Does Treatment Work?

Carl Christensen, MD PhD, FASAM
Medical Director, Dawn Farm
Clinical Associate Professor, WSU School of Medicine
Medical Director, Mich Health Recovery Prof Program
Advisory Board, Families Against Narcotics, Wayne Co.

To Get This PowerPoint and copies of the Articles....

- Email ccmdphd@mac.com
- I will send you a Dropbox link with the PPT and all articles/abstracts

Disclaimers

- Methadone provider, WSU
- Medical Director Dawn Farm (12 step)
- Buprenorphine provider
- Naltrexone provider

Treatment: What Are We Looking For?

- Harm Reduction
- Abstinence
- Recovery

What is Recovery?

A voluntarily maintained lifestyle with:

- Sobriety (abstinence)
- Health (physical, mental and social well-being)
- Citizenship (giving back = spirituality)
- Quality of Life?
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3188817/
What is the Gold Standard of Research?

- Level I: randomized, double blinded, controlled experimental trial
- Level IIA: level I without randomization
- Level IIB: population studies: don’t control the research (case-control and cohort)
- Level IIC: no control group
- Level III: opinions of respected experts (Cochrane and other hot air)

Ethics of Treatment

- Non-maleficence: first, do no harm
- Beneficence: do the right thing
- Autonomy: based on informed consent, the patient chooses their treatment
- JUSTICE: division of medical resources

Addiction is Not Withdrawal.

Addiction is:

- Craving
- Compulsion
- Loss of Control
- Use Despite Consequences
- Chronicity

“Addiction isn’t a Disease”

Addiction is not a disease: A neuroscientist argues that it’s time to change our minds on the roots of substance abuse

Treatment of Opioid Dependence
How Do You Treat Addiction?

Medication Assisted Therapy, opiates

- **Agonists**
  - Methadone
  - Buprenorphine +/- Naloxone
- **Antagonists** (NOT FOR PREGNANCY)
  - Naltrexone
  - Rivea (tablets)
  - Vivitrol (injections)

Benefits of Methadone Maintenance Therapy (MMT)

- Reduction in death rates
- Reduction in IVDU
- Reduction in # of crime days
- Reduced HIV seroconversion / HCV conversion
- Reduction to relapse to IVDU
- Improvement in health, employment & functional level


CAREFUL!

Ball 1988: reduction in IVDU

Ball 1988: resumption of IVDU!

Change in Mortality with MAT

Drug Alcohol Dependence 105 (2009) 9-15
Change in Mortality with MAT
Degenhardt, Drug Alcohol Dependence 105 (2009) 9-15

(b) First two weeks in and out of treatment

<table>
<thead>
<tr>
<th>Drug-related</th>
<th>Suicide</th>
<th>Undetermined</th>
<th>Overdose-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2</td>
<td>20.0</td>
<td>38.9</td>
<td>20.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>METHADONE</th>
<th>BU PRENORPHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In treatment</td>
<td>Out of treatment</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

Take Home Points:

- Mortality appears to decrease (29%) after starting medication assisted treatment.
- Mortality INCREASES after leaving treatment.
- Both the first two weeks IN treatment (methadone) and OUT of treatment (methadone and buprenorphine) are the most dangerous periods.

Mortality and M.A.T (bup and MTD)
122,885 patients: overdose mortality

<table>
<thead>
<tr>
<th>METHADONE</th>
<th>BU PRENORPHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In treatment</td>
<td>Out of treatment</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

Quality of Life with Methadone Maintenance Therapy (MMT): ???

- High mortality (>20%) and continued drug use in patients who attended MMT. J Addict Dis 2011 Jan; 30(1) 17-26
- Patients in Taiwan had improvement in QOL with MMT.
  - Chou et al. BMC Psychiatry 2013; 13: 190
- MMT patients regain cognitive function
  - PLOS ONE 2014: 9(40) e94589

Methadone PILLS: for pain only
2% of prescriptions 30% of deaths

Buprenorphine

- A partial opiate agonist
- Less effective for withdrawal
- Less analgesic effect
- Less respiratory depression
- 4000+ PER YEAR WITH METHADONE
- Few OD deaths with buprenorphine
- Relative Risk of death: >4

- Drug Alcohol Dep 2008: 104, 73-77
Agonist, partial agonist, antagonist....

