Methadone- An Introduction

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Why methadone ???

- Stop withdrawal (40mg)
- Decrease craving
- Block euphoria of heroin or other illicit opioids (80mg)

Pharmacology

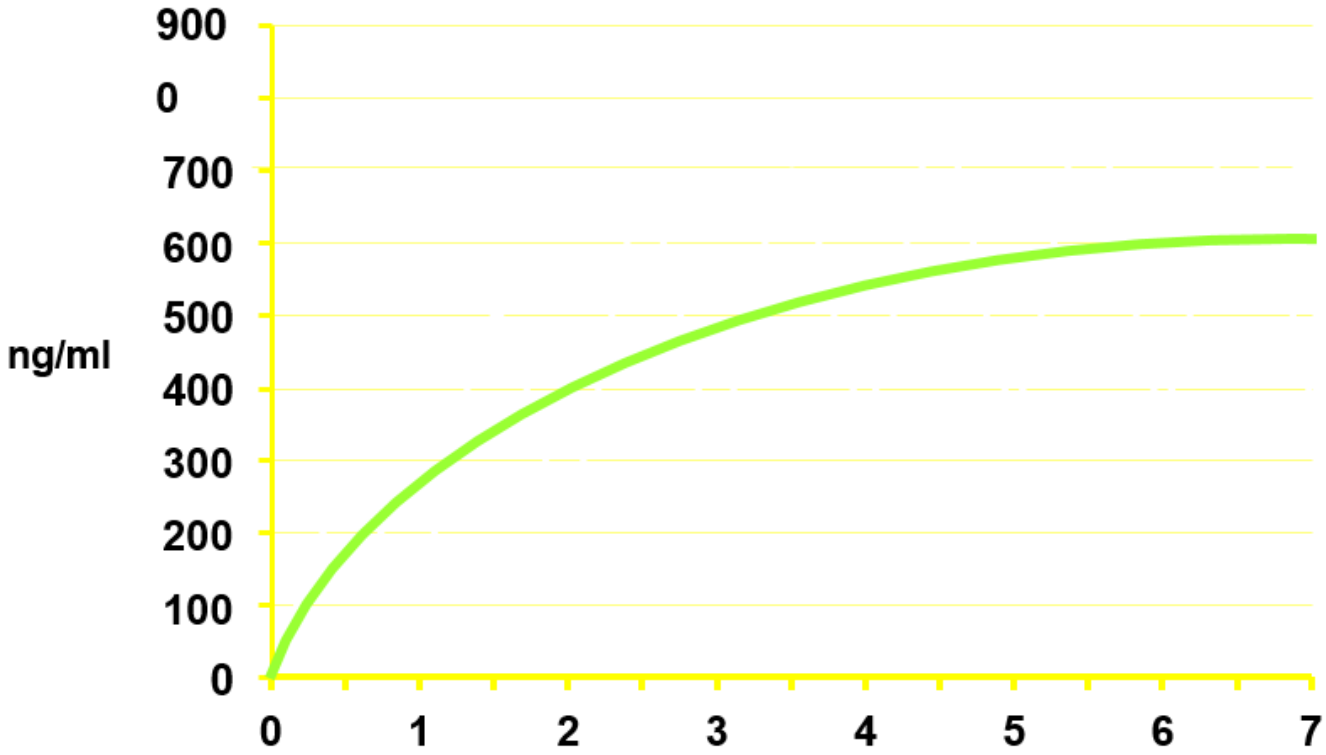
- Agonist at Mu and Delta receptors
- N-methyl-D-asparte (NMDA) antagonist
- Rapid absortion (30 minutes) 85-90% intestine
- Peak 2-6 hours
- Lipophilic, protein bound 70-90%

Pharmacology

- Metabolized by cytochrome P450(CYP)
- Excreted urine and feces, increased with acidic urine (vitamin C)
- Half-life 24-36 hours [range 4-91 hrs]
- Steady state 5-10 days

Steady-State Simulation - Maintenance Pharmacotherapy

Attained after 4-5 half-times, 1 dose / half-life



Adapted from Goodman & Gilman

Time (multiples of elimination half-lives)
Daily dose remains constant to steady-state

Table 1: Factors Affecting Response to Methadone

- Alcohol, tobacco use
- Illicit drug use
- Prescribed and OTC medications or vitamins
- Herbal/alternative products
- Diet, nutritional state
- Psychological stress
- Psychiatric illness
- Physical disorders, disease, infection
- Liver, GI, renal function
- Pregnancy, menopause
- Genetic variations in metabolism

Source: Leavitt 2003

THEREFORE, MUST BE VERY CAREFUL DURING INDUCTION!

