Pharmacotherapy for opioid addiction

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Disclosure slide

- No commercial conflicts to disclose.
Gaps in current treatment of opioid dependence

810,000 to 1,000,000 chronic users of heroin

250,000± patients receiving opioid maintenance treatment (OMT), mostly methadone. (SAMHSA, TEDS)
Number of new non-medical users of therapeutics

(NSDUH, 2002)
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
Outline:

- Opioid maintenance treatment (OMT)
  - Rationale
  - Phases of maintenance
  - Medications for maintenance
- Other pharmacotherapy
  - Tapers and detoxification
  - Symptomatic treatment of withdrawal
  - Antagonists
Four questions patients ask about OMT:

- How is methadone (buprenorphine) better for me than heroin?
- What is the right dose of methadone (buprenorphine) for me?
- How long should I stay on OMT?
- What are the side effects of methadone (buprenorphine)?
Counseling staff
Four questions patients ask about OMT:

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

- Legal
- Avoids needles
- Known amount ingested
Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient

- "Loaded"
- "High"
- "Abnormal Normality"
- "Comfort Zone"
- "Sick"
- Subjective w/d
- Objective w/d

0 hrs. 24 hrs.

Dose Response vs. Time

Opioid Agonist Treatment of Addiction - Payte - 1998
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: High tolerance trough is 400-600 ng/ml, peak no more than twice the trough.
- Not over-sedated
- Blocking dose
Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient

- "Loaded"
- "High"
- "Abnormal Normality"
- Normal Range
  - "Comfort Zone"
  - Subjective w/d
  - "Sick"
  - Objective w/d

Dose Response

Time

0 hrs. → 24 hrs.
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
Average dose range for MMT in the US:

- 80 to 120 mg per day
Phases of Methadone Maintenance treatment:

- Induction: 3-7 days
  - Achieve tissue stores without overdose.
- Stabilization: 2-8 weeks, dose titration
- Maintenance: steady dose
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.

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!
Induction safety, MMT

- Regulation limits first methadone dose to 30mg.
- First day total to 40mg.
- First 7-10 days of treatment is the overdose danger time (rare).
- “Start low and go slow”
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?
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
“How Long???
Long Enough!!”

Tom Payte, MD
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?
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 et al)

- Sweating

- Methadone treatment tied to regulated clinic
Treatment Outcome Data

- 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., vol67, # 5, 6)
Heroin Addiction, Death rates MMT vs Untreated


Opioid Agonist Treatment of Addiction - Payte - 1998
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 infection rates by baseline treatment status. In treatment (IT) n=138, not in treatment (OT) n=88

Pregnancy

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

- Defined in the regs:
  - Short-term = under 30 days
  - Long-term = 30-180 days
Pattern of typical short term detoxification on methadone

Days 1-21 of detoxification

Doses, mg
Example of Pattern of Long-term detoxification with methadone

Stable period, 2 mos.
Outcome of detoxifications:

- Long-term no better than short after detox is over.
- Most patients relapse within six months.

Ref: Sees et al.
Sublingual buprenorphine:

- Partial agonist, sublingual tablet formulated with naloxone.
- Schedule 3, available in office-based practice with certain restrictions.
- Induction – stabilization period only 3 days.
- Strong receptor attachment displaces other opioids.
Comparison of Activity Levels

Mu Receptor Intrinsic Activity

Full Agonist (e.g. methadone)

Partial Agonist (e.g. buprenorphine)

Antagonist (e.g. naloxone)

DRUG DOSE
One slide about LAAM

- Stands for levo alpha acetyl methadol.
- Long acting, allows MWF dosing schedule.
- Listed as a maintenance medication in the regulations.
- Not available in US, nobody marketing it.
- QT lengthened.
Buprenorphine, Methadone, LAAM: Treatment Retention

Study Week

Percent Retained

73% Hi Meth
58% Bup
53% LAAM
20% Lo Meth

Johnson et al, 2000
Buprenorphine, Methadone, LAAM: Opioid Urine Results

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Retained in treatment

Kakko et al., 2003,

Graph showing retention in treatment over treatment duration (days).

- Control, 6-day detox
- Buprenorphine maintenance
Opioid pharmacotherapy, summary:

- Methadone, buprenorphine and LAAM all approved by the FDA for treatment of opiate dependence. (LAAM not currently available from any drug company)
- Best evidence so far supports maintenance.
- Detoxification attempts should have maintenance as a back up in case of relapse.
Naltrexone

- Used as a deterrent, blocks opioid receptor.
- Can be instituted after withdrawal from other opioids.
- Some success in patients who are professionals.
- Danger of overdose if discontinued.
Clonidine

- Off-label use of antihypertensive, helps control opioid withdrawal symptoms
- Part of some supervised withdrawal protocols, pills or patches.
- Main side effect is low blood pressure.
- Buprenorphine taper may supersede.