METHADONE

Methadone Mortality Working Group
Drug Enforcement Administration
Office of Diversion Control
April 2007
Background

- In 2003, SAMHSA convened a multidisciplinary group for a national assessment of methadone-associated deaths.

- This meeting was prompted by
  - Increasing methadone-associated deaths
  - Negative press that regarded methadone as “widely abused and dangerous”
  - Uncertainty regarding the source of methadone (i.e. pain management or narcotic treatment)
  - Uncertainty regarding the cause of deaths

- The Methadone-Associated Mortality Assessment Report was published in 2004 (DHHS publication No. 04-3904).
Methadone-Associated Mortality Assessment Findings

- Nearly all narcotics, including methadone, were increasingly associated with diversion, abuse and deaths.

- Both respiratory depressant effects and/or cardiovascular effects at high doses can be fatal.

- Methadone treatment for narcotic addiction has a proven safety record and actually reduces mortality in this population.
Three primary scenarios were seen in methadone associated deaths:

1) Accumulation to toxic levels of methadone during the start of opioid treatment or pain management due to overestimation of tolerance and methadone’s long, often variable, half-life.

2) Misuse of diverted methadone by individuals with little or no opioid tolerance.

3) Synergistic effects of methadone in combination with other CNS depressants (i.e., alcohol, benzodiazepines or other opioids).
Methadone-Associated Mortality Assessment Findings (cont)

- Methadone is becoming more widely available due to increased use for pain management and a relaxation in regulations regarding take-home doses of methadone from narcotic treatment programs (NTPs).

- There is no comprehensive database of drug-related deaths in the U.S.

- Problems with uniform definition by Medical Examiners preclude uniformity in reporting “cause of death” on death certificates.

- It seemed more likely that the increased availability of methadone was the result of use in pain management as there was not a great increase in NTP patient population. In addition, the increased incidents of death started prior to a change in take-home regulations.
Current Problem

- All available data indicate that methadone continues to be increasingly used, misused, diverted, and abused.
- Significant increases in methadone-related deaths are being reported. In some areas, deaths related to methadone are outpacing other narcotics.
- Federal agencies must address this public health crisis.
On November 27, 2006, the Food and Drug Administration (FDA) put out a public health Advisory stating that methadone use in pain control may result in death and life-threatening changes in breathing and heart beat. Pain relief from a dose of methadone lasts about 4-8 hours but methadone stays in the body much longer, 8-59 hours after administration. As a result, patients may feel the need for more pain relief before methadone is cleared from the body. Methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements. FDA advised that methadone doses for pain should be carefully selected, slowly titrated to analgesic effect and closely monitored by their prescribing physician. The black box warning in the approved labeling for Dolophine Hydrochloride (methadone-containing 5 and 10 mg tablets) has been altered to warn patients not to take a higher dose or take Dolophine more frequently than prescribed.

Note: This advisory has not resulted in any decrease in the numbers of prescriptions for methadone (IMS Health Prescription Audit).
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 Quota History

Source: DEA

Bar chart showing the Methadone Quota History from 1998 to 2006. The y-axis represents Kg and the x-axis represents the years from 1998 to 2006. The chart shows an increase in the quota over time.
Note: In 2006, there were about 35-fold more hydrocodone prescriptions, 10-fold more oxycodone and 2-fold more fentanyl prescriptions compared to methadone prescriptions.
Who is prescribing methadone?

5 and 10 mg tablets Rx
Top Prescribers:
– Anesthesiologists
– Family Practitioners
– Internists
– Osteopaths
– Physical Med. & Rehab
– Neurologists
– Nurse Practitioners

40 mg diskettes Rx
Top Prescribers:
– Family Practitioners
– Anesthesiologists
– Internists
– Osteopaths
– Physical Med. & Rehab
– Nurse Practitioners
– General Practitioners

Source: IMS Health, National Prescription Audit, November 2006
2000 - 2006 Methadone Distribution
Business Activity Comparison

Source: DEA ARCOS 04/2007
2006 Distribution* of Methadone

Source: DEA ARCOS 04/2007

- **5 mg & 10 mg Tablets**: 4,412,651 grams (32%)
- **Liquids**: 5,283,295 grams (39%)
- **40 mg Diskettes**: 3,236,405 grams (24%)
- **All Other**: 655,224 grams (5%)

* Based on total gram amount
Includes NTP's
2006 Distribution* of Methadone to Pharmacies

