

Opioid Dependence Treatment:

Should substitution therapy be
the management of choice?

CON

Karen E. Simone, PharmD, DABAT, FAACT

Director, Northern New England Poison Center

simonk@mmc.org

(207)662-7221



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Objectives

Helpful? For everyone?

- Discuss the concerns associated with opioid substitution therapy **evidence base and outcomes.**
- Identify the characteristics of patients and services that **predict poor opioid substitution therapy results.**

Secondary Objectives

Harmful?

- Review risk of diversion, misuse, abuse and overdose in **adults**
- Describe the risk to **children** in MAT families



Northern New England

Poison Center

1-800-222-1222
www.nnepc.org

Medication-Assisted Therapy

- **Pharmaceuticals:**
 - Methadone
 - Buprenorphine
 - Naltrexone
- **Behavioral therapy**



Northern New England

Poison Center

1-800-222-1222
www.nnepc.org

Benefits of MAT

- **Primary:**
 - Retention in treatment
 - Reduction in opioid use
- **Secondary (reduction in):**
 - Use of other illicit drugs
 - HIV-risky behaviors
 - Crime
 - Heroin craving
 - Mortality



Fullerton, C. A., et al. (2014). "Medication-assisted treatment with methadone: assessing the evidence." *Psychiatr Serv* 65(2): 146-157.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

PROBLEMS



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

State investigating Baltimore methadone clinic after man's death

Firm that runs clinic has recently come under scrutiny for deaths in other states

April 02, 2013 | By Carrie Wells, The Baltimore Sun

The day after her ex-husband's funeral in January, Sabrina Lumpkin started calling every public official she could think of, trying to get someone to pay attention.

Warren Lumpkin, 34, had died in a Southwest Baltimore house of heart complications related to using methadone, the prescription drug typically used to treat heroin addiction, according to an autopsy from the state medical examiner. But Sabrina Lumpkin said he had no such prescription — he took his roommate's methadone the night before he died.

Tweet

1

G+1



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone - Safety

- Patient deaths – rapid escalation
- Community morbidity/mortality
 - Poisoning
 - Small children
 - Adults
 - › Naïve users
 - › Combination with CNS depressants
 - Operating under the influence



