Learning Objectives

Upon completion of this session, participants will be able to:

1. Identify and describe the pharmacology of methadone related to patient safety
2. Apply evidenced-based practice guidelines for methadone dosing in opioid agonist treatment
3. Recognize patient care issues for risk management related to pharmacotherapy for opioid agonist treatment for addiction
Overview

- Medication Errors / Patient Safety
- Methadone Overdose Deaths
- Opioid Pharmacology
- Evidenced-Based Guidelines
- FDA Advisory Warning
- Phases of Treatment
- Risk Management
Patient Safety / Medication Errors

• Patient Safety
  – Reporting, analysis and prevention of medical error and adverse healthcare events
  – Recent recognition since 1990s
  – Greeks 4th Century B.C., Hippocratic Oath

• Patient Safety Initiatives
  – Application of lessons learned from business and industry
  – Advancing technologies
  – Education of providers and the public
  – Economic incentives

Project-Identifying and Preventing Medication Errors, IOM; Report - Preventing Medication Errors: Quality Chasm Series, IOM, July 20, 2006
Patient Safety / Medication Errors

• Data on adverse health outcomes
• Institute of Medicine (IOM), 1999
  – *To Err is Human: Building a Safer Health System*
    • Media focus upon statistics – 44,000 to 98,000 preventable deaths related to medication errors alone
    • Broad national effort, establishment of a Center of Patient Safety, expanded reporting of adverse events, development of safety programs in health care organizations, attention by regulators, health care purchasers, and professional societies
Patient Safety / Medication Errors

• Definition –
  – A preventable adverse effect of care, whether or not it is evident or harmful to the patient (1)
  – Any error occurring in the medication-use process (Bates et al., 1995). Examples include wrong dosage prescribed, wrong dosage administered for a prescribed medication, or failure to give (by the provider) or take (by the patient) a medication. (2)
  – An adverse drug event is defined as any injury due to medication (Bates et al., 1995). (2)

Patient Safety / Medication Errors

• **Causes of health care errors**
  – **Human Factors**
    • *Variations in provider training and experience*
    • Fatigue
    • Diverse patients
    • Unfamiliar settings
    • Time pressures
    • Failure to acknowledge the prevalence and seriousness of medical errors
  – **Medical Complexity**
    • Complicated technologies, powerful drugs
    • Intensive care, prolonged hospital stay
  – **Systems Failures**
    • Poor communications, unclear lines of authority of physicians, nurses, and other care providers
    • Complications increase as patient to nurse staffing ration increases
    • Disconnected reporting systems, fragmented systems
    • Reliance on automated systems to prevent error
    • Not measuring patient safety initiatives to analyze contributory issues and identify strategies for improvement
    • Cost-cutting measures

Paul A, Gluck, MD: *Medical Errors: Incidence, Theories, Myths and Solutions* (Presentation at the Seminole County Patient Safety Summit, April 22, 2006)

Reasons for focus upon Patient Safety

• Methadone (full agonist)
  – Pharmacokinetic and pharmacodynamic profile
  – Patient variability in pharmacokinetics and pharmacodynamics
  – Induction, risk of death
  – Drug-drug interactions
  – Trend of increased utilization
FDA Health Advisory

• November 27, 2006
  – Revision of the package insert

• Sharp rise in unintentional overdose deaths attributed to prescribed methadone
  – NCHS: > 2 million prescriptions in 2003
    • 2,452 unintentional poisoning deaths with methadone listed as a cause; up from 623 in 1999
  – USA Today, reported in Feb 2006, fatal methadone overdoses totaled 3,849, increased 390% from 1999
  – NCHS report 13% of all overdose deaths in 2004 involved methadone, up from 4% in 1999
FDA Health Advisory

• Concern focused upon increasing use of methadone for pain management

• Labeling change with “black box” warnings apply to all methadone medications, including products used to treat opioid dependence, hence those used in OTPs
Recommendations for OTPs

• “Dear Colleague” letter of December 15, 2006 from Dr. Clark

• **Three key points:**
  – Initial Dose
  – Black box warning (4)
  – Patient information sheet
Methadone
Black Box Warnings

• Deaths
• Respiratory depression
• Cardiac complications
• Use as an analgesic

FDA Public Health Advisory, November 27, 2006
Deaths

- Cardiac and respiratory, during initiation and conversion of pain patients to methadone from other opioids
- Drug interactions, licit and illicit; too rapid titration without appreciation of accumulation of methadone; vigilance necessary
- Caution patients against self-medicating with CNS depressants

FDA Public Health Advisory, November 27, 2006
Respiratory Depression

- Chief hazard associated with methadone administration
- Methadone’s peak respiratory depressant effects typically occur later, and persist longer than its peak effects, particularly during induction.
- Can precipitate iatrogenic overdose, particularly during induction and dose titration
Cardiac Complications

• QT prolongation and serious arrhythmias (torsade de pointes) have been observed during treatment with methadone.

• Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

FDA Public Health Advisory, November 27, 2006
Analgesic use

• Methadone for analgesic therapy in patients with acute or chronic pain should only be initiated if the analgesic and palliative care benefit outweighs the risk
Trends Involving Methadone

• Pennsylvania Data
  – Distribution and Utilization
  – Methadone-associated Mortality
State of Pennsylvania
Methadone Drug Profile
2003 – 2007
Distribution* of Methadone to State of Pennsylvania 2003 – 2006

TOTAL GRAMS
(Includes all liquids, powders and tablets)

* Includes sales to Pharmacies, Hospitals, Practitioners, Teaching Institutions and NTP’s

Source: ARCOS
Date Prepared: 04/15/2008

* Includes sales to Pharmacies, Hospitals, Practitioners, Teaching Institutions and NTP’s

- 2003: 367,771 grams
- 2004: 450,761 grams
- 2005: 522,822 grams
- 2006: 601,471 grams
- 2007: 571,758 grams

* Includes all liquids, powders, and tablets.

Source: ARCOS
Date Prepared: 04/15/2008
Yearly Distribution of Methadone (in grams) to State of Pennsylvania by Business Activity 2005 to 2007

- **2005**: 155,160
- **2006**: 316,162
- **2007**: 349,514

Legend:
- Pharmacies
- Narcotic Treatment Programs

Source: ARCOS
Date Prepared: 04/15/2008
### Yearly Distribution of Methadone (in dosage units) to State of Pennsylvania by Business Activity 2005 to 2007

<table>
<thead>
<tr>
<th>Yearly Distribution</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
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</thead>
<tbody>
<tr>
<td>Pharmacies</td>
<td>14,602,700</td>
<td>17,495,160</td>
<td>18,135,370</td>
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<tr>
<td>Narcotic Treatment Programs</td>
<td>3,470,600</td>
<td>3,693,400</td>
<td>3,616,500</td>
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</tbody>
</table>

- **Drug Enforcement Administration, Office of Diversion Control, Pharmaceutical Investigations Section, Targeting and Analysis Unit**
- **Source:** ARCOS
- **Date Prepared:** 04/15/2008
Figure 1. Poisoning and methadone-related poisoning deaths: 1999–2005

Source: CDC/NCHS, data from the National Vital Statistics System.
Figure 2. Age-specific methadone-related death rates: 1999–2005

Source: CDC/NCHS, data from the National Vital Statistics System.
<table>
<thead>
<tr>
<th>State</th>
<th>1999</th>
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<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>Ratio 2005:1999²</th>
<th>Methadone deaths per 100,000 population, 2005</th>
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</thead>
<tbody>
<tr>
<td>United States total</td>
<td>786</td>
<td>988</td>
<td>1,456</td>
<td>2,360</td>
<td>2,974</td>
<td>3,849</td>
<td>4,462</td>
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<td>128</td>
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<td>18</td>
<td>15</td>
<td>39</td>
<td>73</td>
<td>93</td>
<td>114</td>
<td>10.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Source: National Center for Health Statistics
Summary Report of the Meeting:

Methadone Mortality – A Reassessment

Sponsored by the
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration

Washington, DC
July 20, 2007
Methadone-Associated Mortality

- Data Collection-(Methadone as a cause of death)
  - OTPs, capture vital information about all patient deaths, in treatment and completed
    - Technical assistance
  - OTPs, report dispensing data to state Prescription Management Programs (PMP)
    - PMPs should make information available to medical, professionals, “pts don’t tell their PCPs they are using methadone”

Opioid Pharmacology
The form of methadone used clinically in the United States is a racemic mixture (50/50) of two enantiomers—d and l methadone.
Interindividual Variability of the Clinical Pharmacokinetics of Methadone — Implications for the Treatment of Opioid Dependence

Chin B. Eap, Thierry Buclin and Pierre Baumann

The Pharmacokinetics of methadone in healthy subjects and opiate users

Pharmacokinetics

- Absorption
- Distribution
- Binding in tissues
- Biotransformation, metabolism
- Excretion
- Operationally viewed as how the organism handles a drug

Pharmacokinetics
Absorption and Distribution

• Methadone is a liposoluble drug
• Detected in the blood stream within 15-45 minutes after oral administration
• Rapidly distributed to tissues of the brain, gut, kidney, liver, muscle, lung, saliva, amniotic fluid (large volume of distribution), a distribution which predominates over binding to plasma proteins

Pharmacokinetics
Absorption and Distribution

• Long $t_{\text{max}}$ as well as a slower absorption of methadone in opioid users compared with health subjects, may reflect the pharmacological effect of opioids in slowing gastric emptying.

• Absorption is not stereoselective for either enantiomer, $(R)$ or $(S)$.

Pharmacokinetics of Methadone

Extensive Distribution Phase

Large Volume of Distribution

Long elimination phase
Pharmacokinetics

Absorption and Distribution

• Peak plasma concentrations occurs at 2.5-4 hours after dose intake \( (t_{\text{max}}) \) with some differences among patients (range 1-5 hrs), but independent of the dose.

• Second plasma peak occurs approximately 4hrs after administration.

• A second plasma peak may be detected, probably due to enterohepatic recirculation.

