal (cont.)

- **Sedation / tranquilization**
 - Trazodone
 - Doxepin
 - AEDs given for pain also reduce the anxiety component of w/d
 - Others
- **Loperamide (Imodium)**
- **Anti-emetics**

Adjunctive treatment with doxepin

- Doxepin facilitates methadone opioid withdrawal
 - Uncontrolled report
 - Dufficy RG. Milit Med 138:748, 1973
- Doxepin as an adjunct to treatment of heroin addicts in a methadone program was performed over a 14-month period
 - Uncontrolled trial
 - 10% of the program's population utilized a mean of 73 mg of doxepin, usually briefly
 - Beneficial results in 93%
 - Spensley J. Int J Addict. 1976;11(1):191-7.

Rapid opioid taper: 20% every 4 days



Substitution or agonist therapy: Opioid addiction or dependence

**Appropriate for illicit or prescription opioid abuse with
associated physical dependence**

Rationale for agonist therapy:

- Cross-tolerance
- Prevents withdrawal
- Relieves craving
- Blocks euphoric effects of other opioids

Available alternatives:

- Methadone
- Buprenorphine (Subutex)
- Buprenorphine/naloxone (Suboxone)

Finding a resource for referral

- *On the web:* The electronic, searchable version of SAMHSA's updated ***National Directory of Drug and Alcohol Abuse Treatment Programs*** is available on the Web at <http://FindTreatment.samhsa.gov/>
- *In the community:* Contact your state chapter of ASAM (e.g., the Florida Society of Addiction Medicine) about the methadone PCSS. See www.asam.org for contact information.

OPIOIDS FOR CHRONIC PAIN: SUMMARY

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Addiction
Abuse/Dependence

Prescription Drug Misuse

Aberrant Medication Use Behaviors:
A spectrum of patient behaviors
that *may* reflect misuse

