Methadone Maintenance

Judith Martin, MD
Medical Director
BAART Turk Street Clinic
San Francisco, CA

Dr. Martin, Disclosures

- No conflict of interest to disclose.
- No discussion of off-label use.
- Special thanks to Dr. Thomas Payte for allowing me to use some of his great slides.

Physicians Working in MMT Will Know:

- How to safely induce patients to MMT.
- How to adjust methadone dosing for maximum effectiveness.
- How to detect and manage MMT side effects and medication interactions.
- How to work within legal/regulatory framework of 42 CFR part 8.

Safety Considerations in MMT:

- Avoid sedation and respiratory depression (stay within tolerance)
- Minimize side effects of constipation, sweating, hypogonadism
- Alertness to potential medication interactions, QT/cardiac risk
- Minimize diversion, accidental ingestion or dosing errors

Safe Induction: "Start Low go Slow"

- Methadone-related deaths during MMT occur during the first 10 days of treatment and are more common with higher induction doses.
- There is no way of directly measuring tolerance to methadone. Estimate of opioid tolerance is based on history and physical, supported by toxicology tests.

Methadone Deaths in Treatment

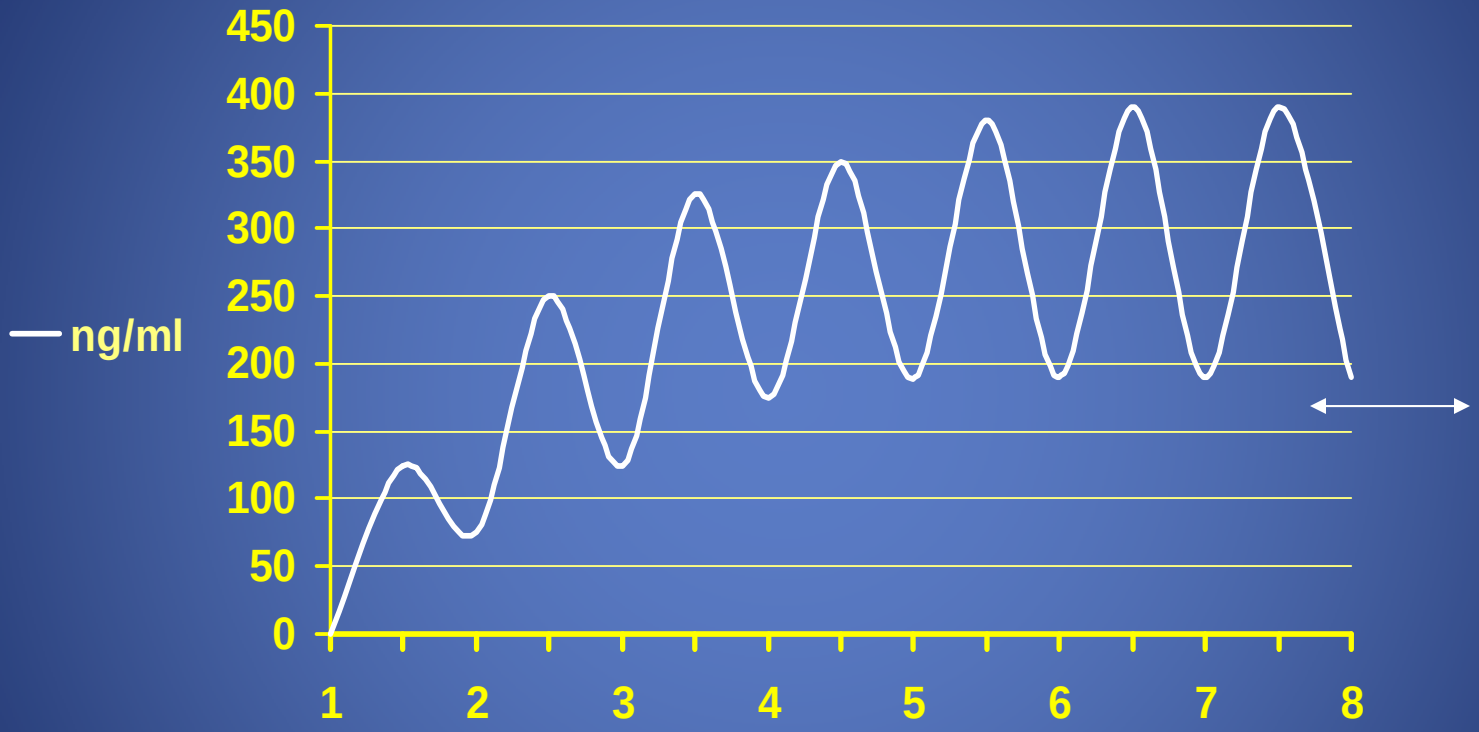
- Induction risk 7 times greater than active heroin use. Methadone induces its own metabolic rate over time. Eventual dose needed will be usually much higher than initial tolerance.
- Most deaths also show benzodiazepines on toxicology. This is true of most unintentional opiate poisonings.