Northern New England

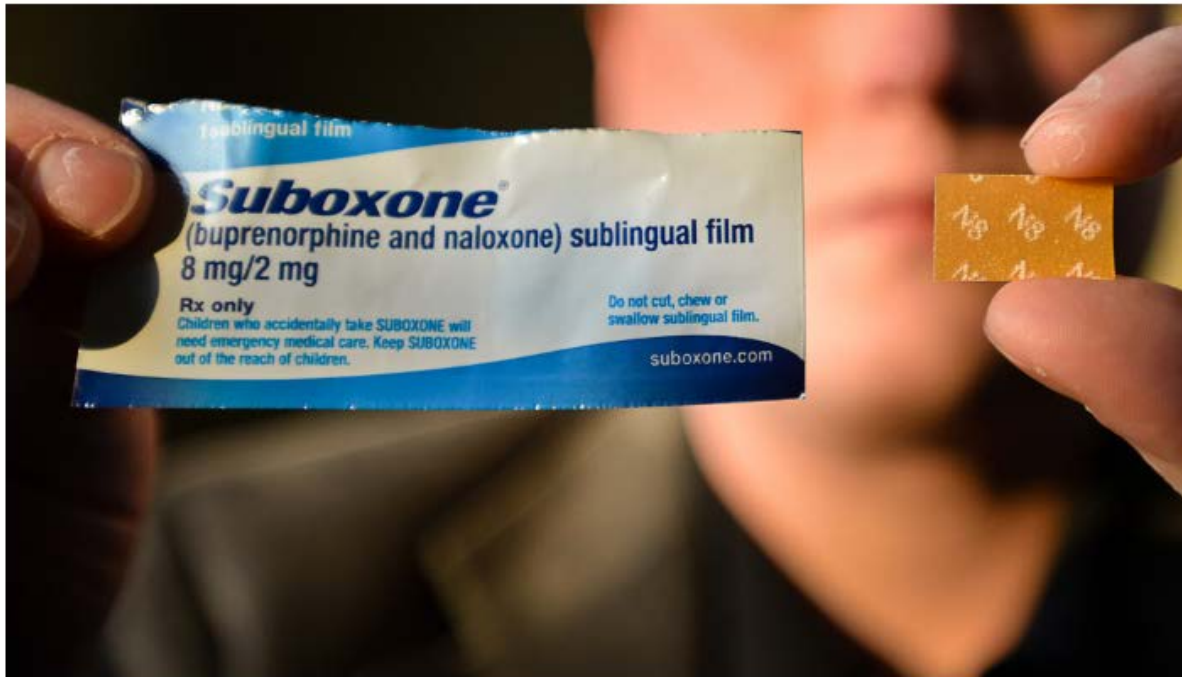
Poison Center

1-800-222-1222
www.nnepc.org

HEALTH | THE DOUBLE-EDGED DRUG

Addiction Treatment With a Dark Side

By DEBORAH SONTAG NOV. 16, 2013



Dissolvable filmstrips of buprenorphine



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

NYT – Buprenorphine Article

Bad Players

- Bad doctors (US national data)
 - 1,350/12,780 (>10%) sanctioned
 - Excessive narcotic prescribing
 - Insurance fraud
 - Sexual misconduct
 - Practicing impaired
- Bad patients
- Drug dealers



Northern New England

Poison Center

1-800-222-1222
www.nnepc.org

NYT – Buprenorphine Article

Underground Market

- Manage withdrawal
- Recreational use
 - Shooting
 - Snorting
 - Sublingual
- Prison heroin



Northern New England

Poison Center

1-800-222-1222
www.nnepc.org

SUCCESS?



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone

How successful is success? Baltimore 40-week Program

- **Plan:**

- Maintenance for 30 weeks
 - Moderate-dose: 40 – 50 mg/day
 - High-dose: 80 – 100 mg/day
- Detoxification for 10 weeks (10%/week)

- **Withdrawn:**

- Maintenance: missed > 3 days, incarcerated, med/psych issues, other
- Detoxification: missed > 3 days, transferred to treatment, other



Strain, E. C., et al. (1999). "Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial." *JAMA* **281**(11): 1000-1005.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone

How successful is success? Baltimore 40-week Program

- **Disappearing patients:**

- Maintenance:

- Moderate-dose: 97 to start, 54 after this phase (56% left)
- High-dose: 95 to start, 57 after this phase (60% left)

- Detoxification:

- Moderate-dose: 54 to start, 11 after this phase (11% left)
- High-dose: 57 to start, 19 after this phase (20% left)

- **Outcome?:**

- Ability to taper off methadone

- No longer-term success measured

66% withdrew due to failure to show up to clinic or incarceration

5% transferred to community treatment



Strain, E. C., et al. (1999). "Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial." *JAMA* 281(11): 1000-1005.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone

How good is good? Swedish Program

- **Swedish methadone program**
 - 1988 – 2000
 - N=848
- **Strict rules:**
 - No abuse of other medications/alcohol
 - No violence toward staff/patients
 - No ongoing criminal activity



Fugelstad, A., et al. (2007). "Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings." *Addiction* **102**(3): 406-412.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone

How good is good? Swedish Program

- **Results:**

- 77 deaths/1000 person years in the program
 - Mostly natural causes (HIV, Hep C)
- 74 deaths/1000 person years of those discharged
 - Mostly unnatural (heroin overdose)
- *2 deaths in the community from leakage of program methadone*



Northern New England
Poison Center

Fugelstad, A., et al. (2007). "Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings." Addiction **102**(3): 406-412.

1-800-222-1222
www.nnepc.org

Methadone

How good is good? Swedish Program

- **Notes:**

- In-program deaths: 77/679
- Discharged: 74/368

- **Take-home messages:**

- Outcomes must look at all patients/all causes
- Strictness of rules may dictate types of deaths
 - Overdose among those discharged OR
 - Overdose with program methadone diverted into community and drug abuse while in the program



Fugelstad, A., et al. (2007). "Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings." *Addiction* **102**(3): 406-412.

