IMPLEMENTING ANTAGONIST-BASED RELAPSE PREVENTION TREATMENT FOR OPIOID-DEPENDENT INDIVIDUALS

Adam Bisaga M.D.
Professor of Psychiatry at CUMC
Columbia University P&S, New York, NY
The ASAM State of the Art Course
October 6, 2016
Disclosure Information

Adam Bisaga, MD
Alkermes - Research Support - Medication Samples
Indivior – Honorarium – Unbranded Educational Activity
Outline

- Introduction to antagonist-based treatment
- Patient selection and treatment initiation
- Maintenance treatment and treatment logistics
Introduction to Antagonist-based Treatment of OUD
Antagonist-based Treatment

- Opioid antagonist attach to the receptor and prevent other opioids from exerting effects
- Naltrexone is a long-acting, high affinity, competitive opioid receptor antagonist with an active metabolite (6-β-naltrexol)
  - At sufficient plasma concentrations (>2 ng/ml) naltrexone fully blocks all opioid effects
- Naltrexone tablet is approved for the blockade of exogenously administered opioids
- Naltrexone injection is approved for prevention of relapse to an opioid dependence following opioid detoxification
Naltrexone: Treatment Components

- Behavioral component: blockade of the positive effects of heroin leads to gradual extinction of craving and drug use
- Pharmacological component: naltrexone decreases reactivity to drug-conditioned cues thereby minimizing pathological responses contributing to relapse
Antagonist vs. agonist based treatment

- Naltrexone is an appealing choice for patients seeking withdrawal from all opioids as a first stage of treatment.
- As naltrexone has a different mechanism of action than agonists, it may address limitations related to treatment with agonists, providing another option for patients with OUD.
## Choosing agonist vs. antagonist based treatment

<table>
<thead>
<tr>
<th></th>
<th>AGONIST</th>
<th>ANTAGONIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintains physiological dependence with withdrawal on stopping</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reinforcing effects promote medication adherence</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Eliminates ongoing illicit opioid use</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Protects against overdose during treatment</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased risk of overdose after treatment dropout</td>
<td>+</td>
<td>+ (XR) ++ (oral)</td>
</tr>
<tr>
<td>Opioid side-effects (constipation, sexual dysfunction, sweating)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Euphoric effects if misused (potential for abuse and diversion)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Risk of overdose when combined with sedatives</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Interferes with opioid-based pain management</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Retention in treatment is often used as a primary outcome of OUD treatment.

Main reason for dropout is relapse and majority of patients retained in treatment with naltrexone are abstinent from opioids.

Treatment retention rate in groups treated with XR-NTX is twice that of the oral group, approximating 50-70% at 6 months.
Efficacy of XR-naltrexone vs. placebo

- Trials comparing XR-NTX vs. placebo injections showed that patients receiving active naltrexone have:
  - Better treatment retention
  - Less opioid use
  - Lower craving for opioids

(Comer et al., Arch Gen Psych, 2006; Krupitsky, et al., Lancet, 2011)
Effectiveness of XR-naltrexone vs. usual treatment

- 308 adults involved in criminal justice system
- Participants treated with XR-naltrexone had
  - less relapse, longer relapse-free survival
  - less heroin use overall and fewer overdoses
- 61% of XR-NTX participants completed 24-weeks of treatment (6 injections)
Patient Selection and Treatment Initiation
Good Candidates for Naltrexone Treatment

- Not interested or able to be on agonist therapies
- Abstinent from opioids but remain at risk for relapse
- Failed prior treatment with agonist
- Less severe forms of a disorder
- Young adults living with involved parents who supervise treatment
- Young adults unwilling to commit to long-term agonist therapy
- Successful on agonist therapy who wish to discontinue medication
When the Patient is Ready to Receive Therapeutic Dose of Naltrexone?

- Therapeutic doses of naltrexone will precipitate severe an prolonged withdrawal in patients who are physically dependent or have large amount of opioids in their system.
- Always confirm absence of opioids and absence of physical dependence prior to the first dose of naltrexone.
  - Urine drug screen must be negative for all opioids.
  - Perform naloxone challenge if unsure.
  - Patient must understand the risks of precipitated withdrawal if underreporting.
Initiating Naltrexone

- Two phases of treatment: 1) withdrawal, 2) naltrexone induction
- Current FDA-sanctioned method involves 7-10 days “washout” between the last dose of opioid and first dose of NTX

- Agonist-assisted + opioid washout
- BUP taper
- Day 0
- Washout
- NTX
- Day 10
- NTX
- Day 15

- Clonidine/BDZ
- Symptomatic only
- Washout
- Day 5
- Day 10
- Day 15
Initiating Naltrexone (cont’d)

- Withdrawal and naltrexone induction can occur at the same time: rapid detoxification/naltrexone induction
- Introducing naltrexone during withdrawal accelerates the process of induction
Maintenance Treatment: Clinical Considerations
Side Effects

- **Serious**
  - Injection site reactions (inflammation, tissue damage)
  - Local tenderness and a small “bump” are common, usually resolve within 1-3 days
  - Serious site reactions are more likely to occur if administered into the fat tissue
  - Depressed mood with suicidal behavior
  - Allergic (eosinophillic) pneumonia
  - Systemic allergic reactions