Pharmacokinetics
Absorption and Distribution

• Absorption rates of methadone from tablets and solution appear comparable.
• Methadone pharmacokinetics are independent of the oral formulation of the drug, shown by a double-blind crossover study with 18 patients in MMT.
• No significant change in:
  – Peak plasma concentrations
  – Trough plasma concentrations
  – area under the concentration-time curve (AUC)

# Pharmacokinetics

## Absorption and Distribution

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>~80% (79 ± 11.7%)</td>
<td>~30% (26 ± 13%)</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>~30 hrs. (30.4 ± 16.3)</td>
<td>~3 hrs. (2.7 ± 1.2)</td>
</tr>
</tbody>
</table>

Opioid Maintenance Pharmacotherapy - A Course for Clinicians
Pharmacokinetics
Absorption and Distribution

• Oral bioavailability of methadone tablets was found to be ~70-80% of doses between 10mg and 60mg with marked inter-subject variation (range 36-100%)
  – Study of (6) pts 25 days in treatment, 30mg 10days, 60mg remaining, slight statistically significant difference (p< 0.05) 95% vs 81%
  – Explained by metabolic induction, intestinal CYP3A4k, influence of intestinal first-pass extraction

• Similar bioavailability for both enantiomers.

Pharmacokinetics
Protein / Tissue Binding

• Plasma concentrations are maintained by the tissue reservoir
• Binds readily to plasma proteins, unbound fraction, pharmacologically active portion averages ~12%, which is variable and may account for some of the differences in patient response to methadone

Pharmacokinetics
Protein / Tissue Binding

• Methadone is highly bound to plasma proteins including
  – Albumin
  – Lipoproteins
  – $\alpha_1$-acid glycoprotein

• ($R$) has a lower proportion binding compared to ($S$), confirmed which means higher free fraction for ($R$)

Pharmacokinetics
Protein / Tissue Binding

• Changes in binding of methadone to plasma proteins can alter its total hepatic clearance

• Possible consequences of changes of plasma protein binding of methadone, resulting from an increase of $\alpha_1$-acid glycoprotein, on the pharmacological action of methadone have been the subject of many studies

Pharmacokinetics
Protein / Tissue Binding

• Variation of methadone binding to plasma proteins, such as those produced by marked changes in $\alpha_1$-acid glycoprotein levels, might significantly alter methadone pharmacokinetics.

• Within each individual, there is a genetic polymorphism of $\alpha_1$-acid glycoprotein.

• However, the pharmacological consequence of this genetic polymorphism, and in particular its clinical significance, remains to be elucidated.

Biotransformation of methadone

Methadone → EDDP → EMDP
Pharmacokinetics
Metabolism and Elimination

• Elimination of methadone is mediated by biotransformation, followed by renal and fecal excretion.
• Methadone is extensively metabolized mainly at the level of the liver, but probably also by intestinal CYP3A4.
• Main metabolite of methadone is (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) EDDP, is inactive.
• Nine other metabolites identified in urine, three in feces.
• Elimination of methadone is mostly due to metabolic clearance.

Age, Renal and Hepatic Diseases

• Methadone clearance does not appear to be markedly affected by age.
• Over 65 years, slight decrease was noted.
• Patients with low renal function increase the fraction of methadone excreted through feces, as in anuric patients occurring exclusively.

Age, Renal and Hepatic Diseases

• Data is limited, some authors recommend to reduce the normal dosage by 50% in patients with end-stage renal disease

• Patients with chronic renal replacement therapy, less than 1% of the daily dose is removed by peritoneal dialysis or hemodialysis, which is due to the high protein binding and extensive volume of distribution; which means that dialysis is not useful for the management of methadone overdose

Age, Renal and Hepatic Diseases

• Study of 11 MMT patients with severe alcoholic liver disease, compared with 9 MMT patients with recent alcohol abuse and no evidence of liver disease
  – Longer half-life was measured in the former group (mean ± SE, 32 ± 5 versus 20 ± 2 hrs, p = 0.04)
  – Higher volume of distribution (mean ± SE, 716 ± 100 versus 458 ± 94L, p = 0.06)
  – Apparent oral clearance was similar

Age, Renal and Hepatic Diseases

• Suggested but unconfirmed
  – Usual methadone maintenance dosage could be continued in stable patients with severe alcoholic liver disease
  – Two studies, patients infected with HCV, suggested require significantly higher dosages of methadone than non-infected patients, due to induction of CYP enzymes

Age, Renal and Hepatic Diseases

• Summary:
  – Above do not suggest a major impact of age, renal of hepatic diseases on methadone pharmacokinetics, clinical experience indicates that some of these patients tend to have an exaggerated response to methadone.
  – Cautious administration is advised, in particular during induction or when methadone is prescribed an analgesic to non-tolerant patients.

Hepatic Disease

• Methadone has not been extensively evaluated in patients with hepatic insufficiency.

• Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

[Dolophine PI 2006].
Metabolism by Cytochrome P450

• Cytochrome P450 enzymes
  – Primary catalysts of drug and chemical biotransformation
  – Twelve cytochrome P450 gene “families”, single cell may contain several

• Major isoforms
  – CYP3A4
  – CYP2D6
  – CYP1A2
  – CYP2C9
  – CYP2C19

Metabolism by Cytochrome P450

- **Inducers** – Accelerate methadone metabolism, shorten the duration of its effects, lower SMLs, and precipitate withdrawal symptoms
- **Inhibitors** – Decrease methadone metabolism, raise SMLs, and extend the duration of its effects
- **Genetic and environmental factors** affect enzymes, influencing high degree of individual variation in the response to methadone

(SMLs) Serum Methadone Levels


Metabolism by Cytochrome P450

• Drug – Drug Interactions:
  Specific and extensive review in (Part 2)
Methadone Pharmacodynamics Overview
Pharmacodynamics

• Study of the biochemical and physiological effects
• Operationally viewed as the effects of drugs on the organism and the mechanism by which drugs produce their effects
• Relationship between drug concentration and effect
• Alteration of cellular function; enzymes, cell membranes, receptors
Pharmacodynamics

Opioid Receptors

• **Mu** – (MOR) Subtypes: $\mu_1, \mu_2$

• **Kappa** – (KOR) Subtypes: $\kappa_1, \kappa_2, \kappa_3$

• **Delta** – (DOR) Subtypes: $\delta_1, \delta_2$
Pharmacodynamics

Methadone

• **Mu receptor – Full Agonist**
  - Binds to the receptor and activates the receptor
  - Increasing the amount or dose of the drug produces increasing receptor-specific effects with a maximum effect
  - Supraspinal analgesia, respiratory depression, gastrointestinal stasis, urinary retention, bradycardia, pruritus, euphoria, physical dependence
Mu Receptor Activity Dose Response Curve

Intrinsic Activity

Log Dose of Opioid

Full Agonist (Methadone)

Partial Agonist (Buprenorphine)

Antagonist (Naloxone)

Opioid Maintenance Pharmacotherapy - A Course for Clinicians
NMDA Receptor

• (N-methyl-D-aspartate)
  – Antagonist against Glutamate
  – Glutamate is an excitatory neurotransmitter
  – Play a major role in decreasing craving and the development of opioid tolerance
  – Possible mechanism for efficacy in treating neuropathic pain
Inter-Individual Variation
Pharmacokinetics and Pharmacodynamics
Inter-individual Variability

- **Pharmacokinetics**
  - Variability of CYP enzyme activities, which are genetically and environmentally determined, probably accounts for a substantial part of the inter-individual variability in clearance and plasma half-life of methadone
  - Possible inter-individual variability of P-glycoprotein activity on methadone disposition should also be considered.

Inter-individual Variability

• Pharmacodynamics
  – Methadone has several mechanisms of action and this probably contributes to the marked inter-individual variability in the relationship between the concentration of methadone and its pharmacological effect when measuring outcomes such as pain relief, rated well being, mood states or withdrawal symptoms.

Inter-individual Variability

• Pharmacodynamics
  – Genetic polymorphisms of various receptors, including the μ opioid receptor or the dopamine D₂ receptor could also contribute to this variability.
Inter-individual Variability

• Despite existence of inter-individual variability, there is a good relationship between dose and plasma concentrations within an individual, provided that no inducing or inhibiting concurrent medications are introduced or removed.

The T1/2 of methadone can vary widely among individuals (5 to 130 hours) and this will be reflected in the rate of accumulation with repetitive dosing.

Fig. 2. Plasma methadone concentrations in 17 opioid users after oral administration of a single dose of methadone. Data are normalised to a 10mg dose of methadone HCl (reproduced from Wolff et al.,[59] with permission from Blackwell Science Ltd.)
Evidenced-Based Guidelines

Methadone Induction Guidelines
## Induction Dosing Guidelines

<table>
<thead>
<tr>
<th>Methadone Dose Range</th>
<th>Country (Ref)</th>
</tr>
</thead>
</table>
| Initial dose not to exceed 30 mg, or 40 mg total first day. | USA (Federal Register 2001)  
  TIP #43 (2005)  
  FDA Advisory 2007  
  AATOD 2008  
  ASAM / CSAM (in progress) |
| Initial dose 10-30 mg if tolerance is low or uncertain; 10-20 mg is more appropriate | UK (Drug Misuse and Dependence Guidelines 2007) |
| Initial dose 10-20 mg if opioid tolerance is low or uncertain; 25-40 mg if tolerance is high | Europe (Verster and Buning 2000) |
| 20-30 mg/d at first, more than 30 mg on first day only in patients with tolerance threshold known to be quite high | EUROPAD Italia (Maremmani et al 2002) |
| Initial dose 20-40 mg, based upon estimated tolerance and documented drug use 3-days prior | Australia (Humeniuk et al 2000) |
| Up to 40 mg | British Columbia |
| 20-40 mg | Alberta, Canada |
| 10-30 mg first three days, high risk patients started on no more than 10-20 mg | Ontario, Canada (College of Physicians 2005) |
| 20-40 mg | Quebec, Canada |
| 10-30 mg | Nova Scotia |
| 10-30 mg | Newfoundland |