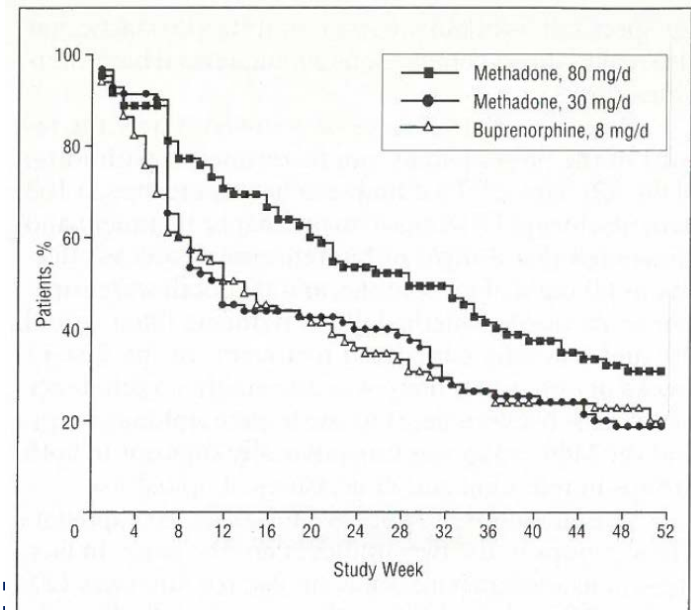
Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone and Buprenorphine

How good is good? California 52-week study

- **Methadone 80 mg (N=75):**
 - 52% retention at 26 weeks
 - 31% retention at 52 weeks
- **Methadone 30 mg (N=75):**
 - 40% retention at 26 weeks
 - 19% retention at 52 weeks
- **Buprenorphine 8 mg (N=75):**
 - 35% retention at 26 weeks
 - 20% retention at 52 weeks



Patients in each group still in treatment at the end of each study week.

60 dropped from program
for 0 opioid-negative
urines after 12 urinalyses



Ling, W., et al. (1996). "A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence." *Arch Gen Psychiatry* 53(5): 401-407.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Buprenorphine

How Good is Good? Sweden 7-year Study

- **Patients (N=170):**

- 148 left after 30 days - 22 (13%) dropped out
- 94 left after 7 years – 54 (45% of the original 170)

- **Outcomes:**

- Drug- and alcohol-free
- Retention in the program (continuous)
- Employment (69% regular, 29% supplemented wages, 2% studying)
- Psychosocial conditions favorable
- No criminal convictions



Ohlin, L., et al. (2015). "Buprenorphine maintenance program with contracted work/education and low tolerance for non-prescribed drug use: a cohort study of outcome for women and men after seven years." *BMC Psychiatry* **15**: 56.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

DIVERSION AND MISUSE



Northern New England

Poison Center

1-800-222-1222
www.nnepc.org

Diversions and Misuse

Australia Survey of People Misusing MAT Opioids (N=544)

- **Removal of supervised doses:**
 - Buprenorphine 19 – 33%
 - Methadone 5%
- **Diversions of doses:**
 - Buprenorphine >> methadone
- **Injection of doses:**
 - Injection once in last 6 months (buprenorphine = methadone)
 - Regular injection (at least weekly):
 - Buprenorphine – 11%
 - Buprenorphine/naloxone tablet – 9%
 - Buprenorphine/naloxone film – 3%
 - Methadone – 3%



Larance, B., et al. (2014). "The diversion and injection of a buprenorphine-naloxone soluble film formulation." Drug Alcohol Depend **136**: 21-27.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Diversions and Misuse

Australia Survey of out-of-treatment People Who Inject Drugs (N=541)

- **Most injected in rank order:**

1. Buprenorphine or methadone (recent 16 – 17%)
2. Buprenorphine/naloxone tablet > film (recent 5 –10%)

- **Reasons for injection:**

- Mostly self treatment (withdrawal) – 56 to 71%
- Also:
 - Substitution for other opioids (methadone, buprenorphine) - 6 to 21%
 - Intoxication (methadone) – 16%
 - Other (financial stress, needing higher dose, faster onset, prefer injection, difficulty not injecting (methadone, buprenorphine/naloxone) - 12 – 21%