Sublingual Buprenorphine/Naloxone for Dependence:

- Available in 3 branded forms:
  - Generic buprenorphine (Subutex®): sublingual OFF MARKET: Medicaid may concerns about diversion.
  - Bunavail®: sublingual buprenorphine + naloxone (Narcan®): prevents IV use*
  - Suboxone®: sublingual buprenorphine + naloxone (Narcan®): prevents IV use*
  - Zubsolv®: prevents IV use*
- ANY of these will precipitate sudden withdrawal: only give when patient is going INTO withdrawal!

Buprenorphine:

- Formulations approved for PAIN:
  - Buprenex®: parenteral, used in the hospital setting.
  - Butrans®: weekly patch, 10 to 20 mcg/hr
  - Belbuca®: buccal film from 75 – 900 mcg/24 hr.

Buprenorphine long-term follow up: Fiellin, 2008

- Of those who remained in treatment:
  - 91% were negative for opioids
  - 96% were negative for cocaine!
  - Satisfaction score: “86%”

Methadone vs. Bupx: Cochrane database

- “Buprenorphine is an effective treatment for heroin use in a maintenance therapy approach compared with placebo. However, methadone maintenance treatment at high dose is associated with higher rates of retention in treatment and better suppression of heroin than buprenorphine maintenance treatment.”
- Methadone, however, has been found to be associated with more frequent overdose and death (4.8 vs 0.9/1000 patient-years) (Bell, 2009)
What about pregnancy?

MOTHER STUDY

The New England Journal of Medicine

Original Article

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée Jones, Ph.D., Kari Klassen, Ph.D., Sarah H. Heil, Ph.D., Suzy M. Stitzer, M.D., Ph.D., More G. Coyle, M.D., Annise M. Anis, Ph.D., O’Grady, Ph.D., Peter Sibley, M.B., B.S., Peter R. Martin, M.D., and Gabrielle Fischer, M.D.

Methadone vs. Buprenorphine: the MOTHER study

<table>
<thead>
<tr>
<th>Measure</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of MS required</td>
<td>10.4</td>
<td>1.1</td>
</tr>
<tr>
<td># of days in hospital</td>
<td>17.5</td>
<td>10</td>
</tr>
<tr>
<td>Duration of treatment for NAS</td>
<td>9.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Birthweight</td>
<td>2878</td>
<td>3093</td>
</tr>
<tr>
<td>% preterm delivery</td>
<td>19</td>
<td>7*</td>
</tr>
<tr>
<td>Positive drug screen at delivery</td>
<td>15%</td>
<td>9%*</td>
</tr>
<tr>
<td>Dropped out (why?)</td>
<td>18%</td>
<td>33</td>
</tr>
</tbody>
</table>

MS = morphine, NAS = neonatal abstinence syndrome

Vivitrol® (naltrexone) for opioid dependence

Krupitsky et al, Lancet 2011; 377: 1506-13
Comer et al, Arch Gen Psychiatry 2006; 63: 210-218

Vivitrol: abstinence

Krupitsky et al, Lancet 2011; 377: 1506-13
Comer et al, Arch Gen Psychiatry 2006; 63: 210-218
**Vivitrol: craving**

- **placebo**
- **vivitrol**

- **p=0.0001 (adjusted)**

**Vivitrol: treatment retention**

- **Placebo effect and/or med free treatment!**
- **Log rank p=0.0042 (adjusted)**

**Vivitrol: treatment retention**

- **Placebo effect and/or med free treatment!**
- **Log rank p=0.0042 (adjusted)**

**Doc, when can I get off this sh*t (medication)?**

**Detoxing During Pregnancy?**

**Luty 2003**

- 101 women underwent detox during pregnancy
- 40 successfully detoxed.
- No adverse fetal effects documented
- But: only 1/101 patients documented to be abstinent at time of delivery!

- Luty et al, J Sub Abuse Treat 24 (2003); 363 - 367
Detox from heroin using buprenorphine: Kakko

- 40 heroin addicts in Sweden were recruited.
- All were given buprenorphine and offered counseling.
- 20 were allowed to taper off.
- 20 remained on buprenorphine and continued counseling.
- A year later.....

Medical Withdrawal vs Maintenance

- N=20
- Both groups received counseling
- High mortality rate in detox group (20%, n=4)

Can you taper off buprenorphine without relapse?

Outcome Phase 1

- Only 43 of 653 patients remained abstinent (6.6%)
- All others relapsed!!
- On to Phase 2!
Phase 2

360 pts → 12 weeks BUP → Taper 1 to 2 weeks
(5 to 12 weeks)

Outcomes Phase 2

• 49% stayed abstinent when they went back on buprenorphine!
• But when they were taken off buprenorphine again, only 8.6% remained abstinent!