Methadone is an Unusual Opioid:

- Slow onset of action: patient starts to ‘feel’ the swallowed dose 30-45 minutes later.
- Delayed peak action: greatest effect from single dose is 2-4 hours post ingestion.
- Tissue stores: methadone deposited in tissue over 3-7 days to reach steady state. This means that during induction, a given dose will have stronger effect and last longer with each day of ingestion.

Steady State: The point at which during each interdose interval the rise and fall of drug concentration for the interdose interval is identical for each dose

(Slide courtesy of Dr. Thomas Payte)



Days/Half-Lives – Methadone half-life= 24-36 hours

Dose constant at 30 mg daily. Interdose interval = 24 hrs (trough to trough)

Peak levels increase daily for 5-6 days with NO increase in dose!

Note: This slide was developed by Dr. Payte to illustrate that it takes several days to know the full effect of a given dose at steady state. It shows one patient's blood levels during induction, at a dose of 30mg. The maximum effect rises with each dose, even though the amount administered to the patient remains the same each day.

Clinical Pointers in Choosing Initial Dose:

- Special caution if:
  - Patient inexperienced with methadone
  - Patient uses benzodiazepines or alcohol
  - Recent abstinence history (example: incarceration)
  - Unable to observe patient for several hours after first dose.
  - Unable to document use or withdrawal on physical exam

Note: There is wide variation in metabolism of methadone, and no blood level or dose that is ‘therapeutic’ for all patients. Patients who are only familiar with short-acting opiates might expect full effect of dose within an hour after taking a dose of methadone, and when they don’t feel relief, add illicit drugs to relieve withdrawal, thus overdosing. Benzodiazepines and alcohol have synergistic sedative effect with methadone, and may cause dangerous sedation or respiratory depression when used with methadone (or other opiates). Tolerance fades when patients are abstinent, for example when they have been in residential programs, or in jail. Also, if the patient has not used opiates in several days and does not have signs of withdrawal, low tolerance should be assumed at induction. Some settings do not offer observation at peak of dose effect, so patients are only seen after dose effect is wearing off. Patient may be in withdrawal 24 hours after an adequate dose because tissue stores have not built up. In this case interview patient about effects at peak, or call on the phone at peak, when trying to adjust the dose during induction. Patients may misrepresent their history. Usually use of needles can be documented on the physical, withdrawal signs, such as pupillary dilation, can be found on physical, and on-site dipstick toxicology tests can support the history of opioid use.

First Dose Limited in Regulation, 42 CFR Part 8.12

- Maximum first dose is limited to 30mg.
- Maximum total dose during first day of treatment is 40mg.

Note: Patients estimated to have high tolerance, for example a history of daily use of 3gm of heroin by injection for a year, with many track marks in different stages of healing, physical signs of withdrawal, and a history of previous MMT(ie patient familiar with methadone effects), would probably benefit from maximum dose, with evaluation for additional dose increases over the first several days. Many patients need lower than maximum dose, for example a patient naïve to methadone treatment who has used hydrocodone tablets for six months and does not have dilated pupils at admission may benefit from a starting dose of 10mg followed by observation.

Induction, Summary.

- Tension between efficacy/safety during induction, safety prevails.
- Tolerance can only be estimated, special care with low potency opioid abusers.
- Start low, go slow until steady state achieved.
- Prescription drug abusers are sometimes used to getting their drugs of abuse from doctors like you!