Larance, B., et al. (2014). "The diversion and injection of a buprenorphine-naloxone soluble film formulation." Drug Alcohol Depend **136**: 21-27.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Diversions and Misuse

New South Wales Australia Community Pharmacy Survey Methadone and Buprenorphine Patients (508/931 responded)

- 442 methadone
 - 12% ever sneaked
 - 43% ever injected
- 66 buprenorphine
 - 32% ever sneaked
 - 15% ever injected
- For both, injectors 10 x more likely to divert/attempt to divert



Winstock, A. R., et al. (2008). "Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia." *Int J Drug Policy* **19**(6): 450-458.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

POISONING



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Buprenorphine and Methadone Exposures

NPDS Data from 2000 - 2008

- **Methadone (N=2,186)**
 - All exposures (6,171, 9 deaths)
 - Children < 6 years of age (2,186, 20 deaths)
- **Buprenorphine (N=1,786)**
 - All exposures (31,609, 654 deaths)
 - Children < 6 years of age (1,786, no deaths)



Boyer, E. W., et al. (2010). "Methadone and buprenorphine toxicity in children." Am J Addict 19(1): 89-95.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Opioid Childhood Exposures

RADARs Data in children < 6 years of age exposed to 7 opioids
#9,179 over 3.5 years

- **Methadone (N=415)**

- 4th most common
- 2nd effects of moderate or greater severity
- 2 deaths (25% of deaths)
 - 4 oxycodone (N=2,036) and 2 hydrocodone (N=6.003)

- **Buprenorphine (N=176)**

- 5th most common
- 1st effects of moderate or greater severity
- No deaths



Bailey, J. E., et al. (2009). "The underrecognized toll of prescription opioid abuse on young children." Ann Emerg Med 53(4): 419-424.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone Pediatric Exposures

French Poison Centers Data in children < 18 years of age exposed 2008 – 2014 since solid form methadone available

- **87 patients:**
 - Children < 6 years (69 accidental, 6 intentional)
- **Clinical Outcomes (N=87):**
 - 5 deaths (4 syrup, 1 capsule)
 - 20 moderate to severe
 - 62 no effect to mild effects
- **Important Points:**
 - Nearly all packages opened by parents first
 - Better outcomes associated with faster parent reaction



Torrents, R., et al. (2015). "Child poisonings with methadone in France: A 6-year prospective national survey since the availability of capsules in 2008." *Clin Toxicol (Phila)* **53**(8): 819-822..



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone

206 methadone deaths from 2001 – 2005 in Victoria, Australia

- **Legality:**

- 161 (78%) legally prescribed
 - Mostly maintenance (N=123)
 - Many in long-term treatment (N=72 > 2 weeks)
 - Take-home doses (N=42)
- 36 (17%) diverted maintenance and pain management
- 9 (4%) unknown

Pilgrim, J. L., et al. (2013). "A review of methadone deaths between 2001 and 2005 in Victoria, Australia." Forensic Sci Int 226(1-3): 216-222.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone

206 methadone deaths from 2001 – 2005 in Victoria, Australia

- **Problems:**

- Combination with CNS depressants (98%)
- Dosing in MAT
 - Initial high dose
 - Rapid dose escalation
- Failure to reduce deaths?
 - Methadone deaths equaled/exceeded heroin deaths
 - Heroin use decreased (↓heroin supply, ↑stimulant abuse)



Pilgrim, J. L., et al. (2013). "A review of methadone deaths between 2001 and 2005 in Victoria, Australia." Forensic Sci Int 226(1-3): 216-222.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Methadone Deaths

36 autopsies from Italy 2005 - 2013

- **20 long-term methadone maintenance patients**
 - 9 take-home
 - 2 apparently selling their methadone
 - 1 took an excessive dose
 - 11 in-clinic (more mixing with ethanol and drugs of abuse)
- **4 induction deaths** (3/4 post incarceration)
- **12 diverted/illegal** (3 naïve)
 - 2 toddler deaths (1/2 possibly intentional)
 - 4 partiers



Vignali, C., et al. (2015). "Methadone-related deaths. A ten year overview." *Forensic Sci Int* **257**: 172-176.

Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Predicting Success

Short-term of Stabilization and Detox with Buprenorphine

Positive Predictors

Negative Predictors

Stabilization Completion – 4 wks

- Non-daily opiate use in past 30 days
- Employment in past 30 days
- Past criminal history

Retention - # wks in tx

- No opiate use in last 30 days
- Past criminal history

Hillhouse, M., et al. (2013). "Predictors of outcome after short-term stabilization with buprenorphine." Journal of Substance Abuse Treatment 44(3): 336-342.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Predicting Success

Buprenorphine over 3 Months

Positive Predictors

- COMPLIANCE
- Older
- Male

*Compliance = taking 22/28 (80%) of days

Negative Predictors

- ↑ Addiction Severity Index Score
 - Psychiatric
 - Legal
 - Family/social

Tkacz, J., et al. (2012). "Compliance with buprenorphine medication-assisted treatment and relapse to opioid use." *Am J Addict* 21(1): 55-62.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Predicting Success

Methadone, Buprenorphine, Other

Positive Predictors

- Prescription opioids
(v. heroin)

Negative Predictors

- ↑ Heroin injection rate
- ↑ Number of prior treatments

Soyka, M., et al. (2011). "The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence.[Erratum appears in World J Biol Psychiatry. 2011 Aug;12(5):397 Note: Lingford-Hughes, Anne [removed]]." World Journal of Biological Psychiatry **12**(3): 160-187.

Weiss, R. D., et al. (2011). "Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial." Arch Gen Psychiatry **68**(12): 1238-1246.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Measuring Success

Physician Survey on Successful MAT (Switzerland)

- Break off as reason for terminating MAT*
- Psychological improvement
- Wish for abstinence from MAT
- Social improvement
- Medical improvement
- Social integration index**

*Patient, physician or loss of contact

**Job, earning a living, flat, partnership, family relations, friends outside drug scene



Vogel, M., et al. (2016). "Evaluation of medication-assisted treatment of opioid dependence-The physicians' perspective."
Drug Alcohol Depend.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

Cost

Table ES2. Two-year costs among 1,000 hypothetical patients treated for opioid dependence.

Outcome/Cost	MMT	BMT	SUB/VIV Taper	SUB/Oral NTX Taper	Vivitrol Alone	Oral NTX Alone
Treatment outcome (per 1,000):						
<i>In treatment</i>	630	523	550	500	416	277
<i>Relapsed</i>	185	292	265	315	400	538
<i>Drug-free</i>	177	176	177	176	173	169
<i>Died</i>	8	9	8	9	12	16
Cost (\$, per patient):						
<i>Drug therapy</i>	699	3,655	8,553	1,249	6,585	665
<i>Other SA services</i>	14,017	7,043	4,146	4,297	2,985	2,446
<i>Other health care</i>	23,926	25,993	25,454	26,441	28,109	30,844
SUBTOTAL	38,642	36,691	38,153	31,988	37,679	33,954
<i>Social costs</i>	92,068	102,337	98,033	105,917	119,239	141,076
TOTAL	130,710	139,028	136,187	137,905	156,918	175,030

MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment; NTX: naltrexone; SUB: Suboxone; VIV: Vivitrol

(2014). Management of Patients with Opioid Dependence: A Review of Clinical, Delivery System, and Policy Options. The New England Comparative Effectiveness Public Advisory Council - Public Meeting June 20, 2014.



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org

The Best Outcome

Are the goals sufficient?

- **Harm reduction only:**
 - Fewer overdoses
 - Not dead yet
 - Fewer infectious disease issues
 - Cellulitis/vasculitis
 - Endocarditis/heart valves
 - Hepatitis C, HIV
 - No additional heart valve replacements
- **Return to a nl life:**
 - Reasonably happy
 - Not using
 - Not demonstrating addictive behaviors
 - Maintaining a job
 - Maintaining a family life/relationships



Northern New England

Poison Center

1-800-222-1222
www.nnepc.org

Conclusion

What is good enough?

- **What are the goals?**
 - Not dead yet and lower cost to society
 - Functioning well at work and home
- **What is the harm to bystanders?**
 - Children
 - Naïve drug users
 - Clients and families



Northern New England
Poison Center

1-800-222-1222
www.nnepc.org