Treatment of Substance Use Disorders

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Proprietary Recipe of Treatment of Any Mental/Substance Use Disorder by Dr. Elena Volfson

• Brain transplant
• Re-parenting
• Administration of common sense and perspective (PO, IM, IV, sublingually, etc.)
• Psychotherapy is the best treatment, unless the patient is actively psychotic, demented or mentally retarded
  • Functional frontal lobes are required for therapy
Outline

• DSM V vs DSM IV substance use disorders/behavioral addictions

• Current epidemiology of substance use in the USA from NSDUH 2013

• Neurobiology of substance use

• Current review of treatment strategies by substances: Alcohol, tobacco, opiates, cannabis, cocaine
DSM-IV and DSM-V Substance Use Disorders

- Eliminated abuse and dependence distinction
- Mild (2-3), moderate (4-5), and severe (>6) out of 11
- Added craving/eliminated legal problems as a criterion
- Specific substances need to be named in diagnoses
Substance Use Disorder DSM-V

- A substance is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control substance use
- A great deal of time is spent in activities necessary to obtain substance, use it, or recover from its effects
- Craving, or a strong desire or urge to use a substance
- Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home

- Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
- Important social, occupational, or recreational activities are given up or reduced because of substance use
- Recurrent use in situations in which it is physically hazardous
- Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Tolerance
- Withdrawal
Validated Screening Tools for Substance Use Disorders in Primary Care

**Alcohol**
- Single item screen
- AUDIT-C
- CAGE
- CARET: Elderly
- GMAST: Elderly
- T-ACE: Pregnant
- CRAFT: Adolescents

**Substances**
- Single item screen
- ASI
- BAM
- DAST
- ASSIST
Past Month Alcohol Consumption 2012

- Current use (not binge)
- Binge use (not heavy)
- Heavy use

Use in Last Month, %

Age, Years

- 12-13
- 14-15
- 16-17
- 18-20
- 21-25
- 26-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- 55-59
- 60-64
- 65+

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Past Month Cigarette Use 2012

Use in Last Month, %

Age, Years


1.2 4.6 13.6 28.2 34.1 33.4 31.9 26.7 24.3 26.0 24.5 21.5 16.9 10.1
Tobacco Use by Women Age >12

Use in Last Month, %

Not pregnant

Pregnant

Years

2002-03
2003-04
2004-05
2005-06
2006-07
2007-08
2008-09
2009-10
2010-11
2011-12

30.7
30.0
29.6
29.5
28.4
27.4
27.5
26.8
25.4
24.6

18.0
18.0
16.6
16.4
16.3
16.3
15.2
16.2
17.6
15.9
Daily or Almost Daily Cannabis Use in Age >12

- Used marijuana on 300 or more days in past year
- Used marijuana on 20 or more days in past month

Years: 2002 to 2012

Use, Millions:
- 2002: 4.8
- 2003: 4.9
- 2004: 4.9
- 2005: 5.1
- 2006: 5.1
- 2007: 5.1
- 2008: 5.5
- 2009: 6.2
- 2010: 6.9
- 2011: 7.1
- 2012: 7.6

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Initiation of Use by Substances 2012 (Excluding Tobacco)

- Marijuana 65.6%
- Pain relievers 17.0%
- Inhalants 6.3%
- Tranquilizers 4.1%
- Stimulants 3.6%
- Hallucinogens 2.0%
- Sedatives 1.3%
- Cocaine 0.1%
- Heroin 0.1%

2.9 million initiates of illicit drugs
Model of Addiction

- Emotion
- Reward/euphoria
- Control
- Craving
- Temporal - Parietal
- Orbital Prefrontal Cortex
- Ventral Tegmentum
- Nucleus Accumbens
- Memory
- Hippocampus

Used with permission from David Oslin, 2012
Model of Addiction

- Emotion
- Control
- Reward/euphoria
- Craving
- Memory
- Antidepressants
- Mood Stabilizers
- Therapy
- Naltrexone
- Acamprosate

12 Step/CBT

Used with permission from David Oslin, 2012
Interpersonal Neurobiology by Dr. Dan Siegel

