Methadone Clinical Toxicology

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TONYAA WEATHERSBEE
We must recognize the terrors of history PAGE B-7

LOTTERY
Jacksonville has a Fantasy 5 winner PAGE B-3

Methadone a growing killer in state

49 people have died in Nassau, Clay and Duval with drug in their systems

By SHANNON HOUGHTON
The Times-Union

It was a cool, drizzly Saturday in Jacksonville, and 21-year-old Destin Alan Curtin had been drinking alcohol all day. He added a dose of liquid methadone to the mix, and when he began to pass out, he took a shower to sober himself up.

His friends last saw him as he headed to bed at 1:30 a.m. April 23. When they went to rouse him the next day, he was pale and clammy — the victim of a methadone overdose.

So far this year, 49 people have died in Nassau, Clay and Duval counties with methadone in their system. The drug was the primary cause of death in eight of those cases.

Methadone was the second deadliest drug in Florida in 2004, according to the Florida Department of Law Enforcement. It's second only to heroin and was trailed by two other prescription drugs, fentanyl and OxyContin.

In recent years, drug officials raised a warning flag of the increasing abuse of methadone, which came onto the market in 1947 and was originally prescribed to help people break heroin addictions, according to the U.S. Drug Enforcement Administration. It's also used as a painkiller.

Despite their efforts, the number of deaths related to methadone abuse has continued to rise.

"Very little of this came from methadone as a displacement drug from heroin," said Jim McDonough, director of the Florida Office of Drug Control. "It came from methadone as used usually in pill form as a pain medication."

People who are prescribed methadone can get addicted fai easily to the controlled substan Jacksonville Sheriff's Office Detect Lorri Hall said, but most receive t drug with a fake prescription or wi out a prescription at all.

Prescription drug abuse produce high that's not as overpowering other drugs, comforting people i believing they can take more of drug or mix it with others.

"There's a whole aura of acceptal ity behind prescription drug abu McDonough said. "It's not like going up an alley and sticking a n dle in my arm, I'm actually going

DRUG continues on B-5

HITTING HOME

Lethal doses

Eighty-four of the 125 people in the Northeast Florida region whose autopsies tested positive for methadone last year had lethal levels of the drug in their systems, according to medical examiner statistics.

Florida Drug Caused Deaths

Interim Report Jan-Jun 2006

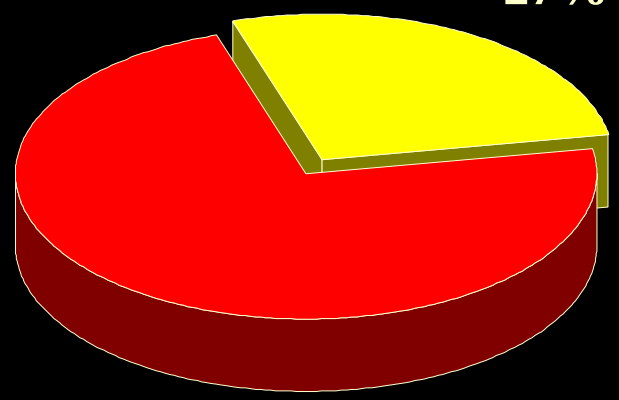
- #1 Cocaine-348
- #2 Methadone-312
- #3 Alprazolam-194
- #4 Oxycodone-185
- #5 Ethanol-160

Florida Drug Caused Deaths Interim Report Jan-Jun 2006

- #6=Morphine-106
- #7=Hydrocodone-106
- #8= Other Benzodiazepines-62
- #9=Diazepam-59
- #10= Fentanyl-51

Methadone Deaths

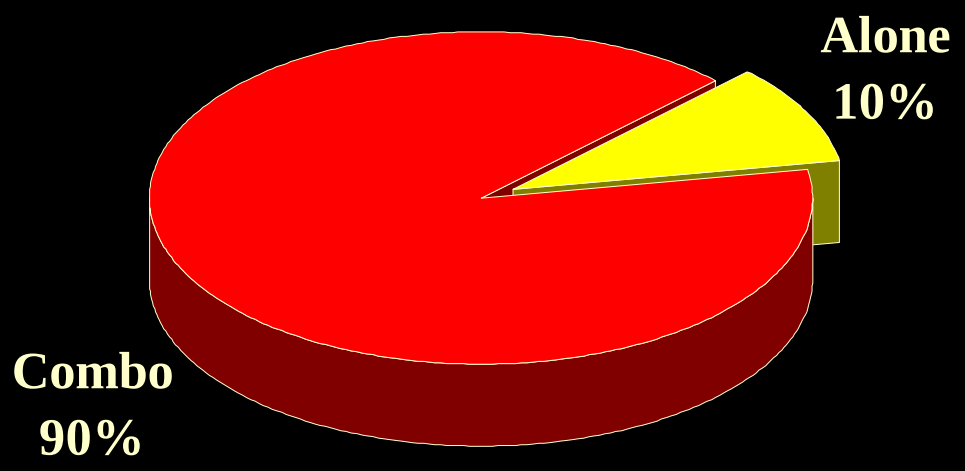
"Lethality"