- **Common**
  - Occur infrequently outside of the first month of treatment when majority of side effects are related to opioid withdrawal
    - nausea
    - tiredness
    - headache
    - dizziness
    - vomiting
    - decreased appetite
    - painful joints
    - muscle cramps
    - insomnia
Testing the Blockade

- Up to a third of patients will “test blockade”, often within 1-2 days after receiving XR-naltrexone
- Most commonly patients will test 1-2 times with small amounts, after which they are “reassured” that blockade works and do not resume use
- Some patients will use large amounts, for few weeks, but rarely persist in the use if they receive full blocking doses of the medication
  - Very few patients try intentionally to “override the blockade”
- Continuous blockade prevents patients from relapsing to physical dependence and many patients prefer to remain on the medication
Managing Relapse

- Some patients have increased craving and may use right before due for the next injection
- Most commonly, the first sign of relapse is delayed/missing injections
  - the blockade wears off 5-6 weeks after the injection
- Increasing treatment intensity may help stabilize the patient
  - more frequent injection (q3 weeks) or oral supplementation may be considered
  - additional therapy, involving network members, may improve adherence
  - Inpatient stabilization and another attempt at antagonist treatment
  - Residential treatment/sober house
- If unable to stabilize consider transition onto agonist
Overdose Risk

- Treatment with agonist or antagonists reduces mortality as compared to drug-free treatment
- The risk of overdose is comparable while patients are in active treatment with MAT (adherent to naltrexone oral/XR, buprenorphine, or methadone)
- Mortality rates differ between patients who discontinue treatment with various medications
  - higher in patients treated with oral naltrexone as compared to methadone
  - higher in patients treated with oral vs. XR-naltrexone
  - comparable in patients treated with XR-naltrexone and methadone
- The long “tail” on the serum XR-naltrexone curve may provide protection during early drug-free period which is often marked by an elevated mortality
Overdose: Patient Education

- There is a significant risk of overdose if patient decides to stop taking naltrexone and resumes opiate use
  - Due to the absence of pharmacological blockade, absence of tolerance, and possibly increased sensitivity to opioids
- To mitigate this risk, provide a detailed description of risks at treatment outset (e.g., treatment agreement) and discuss it during treatment especially in patients who continue use
There are concerns whether treatment with naltrexone increases risk of depression and suicidality through blocking of endogenous opioid activity. Theoretically plausible but there is no systematic clinical evidence that naltrexone increases depression in this population. Depressive symptoms usually improve during abstinence from opioids. Some patients may have increased depressive symptoms, usually during the first few weeks of treatment (protracted withdrawal?). OUD is a risk factor for suicide: 10% vs. 1.3% in the general population. Depression/suicidality warning is included in the package insert for Vivitrol. Suicidality was reported in 5% of patients treated with Vivitrol (10% in oral naltrexone) in open-label long-term US safety study.
PCSSMAT is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society of Addiction Medicine (ASAM) and Association for Medical Education and Research in Substance Abuse (AMERSA).

For More Information: www.pcssmat.org

Twitter: @PCSSProjects

Funding for this initiative was made possible (in part) by Providers’ Clinical Support System for Medication Assisted Treatment (5U79TI024697) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
Naloxone for Opioid Safety

Phillip O. Coffin, MD MIA
San Francisco Department of Public Health
University of California San Francisco
The ASAM State of the Art Course in Addiction Medicine
6 October 2016
Disclosure Information

Phillip O. Coffin, MD MIA

Gilead, Donated ledipasvir-sofosbuvir, Study
Alkermes, Donated ER-naltrexone, Study
Outline

1. Background
2. Settings / Indications
3. Education/patient interaction
4. Formulations
5. Summary
1. Background

The main risk of death from an opioid overdose is prior overdose. A patient who has previously overdosed is 6 times more likely to overdose in the subsequent year.

OTHER FACTORS THAT INCREASE RISK OF OVERDOSE:

- Reduced tolerance: Period of abstinence, change in dose, release from prison
- Genetic predisposition
- Concomitant use of substances: benzodiazepines, alcohol, cocaine

Outcomes of Heroin Overdose

Chemistry

opioid receptors activated
by heroin and prescription opioids

Pain Relief
Pleasure
Reward
Respiratory Depression

opioids broken down and excreted

Reversal of Respiratory Depression
Opioid Withdrawal

Source: projectlazarus.org
Naloxone Programs, 2014

Naloxone/Overdose Legislation

- Naloxone is **not** a controlled substance; prescribing naloxone to a patient is no different than prescribing other routine medications
- States on this map have added legal protections, such as authorizing:
  - Prescribing/dispensing to potential bystanders
  - Third-party administration by lay bystanders
  - Prescribing/dispensing by standing order or directly from pharmacies
- States in green also have laws protecting from prosecution when help is sought

Source: [www.lawatlas.org](http://www.lawatlas.org)
2. Settings / Indications

- Harm reduction programming
- Corrections
- Substance use treatment
- Primary / other medical care settings
Harm Reduction Programming

Predictors of Using Naloxone to Reverse an Overdose  Adjusted Odds Ratio
Use heroin  1.85
Use methamphetamine  1.71
Previously witnessed OD  2.02

Fatal Opioid Overdose Rates by Naloxone Distribution in Massachusetts

In California, counties with naloxone programs had an overall slower rate in the growth in opioid overdose death compared to counties without naloxone programs.13

Naloxone Cost-Effectiveness

**Cost:**

$421\text{ per quality-adjusted life-year gained}$

**Benefit:**

164 naloxone scripts = 1 prevented death

Emerging data suggests that providing naloxone may encourage patients to be safer with their opioid use. If this is the case, the intervention would be cost-saving and 36 prescriptions would prevent one death.