• 3 parts to be reintegrated and healed:

1. **Brain disease:** Abnormalities in reward processing, memory and motivation

2. **Affect dysregulation:** Maladaptive coping mechanisms to soothe fear, pain, loneliness, anger and shame (frustration tolerance)

3. **Intimacy disorder:** Lack of interpersonal connections and attachments (therapist, group, partner/family, higher power)
Vulnerabilities in Development of Substance Use Disorders

- Genetic
- Developmental (maturational)
- Social
- Substance-induced brain plasticity
- Females are more vulnerable than males due to difference in dopamine release
Differences in Behavioral Response in Males and Females

Male:
- D2 and D1
- 10% more D1 than females
- D2 < female-dorsolateral striatum
- High basal DA requires greater stimulated DA for behavioral response

Female:
- D2 and D1
- D1 < than male
- D2 > male in dorsolateral striatum
- Lower basal DA so increase in DA produces greater behavioral response

Downstream changes induced by greater increase in DA result in greater susceptibility for addiction in females

Hu and Becker, 2008
Female Smokers are Much More Sensitive to Cigarette Cues Than Male Smokers

N=5 smokers and 6 non-smokers

N=6 smokers and 5 non-smokers

T. Franklin, 2010
Staged Neuroplasticity of Addiction

- Abstinence
- Social use
- Chronic use
- Regulated relapse: Conscious choice
- Compulsive relapse: Inability to make a conscious choice

Kalivas and O’Brien 2008
Core Addiction Syndrome

• Common neuroplastic changes in response to chronic administration of different substances of abuse

• Addiction is “overlearned” with repeated associations between substances and life events mediated by dopamine release

• Addictive behaviors and chronic relapse vulnerability are maintained by glutamatergic neurotransmission

Kalivas and O’Brien, 2008
Core Addiction Syndrome

- **Hypofrontality**: Subcortical glutamatergic connections assume primacy and reduce cortical control over drug-seeking (automatic behavior)

- Drug-associated stimuli activate PFC excessively, whereas natural reinforcers (sex, food, danger, etc.) elicit poor response - maladaptive process
Neurobiological Changes with Chronic Substance Use

- Motivation/reward system DA/endorphine
- Glutamate/GABA dysregulation
- HPA axis dysregulation
- Sex hormones dysregulation
- Hypofrontality
- Cravings
- Relapse
Pharmacologic Strategies to Treat Addiction

- Dopaminergic (D1-D5)
- Glutamatergic (NMDA, AMPA, KA, metabotropic)
- GABAergic (GABA A and B)
- Cholinergic (Ach M and N)
- Noradrenergic (alpha and beta)
- Serotonergic (14 subtypes)
- Endogenous opioids (mu, delta, kappa, OFQ-N)
- Endogenous cannabinoids (CB1 and CB2)
- Many others (NPY, DARPP-32, galanin, orexin, CRF, substance P, melanocortins, leptin, BDNF, etc.)
Most Effective Treatment for Substance Abuse Disorders

• Combination of medications and therapy

• Treatment of co-morbid mood, anxiety and other disorders

• Free up the frontal lobes by quieting subcortical areas for the therapy

• Therapy: Relapse prevention, motivational interviewing, 12-step facilitation, CBT, family therapy, etc.
Addiction Therapy May be Related to Activation of Frontal Cortex

Boettiger, et.al. 2009 and Crews and Boettiger et.al. 2009
Importance of Simultaneous Treatment for All Substances Involved

- One craving breeds another
- One addiction drives another (priming effect)
- Very important to address tobacco dependence
- Stress increases cravings and relapse
Goal of Addiction Treatment

- Recovery as "a voluntarily maintained lifestyle characterized by sobriety, personal health, and citizenship" J Subst Abuse Treat. 2007;33(3):221

- Restoration of medical and social well-being

- Acquiring or regaining cortical/executive control over one’s behavior and life
Low-Risk Drinking Limits (NIAAA)

• Only if no cardiovascular /liver/kidney disease

• Men age <65
  • Not >2 standard drinks (12 g of ethanol) per day
  • Not >4 drinks on an occasion
  • Not >14 drinks per week