Total Chronic Pain Population

Adapted from Passik. APS Resident Course, 2007

Opioid treatment of chronic pain

Initial Patient Assessment



Trial of Opioid Therapy
Setting Goals



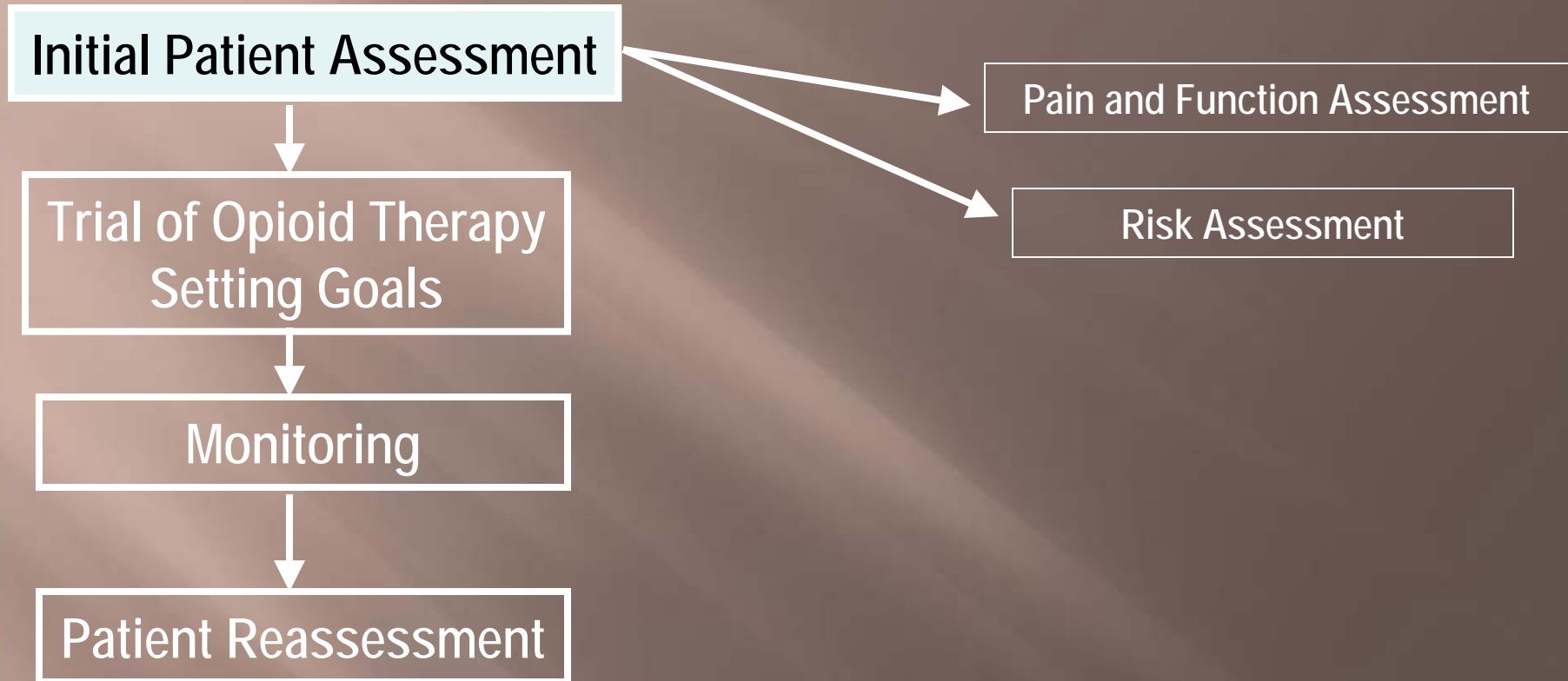
Monitoring



Patient Reassessment

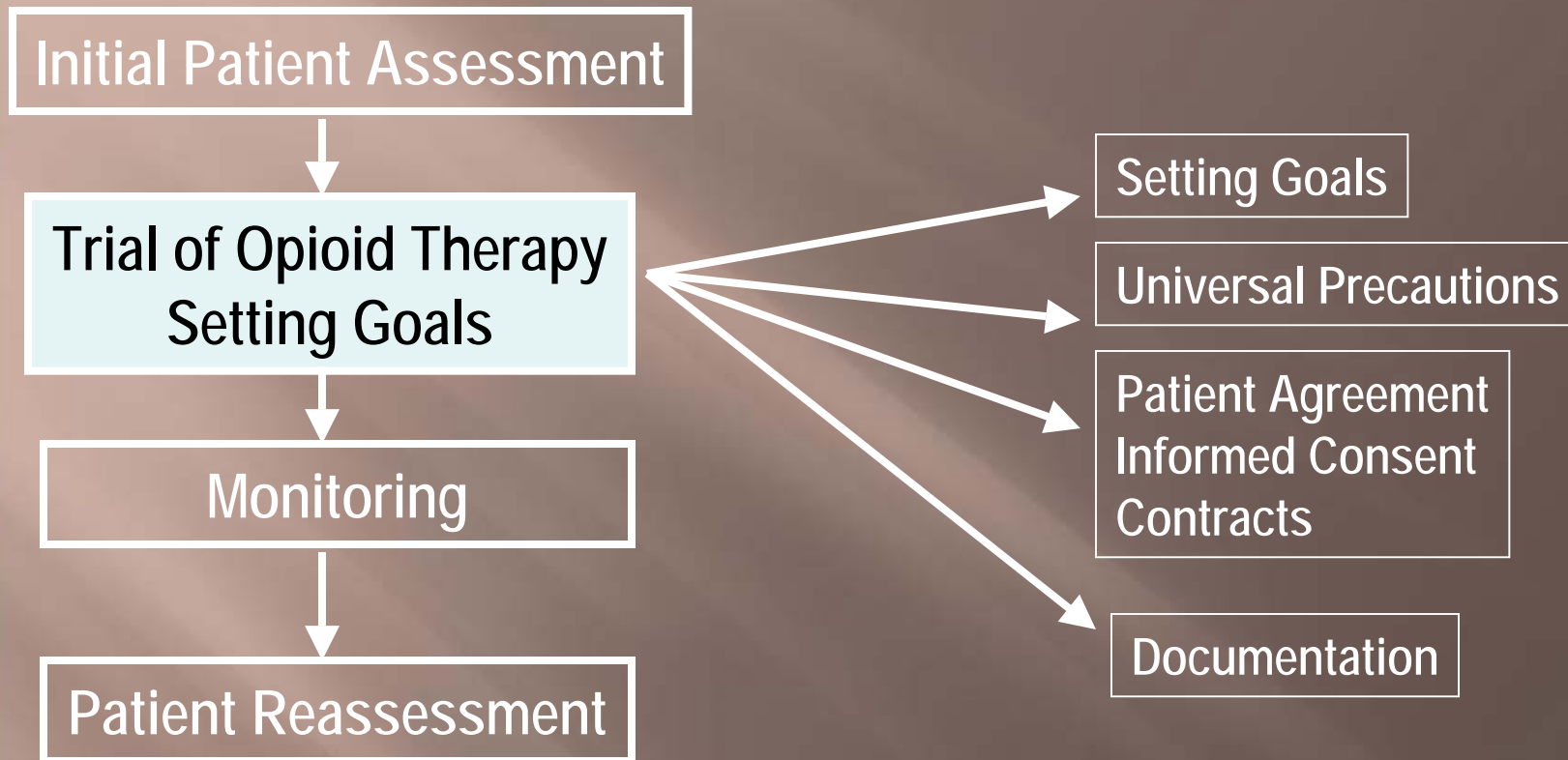
Adapted from Katz NP. Patient Level Opioid Risk Management. PainEDU.org Manual. 2007