Lay Naloxone Reversals Reported During Two Fentanyl Outbreaks in San Francisco, 2015

Source: Drug Overdose Prevention/Education Project, San Francisco
Deaths Caused by Fentanyl in San Francisco, 2015

Source: Office of the Chief Medical Examiner, San Francisco
Corrections

Substance Use Disorder Treatment

Opioid Overdose Deaths Among Persons with OUD in England

<table>
<thead>
<tr>
<th></th>
<th>Deaths / 1000py</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out of Treatment</td>
<td>~4.3</td>
</tr>
<tr>
<td>Residential Treatment</td>
<td></td>
</tr>
<tr>
<td>In</td>
<td>3.9</td>
</tr>
<tr>
<td>1-28 days out</td>
<td>18.8</td>
</tr>
</tbody>
</table>

SAMHSA Guidelines for Naloxone Provision from SUD Treatment Settings

“Overdose prevention, including prescribing or dispensing naloxone, is an essential complement to both detoxification services as well as medically supervised withdrawal”
Primary / Other Medical Care Settings

Expected Opioid-Related ED Visits / Month by Receipt of Naloxone

Opioid / Overdose History of Patients on Opioids for Chronic Pain

<table>
<thead>
<tr>
<th>Patient Characteristics (N=60)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever taken opioids not as prescribed</td>
<td>53%</td>
</tr>
<tr>
<td>Ever witnessed an overdose</td>
<td>53%</td>
</tr>
<tr>
<td>Previously received take-home naloxone</td>
<td>10%</td>
</tr>
<tr>
<td>History of overdose / bad reaction</td>
<td>37%</td>
</tr>
<tr>
<td>Overdose</td>
<td>20%</td>
</tr>
<tr>
<td>“Bad reaction” consistent with overdose</td>
<td>17%</td>
</tr>
<tr>
<td>Perceived risk of personal overdose</td>
<td>Low (2 / 10)</td>
</tr>
</tbody>
</table>

“Overdose” is Often the Incorrect Term

**Interviewer:** How many times would you say you’ve had these bouts of delirium, or you’ve stopped breathing because of opioids?

**Patient:** Ever? 8-10 times.

**Interviewer:** And how many times has [naloxone] been used on you?

**Patient:** Oh boy. That would be really hard to answer. I’d say somewhere in the neighborhood of 12-15 times.

**Interviewer:** So, around 12-15 times someone has given you [naloxone] because you’ve stopped breathing because of opioids?

**Patient:** Yes. Medical staff each time. Because of the opioids, I’ve stopped breathing.

**Interviewer:** Over what period of time?

**Patient:** Over 1 year.

CDC Guidelines for Prescribing Naloxone to Patients on Opioids for Chronic Pain

“Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (>50 MME/day), or concurrent benzodiazepine use, are present.”
3. Education / Patient Interaction

- Using Illicit Opioids
  - Overdose Prevention
  - Personal Overdose Risk
  - Peer Response
  - Empowerment

- On Opioids For Pain
  - Medication Safety
  - Bad Reactions
  - Unintentional Exposures
  - Antidote to risky pain medications
4. Formulations
Historic Formulations

**Vial and syringe**
- Sig: Naloxone 0.4mg IM if overdose, repeat after 3 minutes if no response, #2; IM syringe x2
- Cost: <$30
- Limitations: Comfortable with needles
- Pharmacy: FDA-approved, but no patient information sheet
- NDC: 00409-1215-01 or 67457-0292-02

**Nasal with assembly**
- Sig: Naloxone 2mg/2mL IN if overdose, repeat after 3 minutes if no response, #2; mucosal atomizer device (MAD) x2
- Cost: ~$80
- Limitations: Able to assemble device
- Pharmacy: Off-label use, no patient information sheet, atomizer ordered separately and not covered by insurance
- NDC: 76329-3369-01 (MAD UPC: 4100054145)
Novel Formulations

**Autoinjector**
- **Sig:** Naloxone autoinjector (Evzio) 0.4mg IM, use as directed, #1 kit
- **Cost:** ~$3,700 (retail)
- **Limitations:** None
- **Pharmacy:** FDA-approved, comes with patient information and training device, voice instructions
- **NDC:** 60842-0030-01

**Nasal**
- **Sig:** Naloxone (Narcan) 4mg/0.1mL IN, use as directed, #1 kit
- **Cost:** ~$100
- **Limitations:** None
- **Pharmacy:** FDA-approved, comes with patient information
- **NDC:** 69547-0353-02
5. Summary