Source: DEA ARCOS 04/2007

- **5 mg & 10 mg Tablets**
  - 3,934,446 grams
  - 69.2%

- **40 mg Diskettes**
  - 1,676,225 grams
  - 29.5%

- **Liquids**
  - 58,025 grams
  - 1.0%

- **All Other**
  - 20,255 grams
  - 0.4%

* Based on total gram amount
2006 Distribution* of Methadone to NTP’s

Source: DEA ARCOS 04/2007

Liquids
5,192,096 grams
70.7%

40 mg Diskettes
1,481,873 grams
20.2%

All Other
632,878 grams
8.6%

5 mg & 10 mg Tablets
41,103 grams
0.6%

* Based on total gram amount
2006 Purchases* of Methadone 40 mg Diskettes by Business Activity

Source: DEA ARCOS 04/2007

- 19,275 Pharmacies: 1,676,225 grams (51.79%)
- 810 Hospitals: 45,329 grams (1.40%)
- 58 Practitioners: 44,285 grams (1.37%)
- 424 NTP’s: 1,470,566 grams (45.44%)
- 0 Teaching Institutions: 0 grams (0.00%)
- 0 Mid-Level Practitioners: 0 grams (0.00%)

* Based on total gram amount
2006 Purchases* of Methadone Liquids by Business Activity

Source: DEA ARCOS 04/2007

- 792 NTP’s
  - 5,164,478 grams
  - 97.75%

- 4,410 Pharmacies
  - 58,025 grams
  - 1.10%

- 1,979 Hospitals
  - 60,769 grams
  - 1.15%

- 6 Practitioners
  - 23 grams
  - <0.01%

- 0 Mid-Level Practitioners
  - 0 grams
  - 0.0%

- 0 Teaching Institutions
  - 0 grams
  - 0.0%

* Based on total gram amount
2006 Distribution* of Methadone to Practitioners

Source: DEA ARCOS 04/2007

- 40 mg Diskettes 44,718 grams 87.53%
- 5 mg & 10 mg Tablets 6,331 grams 12.39%
- Liquids 23 grams 0.05%
- All Other 19 grams 0.04%

* Based on total gram amount
DRUG DISTRIBUTION

TOP 5 STATES, January - December, 2006

Methadone 5 mg and 10 mg Tablets

GRAMS PER 100K POPULATION

Includes NTP's

Excludes NTP's
DRUG DISTRIBUTION

TOP 5 STATES, January - December, 2006

Methadone 40 mg Diskettes

Source: DEA ARCOS 04/2007
What problems are associated with methadone products?
Poison Control Data
Drug Exposures

Source: National Association of Poison Control Centers (AAPCC)
2005 AAPCC
Deaths/100 Exposures

Source: National Association of Poison Control Centers (AAPCC)
NFLIS Exhibits

Source: DEA National Forensic Laboratory Information System

There was a 170% increase in methadone exhibits from 2002 to 2006.
This data suggests that on a per prescription basis, methadone is more likely to be involved in illicit activities (diverted and abused) than either hydrocodone or oxycodone.
Methadone Formulations Analyzed in Forensic Laboratories
(Source: 2006 NFLIS and STRIDE)

Data regarding the types of methadone formulations submitted to forensic laboratories show:

– Most laboratories are not reporting the physical form of the exhibits for methadone (59% are unknown/unspecified).

– 41% of the methadone exhibits were associated with a report of drug form. Of those exhibits, 94% were tablets and 6% were liquids.

– The diskettes, if reported, would be reported as tablets as there is no “field” for diskettes.
Methadone ranked 3rd among all opioid analgesics, 4th among all controlled pharmaceuticals, and 8th among all controlled substances.
2005 DAWN ED Estimates by Age

Source: Office of Applied Science, SAMHSA, DAWN

**Methadone**
- Total ED visits – 60,135
- 55% males
- Nonmedical ED Visits – 41,216
- 55% males

**Hydrocodone**
- Total ED visits – 119,138
- 40% males
- Nonmedical ED visits – 51,225
- 43% males
Methadone-related Deaths (1999-2004)

Source: Center for Disease Control (CDC)

- Nationally, all poisoning deaths by all drugs increased by 54%.
- The number of methadone-related deaths increased by 390%: 786 in 1999 to 3,849 in 2004.
- Other opioid (e.g. hydrocodone and oxycodone) deaths increased by 90%.
- Most methadone deaths (73 to 79% depending on the year) were classified as unintentional.
- The rate of methadone deaths in younger individuals (15-24) increased 11-fold.
- The age-specific rates of methadone death are higher for persons age 35 to 44 and 45 to 54 than for other age groups.
Poisoning Deaths in the U.S.