• Women and elderly (age >65)
  • 1 drink per day
  • 7 per week
  • Not >3 drinks on an occasion

“Rethinking drinking” by SAMHSA
Medications for Alcohol Use Disorder

**FDA-Approved**
- Disulfiram
- Acamprosate
- Naltrexone – oral or injectable

**Off-Label**
- Topiramate
- Gabapentin
- Valproic Acid
- Carbamazepine
- Lamotrigine
- Memantine
- Zonisamide
- Levetiracetam
- Baclofen
- Ondansetron
Disulfiram

• Blocks aldehyde dehydrogenase – aversive therapy
• Does not reduce cravings
• Does not prevent relapse
• Problematic compliance
• Effective for cocaine use disorder
Disulfiram Reduces Drinking Days

Acamprosate

- Glutamate antagonist; blocks metabotrophic-5 glutamate receptors
- Reduces protracted withdrawal
- Reduces cravings
Acamprosate Promotes Abstinence

<table>
<thead>
<tr>
<th>Without Relapse, %</th>
<th>Acamprosate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45</td>
<td>25.3</td>
</tr>
</tbody>
</table>

# Meta-Analysis of Acamprosate: Abstinence Improved

**Outcome: Abstinence Rate**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>Peto OR (95% CI Fixed)</th>
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</thead>
<tbody>
<tr>
<td>Besson 1998</td>
<td>14/55</td>
<td>3/55</td>
<td></td>
<td>3.1</td>
<td>4.56 [1.63, 12.76]</td>
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<tr>
<td>Chick 2000</td>
<td>35/289</td>
<td>32/292</td>
<td></td>
<td>12.6</td>
<td>1.12 [0.67, 1.86]</td>
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<tr>
<td>Geerlings 1997</td>
<td>14/128</td>
<td>7/134</td>
<td></td>
<td>4.1</td>
<td>2.16 [0.89, 5.27]</td>
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<tr>
<td>Gual 2001</td>
<td>49/141</td>
<td>38/147</td>
<td></td>
<td>12.9</td>
<td>1.52 [0.92, 2.52]</td>
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<tr>
<td>Ladewig 1993</td>
<td>12/29</td>
<td>7/32</td>
<td></td>
<td>2.8</td>
<td>2.45 [0.83, 7.18]</td>
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<tr>
<td>Paille 1995</td>
<td>45/361</td>
<td>16/177</td>
<td></td>
<td>10.1</td>
<td>1.41 [0.80, 2.48]</td>
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<td>Pelc 1997</td>
<td>52/126</td>
<td>9/62</td>
<td></td>
<td>7.7</td>
<td>3.37 [1.76, 6.44]</td>
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<tr>
<td>Poldrugo 1997</td>
<td>53/122</td>
<td>37/124</td>
<td></td>
<td>12.1</td>
<td>1.79 [1.07, 3.01]</td>
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<tr>
<td>Sass 1996</td>
<td>54/136</td>
<td>23/136</td>
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<td>11.7</td>
<td>3.06 [1.81, 5.18]</td>
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<tr>
<td>Tempesta 2000</td>
<td>62/164</td>
<td>48/166</td>
<td></td>
<td>15.5</td>
<td>1.49 [0.94, 2.35]</td>
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<tr>
<td>Whitworth 1996</td>
<td>27/224</td>
<td>11/224</td>
<td></td>
<td>7.4</td>
<td>2.50 [1.29, 4.87]</td>
</tr>
<tr>
<td><strong>Total (95%CI)</strong></td>
<td><strong>417/1775</strong></td>
<td><strong>231/1549</strong></td>
<td><strong>100.00</strong></td>
<td><strong>1.88 [1.57, 2.25]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: chi-square=17.00; df=10; P=0.074
Test for overall effect: z=6.87; P<0.0001

CI, confidence interval; OR, odds ratio

Naltrexone

• Blocks opiate mu-receptors: Prevents endorphins from binding to GABA-interneurons