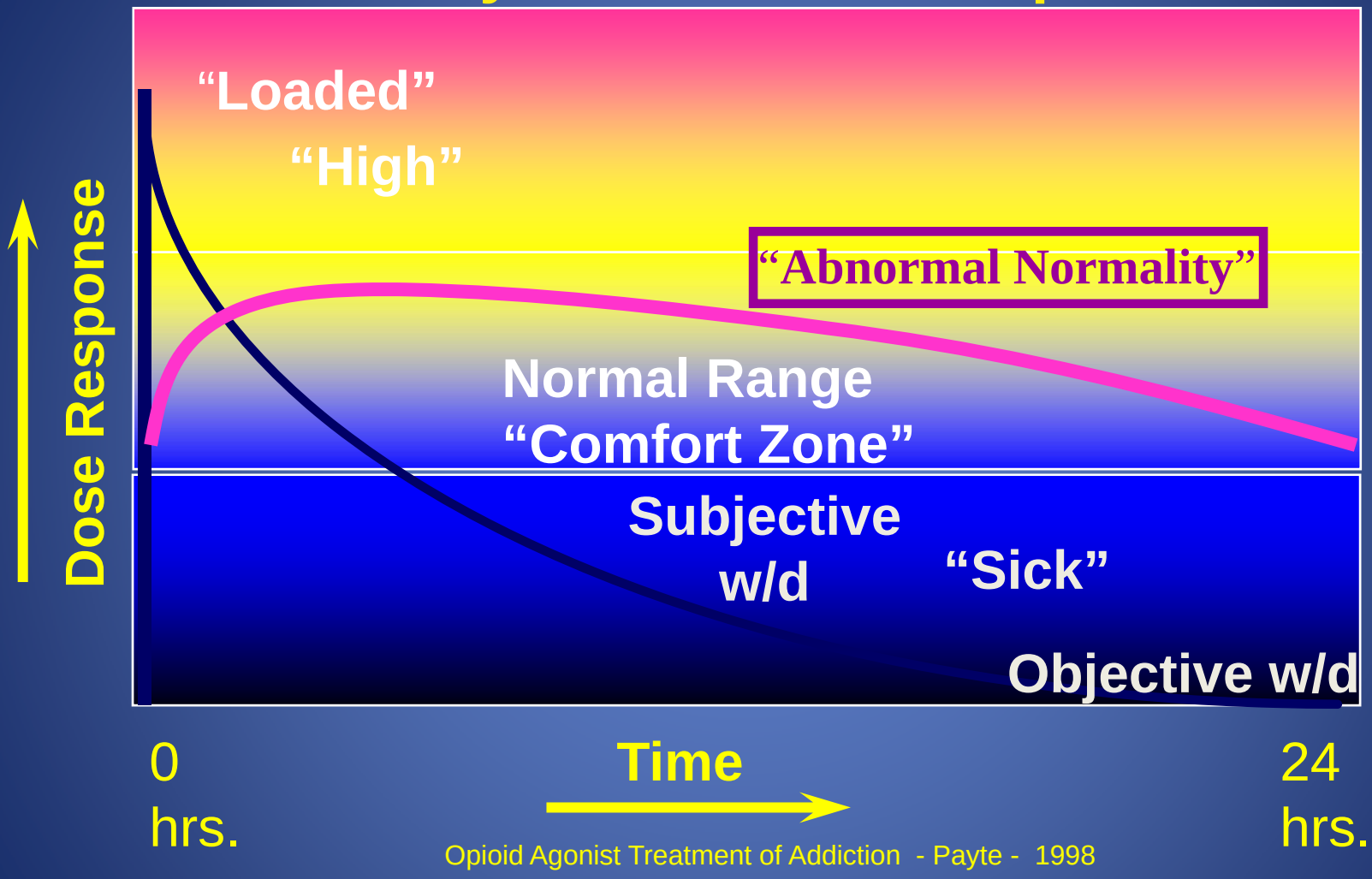
Efficacy Considerations in MMT:

- Relief of physical withdrawal
- Relief of craving
- Blocking dose
- Stability throughout the day (allows normalization of body and mind)
- Engagement in recovery and personal growth activities

Effective Maintenance Dose:

- Opioid withdrawal symptoms and signs, including craving are controlled during the entire 24 hours between doses of methadone.
- Patient is alert, aware of his or her surroundings, able to study, work, carry out family obligations, make progress in treatment goals.
- Illicit opioids are usually not ‘felt’ if use occurs.
- Average maintenance doses in US: 60-120mg/day.