Adapted from Leavitt SB, Methadone Dosing & Safety in the Treatment of Opioid Addiction, ATF 2003
Stages of Pharmacotherapy

• Induction
• Stabilization
• Maintenance
Methadone Induction

• Contraindications:
  – Does not meet DSM-IV-TR criteria
  – Less than 1yr history of opioid addiction
  – Unable to attend program as required
  – Allergic response
  – Cardiac complications
  – Serious and problematic use of alcohol and or sedative hypnotics

Clinical Pharmacology, Chapter 5, (TIP) Treatment Improvement Protocol #43, FDA Public Health Advisory, November 27, 2006
Induction / Initial Dosing

- Administered under supervision
- No signs of sedation or intoxication
- Manifestation of withdrawal symptoms
- Single dose of 20-30 mg Methadone, not to exceed 30 mg
- Same day adjustment, wait 2-4hrs after initial dose (peak effect), 5-10 mg increase
- Maximum dose first day 40 mg
Induction / Initial Dosing

- Dose adjustments during first week, based upon control of withdrawal symptoms 2-4 hrs after dosing
- Caution, overdose deaths
- Cumulative effects of the first several days’ dosing
- Initial doses should be lower, < 20 mg, for patients whose tolerance is expected to be low upon admission
- Loss of tolerance, incomplete tolerance
Methadone Induction

• **Safety** is key
• General considerations:
  – No signs of opioid intoxication or sedation
  – Signs of opioid withdrawal, objective scale, COWS
  – Physical assessment, r/o acute life-threatening condition
  – Other substance use, alcohol, BZDs, pt advised of the danger during induction and maintenance
  – Observation after first dose (30-60 minutes)
Methadone Induction

• Initial Dosing:
  – “Start low and go slow”
  – Amounts of use reported by patients and dosages from previous treatment episodes should not be used to determine the patient’s current induction dose
  – Typical first dose of methadone, 20-30 mg
  – Federal and state regulations stipulate no more than 30 mg, methadone for first dose
  – Federal and state regulations stipulate total first day dose is 40 mg methadone, unless program physician documents in the patient record that 40mg methadone was insufficient to suppress opioid withdrawal symptoms

Clinical Pharmacology, Chapter 5, (TIP) Treatment Improvement Protocol #43, FDA Public Health Advisory, November 27, 2006
Methadone Induction

• Steady State
  – Based upon multiples of the elimination half-life
  – Approximately four to five half-life times are needed to establish
  – 5 to 7.5 days for most patients
  – Individual variation in some patients
“Build-up” To Steady-State

Days/Half-Lives (T-1/2=15-55 hrs. (Baselt))
Dose constant at 30 mg to steady-state
Methadone Induction

- Dose “holding” (first few weeks)
  - Judge dose by how the patient feels during the peak period (2 to 4 hrs after dosing) rather than during the trough period (just prior to the next dose) generally 24 hrs after ingestion
  - Patients waking up “sick” during the first few days of induction are often convinced that they need a dose increase, when in fact more time is needed to reach steady state.
## Phases of Methadone Dosing

<table>
<thead>
<tr>
<th>PHASE</th>
<th>PURPOSE</th>
<th>RANGE IN MG/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose</td>
<td>Relieve abstinence symptoms</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>Early Induction</td>
<td>Reach established tolerance level</td>
<td>Plus or minus 5-10 mg q 3-24 hours</td>
</tr>
<tr>
<td>Late Induction</td>
<td>Establish adequate dose (desired effects)</td>
<td>Plus or minus 5-10 mg q 5-10 days</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Maintain desired effects (steady-state</td>
<td>Ideally 60-120 mg</td>
</tr>
<tr>
<td></td>
<td>occupation opiate receptors)</td>
<td>May be &gt; 120 or &lt; 60</td>
</tr>
</tbody>
</table>

Payte and Khuri
Patients are 6.7 times more likely to die during induction than untreated heroin addicts (Caplehorn & Drummer, 1999).

42% of drug-related deaths occurred during the first week of OMT (Zador & Sunjic, 2000).

10 OMT deaths are reported — All 10 had been in treatment less than 7 days (Drummer, Opeskin, Syrjanen & Cordner, 1992).
## Comparison - Methadone Dosing Schedules

<table>
<thead>
<tr>
<th>Dose Schedule A</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Effect</td>
<td>45</td>
<td>52.5</td>
<td>56.25</td>
<td>58.125</td>
<td>59.0625</td>
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<table>
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<th>Dose Schedule B</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
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<td>50%</td>
<td>30</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Effect</td>
<td>45</td>
<td>62.5</td>
<td>71.25</td>
<td>75.625</td>
<td>77.8125</td>
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<th>Dose Schedule C</th>
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<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>30</td>
<td>50</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
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<td>77.5</td>
<td>98.75</td>
<td>109.375</td>
<td>114.688</td>
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<tr>
<th>Dose Schedule D</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>30</td>
<td>50</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
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<tr>
<td>Effect</td>
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<td>102</td>
<td>121</td>
<td>130.5</td>
<td>135.25</td>
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<thead>
<tr>
<th>Dose Schedule L</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
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<tbody>
<tr>
<td>50%</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
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<td>55</td>
<td>77.5</td>
<td>98.75</td>
<td>119.375</td>
<td>139.688</td>
<td></td>
</tr>
</tbody>
</table>
George B