Source: Center for Disease Control (CDC)

*Other Opioids include drugs like morphine, oxycodone, hydrocodone, hydromorphone
**Other Synthetic Narcotics include drugs like propoxyphene, fentanyl, meperidine

DEA/OD
Methadone deaths expressed as percent of all poisoning deaths

Source: Center for Disease Control
Percent Increase in Poisoning Deaths

Source: Center for Disease Control (CDC)
# States With Highest Number of Methadone Deaths in 2004

*Source: Center of Disease Control (CDC)*

<table>
<thead>
<tr>
<th>Ranking</th>
<th>State</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>1</td>
<td>Florida</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>North Carolina</td>
<td>245</td>
</tr>
<tr>
<td>3</td>
<td>Washington</td>
<td>228</td>
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<tr>
<td>4</td>
<td>Texas</td>
<td>138</td>
</tr>
<tr>
<td>5</td>
<td>Ohio</td>
<td>122</td>
</tr>
<tr>
<td>6</td>
<td>Kentucky</td>
<td>121</td>
</tr>
<tr>
<td>7</td>
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<td>120</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
<td>Tennessee</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>West Virginia</td>
<td>99</td>
</tr>
</tbody>
</table>
# States With the Largest Rate of Increase in Methadone Deaths 1999 to 2004

*Source: Center for Disease Control (CDC)*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total US</td>
<td>623</td>
<td>3,202</td>
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<tr>
<td>West Virginia</td>
<td>4</td>
<td>99</td>
<td>24.8</td>
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<td>Ohio</td>
<td>7</td>
<td>122</td>
<td>17.4</td>
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<tr>
<td>Louisiana</td>
<td>4</td>
<td>64</td>
<td>16</td>
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<td>400</td>
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<tr>
<td>Maine</td>
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<td>52</td>
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Florida Medical Examiner Data
Drug-Deaths

Source: Florida Department of Law Enforcement 2006 Interim Drug Report by Medical Examiners
FDLE ME Reports of Methadone Deaths

Cause of Death
Total Deaths

2000 2001 2002 2003 2004 2005 2006
# Florida Medical Examiners Report

**January – June 2006**

*Source: Florida Department of Law Enforcement 2006 Interim Drug Report by Medical Examiners*

<table>
<thead>
<tr>
<th>Drug Found in Body</th>
<th>Total Occurrences</th>
<th>Cause of Death</th>
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</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>85</td>
<td>51</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>346</td>
<td>106</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Meperidine</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Methadone</td>
<td>428+(546)=974</td>
<td>312+(400)=712</td>
</tr>
<tr>
<td>Morphine</td>
<td>289</td>
<td>106</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>377</td>
<td>185</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>155</td>
<td>38</td>
</tr>
<tr>
<td>Tramadol</td>
<td>59</td>
<td>18</td>
</tr>
</tbody>
</table>
When detected at autopsy, methadone is more likely to be the cause of death (like heroin) than either hydrocodone or oxycodone.
Florida ME Data January-June 2006

Manners of Death for Cases Reported
(Accidental, Homicide, Natural, Suicide or Undetermined)

Oxycodone Deaths
- Accident 85%
- Suicide 18%
- Natural 17%
- Homicide 1%
- Undet. 1%

Hydrocodone Deaths
- Accident 68%
- Suicide 18%
- Natural 28%
- Homicide 3%
- Undet. 2%

Methadone Deaths
- Accident 82%
- Suicide 8%
- Natural 8%
- Homicide 2%
- Undet. 2%
Summary

- Methadone-related deaths continue to escalate.
- The Methadone-Associated Mortality Assessment Report stated that methadone tablets and/or diskettes distributed through channels other than NTPs are most likely the central factor in methadone-associated mortality.
- Current data suggest that medication from pain management is likely the source of methadone for illicit use. However, DEA cannot discount diversion from NTPs.
- Several of the top prescribers of methadone are practitioners with specialties not generally associated with extensive training in pain management.
- DEA is not aware of any methadone-specific CME courses available to physicians or specific guidelines for initiating pain management with methadone.
- More than half of all 40 mg diskettes are distributed to pharmacies.