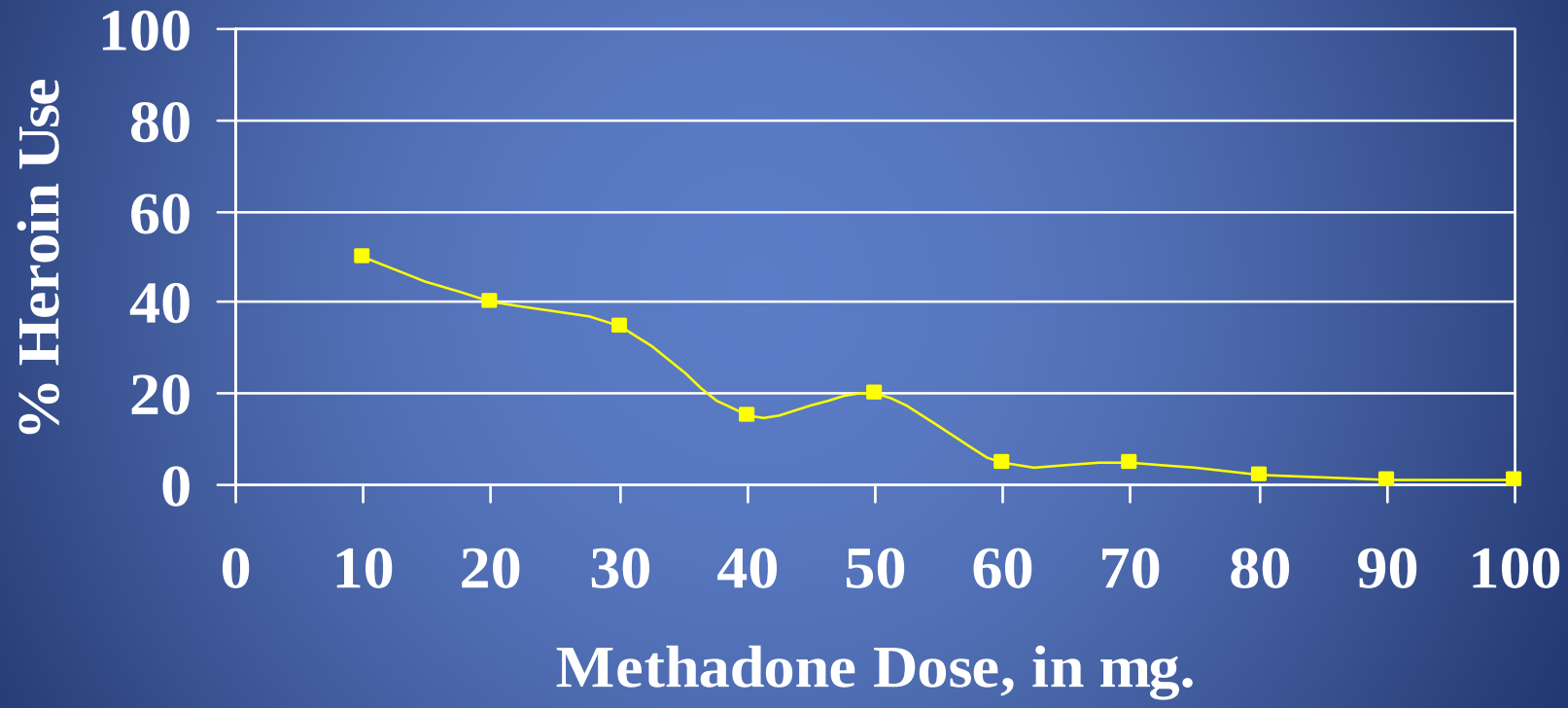
Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient



Opioid Agonist Treatment of Addiction - Payte - 1998

Note: This slide contrasts the rapid impact and fleeting effect of injected or inhaled heroin (blue curve) with steady-state methadone maintenance at the correct dose. The patient is neither intoxicated (loaded) nor in withdrawal (sick). Highest and lowest effect of methadone daily dose are both within that normal range that allows clear thought and action. In early treatment, patients may not be comfortable in the alertness range: they have conditioned themselves to fear alertness, because it indicates impending withdrawal. Dr. Payte indicates this by the 'abnormal normality' box: patients feel most comfortable when they are not completely alert, and may need education about the long-acting properties of MMT.

