

Methadone Maintenance: safe and effective opioid pharmacotherapy

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Opioid abuse and dependence statistics, 2007

Persons who reported abuse or dependence in 2007:

1,707,000 pain relievers

213,000 heroin

2,920,000 total

Persons who received treatment in 2007:

□ 558,000 for pain relievers,

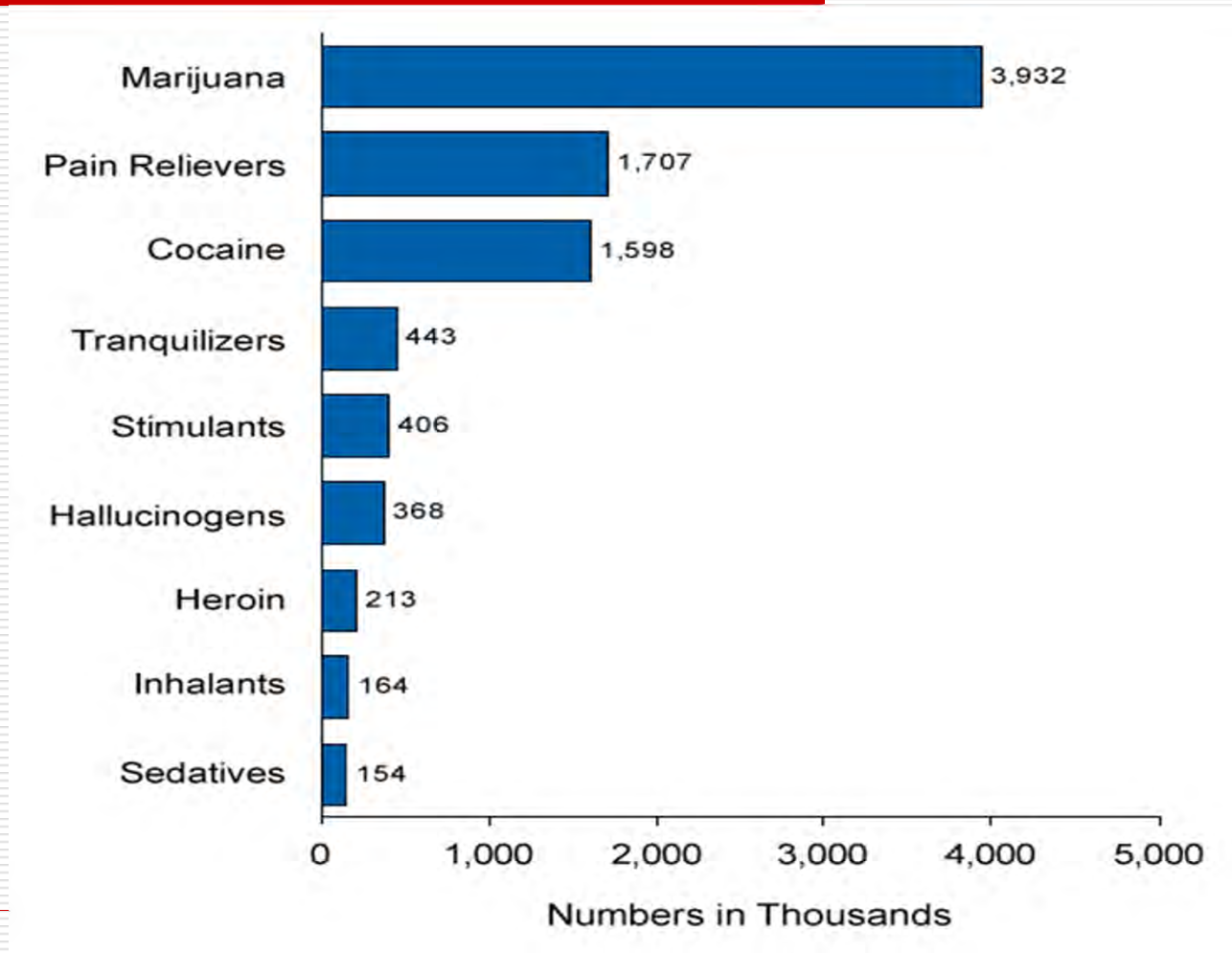
□ 335,000 for heroin,

□ 893,000 total.

(Source: NSDUH, 2007)

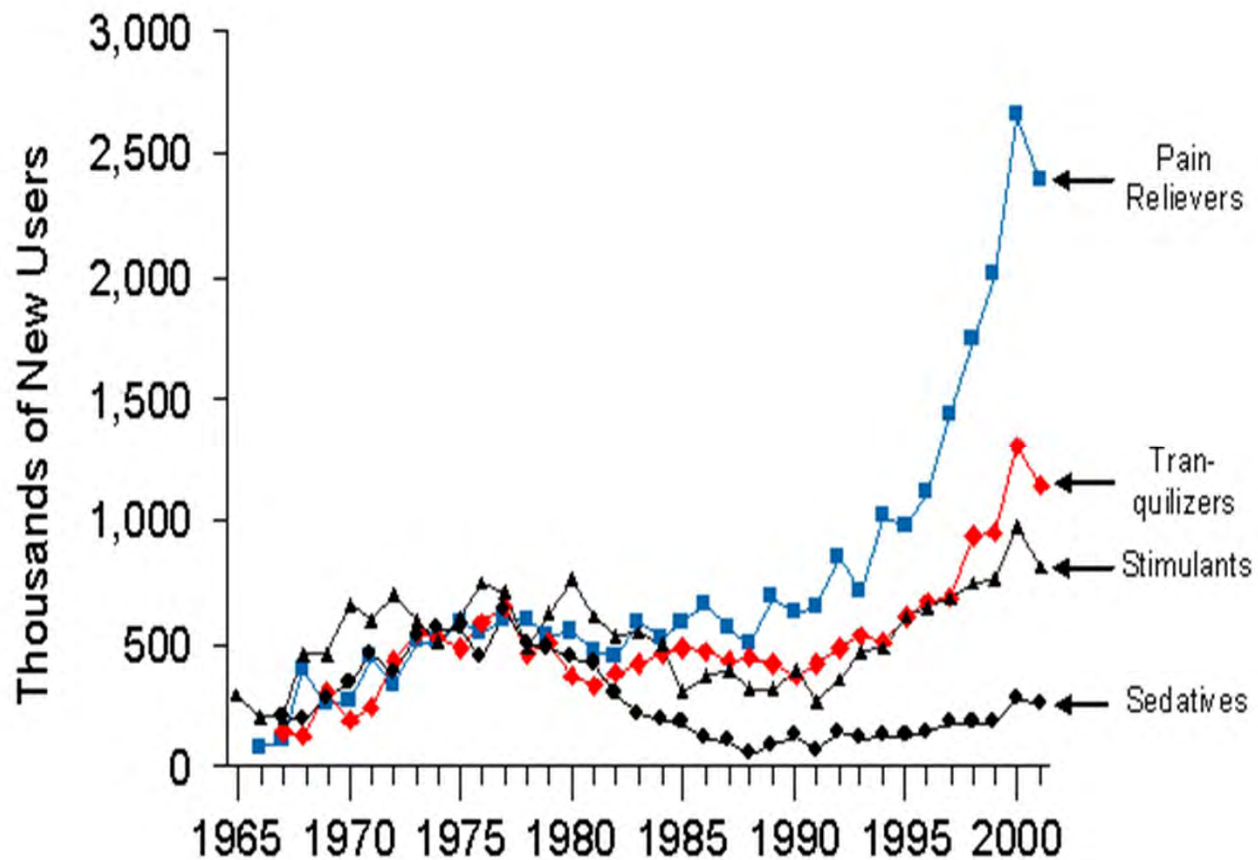
Illicit Drugs 2007

Dependence or Abuse:



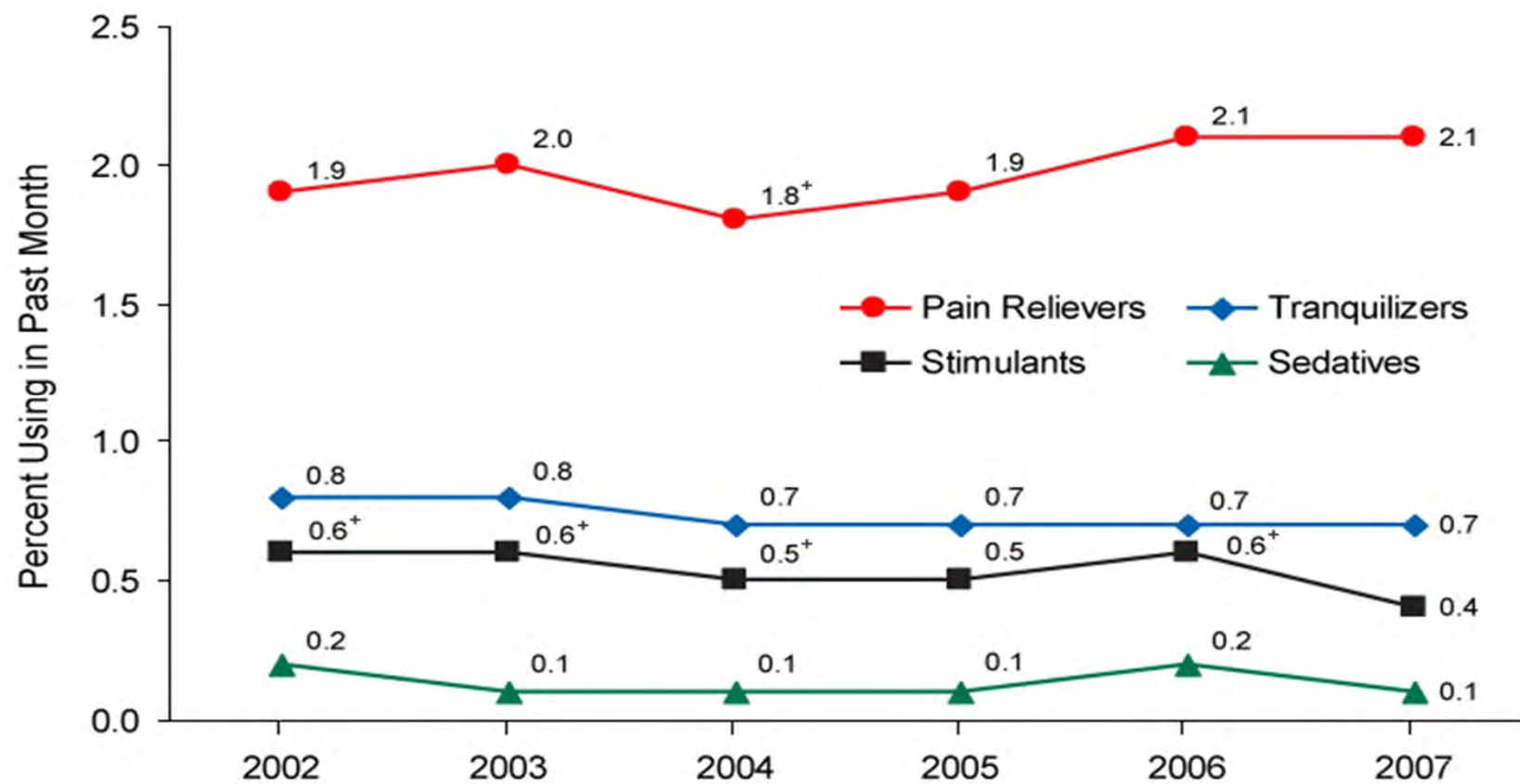
NSDUH, 2007

Number of new non-medical users of therapeutics



(NSDUH,
2002)

Non-medical use of medications, past month.



NSDUH, 2007

Commonly Abused Opioids



Diacetylmorphine (Heroin)

Hydromorphone (Dilaudid)

Oxycodone (OxyContin, Percodan,
Percocet, Tylox)

Meperidine (Demerol)

Hydrocodone (Lortab, Vicodin)

Commonly Abused Opioids (continued)



Morphine (MS Contin, Oramorph)

Fentanyl (Sublimaze)

Propoxyphene (Darvon)

Methadone (Dolophine)