• Blocks subsequent dopamine release: Reduces cravings

• Effective in a subset of alcoholics
Cumulative Rate of Alcohol Relapse

- **Naltrexone HCl (N=35)**
- **Placebo (N=35)**

Volpicelli et al., Arch Gen Psychiatry 1992;49(11):876-80
Meta-Analysis: Oral Naltrexone Reduces Relapse

Outcome: Relapse Rate

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<td>Anton 1999</td>
<td>26/68</td>
<td>38/63</td>
<td></td>
<td>7.5</td>
<td>0.42 [0.21, 0.82]</td>
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<tr>
<td>Chick 2000</td>
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<td>54/85</td>
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<td>9.2</td>
<td>1.09 [0.59, 2.03]</td>
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<tr>
<td>Guardia 2002</td>
<td>8/101</td>
<td>19/101</td>
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<td>Hersch 1998</td>
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<td>15/33</td>
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<td>1.12 [0.42, 2.98]</td>
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<tr>
<td>Kranzler 2000</td>
<td>29/61</td>
<td>31/63</td>
<td></td>
<td>7.1</td>
<td>0.94 [0.46, 1.89]</td>
</tr>
<tr>
<td>Krystal 2001</td>
<td>142/378</td>
<td>83/187</td>
<td></td>
<td>27.4</td>
<td>0.75 [0.53, 1.08]</td>
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<tr>
<td>Latt 2002</td>
<td>19/56</td>
<td>27/51</td>
<td></td>
<td>6.0</td>
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<td><strong>Total (95%CI)</strong></td>
<td><strong>428/1142</strong></td>
<td><strong>445/930</strong></td>
<td></td>
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Test for heterogeneity: chi-square=17.00; df=10; P=0.074
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CI, confidence interval; OR, odds ratio

Naltrexone is Effective in Compliant Patients

- **Placebo:**
  - Non-Adherent: 3.1%
  - Adherent: 1.4%

- **Naltrexone:**
  - Non-Adherent: 5.0%
  - Adherent: 5.2%

Statistical significance: $p = .002$
Extended Release Injectable Naltrexone

- Naltrexone embedded in microspheres
- Elimination: Polymer eventually metabolized and eliminated as CO$_2$ and H$_2$O

Extended-Release Injectable Naltrexone: Pivotal Trial

- Multicenter study, 624 patients
- 3 groups: Placebo, 190 mg, 380 mg
- All patients received BRENDA
- ~8% of patients were abstinent for 1 week prior to treatment
- 6 months of treatment

Garbutt et al. JAMA 2005;293:1617
Reductions in Heavy Drinking with Naltrexone

Garbutt et al. JAMA. 2005;293:1617
Family History Predicts Naltrexone Response

Mu Receptor Polymorphism Predicts Naltrexone Response

Topiramate

- Antagonist at AMPA and kainate GLU receptors
- Allosteric agonist at the GABA-A receptor
- Blocks voltage-dependent Na and l-type voltage-gated Ca channels
- Inhibits carbonic anhydrase
- Enhances K+ conductance
Topiramate Promotes Abstinence From Alcohol

Placebo-Controlled Trial of Topiramate to Reduce Heavy Drinking

• 12-week study of 138 heavy drinkers whose goal was to reduce drinking to safe levels

• Topiramate 100 mg twice daily (N=67) or matching placebo (N=71) with dosage increased gradually over 6 weeks

• Brief behavioral counseling at each visit

• Moderator analysis of rs2832407 in GRIK1

Kranzler et al., Am J Psychiatry, 2014
Within Treatment

- **Placebo group**
- **Topiramate group**

Heaving Drinking Days per Week vs. Study Week

Study Week:
- 0
- 2
- 4
- 6
- 8
- 10
- 12

Heaving Drinking Days per Week:
- 0
- 1
- 2
- 3
- 4
- 5

Chart showing the decrease in heaving drinking days per week over study weeks for Placebo and Topiramate groups.
Within Treatment