Recent Heroin Use by Current Methadone Dose



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

Note: This shows dose-effectiveness in MMT: doses over 60 are frequently required to achieve abstinence from heroin.

Reinstating Treatment After Absence:

- Stability is a goal in treatment, missing days undermines benefits of MMT
- Medical evaluation after absence is usually a ‘safety to dose’ evaluation:
  - Has the patient been in the hospital or ED?
  - Has the patient been incarcerated?
  - Was it a ‘binge’, for example cocaine or alcohol relapse?
  - Is the patient alert? Are there new medications?

When Does Tolerance Wear Off?

- Overdose risk high after incarceration
- Overdose risk after naltrexone treatment
- Overdose risk after detoxification (Strang et al, *BMJ* 2003;326:959–60) is greater for the ‘successfully treated’, ie abstinent.

Reinstating Treatment After Absence: Continued

- What are the difficulties with daily attendance?
- Has the patient lost tolerance? Loss of tolerance has been reported at 3 weeks.
- In general big jumps in dose are not recommended, undermine stability.
- Usually after 3-5 days, dose is lowered and then gradually increased to the regular dose.

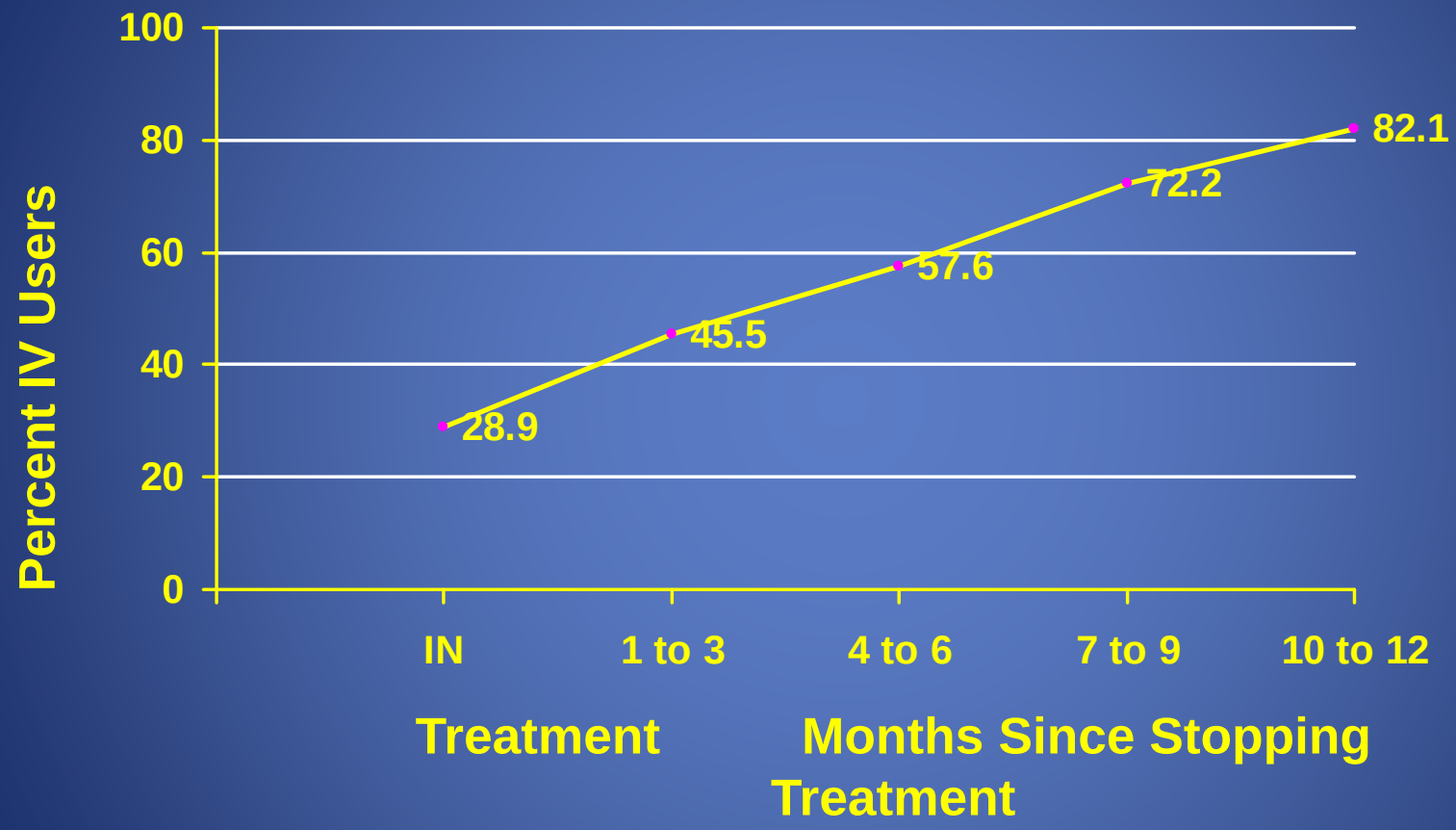
Reinduction Parameters After Absence

- Programs usually have guidelines about re-induction after absence.
- (low level of evidence: protocols vary, no controlled studies)
- Example: absence less than 21 days: re-induce starting at 30mg BUT buildup to regular dose at faster rate than intake. Re-induce as a new patient, after 21 days absence.

Should MMT Ever be Discontinued?

- Opioid addiction is a chronic, relapsing condition, so long-term treatment is indicated.
- Prognosis after withdrawal from MMT is dismal: most patients relapse before 12 mos. (compare this to diabetes, hypertension, epilepsy, etc. – other chronic conditions that require ongoing medication)

Relapse to IV Drug Use After MMT
105 Male Patients who Left Treatment



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

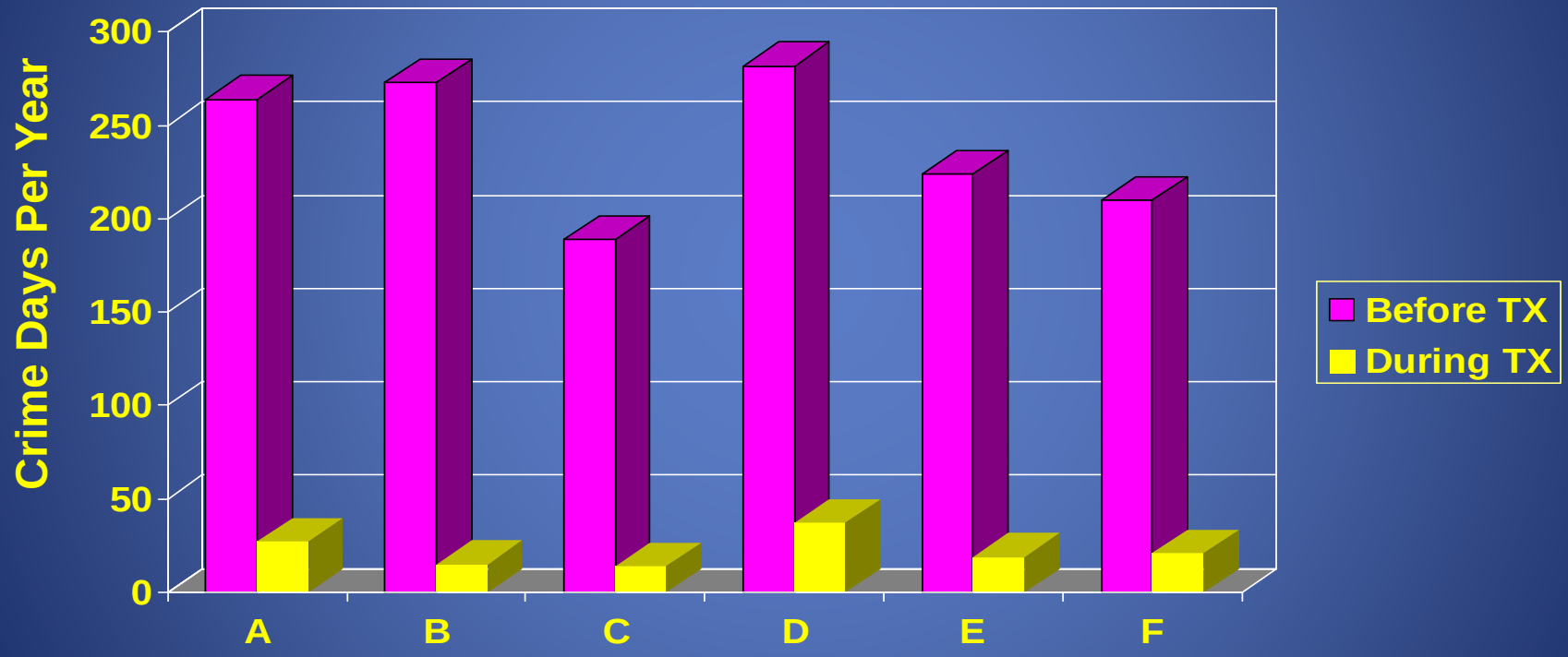
Opioid Agonist Treatment of Addiction - Payte - 1998