Florida Medical Examiners Interim Report Jan-Jun 2006

Methadone Deaths

Polydrug vs Methadone Alone



Florida Medical Examiners Interim Report Jan-Jun 2006

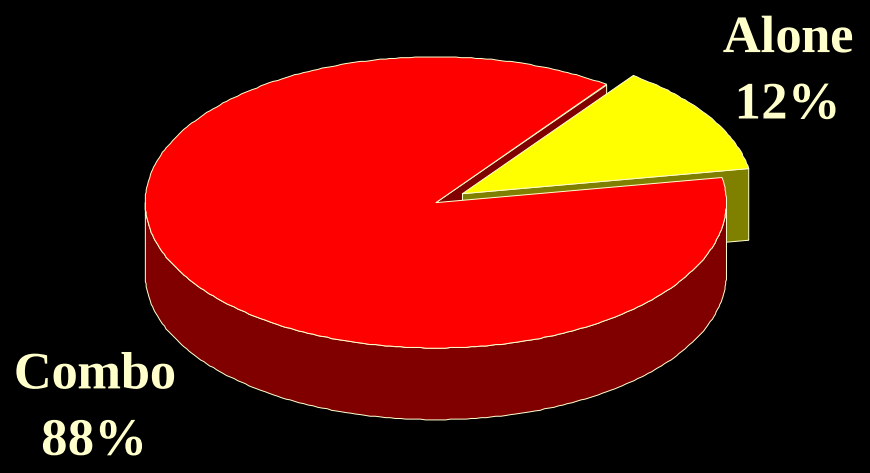
Florida Methadone Deaths 2005

- Total # Detected= 934
- Male= 72.3%
- White= 97%
- Average age of decedent=38.9yrs
- Manner of Death:
  - Accident-78.6%, Natural-9.4%, Suicide-6.4%

Source: Florida Medical Examiners 2005 Raw Data

Florida Methadone Deaths

Polydrug vs Methadone Alone



Florida Medical Examiners 2005 Raw data

Methadone Combination Deaths 2005

- #1 Alprazolam- 40.4%
- #2 Cocaine-32.9%
- #3 Ethanol-21.6%
- #4 Other Benzodiazepines-19.8%
- #5 Oxycodone-16.1%

Methadone Combination Deaths 2005

- #6 Marijuana- 15.3%
- #7 Diazepam- 15.2%
- #8 Hydrocodone-13.4%
- #9 Carisoprodol-7.8%
- #10 Morphine- 6.9%

FORMULARY

Propoxyphene: Is Inadequate Pain Relief Worth the Risk?

Propoxyphene use has been wrought with controversy since its inception. It is well publicized that propoxyphene should only be used for mild to moderate pain, as it is not potent enough for the treatment of severe pain. However, in numerous comparison studies, propoxyphene was found to be no more effective than either acetaminophen or aspirin.[1-5] Safety is also a concern with this drug due to opioid-related adverse events, dangerous overdose-related effects, numerous drug interactions, and the dose adjustment required in the presence of impaired renal or hepatic function. Based on propoxyphene's questionable efficacy and problematic safety profile, several pain management guidelines have deemed it an inappropriate choice for pain management, especially in the elderly.[1,6,7] Despite the considerable data opposing propoxyphene, its use, especially at Shands Jacksonville, continues to be high.[3,4]

Propoxyphene is a member of the opiate class of centrally acting analgesics. It is a synthetic product that is structurally similar to methadone.[8]

ties of several products combined with 650 mg of aspirin compared to 650 mg aspirin alone.[1,2] Propoxyphene napsylate 100 mg plus aspirin 650 mg was among the products reviewed.[1,2] Although pain relief with aspirin alone was superior to placebo, no significant difference in efficacy was found when aspirin alone was compared to the propoxyphene combination.[1,2] A meta-analysis printed in 1997 in *The British Medical Journal* investigated the use of acetaminophen with propoxyphene versus the use of acetaminophen alone.[5] Following the review of 26 randomized trials, the combination of propoxyphene with acetaminophen was no more effective for reducing pain than acetaminophen alone.[5]