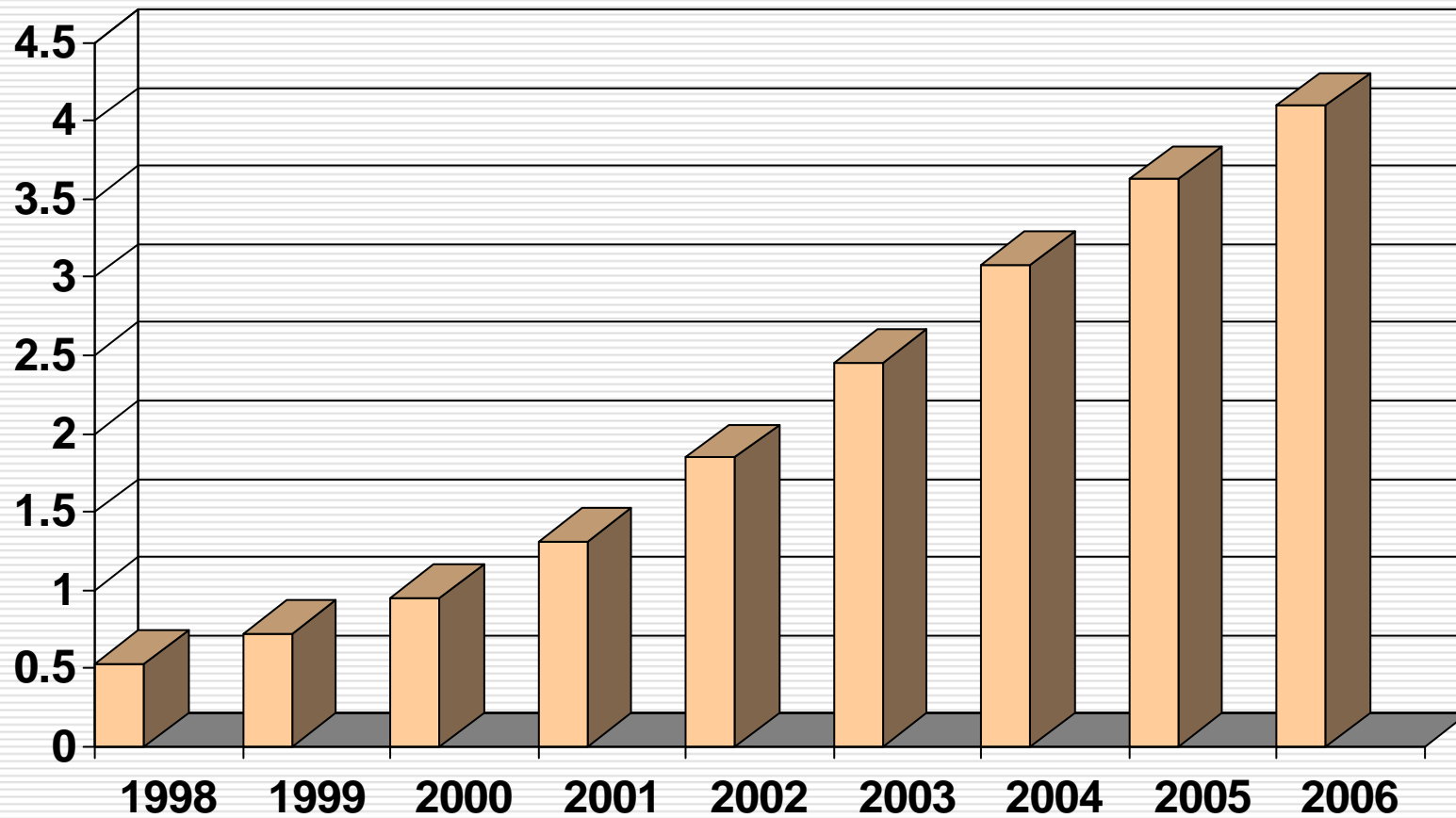
Codeine

Opium

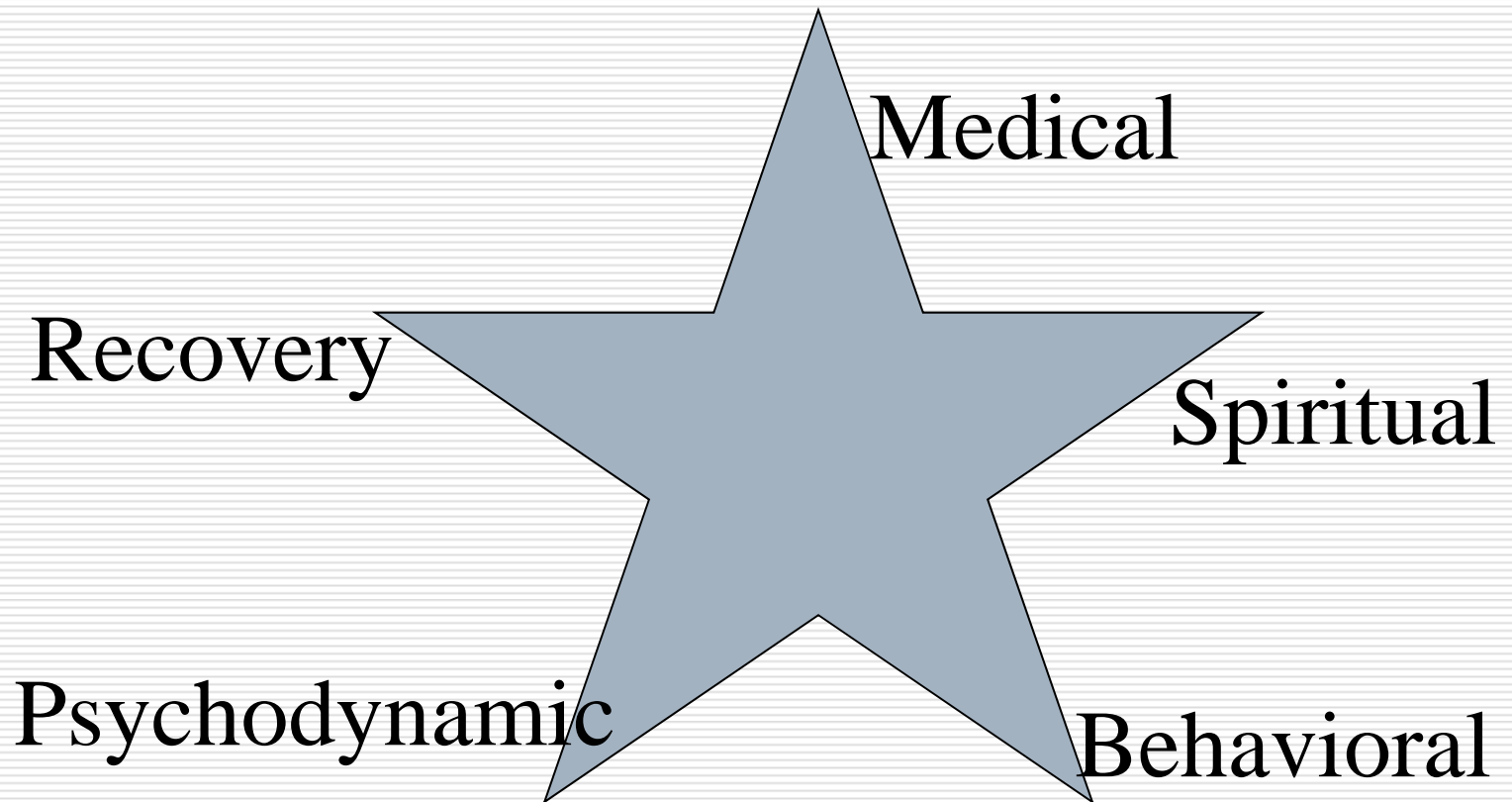
Methadone Prescriptions

Source: IMS Health Prescription Audit

Millions



Talking to patients about addiction treatment approaches



A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

JAMA 1965

Original Articles

Narcotic Blockade

VINCENT P. DOLE, MD; MARIE E. NYSWANDER, MD; AND
MARY JEANNE KREEK, MD, NEW YORK

ARCH INTERN MED 1966

Heroin Addiction—A Metabolic Disease

Vincent P. Dole, MD, and Marie E. Nyswander, MD, New York

ARCH INT. MED. 1967

Methadone for Analgesia

- Methadone exists as a racemic mixture of R- (R-Met) and S- (S-Met) configurations
 - μ activity resides solely with R-Met
 - NMDA antagonist activity with S-Met
 - Highly variable intra and inter patient dose equivalency
 - Analgesic duration of action is 6-8hr in most situations
-

Methadone for Analgesia

Elimination half-life is highly variable

- Typically 14-40h but >100h reported
- Biphasic elimination
 - Alpha phase (analgesic effect) ~6-8h
 - Beta elimination (opioid stability) ~24h
- pH dependent excretion fecal > urinary
<55mg/d and pH < 6; EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) no pH effect

excretion is by kidney

- no dose adjustment needed in dialysis

Methadone Maintenance

- Evidence-based treatment using the medical model
 - Includes interdisciplinary care, mandated counseling
 - Includes behavioral interventions, testing
 - Includes diversion control plans
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THE DOSING WINDOW