- Opioid overdose involves multiple, some modifiable, risk factors
- Naloxone provision is legal, with additional protections in most states
- Indications for naloxone
  - Any person with a history of opioid use disorder, including active users, those in treatment or on-release from corrections
  - Any person who may witness an opioid overdose
  - Patients on long-term opioid therapy for pain with risk factors or receiving >=50MME/day
- Messaging for patients using illicit vs prescribed opioids is distinct
- Naloxone is currently available in four formulations
Naloxone for Opioid Safety
Phillip O. Coffin MD, MIA
San Francisco Department of Public Health
University of California San Francisco
phillip.coffin@ucsf.edu
OPIOID AGONIST THERAPY: THE DURATION DILEMMA

Edwin A. Salsitz, MD, DFASAM
The ASAM State of the Art Course
October 6, 2016
Disclosure Information

Edwin A. Salstiz, MD, DFASAM
No Disclosures
Treatment of Opioid Addiction

- Medication Assisted: Therapy, Treatment, Recovery

- Opioid Full/Partial Agonist Therapy (OAT): Methadone, Buprenorphine,

- Opioid Antagonist Therapy: Naltrexone(po)and IM

- Medication Plus Psychosocial—±Optimal Outcomes

- Drug Free Recovery- “Abstinence Based”

- Mutual Help, CBT, DBT, MI, etc.
Addiction Treatment

Psychosocial  Medication
MEDICATION ASSISTED ADDICTION TREATMENT

“All Treatments Work For Some People/Patients”
“No One Treatment Works for All People/Patients”

-Alan I. Leshner, Ph.D
Former Director NIDA

“Those who do not remember the past are condemned to repeat it.”

-George Santayana 1863-1952
The Lexington Narcotic Farm

The first facility opened on May 25, 1935, outside Lexington, Ky. The 1,050-acre site included a farm and dairy, working on which was considered therapeutic for patients. Morphine and methadone for w/d Rx. With the increased availability of state and local drug abuse treatment programs, The hospital was closed in February 1974.

ONE PROBLEM:

RELAPSE UPON RETURN HOME
Drs. Dole, Nyswander, and Kreek

Dr. Mary Jeanne Kreek, Addiction Laboratory
Rockefeller University
A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine.

From the Rockefeller Institute, and Manhattan General Division of Beth Israel Hospital, New York.

JAMA. 2008;300(19):2303-2305
“The Effectiveness Of Methadone Maintenance Treatment,” Ball & Ross, 1991

Comprehensive Study of 6 Methadone Clinics in NYC, Philadelphia, and Baltimore
Objective: “Open the Black Box of Methadone Maintenance Treatment”
N=617 patients over 7 Years
"Because methadone maintenance involves the giving of drugs to a drug-seeking, suggestible population, the placebo effect is very important and must be examined."
Vaillant, GE. 1974

The Lancet · Saturday 8 September 1979

DOUBLE-BLIND COMPARISON OF METADONE AND PLAECBO MAINTENANCE TREATMENTS OF NARCOTIC ADDICTS IN HONG KONG

JOHN C. VICKNAIR
Beth-Hatil Medical Center, Mount Sinai School of Medicine, New York, U.S.A.

WALDORF WHITFIELD
Medical Service Division, U.S. Pavilion, Athens, Greece, C.E.A.

Summary
In a double-blind study carried out between 1972 and 1973 in Hong Kong 100 heroin addicts volunteered to be admitted for a week's stay to be randomized on 50 mg of methadone or placebo. The two groups were matched for social and medical data, and for the results obtained. At the end of the three-year project, only 1 of the original 5 placebo subjects was still under treatment and 96% of the methadone group were still on treatment. Patients who had dropped out of the study and were randomized for methadone treatment under known conditions had the same results as the original treatment group. (D.P.A.S.) and was designed as a small, double-blind, control study of methadone versus placebo. This report describes the experience of the three-year D.P.A.S. programme.

Patients and Methods

Selection Criteria

100 patients were admitted on a first-come, first-served basis according to the following criteria:
1. Male, aged 18-18 years.
2. Documented history of heroin addiction from at least five years and at least one previous treatment.
3. Evidence of current addiction to heroin as described by three consecutive positive urine samples and properly documented.
4. No history of psychotic or medical illness (e.g. diabetes, tuberculosis, psychiatric, or mental illness.

Procedure

Informed consent for participation in the study was given by all patients.

Those accepted for the trial were admitted to hospital for two weeks for admission to 60 mg of methadone or placebo orally. During the course of treatment, only 4 patients would be admitted at a time, as the admission of the 100 subjects coincided with the results.

Comparison treatment was provided to a clinic usually established for the purpose of the study. This clinic was of the same medical and social services. A medical assistant in charge of pharmacy, a medical research doctor, none of whom had any previous experience with methadone treatment.

On discharge from hospital patients were randomly assigned to either placebo or methadone treatment and were followed up monthly.

% Retained in Treatment

<table>
<thead>
<tr>
<th>Weeks After Admission</th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>76%</td>
<td>10%</td>
</tr>
<tr>
<td>130</td>
<td>56%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Fig. 1—Proportion of subjects retained in study.
Admission to the study occurred over 7 months; at least 128 weeks elapsed between admission of last subject and conclusion of the study.
Mortality in heroin addiction: impact of methadone treatment


1979-1984; N0 Admit to MMTP

Yearly Death Rates: IV ODs
MT=1.4, VD=1.7,
ID=6.91, UC=7.2

Fig. 2. Survivors in cohorts 1+2 (solid line) compared with controls (dotted).