Induction

- MUST determine the presence of tolerance!
- Without tolerance, will result in respiratory suppression, pulmonary edema, and death
- Tolerance develops much more rapidly to euphoria than to constipation, sedation, or respiratory suppression

Tips

- Get a thorough history
- Do a physical exam
- Do an EKG
- Do labwork
- START LOW AND GO SLOW

Methadone induction dosing

- NO MORE THAN 20-30 mg a week increase [Verster and Buning 2000; Strang 1999]
- 4-8 hours post dose critical- do not rely on symptoms at END of dosing interval!
- Often what is needed is time, not a dose increase
- Remember, blood levels will rise upto 7 fold during induction even without a dose change
- Blood levels continue to rise for upto 5 days at any given dose

Table 5: Safety Tips During Induction

- ☐ Document all drug use, abuse, and addiction, noting drugs used, frequency, administration routes, and amounts. Include, to the extent possible, opioid-use patterns during 12 months, 30 days, and 24 hours prior to admission.
- ☐ Document the basis for determining opioid *physical* dependence (e.g., 2 or more objective signs plus subjective symptoms).
- ☐ An instant opioid urine screen is recommended.
- ☐ Adequacy of methadone dose during induction is based primarily on response at 3-8 hours after each dose, not at the end of dosing period (24 hours after last dose) when withdrawal is likely to be present.
- ☐ No further increase is required the following day if the patient was comfortable, without overmedication, during 3-8 hours after dosing.
- ☐ Any indication of overmedication during the 3-8 hour post-dose period is a basis for dose reduction, regardless of condition at 24 hours. (Reminder: overmedication can include feeling "good" with increased energy.)
- ☐ If a patient who was normal at 3-8 hours insists on the need for dose increase, give same dose as previous day and reassess the patient in 2-4 hours.
- ☐ Inform patient that peak blood levels of methadone increase daily even if the dose stays the same until steady-state is achieved. Patient may need *more time, not more methadone*.
- ☐ Remember: patients may provide false information at any time in a misguided attempt to get more methadone. Results can be fatal.
- ☐ Patients and their "significant others" (with permission) must be informed about signs/symptoms of methadone toxicity. Overmedicated patients are never allowed to "sleep it off" – help is needed immediately.

Modified from Payte 2000.

ONGOING METHADONE MAINTENANCE

What is an optimal dose?

- <u>One person's optimal dose is not another person's</u> optimal dose
  - Usually 80-120, but much variability
  - Remember, patients on higher doses exhibit superior outcomes in terms of abstinence, treatment retention, and psychosocial rehabilitation [Payte et al., 2003]
  - High dose maintenance=REDUCED risk of fatal heroin overdose during treatment [Caplehorn, 1996]
  - Dole: "As with antibiotics, the prudent policy is to give enough medication to ensure success." [1988]