Note: When patients taper off of methadone maintenance, relapse is almost universal. There is no way to predict who are the 18% of patients who will not relapse within a year. During medically supervised withdrawal, close observation and keeping open the possibility of resuming therapeutic doses promptly is indicated.

Treatment Outcome Data: Methadone Maintenance

- 4-5 fold reduction in death rate
- 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., vol 67, # 5, 6)

Crime Among 491 Patients Before and During MMT at 6 Programs



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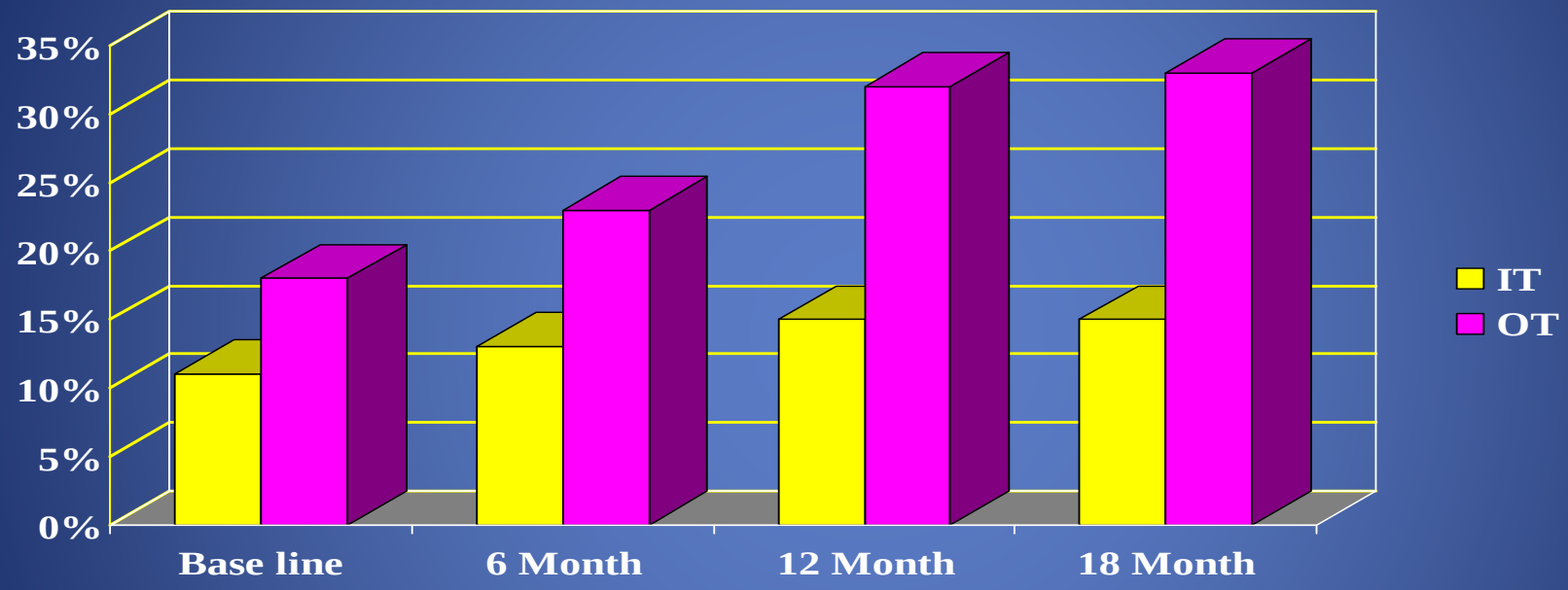
Note: This shows criminal activity at six different methadone maintenance programs, comparing rates before treatment (pink) to during treatment (yellow).