- 37 yo, opioid dependence, heroin, age first use 27; cocaine, age first use 21; ETOH age first use 12
- Intake, reported daily heroin, for past 3yrs, varying amounts, based upon how much money available; denied cocaine
- UDS + opiates
- +HCV, HBV
<table>
<thead>
<tr>
<th>Day</th>
<th>1/12/07</th>
<th>1/13/07</th>
<th>1/14/07</th>
<th>1/15/07</th>
<th>1/16/07</th>
<th>1/17/07</th>
<th>1/22/07</th>
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<tbody>
<tr>
<td>Dose Schedule</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>COWS not available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father called clinic, advised of patient’s demise on 1/17/07; funeral was at 1:00 pm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Barbara B

- 26 yo, opioid addiction 3-4 yrs, heroin, prescription opioids
- Intake reported IDU with heroin, 3 bags, (2) Percocet tabs in the early am
- Exam demonstrated physiological withdrawal: signs and symptoms, COWS 21, + UDS for opiates
- +HCV, HBV, MDD, PSTD
## Barbara B

<table>
<thead>
<tr>
<th>Dose Schedule</th>
<th>Observation</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8/7/07</td>
<td>8/8/07</td>
<td>8/9/07</td>
<td>8/10/07</td>
<td>8/11/07</td>
<td>8/12/07</td>
<td>8/13/07</td>
</tr>
<tr>
<td>30</td>
<td>COWS = 21</td>
<td>18hrs, restless sleep, nausea, sweats, dilated pupils</td>
<td>50</td>
<td>50</td>
<td>70</td>
<td>70</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22hrs, visibly ill, clammy, pupils dilated</td>
<td>Clinic ~10 am, home, asleep on Sofa ~11 am, found unresponsive by family, 911 call</td>
<td>ICU Narcan</td>
<td>D/Ced to home, RTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stabilization
Methadone Stabilization

• Differentiation between “Stabilization” and “Steady State”
  – **Steady State**: achieved when a treatment medication is eliminated from the blood at the exact rate that more is added
  – **Stabilization**: achieved when the patient no longer exhibits withdrawal, drug-seeking behavior or craving
  – Correct steady state medication dosage contributes to a patient’s stabilization
  – Stabilization phase concentrates upon finding the right dosage for each patient

TIP #43: Chapter 5 – Clinical Pharmacology
Methadone Stabilization

• Desired responses
  – Prevention of withdrawal
  – Elimination of drug hunger, craving
  – Blockade of euphoria
Optimal Dosage
Optimal Dosage

• Several studies, randomized, double-blind design, shown pts receiving methadone dosage in the range of 60-100mg/d performed significantly better on measures of:
  – Retention in treatment
  – Opioid use
  – Opioid craving
  – Compared to 20-50mg/d

Optimal Dosage

- Study, 238 heroin dependent, clear inverse correlation between dosage increase and risk of leaving treatment.
- Relative risk of leaving treatment was halved in the group receiving 60-79mg/d as compared to group < 60m/d, and halved again for the group at 80mg/d or >.

Optimal Dosage

• Despite the compelling evidence of the necessity of effective dosages of methadone, it is a real public health problem that low dosages are still prescribed in many places, not for pharmacological but for political, psychological, philosophical or moral reason.

Optimal Dosage

- Dose policy may vary between countries, states and clinics and is sometimes based upon the belief that prescribing of high dosages would be too permissive.
- Besides the irrationality of prescribing dosages that are marginally adequate, the policy of using low dosages creates inequality between patients, whose metabolic clearance is genetically and environmentally determined.

Optimal Dosage

• TIP #43
  – Consensus panel recommends that a maintenance dosage of methadone not be predetermined or limited by policy if that policy does not allow for adjustments for individual patients.
Optimal Dosage

• Even though evidence demonstrates that methadone dosages ranging between 60-100mg are effective for the majority of pts, dosages > 100mg are required for optimal benefit in some patients.
• Dole observed long ago that 100mg/d of methadone is not sufficient for some pts, and his original study, establishing the efficacy of methadone for decreasing heroin use, was conducted with daily dosages ranging from 50 to 150 mg/d
Optimal Dosage

• Thus, in the absence of prospective randomized studies examining the efficacy of methadone >100mg/d, observations suggest that more studies are needed.