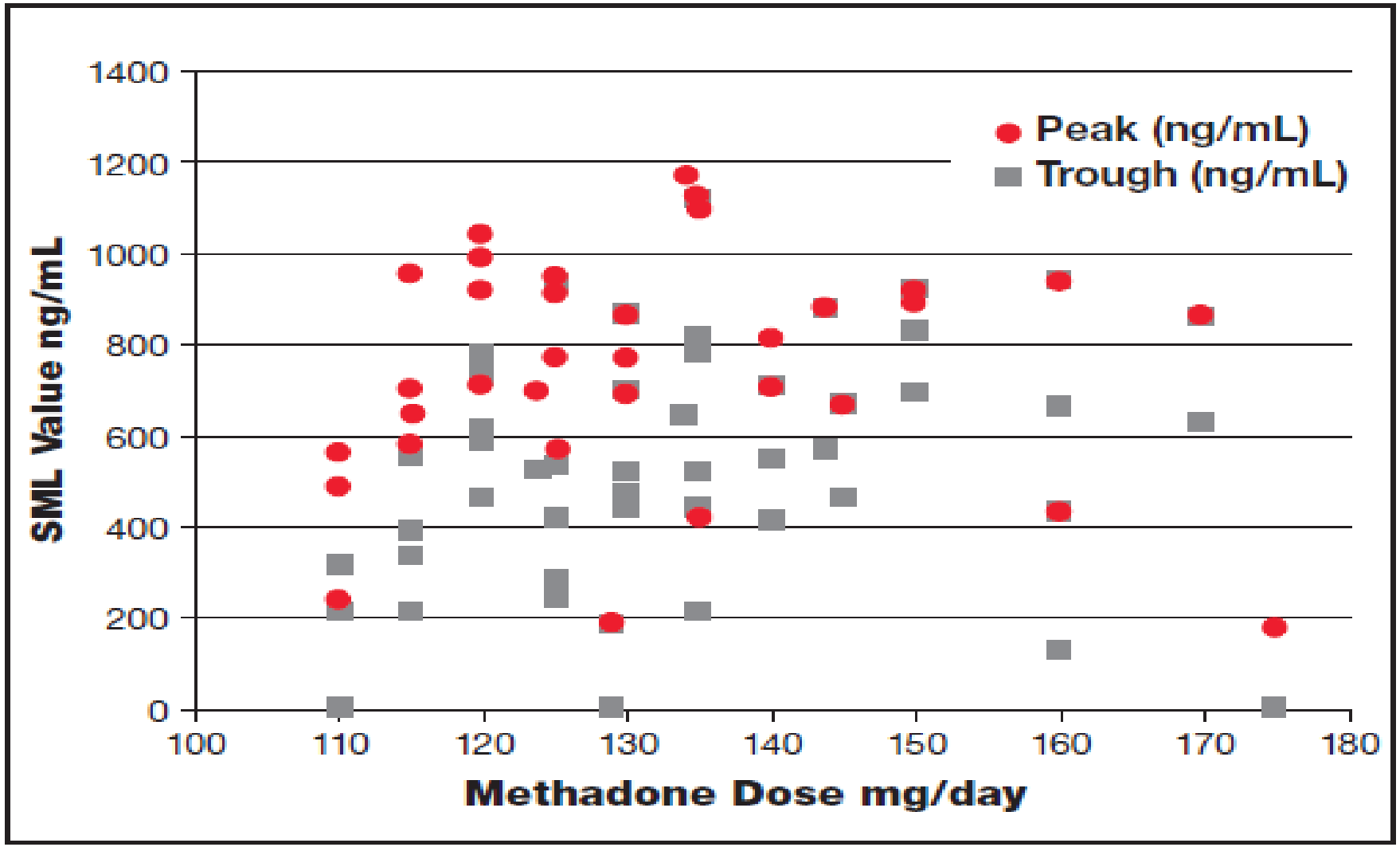


Figure 2: Lack of correlation between methadone dose and either trough *or* peak SML values in methadone-maintained patients (Dorsey 2003).