Opioid treatment of chronic pain (cont.)



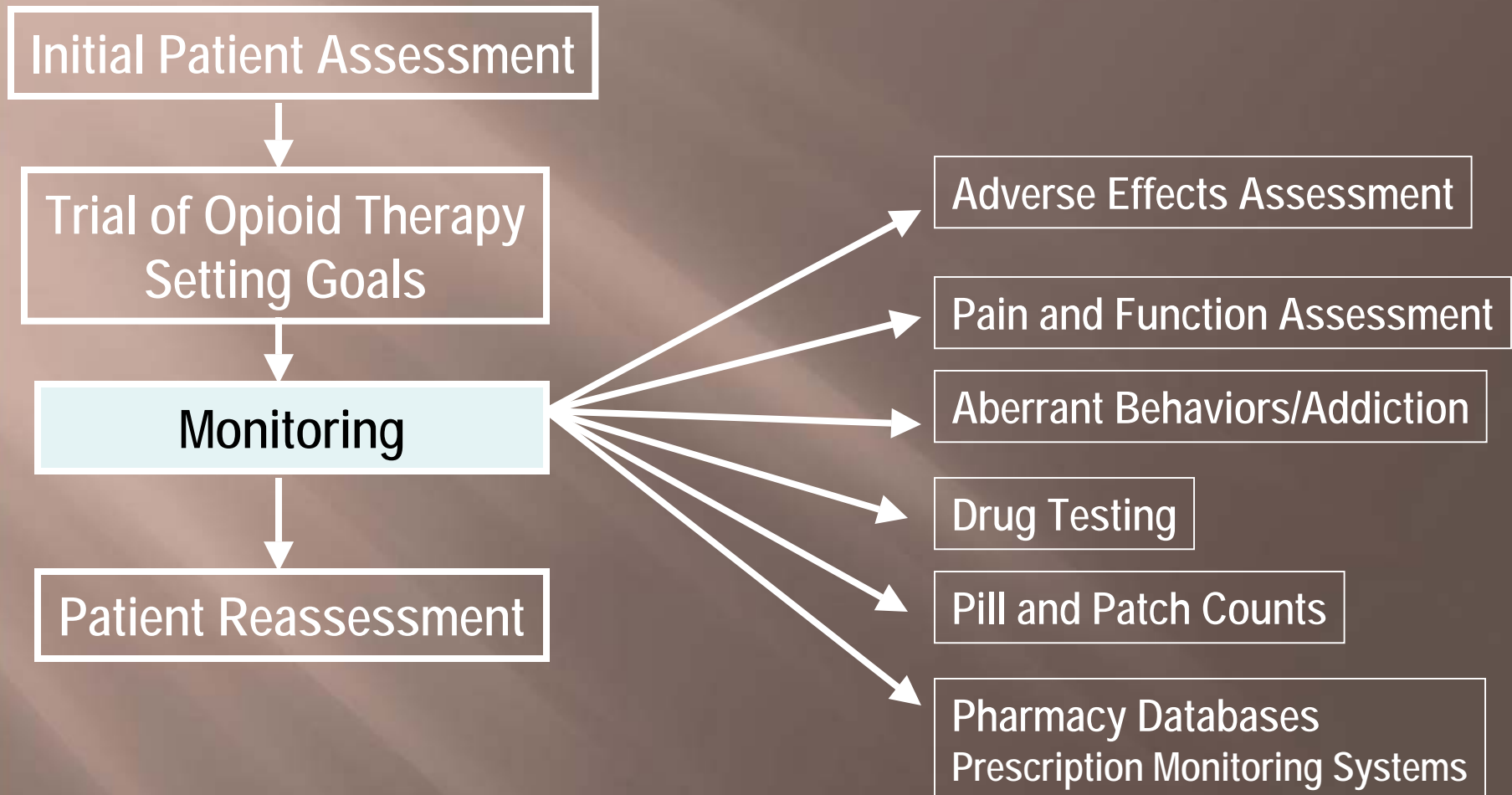
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Opioid treatment of chronic pain (cont.)