• Based upon data presently available and on the inter-individual variability of methadone pharmacokinetics and blood concentrations for a given dosage, opinion is that no convincing data argue against the use of methadone dosages higher than 100mg/d, provided all necessary steps are taken to ensure the safety of treatment.
Methadone Maintenance

- Patient is responding optimally and routine dosage adjustments are no longer needed
- Individual variation – some patients will require frequent or occasional adjustments
  - Periods of increased stress
  - Strenuous physical labor
  - Negative environmental factors
  - Greater drug availability
  - Pregnancy

Clinical Pharmacology, Chapter 5, (TIP) Treatment Improvement Protocol #43
Common Dosing Issues
SMLs – Serum Methadone Levels

TDM – Therapeutic Drug Monitoring
SMLs

The Relationship Between Mood State and Plasma Methadone Concentration in Maintenance Patients

Dyer KR, White JM, Foster DJR, Bochner F, Menelaou A, Somogyi AA. Royal Adelaide Hospital, Adelaide, Australia


This study demonstrates that significant mood changes occur in response to changes in methadone concentration, and these are more pronounced in “non-holders” (early onset withdrawal) than “holders” (stable for 24 hours).
The difference in w/d severity between self-reported holders and non-holders was not related to either methadone dose or trough plasma methadone concentration, demographic or other individual characteristics but, rather; to the significantly more rapid rate of decline in plasma concentration during the period from the peak concentration until the trough.

...high peak/trough ratio
**Fig. 1.** Mean (± SEM) plasma methadone concentration-time profile during a single 24-hour interdosing interval in 18 methadone patients.
Serum Methadone Levels:

- Do NOT indicate adequacy of dose
- Do not predict methadone toxicity
- Define Peak to Trough ratio, the rate of decline or metabolism
- Define the optimum dosing interval to maximize benefits of OMT
- Clinical Picture / Dose Incongruities
- Suspected Drug Interactions
- Justification of “unusual” dose levels/schedules
- Monitor effectiveness of divided dose schedules
Interpretation of Serum Methadone Levels

Peak or trough Levels alone are of negligible clinical utility in determining adequacy or toxicity of a given dose.

*Dose adequacy is determined clinically!*

Optimum levels for cross-tolerance ("Blockade") are not clear, thought to be >400 ng/ml but or more but does occur at lower levels, such as 200 ng/ml.

Peak/Trough Ratio ideally less than 2, 700/400=1.75, values > 2 suggest rapid metabolism, 800/200=4

*Rate of change!*

Opioid Maintenance Pharmacotherapy - A Course for Clinicians
There is linear relationship between dose and methadone levels but NOT to clinical response.

Optimum Dose? ...NOT!

Payte & Khuri - Adapted from Wolff et al 1991

Opioid Maintenance Pharmacotherapy - A Course for Clinicians
SMLs

• “400 ng/ml” – (trough), adequate therapy for stabilization

• No study clearly demonstrated the existence of such a threshold Eap, et al

• Recommended SML ranges have not been validated against self-reported clinical symptoms Hiltunen, et al


Therapeutic Drug Monitoring

- Not necessary for all patients
- Careful clinical follow up of objective signs and subjective symptoms is sufficient for dosage titration
- Useful in selected situations
  - Dosages >100mg, with fear of overdose and potential cardiotoxicity

Therapeutic Drug Monitoring

• Useful in cases of treatment failure, persistent withdrawal symptoms or use of illicit opioids
  – Target values of 250 µg/L or 400 µg/L can be recommended for (R)- or (R,S)-methadone
  – Should only be used after a sufficient period of adequate dosages (at least 60mg/day, but preferably 80-100mg/day)

Chin B. Eap, et. al, Interindividual Variability of the Clinical Pharmacokinetics of Methadone – Implications for the Treatment of Opioid Dependence
 Therapeutic Drug Monitoring

— Author’s experience, demonstration in patients of low methadone blood concentrations, presumably due to high clearance, can be of value for overcoming the fear of the prescriber and/or of the patient to increase the dosage.

Therapeutic Drug Monitoring

• Concurrent Medications and Pregnancy
  – Introduction of drug known to induce methadone clearance, simple TDM before and after the introduction of inducing agent can be helpful for titrating the dosage; allows for quicker titration, which might take months ordinarily, slow titration, to avoid overmedication
  – Convincing pts of need to increase, ART meds, etc.
  – Also useful for dosage decrease, inhibitor of methadone clearance, help convince pt

Therapeutic Drug Monitoring

- The extent of a drug interaction is difficult to predict.
- On prescribing a drug that inhibits a particular isoform of the CYP family, it is expected that a patient with a low CYP activity will not be affected to the same extent as another with a high CYP activity.

Therapeutic Drug Monitoring

• Diversion of methadone
  – TDM may be useful for checking compliance
  – Blood concentrations tend to remain stable within the same individual provided the drug is taken in steady-state conditions and that the samples are drawn at similar time points during the elimination phase, preferably just prior to intake of the next dose.

Therapeutic Drug Monitoring

• Concentrations of Methadone can be measured after a period during which the intake of methadone is controlled and supervised, daily 4-7 consecutive days.
• If necessary, this reference value can then be used to assess a change in compliance during take-home periods.
• Patient serves as his/her own control and methadone blood concentrations cannot easily be used to determine a theoretical dosage.