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

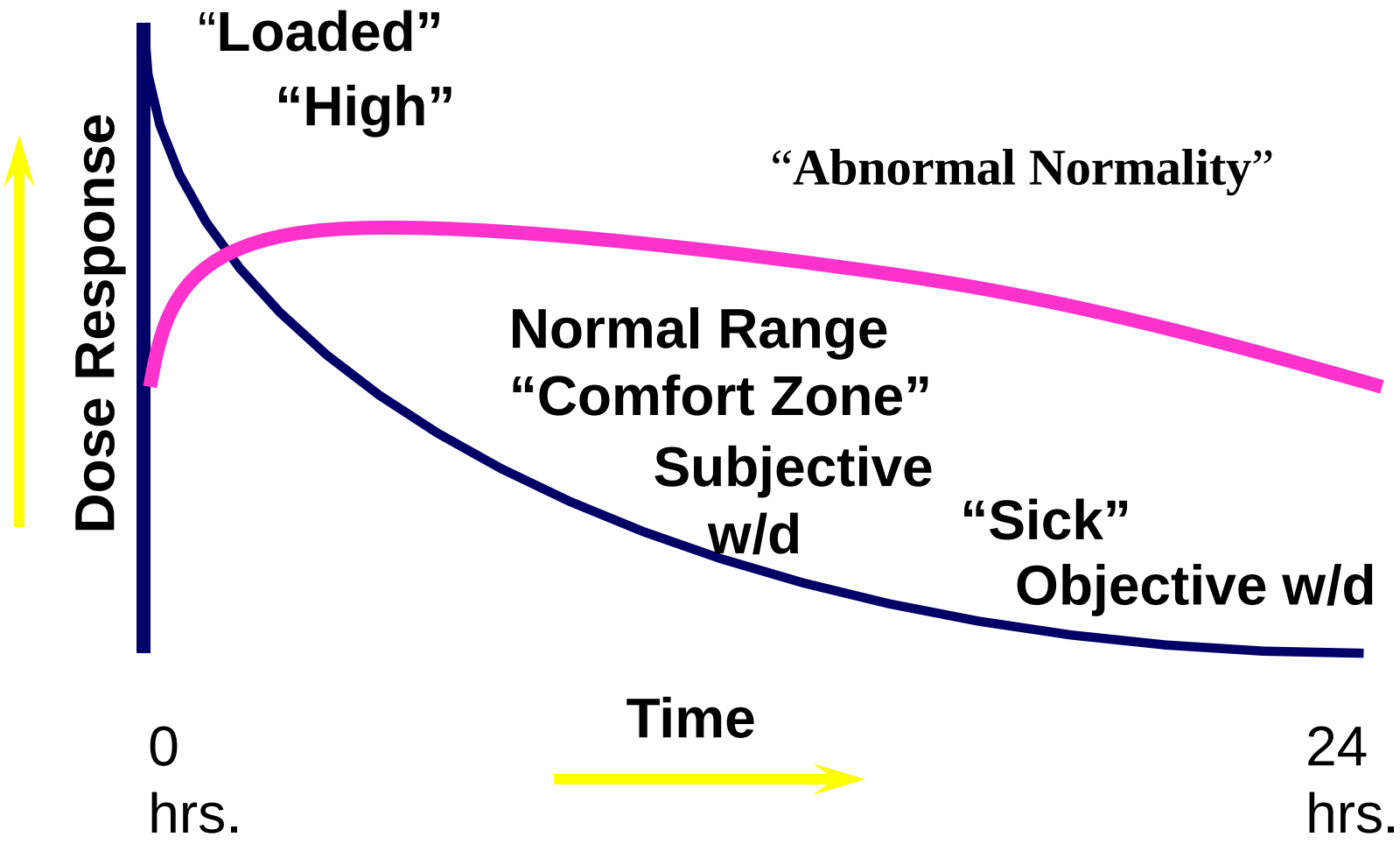


Table 2: Signs/Symptoms of Opioid Withdrawal (Abstinence Syndrome) & Overmedication	
Overmedication Signs and Symptoms	Sedation ("nodding-off," drowsy), miosis (pinpoint pupils), itching/scratching, hypotension, respiratory depression (severe in overdose), depressed mental status, flushing, spasticity. Also, mild euphoria/invigoration (temporary).
Therapeutic Comfort Range	**No withdrawal or overmedication. Ultimately, no craving or illicit opioid use.**
Withdrawal Subjective Symptoms	Drug craving, anxious feelings, depression, dysphoria, irritability, fatigue, insomnia, hot/cold flashes, myalgia/arthralgia (aching muscles/joints), anorexia, nausea, abdominal cramps, restlessness.
Withdrawal Objective Signs	Illicit opioid use, mydriasis (dilated pupils), piloerection ("goose flesh"), diaphoresis (perspiring), muscle tremors/twitching (shaking), diarrhea, vomiting, lacrimation, rhinorrhea, sneezing, yawning, anxiety (outward signs), fever, tachycardia, hypertension.