Propoxyphene, despite providing less pain relief, is still associated with

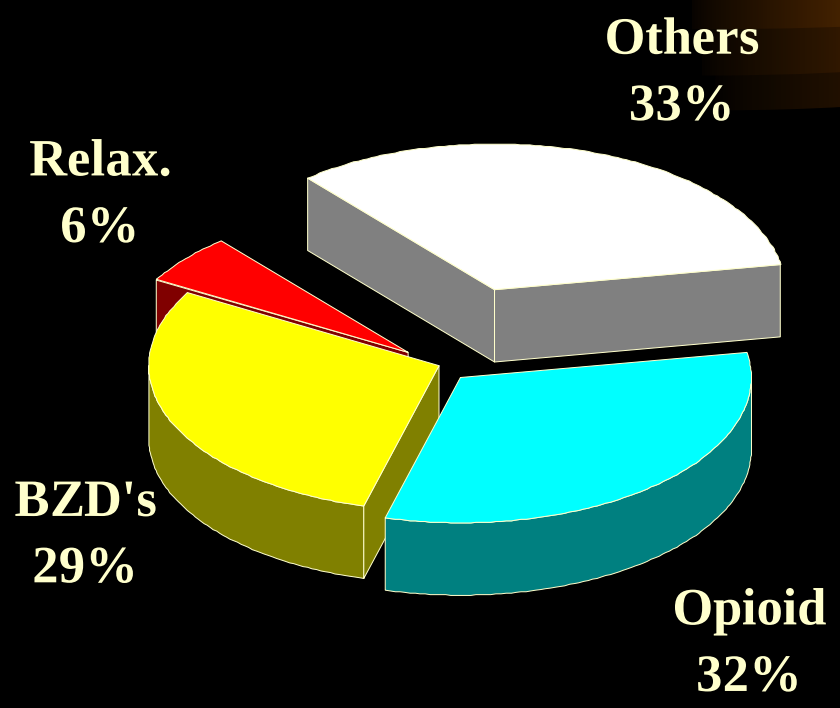
Based on propoxyphene's questionable efficacy and problematic safety profile, it is an inappropriate choice for pain

phene use is its increased toxicity in overdose. Propoxyphene overdose is significantly more hazardous compared to other opioid medications. In addition to CNS and respiratory depression common in opioid overdose, the hepatic metabolite of propoxyphene, norpropoxyphene, produces myocardial sodium channel blockade. This manifests as QRS widening and negative inotropy.[10] Seizures are also reported to occur subsequent to propoxyphene overdose, an effect not typically expected with an opioid overdose.[10]

The Jacksonville District Medical Examiners identified 34 deaths occurring in 2004 where propoxyphene was present. Propoxyphene was determined to be the cause of death in 13 of those cases. St. Petersburg was the only Florida district with more total deaths (39) and deaths caused by propoxyphene (22) in 2004. Accident was determined to be the manner of death in 51% of the cases, whereas suicide was the method in 24% of the case reports.[11] These statistics highlight propoxyphene's questionable safety profile.