Adapted from Katz NP. Patient Level Opioid Risk Management. PainEDU.org Manual. 2007

Opioid treatment of chronic pain (cont.)



Adapted from Katz NP. Patient Level Opioid Risk Management. PainEDU.org Manual. 2007

Aberrant medication use behavior less likely to be indicative of addiction

Yellow Flags

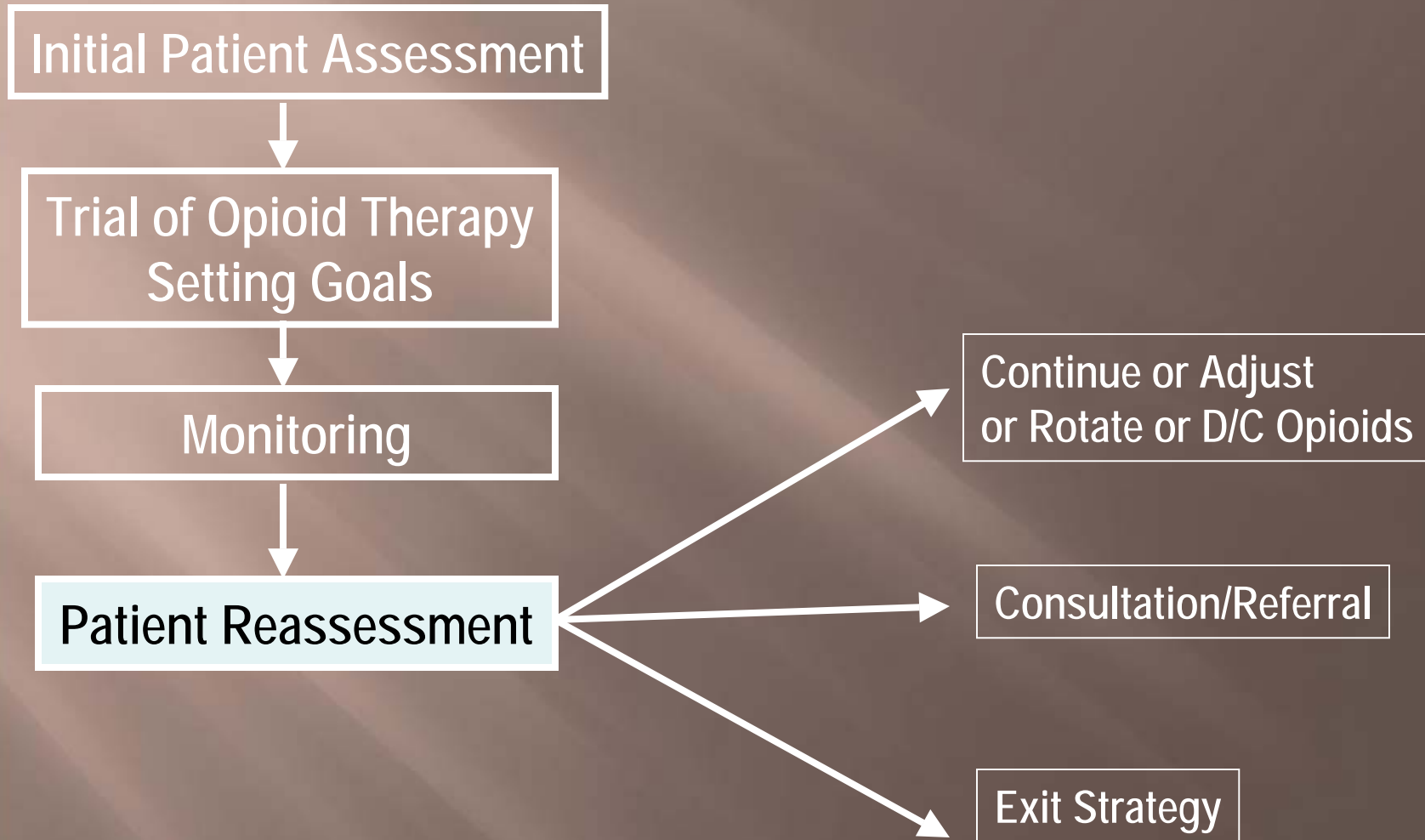
- ▣ Complaints about need for more medication
- ▣ Drug hoarding
- ▣ Requesting specific pain medications
- ▣ Openly acquiring similar medications from other providers
- ▣ Occasional unsanctioned dose escalation
- ▣ Nonadherence to other recommendations for pain therapy