Fig. 3. Cohort 2 (voluntary discharge; upper solid line) contrasted to cohort 3 (involuntary discharge; lower solid line) and controls (dotted line).
Conclusions:
“...inform the public that dependence is a medical disorder that can be effectively treated with significant benefits for the patient and society.”

Recommendations:
Expand Access to MMT
CJS ↑Access
Education of Providers
↓ Regulations
↑ Funding
Parity with all medical/psych disorders
Pregnancy ↑Access
Methadone Maintenance vs. 180 Day Detoxification


- 75% retention
- 75% UTS negative
- 20% mortality in placebo group

Graph showing treatment duration vs. remaining in treatment with Buprenorphine and control groups.
### Prescription Opioid Addiction Treatment Study “POATS”

#### Table 2. Successful Opioid Use Outcome by Counseling Condition (SMM vs SMM+ODC) at 3 Time Points

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Observed, No./Total No. (%) [95% CI]</th>
<th>GEE Model-Based Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMM</td>
<td>SMM+ODC</td>
</tr>
<tr>
<td>End of phase 1</td>
<td>24/324 (7.4) [4.8-10.8]</td>
<td>19/328 (5.8) [3.5-8.9]</td>
</tr>
<tr>
<td>Phase 2, end of treatment</td>
<td>84/180 (46.7) [39.2-54.2]</td>
<td>93/180 (51.7) [44.1-59.2]</td>
</tr>
<tr>
<td>Phase 2, 8-wk posttreatment follow-up</td>
<td>13/180 (7.2) [3.9-12.0]</td>
<td>18/180 (10.0) [6.0-15.3]</td>
</tr>
</tbody>
</table>

Abbreviations: GEE, generalized estimating equation; ODC, opioid dependence counseling; OR, odds ratio; SMM, standard medical management.

<sup>a</sup>The reference category is SMM+ODC.

<sup>b</sup>Adjusted for chronic pain at baseline and lifetime history of heroin use.

<sup>c</sup>Adjusted for chronic pain at baseline, lifetime history of heroin use, and phase 1 randomization.
Primary Care-Based Buprenorphine Taper vs Maintenance: Prescription Opioid Use Disorder

Figure 2. Treatment Retention and Mean Buprenorphine Dosage for Patients With Prescription Opioid Dependence

Results: Completion of 14 week trial: taper 11% vs maintenance 66%
Mean percentage of urine negative for opioids: taper 35% vs maintenance 53%

Fiellin DA et al. JAMA Intern Med 2014
Buprenorphine: Recurrent Relapse

30 y.o. male. Buprenorphine was effective. Significant psychosocial problems, including high stress job, and many co-workers misusing prescription oxycodone. Unable or unwilling to access counseling, and dispute with wife over maintenance paradigm. Advised to return for treatment. Lost to F/U.

<table>
<thead>
<tr>
<th>Name</th>
<th>DOB</th>
<th>Dose</th>
<th>Start</th>
<th>End</th>
<th>Drop Comments</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICHAEL</td>
<td>12/22/79</td>
<td>Suboxone 8mg qd Film</td>
<td>2/21/12</td>
<td>5/13/2012</td>
<td>XXX drop out 1</td>
<td>oxycodone, oxycontin</td>
</tr>
<tr>
<td>MICHAEL 2</td>
<td>12/22/79</td>
<td>Suboxone 8mg qd Film</td>
<td>4/13/2012</td>
<td>6/19/09</td>
<td>XXX drop out 2</td>
<td>Relapse oxycodone IR ER</td>
</tr>
<tr>
<td>MICHAEL 3</td>
<td>12/22/79</td>
<td>Suboxone 8mg Film</td>
<td>6/19/09</td>
<td>7/23/10</td>
<td>XXX drop out 3</td>
<td>Relapse oxycodone IR ER</td>
</tr>
<tr>
<td>MICHAEL 4</td>
<td>12/22/1979</td>
<td>Suboxone 8mg Film</td>
<td>4/13/2012</td>
<td>7/23/10</td>
<td>XXX drop out 4</td>
<td>Relapse oxycodone IR ER</td>
</tr>
</tbody>
</table>
Duration: Potential “Pleiotropic” Benefits

Gavin Bart MD, FACP, FASAM
Prevalence of HIV-1 (AIDS Virus)
Infection in Intravenous Drug Users

50 – 60% Untreated, street heroin addicts: Positive for HIV-1 antibody
9% Methadone maintained since<1978 (beginning of AIDS epidemic): less than 10% positive for HIV-1 antibody

Kreek, 1984; Des Jarlais et al., 1984; 1989
Relapses

- May be delayed and gradual
- ODs and OD death, e.g., fentanyl contamination
- Relationships
- Employment
- Child Custody
- Criminal Justice System
- New Infectious Agent
- Shame and guilt
- Etc.
As compared to active IV heroin users the methadone patients gained weight, and had less sexual dysfunction, Chronic liver disease was common, and antedated methadone treatment. “No clusters of unusual medical complications were observed.” *(EKGs not done)*
Total Years on Methadone

- 0 yrs. (0%)
- 1-10 yrs. (0%)
- 11-20 yrs. (6%)
- 21-30 yrs. (21%)
- 31-40 yrs. (36%)
- 41-50 yrs. (36%)