Abstinent Days per Week

- Placebo group
- Topiramate group

Study Week
Heavy Drinking Days

- **Placebo group**
- **Topiramate group**

### CC Genotype

- Heavy Drinking Days per Week
- Study Week 0, 2, 4, 6, 8, 10, 12

### AC Genotype

- Heavy Drinking Days per Week
- Study Week 0, 2, 4, 6, 8, 10, 12

### AA Genotype

- Heavy Drinking Days per Week
- Study Week 0, 2, 4, 6, 8, 10, 12
Abstinent Days

- **Placebo group**
- **Topiramate group**

**CC Genotype**

**AC Genotype**

**AA Genotype**

Abstinent Days per Week

Study Week
Study of Veterans: Philadelphia, VA

- Prevention Only:
  - 0: 60%
  - 1: 10%
  - 2: 10%
  - 3: 10%
  - 4: 10%

- Heavy Drinking:
  - 5: 5%
  - 6: 5%
  - 7: 5%

- Addiction:
  - 8: 1%
  - 9: 1%
  - 10: 1%
  - 11: 1%
  - 12: 1%
Alcohol Care Management: Brief Intervention

- Provider: BHS - nurse, psychologist, SW
- BHS meets with patient for 18 sessions over 6 months either in person or by telephone
- Collaborates with PCP to:
  - Increase motivation to abstain
  - Be supportive and optimistic
  - Encourage naltrexone
  - Encourage AA attendance
  - Provide education
    (health risks and detrimental outcomes)
Relapse to Heavy Drinking

Oslin et al, 2014
Tobacco Use Disorder Treatment

• No contraindications for NRT (ICU, CVD, pregnancy)
• Patients may smoke while using the patch
• Gradual replacement of cigarettes may work better than fixed quit date
• Pre-cessation NRT improves odds of quitting
• Need to give enough of NRT (2-4 mg per cigarette)
• Many patients need long-term NRT (up to 6 months or longer)
• Women metabolize nicotine faster – need higher doses
Nicotine Levels Obtained From Various Forms of Replacement

Plasma Nicotine, ng/ml

Minutes

Patch 21 mg
Gum 4 mg
Cigarettes 1-2 mg
Nasal spray 1 mg
Pre-Cessation NRT

• Meta-analysis (2008): Effectiveness of and abstinence rates for smokers not willing to quit (but willing to change their smoking patterns or reduce their smoking) after receiving NRT compared to placebo (n =5 studies)
  • Placebo 3.6% (OR1)
  • Nicotine replacement (gum, inhaler, patch)
  • 8.4% (5.9-12.0) (OR 2.2)
  • www.surgeongeneral.gov/tobacco/gdlnrefs.htm
  • www.cochrane.org
Treatment of Tobacco Dependence with Varenicline (Partial Nicotinic Agonist)

- Varenicline > bupropion (RR 1.52)
- Varenicline > placebo (RR 2.33)
- Varenicline > solo NRT (RR 1.33)
- Combination NRT > varenicline

Cochrane review, 2010
Varenicline and Bupropion

- Partial agonist and agonist/modulator on nicotinic receptor

- 2008 FDA suicidal warning on both: 90% of suicides on varenicline, 7% on bupropion and 3% on NRT (Moore, T et al, 2011)

- Varenicline is contraindicated in pilots and traffic controllers (FAA)

- Varenicline may exacerbate CVD (FDA 2011) but 2012 meta-analysis does not confirm it (Prochaska, J et al, 2012)

- Both can be safely used in combination (Ebbert, J et al, 2008)
Cannabis: Clinical Issues

• 60 cannabinoids and cannabinoid-antagonists, only one is THC
• Highly comorbid with other substance use and mental disorders
• Associated with early onset of psychosis (*Large, M et al, 2011*), may be causal
• Respiratory effects comparable to tobacco (*Moore, B et al, 2005*), more carcinogens
• Associated with higher incidence of motor vehicle accidents (impairment beyond 24 hours)
• Use declines with age
• Approved in 28 states for medical or recreational use (prevalence doubled 2002-12)
Cannabis: Treatment