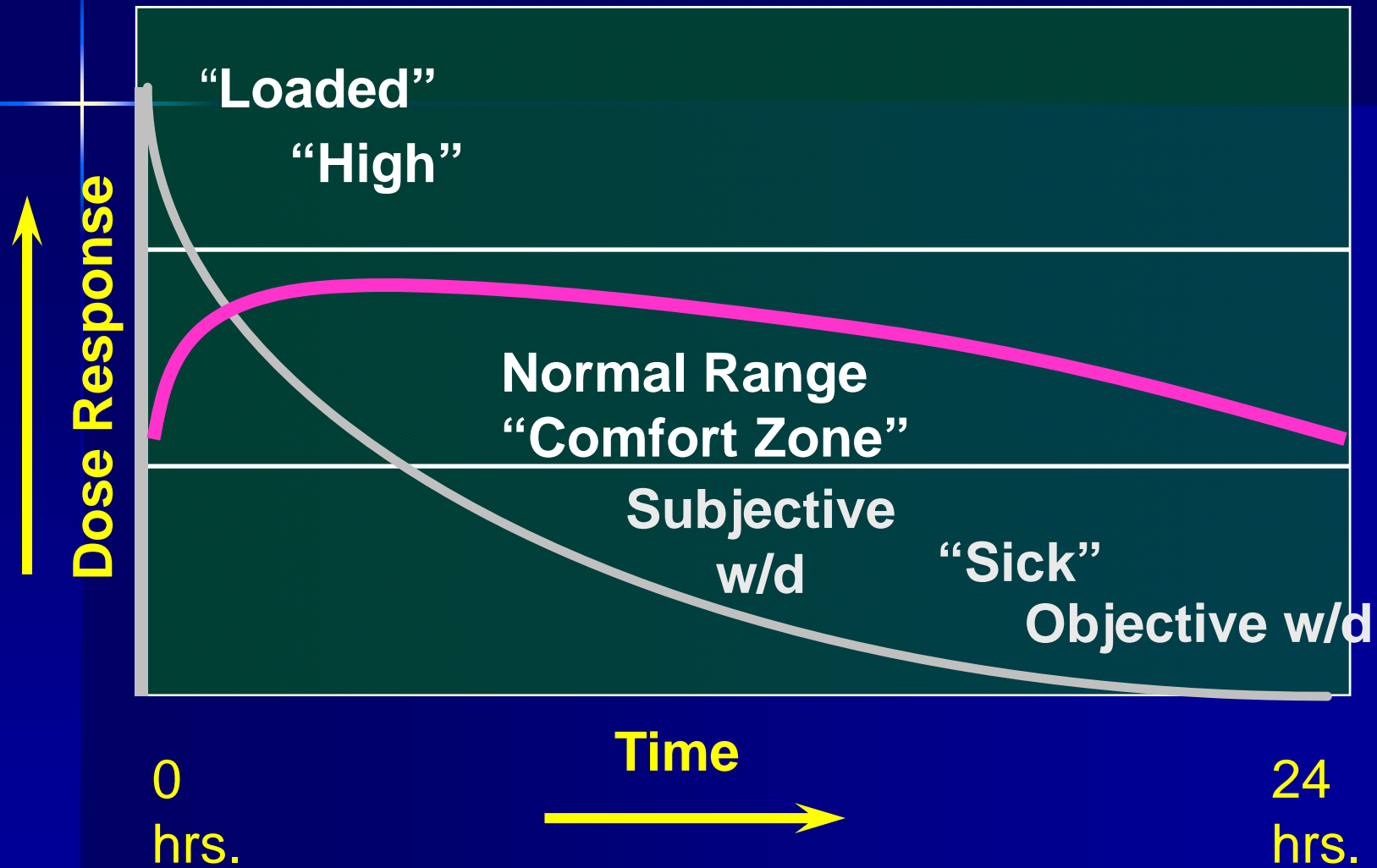
Four questions patients ask:

- How is methadone better for me than heroin?
 - What is the right dose of methadone for me?
 - How long should I stay on methadone?
 - What are the side effects of methadone?
-

How is methadone better than heroin?

- Legal
 - Avoids needles
 - Known amount ingested
-

Methadone Simulated 24 Hr. Dose/Response At steady-state in tolerant patient



How is methadone better than heroin?

- Legal
 - Avoids needles
 - Known amount ingested
 - Slow onset: no “rush”
 - Long acting: can maintain “comfort” or normal brain function
 - Stabilized physiology, hormones, tolerance
-

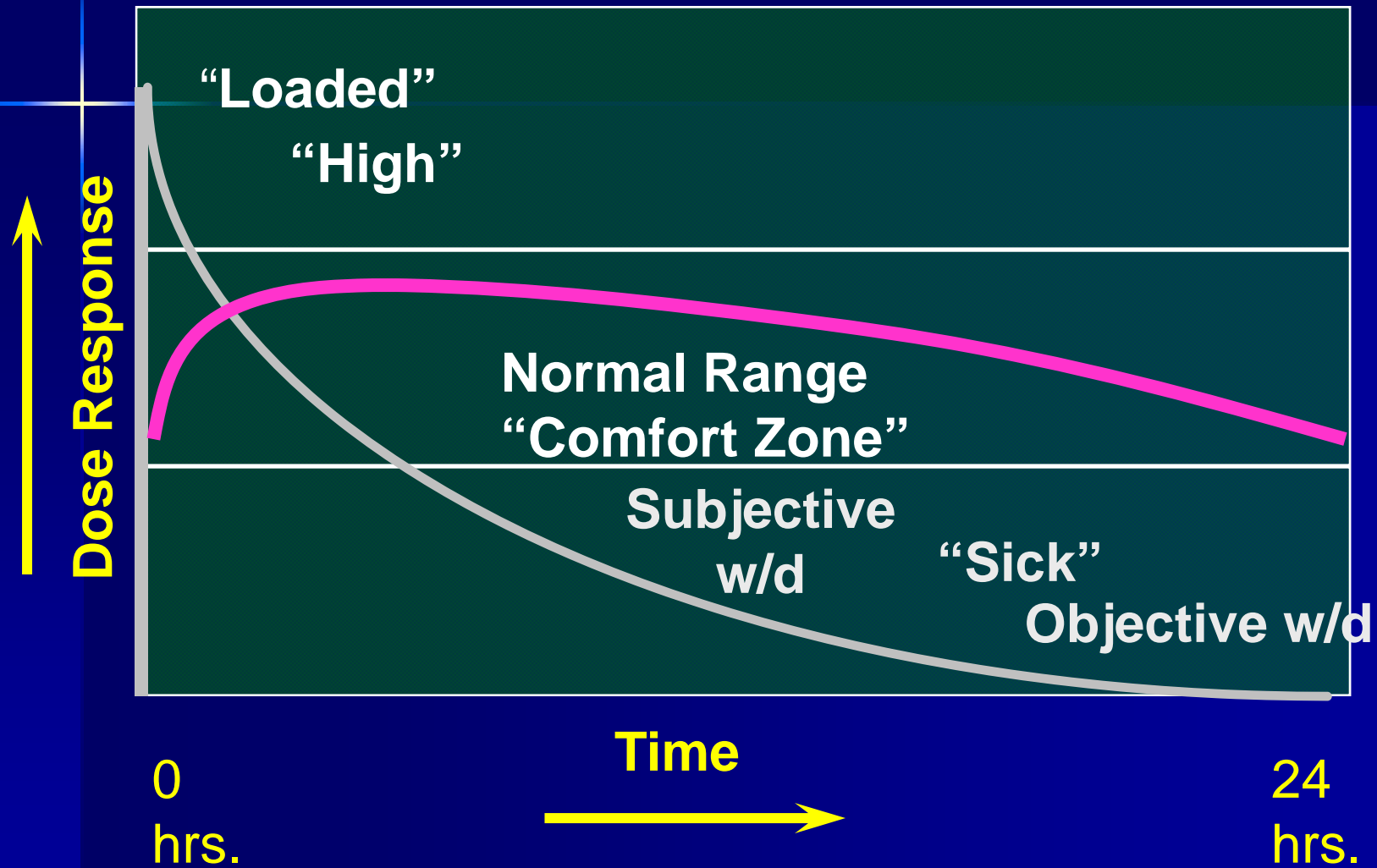
Four questions patients ask:

- How is methadone better for me than heroin?
 - *What is the right dose of methadone for me?*
 - How long should I stay on methadone?
 - What are the side effects of methadone?
-