Sources: Health Canada 2001; Leavitt et al. 2000; Strang 1999.

SAFETY

Safety and Toxicity

- No long term damage to heart, lung, kidney, liver, brain or other organs (Kreek, 2000)
- Normalize hypothalmic-pituituary-adrenal axis
- Normalize immune system
- Does not rot teeth

Side effects

- Sweating 50%
- Constipation
- Ankle edema (ADH)
- Sedation
- Decreased sexual desire
- Insomnia

Side effects

- Urinary retention
- Respiratory depression (children)
- <u>No effect</u> on psychomotor functions
- QT interval and torsades de pointes
- Care in initiation of methadone

Consensus Recommendations [2009]

Table 2. **Consensus Recommendations**

Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.

Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.

Recommendation 4 (Risk Stratification): If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.

Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

QTc = rate-corrected QT.

PREGNANCY AND BREASTFEEDING

Pregnancy

- Methadone has a very long safety record during use in pregnancy; recent studies have also shown the efficacy of buprenorphine [Jones et al., 2010]
- Removes mother from drug using environment
- More likely to get prenatal obstetrical care Reduces obstetrical complications Improves maternal and fetal nutrition
- Increases birth weight
- NO teratogenicity
- Need for enhanced psychosocial services

Nursing considerations

- Methadone and buprenorphine excreted in breastmilk
- Benefits of breastfeeding outweigh the risks of medications, and nursing should be encouraged unless other contraindications present
- Methadone in breastmilk may help with NAS
- Buprenorphine not orally well absorbed, and not likely to help with NAS

EFFICACY DATA

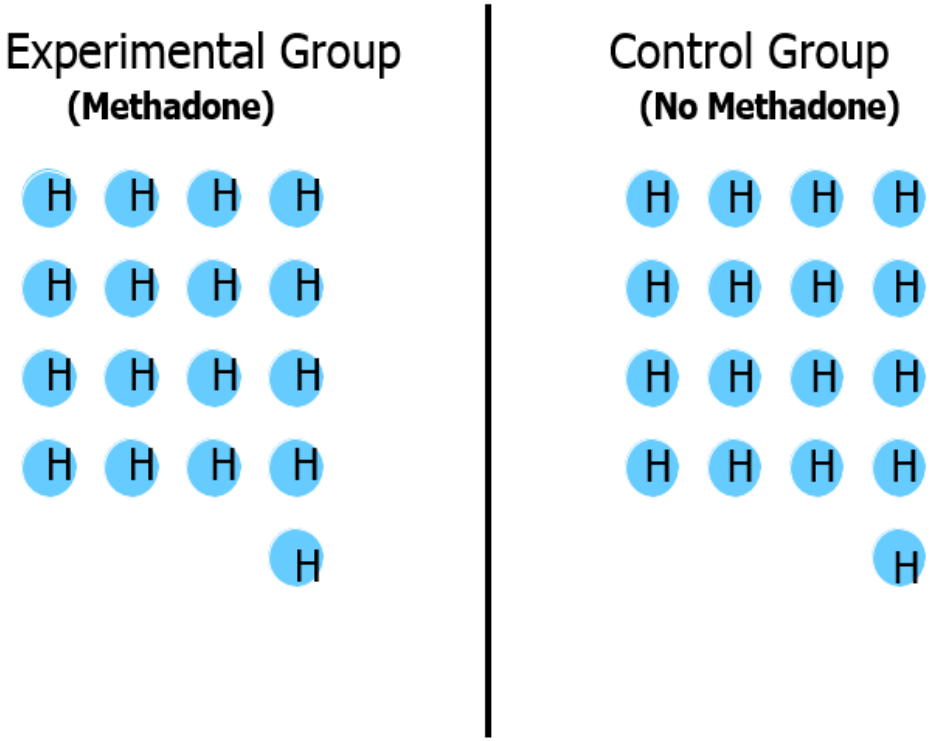
Methadone outcomes

- ↓ Heroin use by 50%
- ↓ HIV 4 fold
- ↑ Employment 24%
- ↓ 60% criminal activity
- Less incarceration
- More child support payments
- 3x as likely to remain in treatment
- Improved hepc treatment adherence
- Mortality reduced
- Cost effective
- Drug users out of methadone treatment 6x more likely to become HIV positive than those in methadone treatment [Metzger et al., 1993]