Courtesy A.W.
Occupations of OBOT OAT Patients

- Teacher
- Electrician
- Plumber
- Social Worker
- Psychologist
- Chauffer
- Computer/IT
- Drug Counselor
- Accountant
- Retail Manager
- Home Security Systems
- Restauranteur
- Fish Dept. Manager
- Movie Editing
- Student (Ph.D.)
- HVAC Tech.
- Stamps
- School Principal
- Artist
- Advertising VP
- Bus Driver—MTA*
- Sanitation Driver*
- Con Ed Utility*
- Subway Signal—MTA*
- Sales
- Secretarial
- Administrator
- Piano Teacher
- Elevator Repair
- Lawyer
- Physician
- Landscape
- Car Salesman/Repair
- Videographer
- Heavy Equipment
- Contractor
- Entrepeuner
- Musician
- Nurse

* Safety Sensitive—Employer’s OK
What If There Were a Methadone or Buprenorphine for:

- Methamphetamine and Cocaine Addiction?
- Alcohol Addiction?
- Tobacco Addiction?
- Benzodiazepine Addiction?
- Food Addiction?
- Pathological Gambling?
Final Comments: OAT Duration

- The scientific evidence base, and 50 years of clinical experience overwhelmingly support maintenance in the OAT treatment paradigm.
- The goal of OAT maintenance is not to see how fast a patient can “get off” medication.
- The goal is normalization and stabilization of the brain, establishing durable and safe hedonic tone, and functioning at maximal potential at home and at work.
- Like most chronic medical therapies, the medication only works, when it is taken.
- “If It Ain’t Broke, Why Fix It?”
Actor Philip Seymour Hoffman, who was found dead February 2, 2014 on the bathroom floor of his New York apartment with a syringe in his left arm, died of acute mixed drug intoxication, **including heroin**, cocaine, benzodiazepines and amphetamine, the New York medical examiner's office said Friday.
References

Development Of An FDA-Approved Intranasal Naloxone Product For Opioid Overdose

Phil Skolnick, Ph.D., D.Sc. (hon.)
Director, Division of Therapeutics & Medical Consequences
National Institute on Drug Abuse, NIH
Disclosure Information

Phil Skolnick, Ph.D., D.Sc. (hon.)
No disclosures
National Overdose Deaths
Number of Deaths from Prescription Opioid Pain Relievers

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Heroin

Source: National Center for Health Statistics, CDC Wonder
An Improvised Intranasal Naloxone Kit
Critical Tasks for Assembling An Improvised Nasal Naloxone Kit

Table 2  Adherence to instructions-for-use for NAI and NXN

<table>
<thead>
<tr>
<th>NAI instructions</th>
<th>NXN instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Remove from outer case</td>
<td>(1) Remove medication and atomizer</td>
</tr>
<tr>
<td>(2) Pull off red safety guard</td>
<td>(2) Pull off both yellow caps from syringe</td>
</tr>
<tr>
<td>(3) Place black end onto patient’s outer thigh</td>
<td>(3) Pull off purple naloxone cap from naloxone cartridge</td>
</tr>
<tr>
<td>(4) Press firmly to activate</td>
<td>(4) Attach atomizer onto syringe by the hold wings on the atomizer</td>
</tr>
<tr>
<td>(5) Hold for at least 5 s</td>
<td>(5) Screw naloxone cartridge into syringe</td>
</tr>
<tr>
<td></td>
<td>(6) Place atomizer tip into patient’s nostril</td>
</tr>
<tr>
<td></td>
<td>(7) Push cartridge to administer some naloxone into one nostril</td>
</tr>
<tr>
<td></td>
<td>(8) Push cartridge to administer approximately 1 mL naloxone into the other nostril</td>
</tr>
</tbody>
</table>

*NAI naloxone 0.4 mg auto-injector, NXN naloxone nasal atomization kit
a Participants can perform steps 2–3 and 4–5 out of sequence*

High Error Rate Associated With Improvised Nasal Naloxone Kits—Even After Training!

Table 4 Critical task success for NAI and NXN

<table>
<thead>
<tr>
<th>Summary</th>
<th>Phase 1</th>
<th>Phase 3</th>
<th>Comparison between phases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>using RMAN (z &lt; 0.0001).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task completion time for NAI was 0.9 ± 0.25 min for phase 1 (untrained) and 0.5 ± 0.15 min for phase 3 (post-training). NXN task completion time for phase 1 was 6.0 ± 4.76 min and 2.0 ± 2.15 min for phase 3.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Yes | 0 (0.0%) | 24 (57.1%) | <0.0001 |
| No | 42 (100.0%) | 18 (42.9%) | <0.0001 |