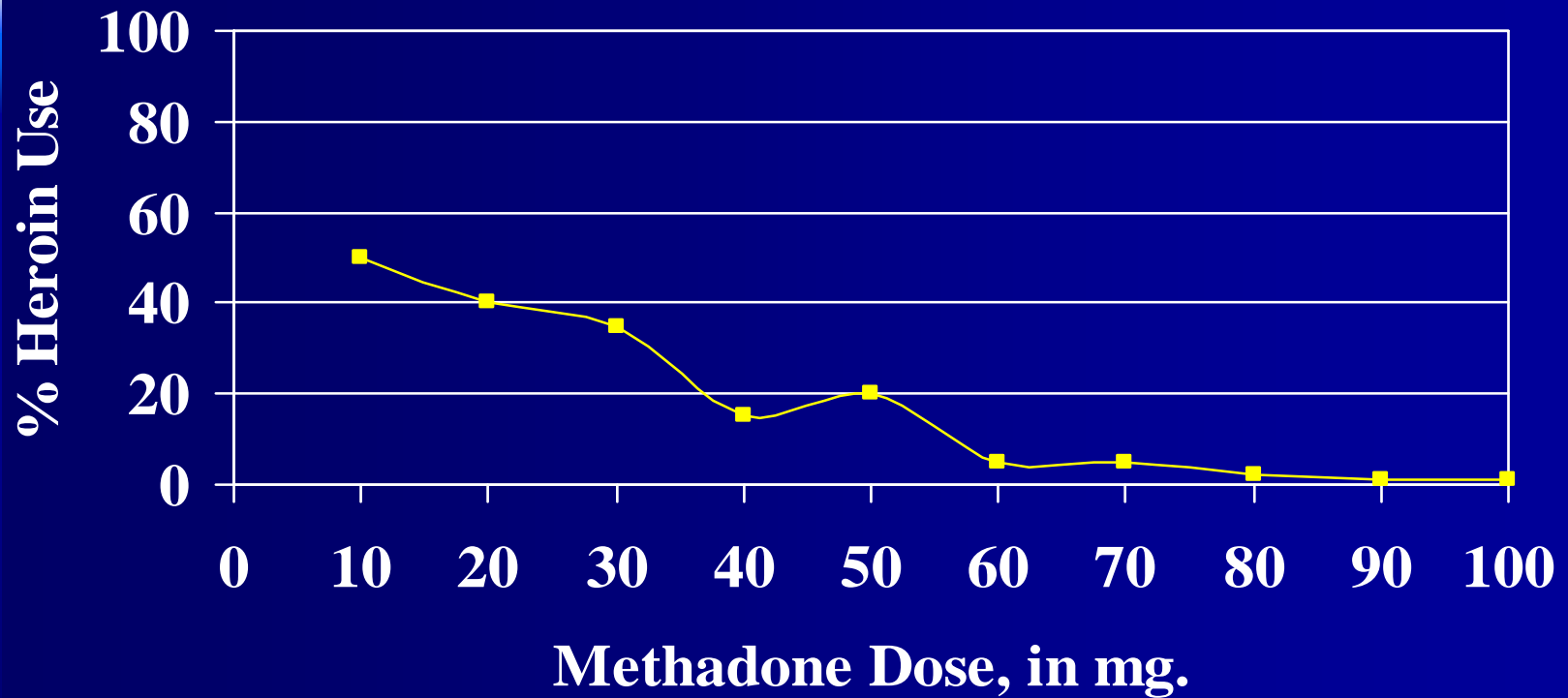
What is the right dose?

- Eliminate physical withdrawal
 - Eliminate 'craving'
 - Comfort/function: if blood levels done, peak lower than twice the trough.
 - Not over-sedated
 - Blocking dose
-

Methadone Simulated 24 Hr. Dose/Response At steady-state in tolerant patient



Recent Heroin Use by Current Methadone Dose



Ref: J. C. Ball, November 18, 1988
Slide adapted from Tom Payte

“How Much????”

Enough!!!”

Tom Payte, MD



SERUM METHADONE LEVELS

Uses

Benefits

Limitations

Methadone-Drugs interactions

Alter extent and duration of effect

Associated with changes in SMLs.

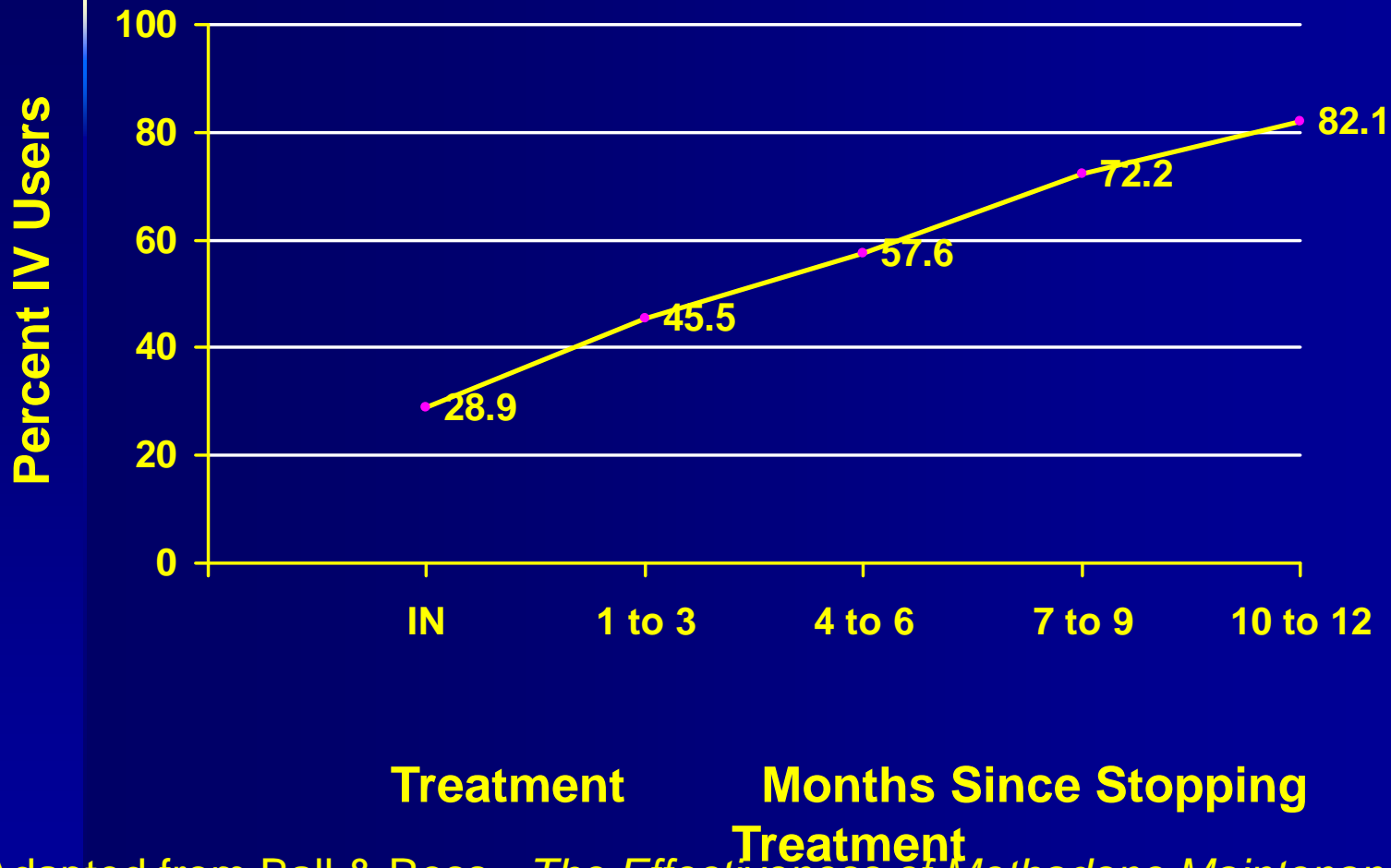
Variations in SMLs are often associated with drug interactions but may be seen without the presence of other drugs.