Therapeutic Drug Monitoring

• Any changes in methadone concentrations could reflect a modification of compliance

• Such changes could also result from a changed methadone clearance due, for example, to the intake of concurrent medications

Split doses

• Patients receive divided daily dose, generally 2-3 times per day
• Goal is to achieve the peak-to-trough ratio in blood level concentrations to avoid withdrawal symptoms
• Consideration for clinical stability and responsibility to handle take-homes, risk/benefit
Rapid Metabolizer - High Single and Split Dose Simulation

- **Single**
- **High Single**
- **Split Dose**
- **Minimum**
- **'Normal' Ceiling**

**ng / ml**

- **High**
- **Normal**
- **Sick**

**Hours**

0 4 8 12 16 20 24
Contingency Contracting

• Consensus (TIP #43)
  – Any manipulation of dosage as either a positive or negative consequence of behavior is inappropriate and has no place in MAT.
  – Only relevant consideration is involving take-home medication, which is controlled by Federal regulations
  – Controversial
Overmedication

- “Nodding” or falling asleep at inappropriate times, feeling “loaded”
- Nausea, particularly in newer patients
- Scratching face, nose continuously
- Sedation may be unapparent in some, feeling mildly stimulated
- Physical reminder of intoxication, discouraging, frightening, relapse triggering

Clinical Pharmacology, Chapter 5, (TIP) Treatment Improvement Protocol #43
Vomited Doses

- **Consensus**
  - Witnessed emesis, replacement
  - Emesis > 30 minutes after dosing, reassurance
  - Emesis 15-30 minutes after dosing, 50% replacement
  - Emesis 15 or < minutes after dosing, whole dose
  - Risk of toxicity with repeated doses, persistent vomiting

Clinical Pharmacology, Chapter 5, (TIP) Treatment Improvement Protocol #43
Missed Doses

• 1 – 2 Missed Doses
  – Less than 3 consecutive days absent, the dosage can remain unchanged

• 3 – 5 Missed Doses
  – > 3 consecutive days absent, dosage reduction or re-induction is advised, tolerance may be altered due to absence
    – Increases 5 – 10 mg per dose up to the previous level

• Recurrent pattern of irregular attendance
  – Case consultation to address non-adherence is recommended
Take-home Medication

- Federal Regulations (42 CFR, Part 8 § 12(i))
- Pennsylvania Chapter §715.16 Code of Regulations
- Dear Colleague Letter – January 24, 2008, restatement of SAMHSA policy when the OTP is closed for business, Sundays and holidays, etc.
Take-home Medication

• Medical Director responsibility

• Exceptions
  – Unusual circumstances of hardship
  – Medical conditions
  – State and Federal requirements, forms and procedures, etc.

• Routine
  – Pennsylvania Chapter §715.16 Code of Regulations
Take-home Medication

- Controversial
- Patient stability
- Unsupervised, decreased clinic attendance
- Specific rationale
- Potential for rehabilitation – employment, education, childcare, care giver responsibility, important endeavors
- Regular review of the specific rationale
- Drug Testing (Part 2)
Medically Supervised Withdrawal

• Voluntary Tapering
• “I want to detox”, “I want to get off the stuff”
• Likelihood of success, depends upon individual factors such as motivation, social support, physical and psychological well being
• Adequate therapeutic trial or length of stay in treatment
• Stabilized patient

Clinical Pharmacology, Chapter 5, (TIP) Treatment Improvement Protocol #43
Medically Supervised Withdrawal

• Informed consent process
• Relapse prevention strategies
• Self-help meetings
• Methadone dosage reduction
  – (5-10%) increments every 1 – 2 weeks, adjusting as needed for patient conditions and comfort
  – “40 and below” – less steady state occupancy of opiate receptors, symptomatic
Medically Supervised Withdrawal

• Drug screen monitoring, substituting other drugs to compensate for withdrawal
  – (+) opiate, taper discontinued
  – Opinion, ? (+) BZDs, THC, cocaine, ETOH
  – (AMA) protocol

• “Blind detox”
Involuntary Discharge

- Decision made in the best interest in the health and safety of the patient
- **Pennsylvania Chapter §715.21 Code of Regulations**
  - Policy and procedure
  - Failure to retain in treatment despite all other efforts
  - **Specific conditions:**
    - Committed or threatened to commit acts of physical violence
    - Possession of a controlled substance without a prescription, or sold or distributed controlled substances
    - Absent for 3 or more consecutive days without cause
    - Failed to follow treatment plan objectives
  - **Minimum 7 day taper**, except for committed or threats to commit act of physical violence
Involuntary Discharge

• Specific Conditions
  – Non-adherence with clinic attendance, repeated pattern that is serious (missed dosing days)
  – Intoxication, precarious or dangerous to continue methadone
  – Failure of progress in treatment such that a higher level of care is required, continued use of methadone poses a danger to the patient
  – Transfer to another program
Risk Management

• OTP – Risk Management Programs
  – Legal and liability concerns
  – Patient deaths related to overdose
  – Dosing and monitoring issues
    • Induction
    • Maintenance, complex needs, co-occurring disorders, polydrug use
    • Take-home bottles
    • Liability for patients’ actions / behavior
  – Impaired driving concerns
Risk Management

- Staff training
  - Knowledge and competency
- Policy and Procedure
- Guidelines / Standards
  - “Standard of care” that will be used to measure OTPs in assessing whether they meet their “duty of care”
- Patient informed consent / education
  - Minimize risk