Conclusions

• Buprenorphine was effective (≈ 50%) at treating prescription pill addiction.
• Chronic pain was not a barrier to success.
• Less than 10% were able to remain abstinent during 2 attempts to taper off buprenorphine.

Conclusions

• “MAT” is effective at decreasing opioid use.
• Stopping MAT will usually result in relapse & increased chance of death.
  • Why would you expect otherwise?
• Methadone is better at keeping you in treatment. Buprenorphine has a superior safety profile.
• Vivitrol® (injectable naltrexone) is effective at reducing opioid use.

Abstinence Based Programs

• The previous administration favored MAT; no one is sure what the current administration will do.
• Advocates of abstinence based programs are often “on the ropes” and accused of religiosity and cultism (Glaser)
• Accusations of 1 to 5% success have been made with claims of greater harm than “spontaneous remission”.
• Any exceptions to this?

Physicians Health Programs*
(php): the Gold Standard

* Physicians Health Programs (PHP) are considered the gold standard in addiction treatment.
PHP

- Physicians, nurses, pharmacists (varies by state)
- Evaluation, treatment (IOP/residential)
- Require mutual help groups: 12 step or SMART
- Monitor –weekly
- 3 to 5 year contracts
- Similar to pilots and lawyers
- MOST do not allow MAT
- Immediate intervention for positive urine drug screens.

80-90% SUCCESS!

Drug Testing

- The majority (29%) had no positive tests for alcohol or other drugs during the monitoring period
- 14% had just one positive test
- 7% had more than one positive test
- Similar in all four groups
- This means that regardless of their drug of choice about two thirds of the physicians who had a positive test for alcohol or other drugs never had a second or subsequent positive test.

Comparison to Bupx

<table>
<thead>
<tr>
<th>Suboxone Maintenance*</th>
<th>PHP Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>Anticipated</td>
</tr>
<tr>
<td>Other Substance Use</td>
<td>Common (alcohol, MJ etc)</td>
</tr>
<tr>
<td>% Ustines Positive at 6 months</td>
<td>Opiates 50%</td>
</tr>
<tr>
<td></td>
<td>Cocaine 40%</td>
</tr>
<tr>
<td></td>
<td>Benzos 10%</td>
</tr>
</tbody>
</table>

Fudala, et al. Office-Based Tx of Opiate Addiction w/ Suboxone. NEJM 2003

Why do PHPs work?

- “They work because doctors have more to lose”.
- “They work because doctors are smarter”
- “They work because doctors can afford treatment”
- “They work because doctors get special treatment”

Hawaii’s HOPE program


Swift and Certain (SAC)

Why does it work?

- Chronic disease model - 3 to 5 years of monitoring and treatment.
- Mutual help groups (12 step and SMART)
- Caduceus groups - reduce isolation
- Rapid response through drug screens & workplace
- Leverage (including negative reinforcement)

What Happens When you Stop Monitoring?

What Happens When you Stop Monitoring?

PHPs: More Harm than Good?

The Opioid Epidemic & Naloxone (Narcan®) Rescue

Developed for Families Against Narcotics
http://www.familiesagainstnarcotics.org/
Naltrexone vs. Naloxone

<table>
<thead>
<tr>
<th>Naltrexone</th>
<th>Naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral (Rivex®) or IM (Vivitrol®)</td>
<td>• IV, IM, SC or IN (Narcan®, Evzio®)</td>
</tr>
<tr>
<td>• Slow onset</td>
<td>• Rapid onset</td>
</tr>
<tr>
<td>• Long acting (hours to weeks)</td>
<td>• Short acting (minutes)</td>
</tr>
<tr>
<td>• Tightest binding to brain</td>
<td>• Less tightly bound</td>
</tr>
<tr>
<td>• Used for PREVENTION of overdose (FDA)</td>
<td>• Used for TREATMENT of overdose (FDA)</td>
</tr>
</tbody>
</table>

What Does Narcan NOT Do?

• It will not reverse an overdose from alcohol, sedatives (Benzodiazepines such as Xanax, Valium and Klonopin), muscle relaxants, or stimulants like Cocaine or Amphetamines.

• If there is more than one drug involved (usually Benzodiazepines and Opioids), it may partially revive the patient until EMS arrives.

Naloxone formulations: (0.4 mg)

Intranasal (I.N.): ADAPT (4mg/2mg!)

Who is at Greatest Risk?