Four questions patients ask:

- How is methadone better for me than heroin?
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-

Relapse to IV drug use after MMT

105 male patients who left treatment



Adapted from Ball & Ross - *The Effectiveness of Methadone Maintenance Treatment*, 1991

“How Long???”

Long Enough!!”

Tom Payte, MD

Four questions patients ask:

- How is methadone better for me than heroin?
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 - How long should I stay on methadone?
 - *What are the side effects of methadone?*
-

Opiate effects, physical

- Predictable physical effects of administering opiates:
 - **Tolerance:** the body becomes efficient in processing the drug and requires ever higher doses to produce the desired effect.
 - **Dependence:** when the drug is discontinued there are typical withdrawal signs and symptoms.
-

Side effects of methadone:

- ❑ General opiate effects:
 - Sedation/stimulation
 - Maintained phys. dependence (stable)
 - hypogonadism (not as severe as with heroin, may be dose dependent)
 - ❑ Constipation
 - ❑ Slight QTc prolongation on ECG (Martell etal) * 2% at significant risk of arrhythmia.
 - ❑ Sweating
 - ❑ Methadone treatment tied to regulated clinic
-

Side effects of methadone: overdose risk

Induction period most dangerous:
first dose 30 or lower.

Build slowly in first 10 days, but
according to symptoms **AT PEAK!**

Hydrocodone, codeine or opium users
may stabilize at lower doses.

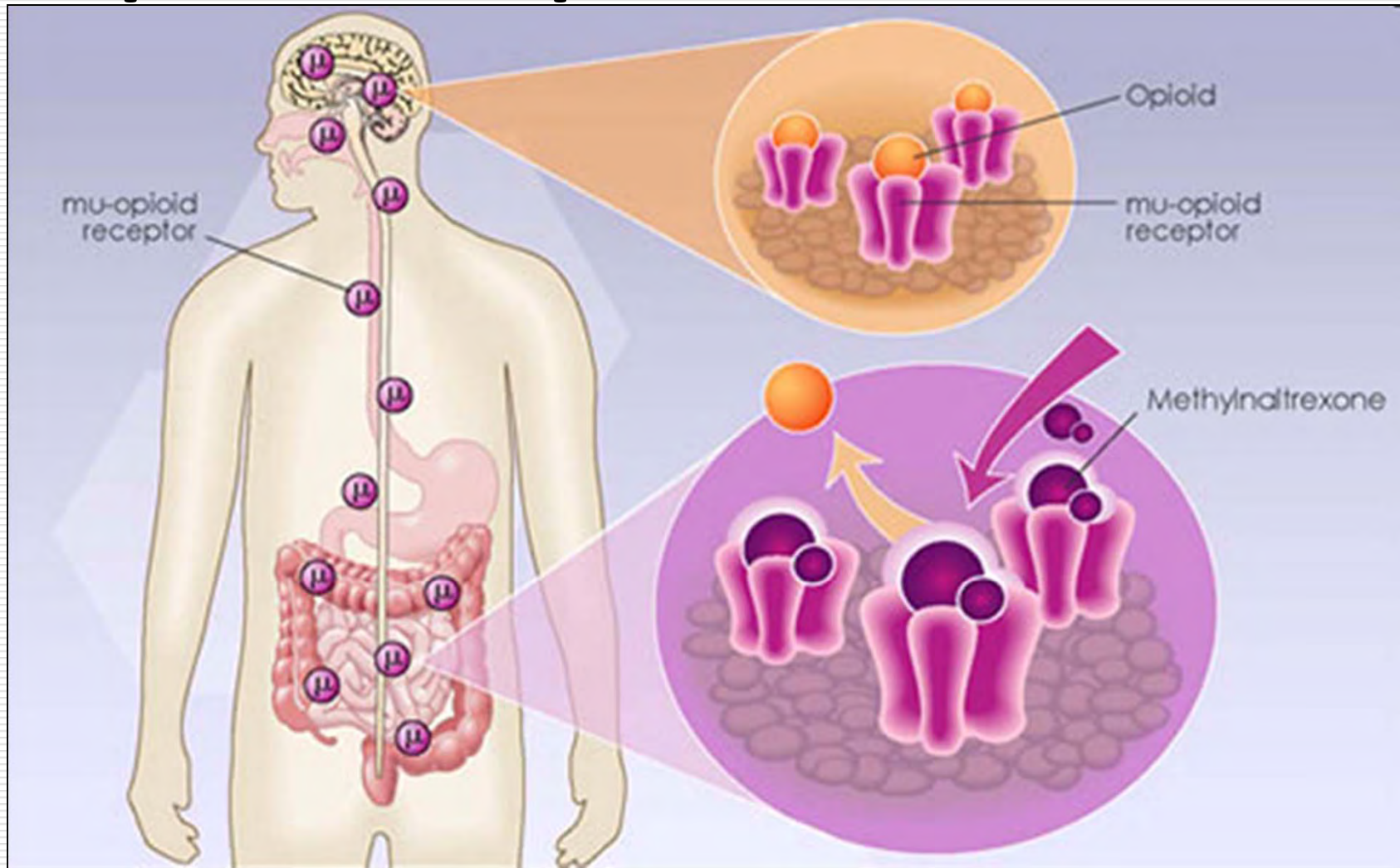
Methadone Dose

- Drug is not holding me
 - Look for medication interactions
 - Other substance use
 - Psychiatric illness
 - Is the dose adequate?
 - What does the patient look like 3 hours after their last dose?
 - Caution about increasing the dose if the patient is using alcohol or benzodiazepines
-

Opioids and Constipation

- ❑ Constipation is a recognized adverse effect of strong opioids (Gray & Spence, 2005)
- ❑ Opioids increase nonpropulsive contractions in middle of small intestine and decrease longitudinal propulsive peristalsis - motions critical to moving food through the intestines. This causes food to stop its route through the digestive tract.
- ❑ Reduce digestive secretions and decrease the urge to defecate.
- ❑ Opioids cause constipation by reducing gut peristalsis and increasing muscle tone (Gray & Spence, 2005), and may alter production and resorption of gut secretions (Burleigh, 1991)
- ❑ Opioids slow down gastric emptying and propulsive motor activity of the intestines, thus decreasing the rate of intestinal transit and producing constipation (Yuan et al., 2000)
- ❑ 40% to 80% patients on palliative care have constipation (Curtis et al., 1991; Sykes, 1998)
 - Increases to up to 90% when patients are treated with opioids (Sykes, 1998; Twycross & Lack, 1983)

Opioid Receptors in Gut

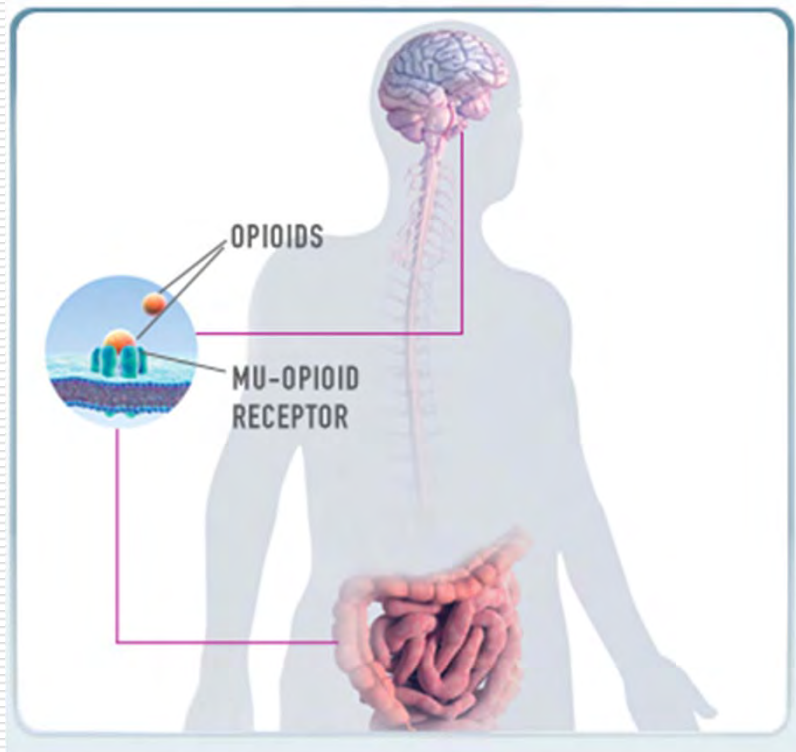


**Image borrowed from Wyeth library. (<http://www.medicalnewstoday.com/info/oic/treatment-for-opioid-induced-constipation.php>)*