- No FDA approved medications
- Oral THC 10 mg 5 times daily and Divalproex 1500 mg daily \( (\text{Haney, M et al, 2004}) \)
- Dronabinol \( (\text{Levin, F et al, 2008}) \)
- Gabapentin 1200 mg daily \( (\text{Mason, B et al, 2012}) \)
- Mirtazapine 15-45 mg nightly \( (\text{Benyamina, A, 2008}) \)
- NAC (N-Acetylcysteine): 1200 mg twice daily for 8 weeks and contingency management – beats placebo in negative urines OR 2.4 \( (\text{Gray, K et al, 2012}) \)
FDA-Approved Opioid Use Disorder Medications

- Methadone
- Buprenorphine/Naloxone: SL, buccal or implantable
- Naltrexone: Oral or injectable/implantable
- Hand-held naloxone injection device (Evhzio) and intranasal formulation (2014)
Methadone

- Full agonist
- Strict federal, state and local control
- Limited to methadone clinics
- Too little availability
Buprenorphine

• Partial mu opiate agonist, kappa antagonist
• Parenteral analgesic since 1972
• Combination with naloxone reduces diversion
• Available for office use SL since 2002 due to safety
• Requires training/waiver
• Compliance and diversion are problematic
• Implantable/injectable formulations are developing
• Patch (Butrans) approved only for chronic pain
Buprenorphine is as Effective as Methadone

- 12 or more consecutive clean urines

Naltrexone

- Compliance impacts effectiveness
- Does not stop withdrawal
- Anti-craving effect
- Very effective in certain populations
- Extended release: Injectable or implantable
- Resets receptors to the original level of tolerance – risk of overdoses is increased after use
Extended Release Naltrexone for Opioid Dependence

• 250 patients
• 6 month trial
• Double blind placebo controlled
• 380 mg extended release naltrexone monthly

Total abstinence (100% opioid-free weeks) during weeks 5-24 was reported in 45 (35.7%) of subjects in the XR-NTX group vs 28 (22.6%) subjects in placebo group ($P=0.0224$).
Naloxone

Injection device (Evzio) or autoinjection device

- FDA approved in 2014
- 0.4 mg/1mL IV, IM or SC
- Verbal instructions like in AED
- Further medical attention recommended (T1/2 up to 2 hours)

Intranasal spray (Narcan)

- FDA approved in 2015
- 4 mg dose intranasally (2 mg in 1mg/1 mL in each nostril)
- Usually 2 doses are recommended
- Further medical attention recommended (T1/2 up to 2 hours)
Cocaine: Treatment

• No FDA approved medications

• Disulfiram (250 mg daily) was effective in 4 trials (Carroll, K et al, 2004), not effective in 1 (Olivetto, A et al, 2011)

• Modafinil (200-400 mg daily) decreased cocaine intake in 1 controlled clinical trial (Dackis, C et al, 2005) but not in a second larger trial (Anderson, A et al, 2009)

• Anticonvulsants are effective
  • Topiramate (200 mg daily) (Kampman, K 2004), tiagabine (12 or 24 mg daily) (Gonzales, 2007), and vigabatrin (3 g/day) (Brodie, 2009)
  • Gabapentin (1800-3200 mg/day) not effective (Brodie, 2009)
Cocaine: Treatment

• Citalopram 10 mg daily (Moeller, F et al, 2007)

• Ondansetron 4 mg twice daily (Johnson, B et al, 2006)

• Agonist substitution with amphetamines (Mooney et al, 2009; Shearer, J 2008)

• Bupropion 300 g daily with contingency management (Poling, J 2006)

• Naltrexone 100 mg daily (Schmitz, J et al, 2009; Pettinati, H et al, 2008; Schmitz, J et al, 2003, Hersh D, 1998)

• Buprenorphine/Naloxone 16-32 mg daily (Montoya, I et al, 2004)

• Beta-blockers (Propranolol) reduces cravings (Leri, 2002), reinforcing effects (Sofuoglu, 2000), withdrawal (Kampman, 2001)
Conclusions

• Substance use disorders can be effectively managed by applying a chronic disease model/integrated care approach

• Combination of therapy with medications works the best

• Simultaneous treatment of all disorders is likely to increase success

• Deeper understanding of neurobiology of substance use will improve patient outcomes