Comparison of NAI and NXN within each phase*

N/AI naloxone 0.4 mg auto-injector, NXN naloxone nasal atomization kit
* McNemar’s Test
Abstract: To investigate the pharmacokinetics of naloxone in healthy volunteers, we undertook an open-label crossover study in which six male volunteers received naloxone on five occasions: intravenous (0.8 mg), intramuscular (0.8 mg), intranasal (0.8 mg), intravenous (2 mg), and intranasal (2 mg). Samples were collected for 4 hours after administration for 128 samples in total. A population pharmacokinetic analysis was undertaken using NONMEM. The data were best described by a three-compartment model with first-order absorption for intramuscular and intranasal administration, between-subject variability on clearance and central volume, lean body weight on clearance, and weight on central volume. Relative bioavailability of intramuscular and intranasal naloxone was 36% and 4%, respectively. The final parameter estimates were clearance, 91 L/hr; central volume, 2.87 L; first peripheral compartment volume, 1.49 L, second peripheral compartment volume, 33.6 L; first intercompartmental clearance, 5.66 L/hr; second intercompartmental clearance, 29.8 L/hr; Ka (intramuscular), 0.65; and Ka (intranasal), 1.52. Median time to peak concentration for intramuscular naloxone was 12 minutes and for intranasal, 6 to 9 minutes. A combination of intravenous and intramuscular naloxone provided immediate high and then detectable concentrations for 4 hours. Intranasal naloxone had poor bioavailability compared with intramuscular. Combined intravenous and intramuscular administration may be a useful alternative to naloxone infusions.

Key Words: naloxone, pharmacokinetics, population pharmacokinetics, therapeutic drug monitoring

(Ther Drug Monit 2008;30:490-496)
Objective: Deliver Naloxone In A Small Volume In An Intuitive Device
Pharmacokinetic Profile of IN and IM Naloxone: The Basis of Approval For Narcan® Nasal

P. Kreiter et al., J. Clinical Pharmacol., 2016
Table 7. Human Factors Study: Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Endpoint Type</th>
<th>Study A 2 Sprays Arm 1—QSG Reviewed Prior to Test (N = 32)</th>
<th>Study A 2 Sprays Arm 2—QSG Not Reviewed Prior to Test (N = 31)</th>
<th>Study B 1 Spray QSG Not Reviewed Prior to Test (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (n)</td>
<td>95% CI</td>
<td>% (n)</td>
</tr>
<tr>
<td>1a) Check for a response</td>
<td>Secondary</td>
<td>93.8 (30)</td>
<td>79.2–99.2</td>
<td>77.4 (24)</td>
</tr>
<tr>
<td>2a) Insert nozzle into nostril</td>
<td>Primary</td>
<td>100.0 (32)</td>
<td>89.1–100.0</td>
<td>100.0 (31)</td>
</tr>
<tr>
<td>2b) Press plunger to release dose into nose (Location and Dose Release Combined)</td>
<td>Primary</td>
<td>90.6 (29)</td>
<td>75.0–98.0</td>
<td>90.3 (28)</td>
</tr>
<tr>
<td>3a) Call 911</td>
<td>Secondary</td>
<td>75.0 (24)</td>
<td>56.6–88.5</td>
<td>80.6 (25)</td>
</tr>
<tr>
<td>3b) Move to recovery position after administering dose</td>
<td>Secondary</td>
<td>68.8 (22)</td>
<td>50.0–83.9</td>
<td>48.4 (15)</td>
</tr>
<tr>
<td>4a) Wait 2–3 minutes</td>
<td>Secondary</td>
<td>59.4 (19)</td>
<td>40.6–76.3</td>
<td>54.8 (17)</td>
</tr>
<tr>
<td>4b) Readminister using new unit (if needed)</td>
<td>Secondary</td>
<td>80.0 (24)</td>
<td>61.4–92.3</td>
<td>70.0 (21)</td>
</tr>
<tr>
<td>Success threshold, lower bound only</td>
<td></td>
<td></td>
<td>69%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose

Philip Krieter, PhD¹, Nora Chiang, PhD¹, Shwe Gyaw, MD¹, Phil Skolnick, PhD, DSc (hon)¹, Roger Crystal, MD², Fintan Keegan, MSc³, Julie Aker, MT (ASCP)⁴, Melissa Beck, BA⁴, and Jennifer Harris, BA⁴
Further Questions?

- Please reach out to Dr. Skolnick at NIDA
  - Phil.Skolnick@nih.gov
  - 301.827.5979
Duration of Treatment and Tapering Strategies for Opioid Use Disorder

Eric C. Strain, M.D.
Johns Hopkins University School of Medicine
Disclosure Information

Eric C. Strain, M.D.:

Advisory Groups (Honoraria): Egalet, Indivior Pharmaceuticals, The Oak Group, Pinney Associates, Relmada Therapeutics, Zogenix
Outline For This Talk

- How long should a patient remain on opioid treatment?
- What’s the optimal strategy for tapering off an opioid?
- Summary and conclusions
Some Assumptions For The Talk

- Talking about Opioid Use Disorder (OUD), aka opioid dependence
- Treatment with buprenorphine or methadone
- Will refer to “tapering” or “medically supervised withdrawal,” but recognize it is hard to banish “detox” from the lexicon
I. How Long Should A Patient Remain On Opioid Treatment?
How Long To Treat?

- We know remarkably little about this topic
- A dearth of good studies (in part, may be related to the five year funding cycle of NIH grants)
- As is often the case in the area of substance use disorders, a lack of data never stops us from having opinions
How Long To Treat?