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

Opioid Maintenance Pharmacotherapy - A Course for Clinicians - 1997

Note: This slide shows protection from HIV sero-conversion by enrollment in MMT: the longer the treatment the more relative protection from HIV.

Special Populations and MMT

- Pregnancy
- Chronic pain
- Polysubstance use
- Needle related chronic conditions: HIV and Hepatitis

Pregnancy

- MAT treatment of choice for pregnant, opioid-abusing women.
- Efforts to avoid intra-uterine fetal withdrawal.
- May require divided doses because of altered metabolism.
- Neonatal withdrawal occurs within 72 hours, not all infants need treatment.
- Breastfeeding recommended if not HIV positive.

Pain in Patients on MMT

- Single daily dose as used in MMT does not control chronic pain. Analgesic effect is 8-12 hours.
- Up to 60% of MMT patients have chronic pain (Jamison 2000, Rosenblum 2003)
- If patient meets criteria for take-homes, consider divided doses for enhanced pain control. (Second daily dose usually counted as a ‘take-home’ dose).

Polysubstance Use:

- If patient has reduced or eliminated illicit opiate/needle use in MAT, very few indications for discharge.
- Sedative use (benzodiazepines/alcohol) may become a safety issue, require lower or with-held doses and reduce effectiveness of treatment.
- Stimulant use is usually a retention issue: patient has many missed days, arrested, etc.

Medication Interactions:

- Methadone effects change when blood levels change.
- Inactive metabolite, so metabolism-sensitive (liver enzymes) CYP 350
- In general, changes in dose are determined clinically, when symptom/signs appear after new medications added or withdrawn.

Medication Interactions, Special Attention: Monitor Patient

- Anticonvulsants (dilantin, phenobarbital)
- HIV medication (efavirenz)
- Rifampicin
- QT prolonging drugs (antipsychotics)
- Lots of others!

Regulations and MMT:

- Diagnosis of opioid dependence (addiction) required
- First day dosing limited in regulation
- Restriction of unobserved doses
- Specially licensed facility, accrediting standards.
- Diversion control plan
- Mandated testing and counseling

Note: Methadone maintenance programs have a DEA license and an approved DEA safe for storing methadone. There are medication reconciliation standards as well as clinical care standards. Some of the regulation is specifically therapeutic for the patient, some of the regulation protects the community from diversion of a potentially deadly schedule 2 narcotic. Physicians working in methadone clinics find themselves involved in both. Clinical decision is limited and documentation requirements are high.

Note: Observed dosing is required by Federal regulation. Nurse or pharmacist observe dose. Diversion control plan usually calls for liquid doses with added water, speaking before and after dosing to avoid 'cheeking' and diverting dose.

THE DOSING WINDOW

What About Take-homes?

- 8 criteria for takehomes defined in 42CFR part 8.
- In general, patients with positive toxicology do not qualify, homeless or unemployed patients do not qualify, patients who do not comply with counseling, or who miss doses do not qualify.
- Take homes are gradually built up from one per week to monthly.
- Physicians are often involved in ‘exception’ take-home decisions.

Note: The famous ‘eight points’ that must be considered for takehomes are: (i) Absence of recent abuse of drugs (opioid or nonnarcotic), including alcohol; (ii) Regularity of clinic attendance; (iii) Absence of serious behavioral problems at the clinic; (iv) Absence of known recent criminal activity, e.g., drug dealing; (v) Stability of the patient’s home environment and social relationships; (vi) Length of time in comprehensive maintenance treatment; (vii) Assurance that take-home medication can be safely stored within the patient’s home; and (viii) Whether the rehabilitative benefit the patient derived from decreasing the frequency of clinic attendance outweighs the potential risks of diversion.

Exception Take-homes Require Approval:

- Physician has to certify that patient meets the eight points of regulation
- Approval from CSAT typically has contingency statements, for example no benzo use, etc.

Examples of Patients who may Need Exception Take-homes:

- Patients in residential treatment
- Patients on dialysis
- Patients dependent on oxygen, portable tanks are small
- Patients in wheelchair, or with difficulty ambulating
- Patients with rapid metabolism requiring more than one daily dose

Review Learning Objectives: Physicians Working in MMT will know:

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