Symptoms of Opioid-Induced Constipation (OIC)

- Common physical symptoms of OIC include:
 - Stools that are hard and dry
 - Difficulty such as straining, forcing, and pain when defecating
 - A constant feeling that you need to use the toilet
 - Bloating, distention, or bulges in the abdomen
 - Abdominal tenderness
 - Other symptoms of OIC include:
 - Feeling of sickness or actual sickness
 - Tiredness, weakness, lethargy
 - Loss of appetite
 - Depression
-

Effects of opioids on the gastrointestinal tract include:



□ Small intestine

- Decreased propulsive contractions
- Increased water absorption

□ Large intestine

- Decreased propulsive peristalsis
 - Increased nonpropulsive contractions
 - Increased anal sphincter tone
 - Decreased reflex relaxation response
 - Increased transit time
-

Managing Opioid Induced Constipation (OIC)

- ❑ ~~Nonpharmacologic management: increase fluid intake, physical activity when feasible~~
- ❑ Pharmacologic management: laxatives
 - Stool softeners help combine fat and aqueous substances into stool
 - Cathartic or stimulant laxatives stimulate peristalsis through direct effect on bowel
 - Osmotic or saline laxatives promote fluid retention in bowel, res

BEHAVIOR MODIFICATIONS	PHARMACOLOGIC TREATMENTS	RECTAL INTERVENTIONS
Promote adequate fluid intake Promote activity	Laxatives <ul style="list-style-type: none">-Stimulants-Stool softeners-Osmotic agents	Enemas Manual disimpaction

*Source: Wyeth.com

Relistor (methylnaltrexone)

- ❑ Relistor is a special narcotic drug that blocks certain effects of other narcotic medicines.
- ❑ It reduces constipation caused by narcotic medications that are often used to treat pain in people with terminal illness.
- ❑ Relistor works by preventing this side effect without reducing the pain-relieving effects of the narcotic.
 - It is usually given after laxatives have tried without successful treatment of constipation.



Methylnaltrexone cont.,

- ❑ Methylnaltrexone is the first quaternary ammonium opioid receptor antagonist that does not cross the blood-brain barrier in humans (Yuan et al., 2000)
 - ❑ It offers the therapeutic potential to reverse side-effects of opioid pain medications without disturbing opioid's analgesic effect (Yuan et al., 2000)
 - ❑ Intravenous methylnaltrexone can induce laxation and reverse slowing of oral cecal-transit time in patients taking high opioid dosages (Yuan et al., 2000)
-

Treatment Options for Opioid-Induced Constipation

	Treatment Option	Mode of Action	Examples	When effective
Oral	Stimulant Laxative	Increased intestinal motility by stimulating peristalsis	Senna bisacodyl, sodium picosulphate	8 to 12 hrs
	Softening Laxative	Softens stools by acting like detergents to reduce surface tension, improve water penetration of stools	Docusate	1 to 2 days
	Osmotic Laxative	Increases amount of water in large bowel. Increases stool mass and stimulates peristalsis.	Lactulose, macrogols (polyethylene glycol)	12 to 48 hrs
	Bulk-forming laxative	Absorbs water to soften stools but also increase faecal bulk, which stimulates peristalsis.	Methylcellulose, ispaghula husk	full effect may take a few days to develop.
	Combination Laxatives	Combine laxatives with different modes of action. Combination of stimulant and softening laxatives generally used.	Co-danthramer, co-danthrusate, magnesium hydroxide with liquid paraffin	6 to 12 hrs
Subcutaneous	Peripheral opioid antagonist	Displaces opioid from peripheral mu (μ)-opioid receptors in the gastrointestinal system.	Methylnaltrexone bromide	30 to 60 mins
Rectal	Suppository	Stimulates rectum due to mild irritant action (glycerol), or stimulates peristalsis (bisacodyl)	Glycerol, bisacodyl	Glycerol: 1 to 6 hrs; bisacodyl: 30 to 60 mins
	Osmotic enema	Softens stool and stimulates peristalsis	Sodium citrate microenema, phosphate	20 minutes

Assessing Opioid-Induced Constipation in Patients

- A full assessment of constipation among cancer patients and/or patients treated with opioid analgesics should include:
 - History of bowel movements (both before and after therapy)
 - Symptoms due to constipation
 - Physical examination (including a digital rectal exam)

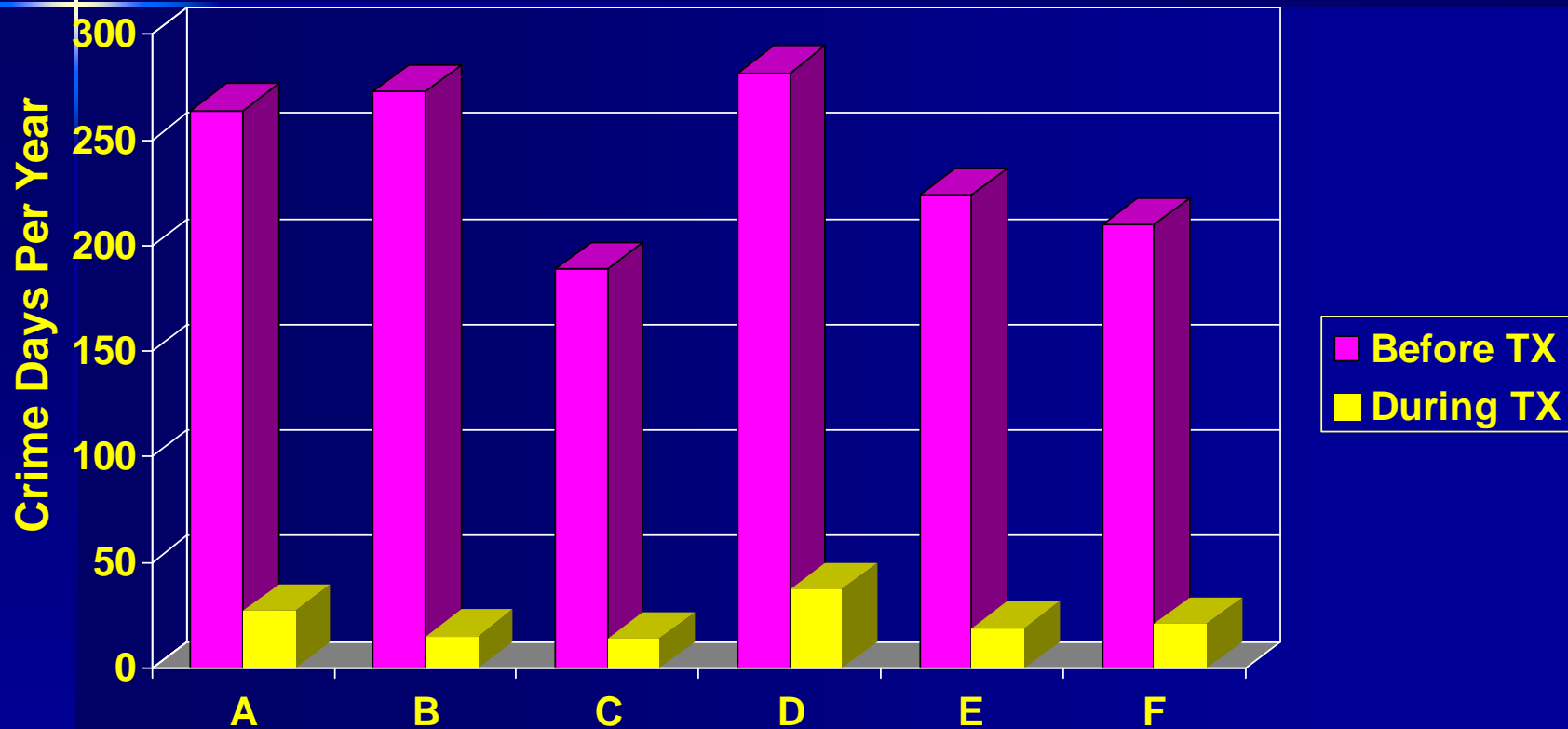
(Daeninck & Bruera, 1999)