- From the NIDA website:

  “Individuals progress through drug addiction treatment at various rates, so there is no predetermined length of treatment. However, research has shown unequivocally that good outcomes are contingent on adequate treatment length. Generally, for residential or outpatient treatment, participation for less than 90 days is of limited effectiveness, and treatment lasting significantly longer is recommended for maintaining positive outcomes.”
How Long To Treat?

- From the NIDA website:
  
  “For methadone maintenance, 12 months is considered the minimum, and some opioid-addicted individuals continue to benefit from methadone maintenance for many years.”

How Long To Treat?

- Patients generally benefit from being in **good quality** methadone/buprenorphine treatment
- However, we do know that many drop out of treatment
How Long To Treat?

- Perhaps the question is not how long to treat with medication assisted treatment (MAT), but why to stop treating with it.
- When should we stop treatment?
When Should MAT Stop?

- Patient preference
- Early in course of illness/younger age
- Intervening factors that contradict treatment (e.g., other illness)
- Adherence issues
How long to treat?

- **Conclude:**
  Virtually no data driven recommendations. In general, longer is better, and there are now patients for years (decades) on methadone and buprenorphine. No clear evidence of adverse effects to long-term use of these medications.

  Unless a compelling reason to stop the medication, would recommend they be continued.
II. What’s the optimal strategy for tapering off an opioid?
Tapering

- Does it work?

Cochrane review from 2005 had a hard time coming to conclusions about methadone tapering/withdrawal (compared to other medications)

Amato et al., Cochrane Database Syst Rev, 2005
Methadone Tapering

Three studies to review today:

Senay et al. (Arch Gen Psychiatry 1977)
Sees et al. (JAMA 2000)
Kakko et al. (Lancet 2003)
Methadone Tapering - Senay et al. 1977

- 127 volunteers – stable methadone patients
- Randomly assigned to one of four groups:
  - Known Maintenance (N=33)
  - Blind Maintenance (N=31)
  - Blind Rapid Withdrawal (10% decrease/wk; N=33)
  - Blind Gradual Withdrawal (3% decrease/wk; N=30)

Subjects on relatively low doses of methadone (average dose was 31 mg/day, range 6-80 mg)

Participants could request interruptions in methadone withdrawal (no dose decrease for a week), and could also request a temporary dose increase

All subjects started withdrawal after 30 weeks
Study Completion*

*significantly different (p<0.001)

From: Senay et al. 1977

- Known Maintenance: 76%
- Blind Maintenance: 94%
- Rapid Withdrawal: 0%
- Gradual Withdrawal: 24%
Weekly Methadone Dose

- Projected Dosage Levels
- Known Maintenance (KM)
- Blind Maintenance (BM)
- Rapid Withdrawal (RW)
- Gradual Withdrawal (GW)
Methadone Tapering-Senay et al.

♦ How did patients do after withdrawal?
  ♦ 23 (70%) patients in Rapid Withdrawal and 16 (53%) patients in Gradual Withdrawal groups reached 0 mg for at least one week
  ♦ At one month follow-up:
    ♦ 17/23 (74%) of Rapid Withdrawal patients relapsed or were back in methadone treatment
    ♦ 6/16 (38%) of Gradual Withdrawal patients relapsed or were back in methadone treatment
Methadone Tapering - Senay et al.

Conclusion:

- Gradual withdrawals better than rapid ones
- Withdrawal not highly effective if goal is abstinence
- Role of expectancy important (and other studies suggest better to keep patient informed during withdrawal rather than conducting withdrawal blindly)
179 opioid dependent volunteers

Randomly assigned to one of two groups:

- Standard Methadone Maintenance (N=91)
- 180 Day Methadone Detoxification (N=88) Both groups started at 30 mg/day, increased to 80 mg/day with a maximum dose of 100 mg/day
- Discharged from study if missed 7 consecutive days of dosing

Study Design

Induction and Maintenance
(mean dose, 87 mg/day)

Withdrawal

Induction & Maintenance
(mean dose, 84 mg/day)

Withdrawal
Non-methadone Treatment

Study Period

From: Sees et al. 2000
Survival Function by Treatment Group

Proportion of Patients in Treatment

- M180
- MMT
Heroin Use in Previous 30 Days

![Graph showing Heroin Use in Previous 30 Days for M180 and MMT.]
Methadone Tapering-Sees et al.

Conclusion

- Maintenance more effective than withdrawal for outcomes of retention and heroin use
- High rates of illicit opioid use in the maintenance group
Methadone Tapering-Kakko et al. (Lancet 2003)
Buprenorphine Maintenance/Withdrawal: Retention

(Kakko et al., 2003)
Methadone tapering - Kakko et al.

Conclusion:

- Maintenance more effective than withdrawal even in the context of enriched psychosocial services
Methadone Tapering—Overall Conclusions

- Maintenance treatments overall produce better outcomes than tapers/withdrawals
- At an individual level, some patients want withdrawal
- Not clear evidence of superiority of methadone vs. buprenorphine (inconclusive)
- Slower tapers better than quicker ones
- May be better to keep patient informed (vs blind)
Summary

1. How long to treat: Keep treating until there is a reason not to treat

2. Optimal way to taper: If indicated to taper, go slow, keep patient informed, be willing to stop tapers if not going well
Acknowledgements

- Support of NIDA
- Patients and staff at the Behavioral Pharmacology Research Unit at Johns Hopkins University School of Medicine

- Thank You