• Abstinence > 2 weeks: treatment; jail; relapse.
• Discontinuing MAT: methadone; buprenorphine; Vivitrol® (naltrexone).
• Mixing opioids with sedatives: alcohol, benzodiazepines, muscle relaxers
• FENTANYL
  • 50% of UDS samples with heroin are pos for Fentanyl

Fentanyl on Urine Drug Screen
Pregnant Patient

1. Illicit Drugs
   Marijuana, Methadone (FDA)

2. Medications Or Metabolites Detected But Not Listed On Requisition
   Opiates: Fentanyl, Hydromorphone

Carl Christensen, MD
www.christensenrecovery.com
How To Do A Naloxone Rescue

- Make Sure They are Not Breathing
- (always) Call 911
- Do Rescue Breaths (not compressions)
- Give Naloxone
- Resume Rescue Breaths
- Repeat Naloxone every 3 mins
- To review videos: go to ccmdphd on YouTube

Rescue Breathing

- Flat on Back
- Tilt the head back
- If no mask-pinch nose
- Give 2 breaths, one second each.
- Chest wall should move 1 inch
- Abdomen should NOT move

Which One Is Better?

<table>
<thead>
<tr>
<th>Time to “Come To”</th>
<th>Time to Resume Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid: IM</td>
<td>Dotted: IN</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After EMS arrives.....

- Watch out for needles!
- Clean up all blood!
- You now have a “window of opportunity”.....

Treatments for Alcohol Dependence

- Alcoholics Anonymous
- Anti-AA (SMART, Rational Recovery, etc)
- CBT
- MET
- Medications for Alcohol Dependence

Cochrane Database?

- AUTHORS' CONCLUSIONS: No experimental studies unequivocally demonstrated the effectiveness of AA or TSF approaches for reducing alcohol dependence or problems compared with other treatments, but there were some limitations with these studies. Furthermore, many different interventions were often compared in the same study and too many hypotheses were tested at the same time to identify factors which determine treatment success.
  - Ferri, 2006.
  - WHY?
AA Effectiveness – Faith Meets Science

Lee Ann Kaskutas, Dr.P.H.
Alcohol Research Group, Emeryville, CA
School of Public Health, UC Berkeley

Presented at the Annual Meeting and Conference of the Federation of State Physician Health Programs (FSPHP)
April 25, 2012
Fort Worth, TX

Abstinence & AA exposure

Ouimette et al., J Stud Alcohol 1998
Thurstin et al., Int J Addict 1987

Abstinence & meeting amount

Moos et al., J Clin Psychol 2001

Abstinence & meeting frequency

Going on two years: LA

Project MATCH

- Randomized patients to CBT, MET and TSF
  - CBT: cognitive behavioral therapy
  - MET: motivational enhancement therapy
  - TSF: twelve step facilitation
- No differences were found between groups. There was no control group.
- It has been argued that natural recovery would be as effective. (Stanton Peele)

Project MATCH

- "Everybody can now project their own views about alcoholism onto this study."
  - G Marlatt, PhD*
- “The study would be stronger with a control group, but is not invalid without one.”**

* https://en.wikipedia.org/wiki/Project_MATCH
**https://stats.stackexchange.com/questions/268318/3treatments-without-a-controlgroup
The 10 Year Course of AA Participation and Long-Term Outcomes: A Follow-up Study of Outpatient Subjects in Project MATCH

Maria E. Pagano, Ph.D., Case Western Reserve University School of Medicine, Department of Psychiatry, Division of Child Psychiatry, WO Walker Building, 10524 Euclid Ave., Cleveland, OH, 44106
William L. White, M.A., Chestnut Health Systems, 3329 Sunset Key Circle #203, Punta Gorda, FL, 33955
John F. Kelly, Ph.D., Center for Addiction Medicine, Department of Psychiatry, Harvard Medical School, 60 Staniford St., Boston, MA, 02114
Robert L. Stout, Ph.D., Decision Sciences Institute, Pacific Institute for Research Evaluation, 1005 Main Street Pawtucket, RI, 02860
Rebecca R. Carter, B.A., and Case Western Reserve University School of Medicine, Department of Psychiatry, Division of Child Psychiatry, WO Walker Building, 10524 Euclid Ave., Cleveland, OH, 44106
J. Scott Tonigan, Ph.D., The University of New Mexico, Center on Alcoholism, Substance Abuse, and Addiction, 2650 Yale SE, Albuquerque, NM, 87106

Abstract

This study investigates the 10-year course and impact of AA-related helping (AAH), step-work, and meeting attendance on long-term outcomes. Data were derived from 226 treatment-seeking alcoholics recruited from an outpatient site in Project MATCH and followed for 10 years post-treatment. Alcohol consumption, AA participation, and other-oriented behavior were assessed at baseline, end of the 3-month treatment period, and one year, three years, and 10 years post-treatment. Controlling for explanatory baseline and time-varying variables, results showed significant direct effects of AAH and meeting attendance on reduced alcohol outcomes and a direct effect of AAH on improved other-oriented interest.