Aberrant medication use behavior more likely to be indicative of addiction

Red
Flags

- ▣ Deterioration in functioning at work or socially
- ▣ Illegal activities-selling, forging, buying from nonmedical sources
- ▣ Injection or snorting medication
- ▣ Multiple episodes of “lost” or “stolen” scripts
- ▣ Resistance to change therapy despite adverse effects
- ▣ Refusal to comply with random drug screens
- ▣ Concurrent abuse of alcohol or illicit drugs
- ▣ Use of multiple physicians and pharmacies

Opioid treatment of chronic pain (cont.)



Adapted from Katz NP. Patient Level Opioid Risk Management. PainEDU.org Manual. 2007

Key steps:

- ▣ Assess for pain, function, risk
- ▣ Set realistic goals
- ▣ Use agreements and informed consents
- ▣ Monitor, monitor, monitor...
- ▣ Not all aberrant medication taking is addiction
- ▣ Patients with addiction lose control
- ▣ Reassess, reassess, reassess..
- ▣ Make needed adjustments
- ▣ Document, document, document...

Case Discussion,
Part 1:
Deciding Whether
to Prescribe

Learning objectives:

1. Identify indications and contraindications to the use of opioids to treat chronic pain.
2. Learn useful techniques for initiating the prescribing of opioids to treat chronic pain.
3. Develop monitoring strategies for use with patients to whom opioids have been prescribed for chronic pain.
4. List the reasons to stop prescribing opioids for chronic pain.

Mr. Smith, part 1

ID: The patient is a 41-year-old married man, father of three, working as an electrician.

He presents from your recently retired senior colleague's patient panel, with a CC of "need my back pain prescriptions refilled, and they are not working as well any more."

Mr. Smith, part 1 (cont.)

HPI: Low back pain off and on for >12 years, chronic in nature for past 6 years, vague radiation from the R L/S region to the right upper thigh, worsened by lifting and bending, interfering in the past with ability to work.

Mr. Smith, part 1 (cont.)

HPI: Normal neurological exam, L/S MRI from 3 years PTA with mild degenerative changes.

Ortho evaluation at the time indicated no intervention indicated.

Tried physical therapy on 2 occasions without improvement.

Mr. Smith, part 1 (cont.)

Medications include Naprosyn 1500 mg/d, acetaminophen 2000 mg/d, and Vicodin HP 1-2 tabs tid prn #60/month.

Mr. Smith, part 1 (cont.)

Clinical Decision Point #1: Would you continue the Vicodin at the first office visit?

If no – why not?

If yes – why?

(“I don’t know” is not an option!)

Mr. Smith, part 1 (cont.)

Is this patient a good candidate for long-term treatment with opioids?

If yes, why?

If no, why not?

If “I don't know,” then what further information would you need before deciding?

**Case Discussion,
Part 2:
Patient Monitoring
and Responding to
“Yellow Flags”**

Mr. Smith, part 2

ID: The patient is a 41-year-old married man, father of three, working as an electrician.

He presents from your recently retired senior colleague's patient panel, with a CC of "need my back pain prescriptions refilled, and they are not working as well any more."

Mr. Smith, part 2 (cont.)