Treatment Outcome Data

- ❑ 4-5 fold reduction in death rate (except first week)
- ❑ reduction of drug use
- ❑ reduction of criminal activity
- ❑ engagement in socially productive roles
- ❑ reduced spread of HIV
- ❑ excellent retention

(see: Joseph et al, 2000, Mt. Sinai J.Med)

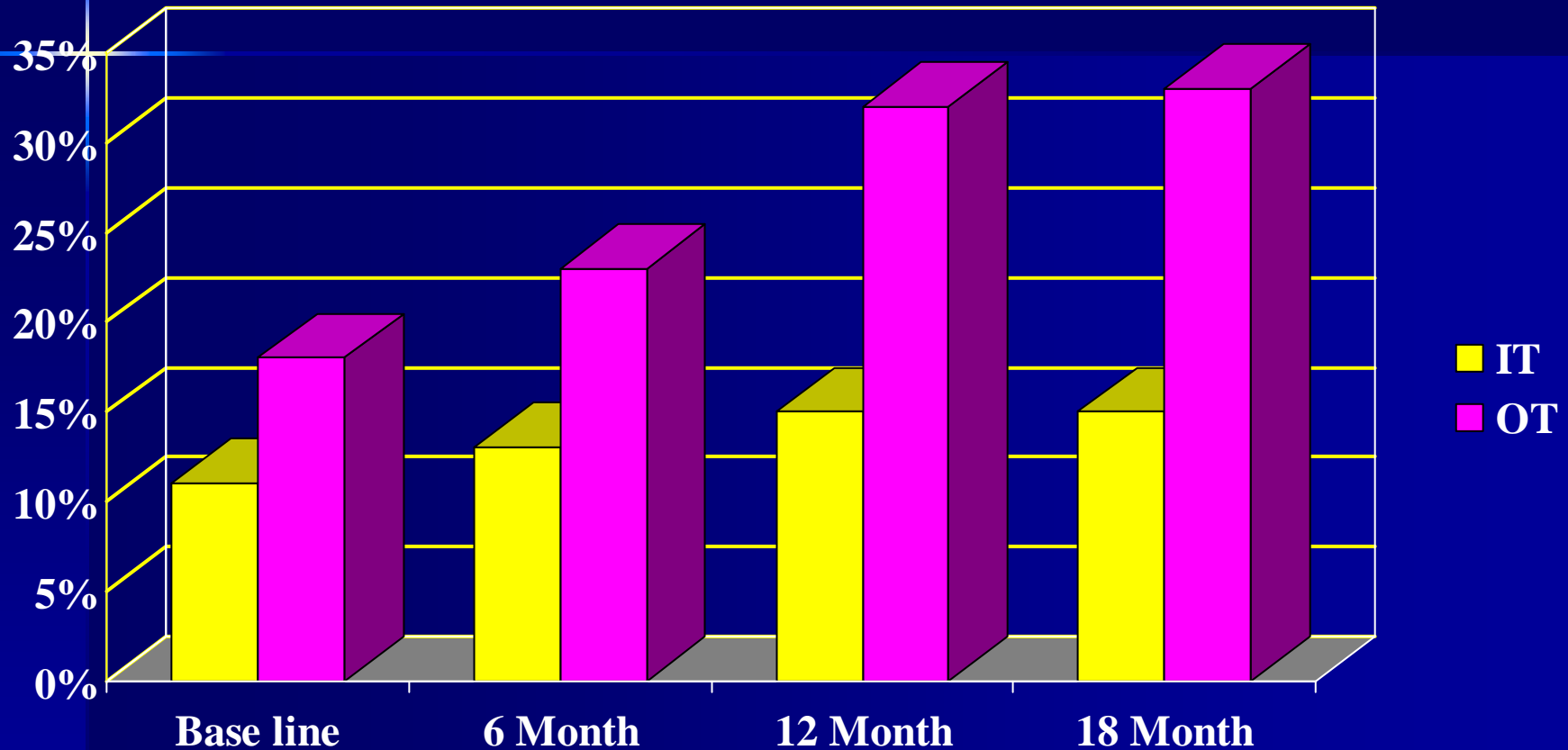
Crime among 491 patients before and during MMT at 6 programs



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

Opioid Agonist Treatment of Addiction - Payte - 1998

HIV CONVERSION IN TREATMENT



HIV infection rates by baseline treatment status. In treatment (IT) n=138, not in treatment (OT) n=88

Source: Metzger, D. et. al. J of AIDS 6:1993. p.1052

Other drugs of abuse: how do they affect MMT?

- ❑ Stimulants: patients do poorly
 - ❑ Alcohol: additive sedation, complicate Hep C.
 - ❑ Benzodiazepines: synergistic sedation
 - ❑ THC: no effect on major outcomes
 - ❑ Opioids: usually blocked, tolerance
-

Pregnancy

- ❑ MMT treatment of choice for pregnant, opioid-abusing women.
 - ❑ Efforts to avoid intra-uterine fetal withdrawal, including divided dose.
 - ❑ Neonatal withdrawal occurs within 72 hours, at least 45% need treatment.
 - ❑ Breastfeeding recommended if not HIV positive.
-

Pain in patients on MMT

- Methadone is prescribed for pain treatment in twice or three times daily doses.
 - Up to 60% of MMT patients have chronic pain (Jamison 2000, Rosenblum 2003)
 - Divided doses may be indicated.
-

Pharmacotherapy in context: correct glossary

- Abstinence** includes pharmacotherapy
 - Maintenance**, not substitution or replacement (new term also: MAT)
 - Tapering from maintenance**, not detoxification, (also 'medically supervised withdrawal', or MSW)
 - Discontinuation**, not discharge
 - Toxicology screens: pos/neg**, not clean/dirty)
-

Current Methadone Use

- As a schedule II substance, methadone manufacturers must obtain a quota from DEA. From 1998 thru 2006, the quota for methadone has increased by about 250%.
- Increased use is primarily associated with increased use for pain management not narcotic treatment.
- Prescriptions for methadone have ~~increased by nearly 700% from 1998 thru 2006.~~

Methadone Associate Deaths (MAD) in the Press 2002-2003

*Methadone, Once the Way Out,
Suddenly Grows as a Killer Drug*

*Overdose increases
linked to methadone*

*Abuse of drug spreading,
so let's restrict the amount*