More benefits of maintenance treatment

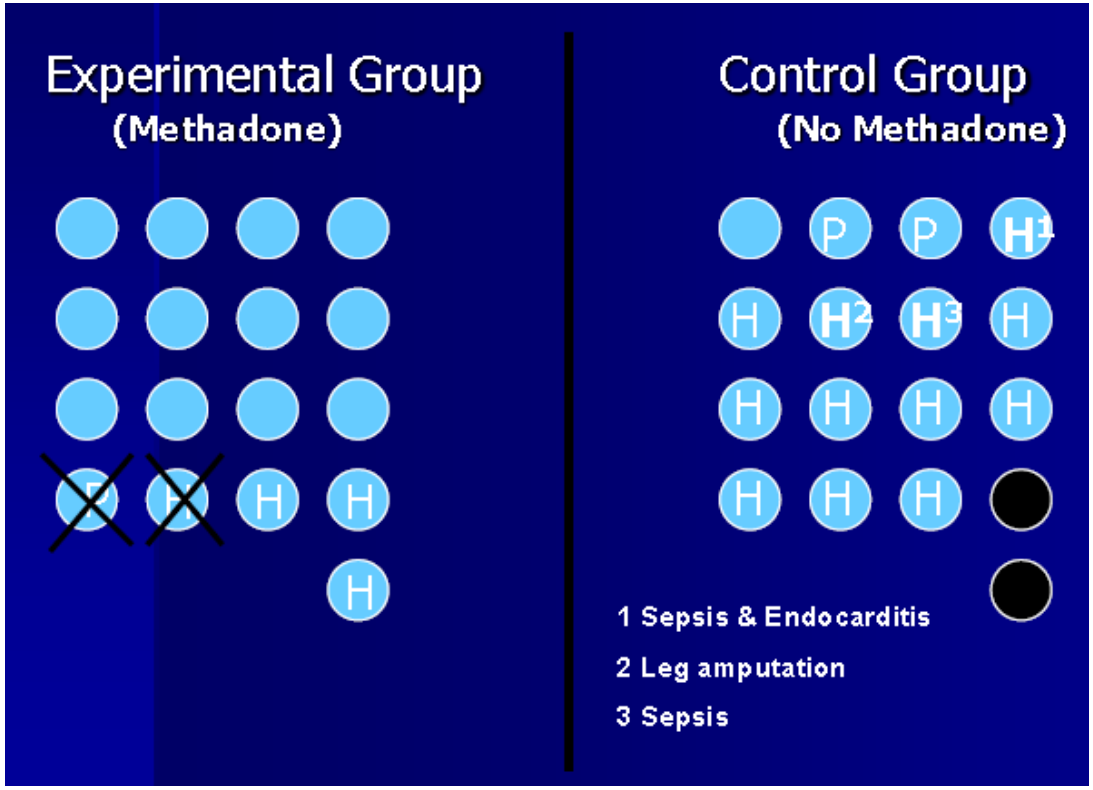
- Decreased IV drug use
- Decreased needle sharing
- Decreased cocaine use
- Decreased unprotected sex
- Decrease in multiple sex partners
- Decrease in commercial sex work

EFFECTIVENESS OF TREATMENT BEFORE



Situation before the randomization study: Each circle represents an individual 20 to 24 yrs. old. “H” indicates regular intravenous heroin abuse. The left half represents the experimental group, which will be accepted for methadone maintenance treatment; the right half represents the controls who will not be given methadone maintenance.