HPI: Low back pain off and on for >12 years, chronic in nature for past 6 years, vague radiation from the R L/S region to the right upper thigh, worsened by lifting and bending, interfering in the past with ability to work.

Mr. Smith, part 2 (cont.)

HPI: Normal neurological exam, L/S MRI from 3 years PTA with mild degenerative changes.

Ortho evaluation at the time indicated no intervention indicated.

Tried physical therapy on 2 occasions without improvement.

Mr. Smith, part 2 (cont.)

- **More Data:** You receive a Functional Impairment Assessment indicating severe limitations regarding work performance, and a letter from Mr. Smith's employer requesting any assistance possible.

Mr. Smith, part 2 (cont.)

More Data: You also receive results of screening for contraindications:

1. The CAGE is 0/4 and a urine drug screen shows only low levels of hydrocodone.
2. The State Pharmacy Board website is negative for evidence of multi-sourcing.
3. Mr. Smith's spouse verifies his functional impairment, reporting that it is even a little worse than the patient's self-report. She also provides a 0/4 F-CAGE

Mr. Smith, part 2 (cont.)

More Data: Mr. Smith's medical record review from primary care, pharmacy, rheumatology consult (from three years ago) and orthopedic evaluation (from two years ago) verify the diagnosis and imply stability in adhering to prior treatment plans.

Mr. Smith, part 2 (cont.)

Clinical Decision Point #2:

You decide that a trial of long-term opioid therapy is indicated and that there are no contra-indications, so you offer this option to the patient, using a process of informed consent.

Mr. Smith, part 2 (cont.)

- Would you change his opioid analgesic or continue the Vicodin? Why or why not?
- Would you prescribe methadone? Why or why not?

Mr. Smith, part 2 (cont.)

- What points will your Informed Consent Form cover?

Mr. Smith, part 2 (cont.)

What will your monitoring strategy consist of?

1. What are your goals for monitoring?
2. How will you know if the opioid is helping or harming the patient?

Mr. Smith, part 2 (cont.)

3. How would you delegate responsibility for this monitoring strategy?
4. How would you ensure documentation of the monitoring?

Case Discussion, Part 3:

Responding to “Red Flags” and Exit Strategies

Mr. Smith, part 3

ID: The patient is a 41-year-old married man, father of three, working as an electrician.

He presents from your recently retired senior colleague's patient panel, with a CC of "need my back pain prescriptions refilled, and they are not working as well any more."

Mr. Smith, part 3 (cont.)

HPI: Low back pain off and on for >12 years, chronic in nature for past 6 years, vague radiation from the R L/S region to the right upper thigh, worsened by lifting and bending, interfering in the past with ability to work.

Mr. Smith, part 3 (cont.)

HPI: Normal neurological exam, L/S MRI from 3 years PTA with mild degenerative changes. Ortho evaluation at the time indicated no intervention indicated.

Tried physical therapy on 2 occasions without improvement.

Mr. Smith, part 3 (cont.)

You choose to increase your monitoring of Mr. Smith, with a urine drug screen at each monthly visit.

Double-checking with the PT program at the hospital, you learn that Mr. Smith did not keep any PT visits after the initial assessment and the first or second follow-up session. Mr. Smith says he did not follow up with PT because “they said he was done ... and anyway they were not teaching anything new.”

Mr. Smith, part 3 (cont.)

After 10 weeks, you have the staff call the patient back for a medication check between regularly scheduled visits.

Mr. Smith refuses to come to the office, stating that “the call-back provision was not on the contract he signed.”

Mr. Smith, part 3 (cont.)

The next day, you call Mr. Smith and remind him that the Informed Consent form indicated that in an effort to keep him safe and functioning, he agreed to follow through on anything that was part of his treatment plan.

You advise him that the call-back appointments are now part of his treatment plan because of the toxicology test results.

Mr. Smith, part 3 (cont.)

Mr. Smith reluctantly agrees to come in and to bring the rest of the prescribed meds.

When he does, the number of sustained-release morphine tablets is below the number expected.

His urine drug screen is positive for non-prescribed benzodiazepines, hydromorphone and THC (marijuana).

Mr. Smith, part 3 (cont.)

Clinical Decision Point #3: Responding to “red flags”:

1. What are your clinical options at this point?
2. What would you choose to do, and why?