ED Visits & Rx Drug Abuse

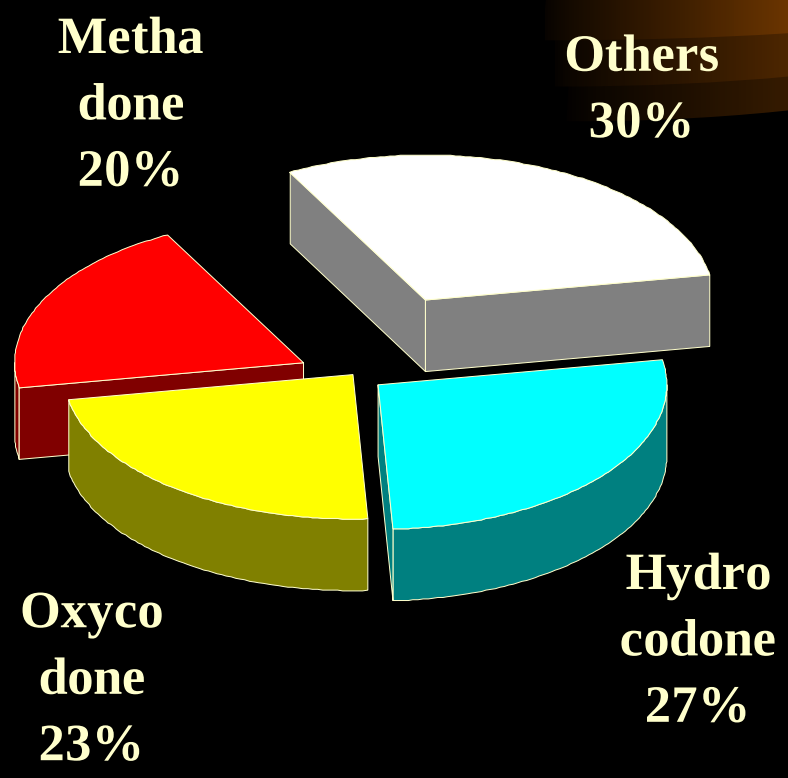
Drug Abuse Warning Network 2004



The DAWN Report Issue 23, 2006

Rx Opioid Drug Abuse& ED Visits

Drug Abuse Warning Network 2004



n=158,281 opioid related ED visits

Opioids

- Morphine/Codeine
- Diacetylmorphine (Heroin)
- Oxycodone/Hydrocodone/Hydromorphone
- Methadone/Fentanyl/Diphenoxylate/ Loperamide/Meperidine/Tramadol
- Others:
  - buprenorphine, propoxyphene, LAAM, dextromethorphan

Opioids
Mechanisms

- Opioid Receptors
  - mu & delta= analgesia, euphoria, CNS depression, respiratory depression
  - kappa & sigma= some analgesia, dysphoria, hallucinations.
- Toxicologic Mechanism:
  - extension of pharm mech's
  - contaminants
  - others

Methadone Toxicity Case Report

- 43M w/ szs, ataxia, cognitive decline x 3mo
- Liquid methadone-carry home privileges
- Injecting after boiling in aluminum pot
- Aluminum level 60X normal
- Tx=deferoxamine chelator

Clin Tox 2006:44:307-314.

Opioid Overdose

Clinical Manifestations

- Vital Signs
  - decr Pulse, BP, Resp
- Classic Triad:
  - CNS/resp depression, hypotension, miosis
- Neuro:
  - Sedation, convulsions
- Pulmonary:
  - Resp depr, apnea, bronchospasm, pulmonary edema
- GI/GU:
  - Decr GI motility, n&v, urinary retention

Opioid Overdose

- Treatment
  - symptomatic/supportive care
  - airway
  - hypotension
  - neurotoxicity (convulsions)
  - cardiotoxicity
  - naloxone

Naloxone (Narcan)

- Indications:
  - Altered mental status/coma-->unk. cause,
  - Opioid or clonidine overdose
- Dose:
  - Adults: 0.1-10mgs IV repeat PRN
  - Children: 0.1mg/kg IV repeat PRN
- Cautions/Warnings:
  - short duration, arousal complications, w/d
  - larger doses with methadone & propoxyphene

Methadone

- Synthetic opioid
- Long ½ life/duration of effect
- Tox Screens
- High & prolonged dosing of naloxone required
- Increasing use, increasing #'s of overdoses
- Florida's 2nd most common cause of drug deaths
- Opioid addiction maintenance

Methadone vs Other Opioids

- Slowest onset
- Longest duration
- Longest ½ life
- High potency
- Toddler Deaths:
  - AAPCC TESS data 1983-2002=12 methadone deaths
  - Hydrocod.,oxycod.,morph., propox combined=9 deaths
- One methadone tab generally dangerous to toddler

Poison Center Recommendations Asymptomatic Toddler Exposures

Drug	Observe in ED (4-6h)
Meperidine	12.5mg/kg
Tramadol	10mg/kg
Codeine	5mg/kg
Morphine	2.5mg/kg
Hydrocodone/Oxycodone	0.42mg/kg
Hydromorphone	0.31mg/kg
Methadone	Any amount
Fentanyl/propoxyphene	Any amount

“….Methadone’s peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects…..”

-Methadone Package Insert Box Warning-
November 2006

“….Patients tolerant to other opioids may be incompletely tolerant to methadone…..”

-Methadone Package Insert - Nov 2006

Methadone Cardiac Toxicity

- QTc prolongation-→Torsades de Pointes
- Mechs: brady &/or delayed repolarization
- Predisposers:
  - Decreased potassium
  - Hepatic/cardiac abnormalities
  - Other QTc prolonging meds
  - Drug interactions w/ methadone
  - High methadone doses

Methadone Summary

- Increasing use
- Long ½ life/duration of effect
- Tox Screens
- High potency/ poor cross tolerance
- Polydrug overdoses—incr interxn→ incr toxicity
- Cardiac toxicity (QTc prolongation-Torsades)
- High & prolonged dosing of naloxone required