THE EFFECTIVENESS OF TREATMENT AFTER 2 YEARS



Two years after acceptance or decline:

= no drug abuse;

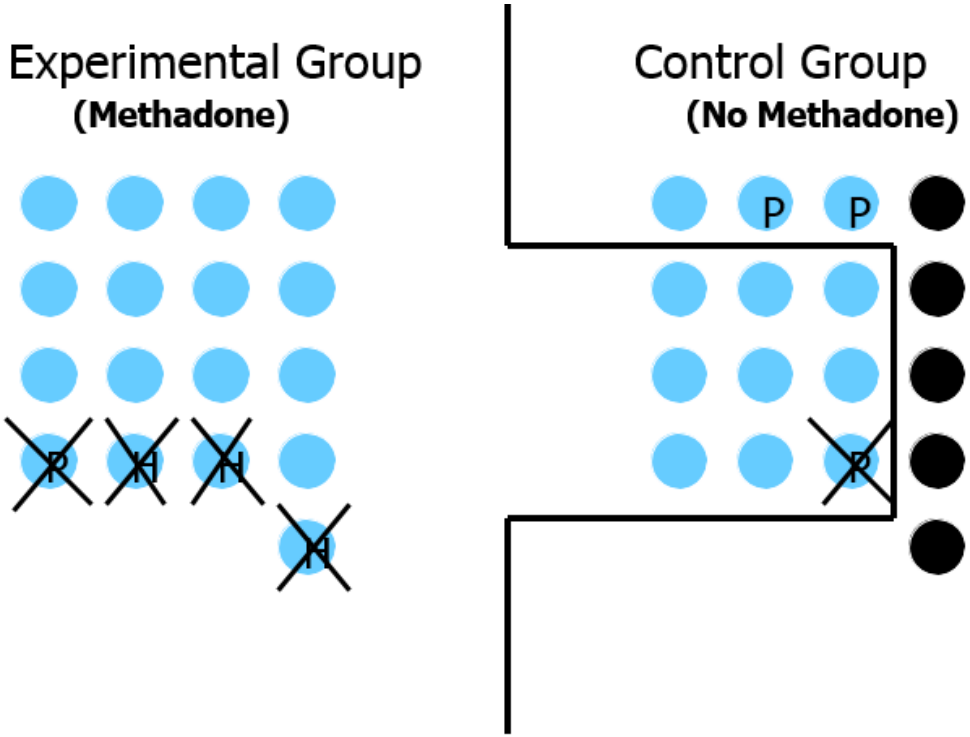
H = abuse of heroin or (in the experimental group) hypnotic depressants;

P = subject in prison;

= subject deceased;

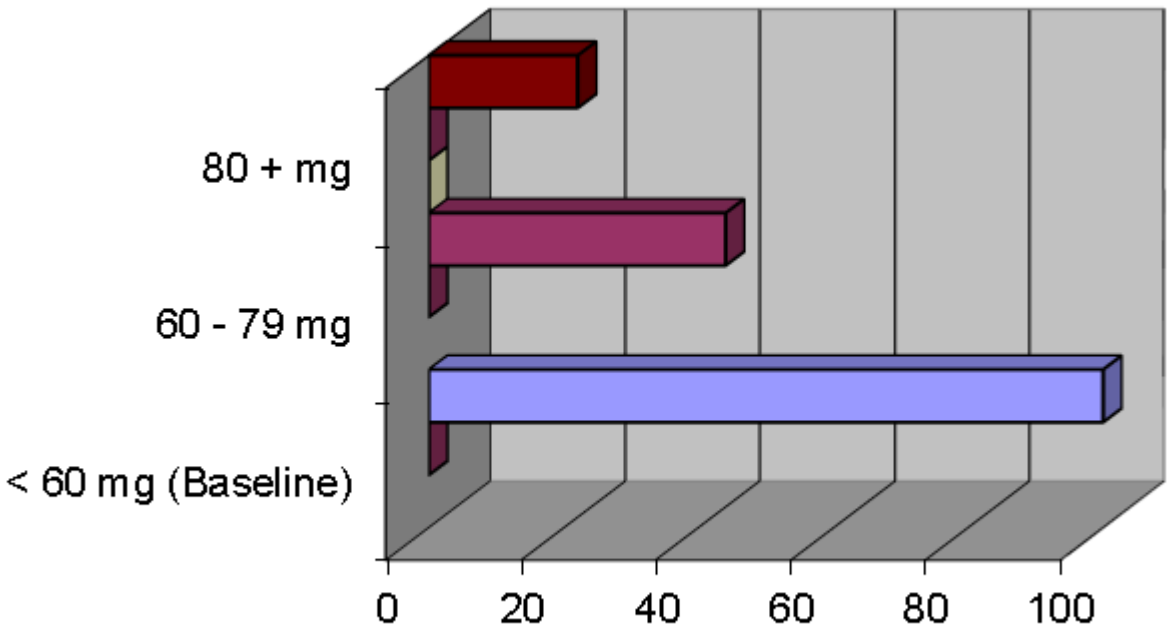
= patient has been expelled from treatment