Keywords

Alcoholics Anonymous; Project MATCH; Meeting Attendance; Step-work; AA-related helping

INTRODUCTION

Alcoholics Anonymous (AA) has distinguished itself within the alcohol problems arena through its membership size and geographical dispersion (more than 2.1 million members). Correspondence to: Maria E. Pagano, mxp123@case.edu.

Medications for alcohol dependence

Alcohol Metabolism and Disulfiram

Ethanol: Æ Acetaldehyde Æ CO2

1: alcohol dehydrogenase:
   • M-W, younger, white, protective
   • metabolizes 1 drink/hour

2: aldehyde dehydrogenase:
   • Detoxifies acetaldehyde
   • Inhibited by Disulfiram (Antabuse)

Naltrexone (Rivea®, Vivitrol)

• Blocks the opiate (µ) receptor
• Prevents you from using opiates
• Also blocks your endogenous (own) opiates: endorphins
• Opiate receptors responsible for alcohol craving
• Oral naltrexone: Has been shown to reduce drinking (but only in research studies)

Injectable naltrexone: O’Malley 2007

Injectable naltrexone: O’Malley 2007

High dose 380 mg
Low dose 190 mg
Placebo

O’Malley 2007

High dose 380 mg
Low dose 190 mg
Placebo

O’Malley 2007
Acamprosate (Campral®)

- Thought that it worked through GABA
- Not known how it works-NMDA/Glutamate
- May decrease “number of drinking days”
- May reduce craving
- Often being used by patients being admitted to detox units.

The COMBINE trial

- Combinations of:
  - CBT
  - Placebo medication
  - Naltrexone
  - Acamprosate

COMBINE Trial: take a pill!!!!

- Patients receiving naltrexone or CBI+placebo had higher percent days abstinent (80.6 and 79.2) compared to the other groups; the combination of naltrexone and CBI was not more effective (77.2) than either intervention alone.
- Acamprosate, alone or combined with naltrexone or CBI, was not more effective than placebo.
The Sinclair Method:
“pharmacologic extinction”

- Taking/injecting naltrexone BEFORE you stop drinking leads to craving → relapse.
- Taking oral naltrexone one hour before drinking leads to extinction of reward (pleasure)
- Other activities are not affected
- Claims better response than with abstinence based tx.
- NOT designed for those who should not drink at all!

Baclofen

- Used for muscle spasticity in spinal cord injuries
- Acts similar to alcohol and benzodiazepines, but binds to its own site in the brain.
- Withdrawal cannot be treated; withdrawal seizures may occur.
- Has been used at high doses for alcohol dependence.
- Reports of decrease in daily drinking with high dose.
- Reports of poisoning with high dose.

Why Treat Addiction?

Drug Dependence, a Chronic Medical Illness:
Implications for Treatment, Insurance, and Outcomes Evaluation
A. Thomas McLellan; David C. Lewis; Charles P. O’Brien; et al.

- Only about 40% of patients will be abstinent at one year after treatment.
- Failure rates may be due to lack of aftercare, often due to insurance difficulties
- Low economic status, psych comorbidity and lack of family/social supports also predict relapse.
- Relapse is often viewed as “inevitable” and drug dependence as “hopeless”*

Drug Dependence, a Chronic Medical Illness: McLellan 2000

- ONLY 60% OF TYPE I DIABETICS ADHERE TO MEDICATION SCHEDULE
- LESS THAN 40% OF ASTHMATICS ADHERE TO TREATMENT REGIMEN
- LESS THAN 40% OF HYPERTENSIVES ADHERE TO THEIR TREATMENT REGIMEN
- DRUG DEPENDENCE =40 TO 60% ADHERENCE

Addiction: a chronic illness

- If you were to stop taking your insulin, and you wound up in a coma in the ICU, your doctor would say:
  “you need to go back on insulin! You could have died!”
- If you were to stop your Suboxone/methadone/12 step treatment, and wind up in the ICU, your doctor would say:
  “You’re an addict. You’re hopeless!!!!!!”
Chronic, Treatable but Incurable Diseases

- Obesity
- Hypertension
- Diabetes
- Asthma
- Addiction

Families Against Narcotics

Contact info: Carl Christensen

- ccmdphd@mac.com
- Voice mail: 734 448 0226
- Christensen Recovery Services: www.christensenrecovery.com