THE EFFECTIVENESS OF TREATMENT AFTER 5 YEARS



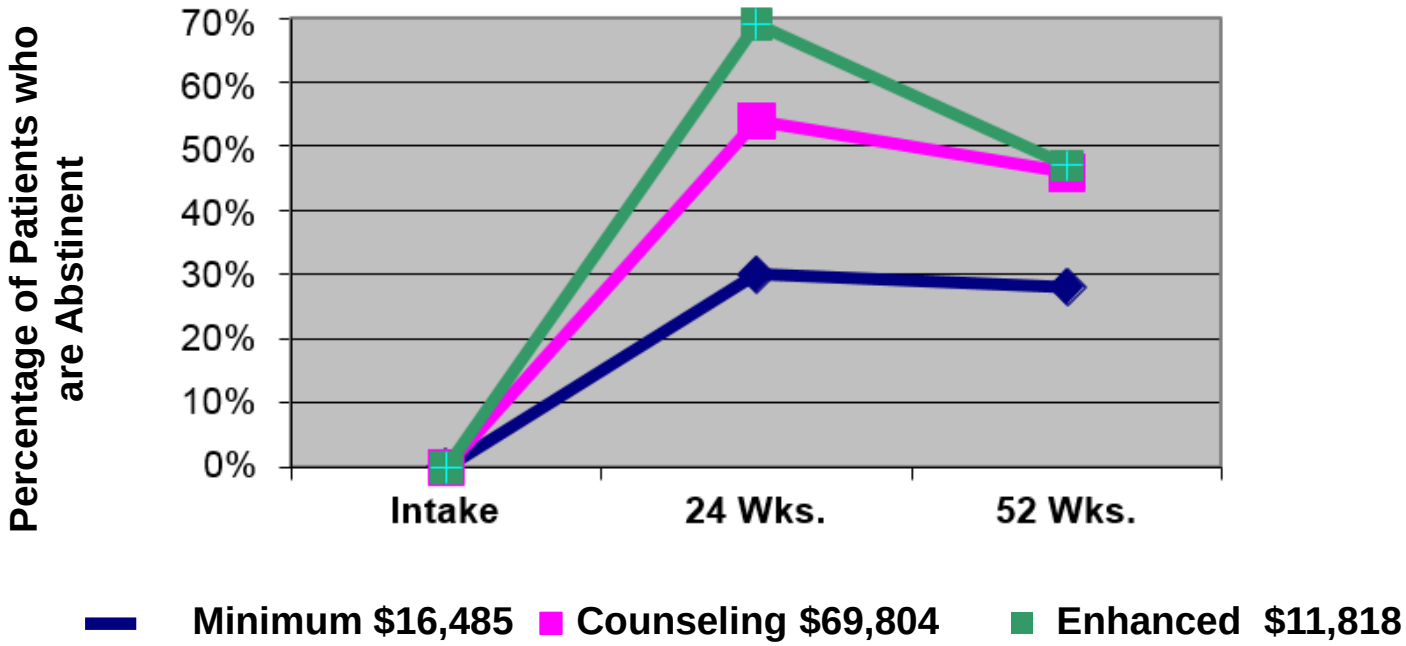
Five years after admission: nine persons from the original control group have been accepted into the methadone maintenance program.

Retention in Treatment Relative to Dose:
Relative Risk of Leaving Treatment



Adapted from Caplehorn & Bell – The Medical Journal of Australia Opioid Maintenance Pharmacotherapy – A Course for Clinicians

Opiate Abstinence by Level of Treatment



Annual Cost per abstinent client