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Pharmacologic Management of Opioid and Alcohol Use Disorders in the Outpatient Setting

SPEAKERS
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Learning Objectives

1. Describe and contrast the mechanism of action of naltrexone and acamprosate in the treatment of alcohol use disorder.
2. Use buprenorphine/naloxone to treat opioid use disorder.

Outline

1. Introduction to Alcohol Use Disorders
2. Alcohol: Disulfiram
3. Alcohol: Naltrexone
4. Alcohol: Acamprosate
5. Introduction to Opioid Use Disorders
6. Opioids: Methadone
7. Opioids: Naltrexone
8. Opioids: Buprenorphine
9. New Directions
10. Conclusions

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Alcohol Use Disorders

Brief Intervention

1. Be empathic and curious.
2. State your medical findings.
3. Educate about alcohol use disorders.
4. Advise.
5. Follow up.
6. Refer, if absolutely necessary.

Levounis, Zerbo, and Aggarwal, *Pocket Guide to Addiction Assessment and Treatment*, 2016.

Neurotransmitter Systems

- GABA → CNS Inhibition
- Glutamate → CNS Excitation
- Opioid → Euphoria
- Dopamine → Pleasure & Reward
- Serotonin → Impulsivity
- Cannabinoid → Pleasant Feeling

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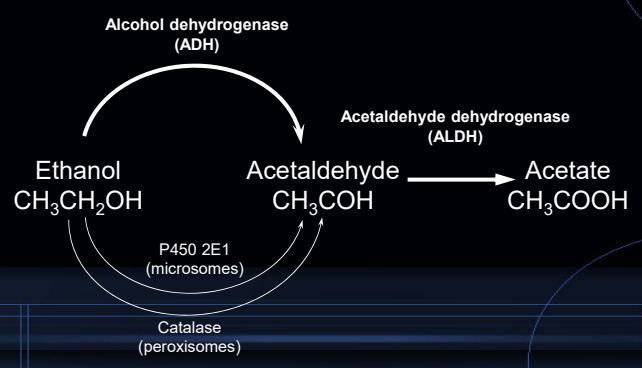
Disulfiram

Oxidation of Alcohol



Mechanism of Action

- Alcohol → Acetaldehyde → Acetate
- Disulfiram irreversibly binds to acetaldehyde dehydrogenase inhibiting the metabolism of acetaldehyde to acetate.
- Acetaldehyde accumulates resulting in a violent reaction (nausea, vomiting, flushing).

Effectiveness

- Supervised disulfiram may be helpful.

Diehl, *Alcohol and Alcoholism*, 2010.

Dosing and Safety

- 250-500 mg po daily.
- Some liver toxicity. Some caution with coronary artery disease.
- Inhibits hepatic microsomal enzymes and increases drug levels of phenytoin, warfarin, isoniazid.

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Naltrexone

Mechanism of Action

- Reduces positive reinforcement (reward craving).
- The patient does not experience the full euphorogenic and reinforcing effect of alcohol.
- Prevents a slip from becoming a full-blown relapse.

Effectiveness

- Reduces relapse to heavy drinking.

HEAVY DRINKING = 5 or more drinks/day for a man - 4 or more drinks/day for a woman.
Srisurapanont, *Cochrane Database Systematic Review*, 2005.

Dosing and Safety - Oral

- 50 mg po daily.
- Liver toxicity. Follow Liver Function Tests.
- Antagonizes opioid-containing agents, but no other significant drug-drug interactions.

Dosing and Safety – Injectable

- 380 mg IM a month.
- Same as oral naltrexone, plus injection site reactions.

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Acamprosate

Mechanism of Action

- Reduces negative reinforcement (abstinence craving).
- Neuroadaptation and upregulation of the glutamate system in alcoholism.
- Acamprosate interferes with the glutamatergic system.

Effectiveness

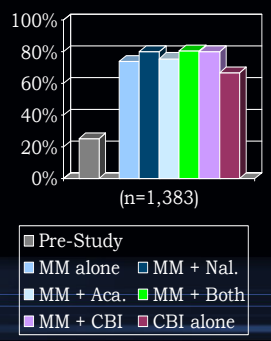
- Improves abstinence.
- The US trial showed efficacy only in patients motivated for abstinence.

Kranzler, *American Journal of Addictions*, 2008; Mason, *Journal of Psychiatric Research*, 2006.

Dosing and Safety

- 666 mg po three times a day.
- Excreted by the kidneys, no liver metabolism. Mild diarrhea (16% acamprosate vs. 10% placebo).
- No drug-drug interactions.

The COMBINE Study



- Percentage of abstinent days per month during a 16-week treatment trial with:
  - Naltrexone 100 mg po QD,
  - Acamprosate 1 g po TID.
- **All** treatment groups had an increase in % days abstinent. Overall effect was from 25% to 73%.

Adapted from Anton RF, *JAMA*, 2006.

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Opioid Use Disorders

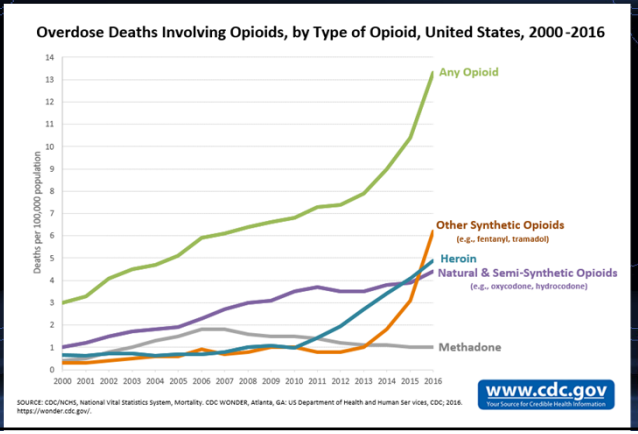
Opium since Ancient Times

Morphine circa 1887

From Pills to Heroin

See Fig 1 in Compton W, *New England Journal of Medicine*, 2016.
https://www.nejm.org/doi/10.1056/NEJMra1508490

From Heroin to Fentanyl



Opioid Intoxication

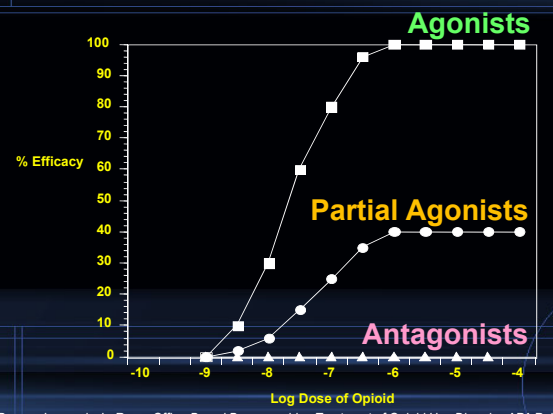
1. Constricted pupils
2. Constipation
3. Nausea and vomiting (often projectile)
4. Respiratory depression
5. Coma and death

➢ Treat with naloxone.

Levounis, Zerbo, and Aggarwal, *Pocket Guide to Addiction Assessment and Treatment*, APA Publishing, 2016.

Naloxone Autoinjector

Medications



Renner, Levounis, LaRose, *Office-Based Buprenorphine Treatment of Opioid Use Disorder*, APA Publishing, 2018.

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Methadone

Mechanism of Action

Mu receptor < **Full agonist binding …**

1. activates the mu receptor
2. is highly reinforcing
3. is the most abused opioid type
4. includes methadone

Renner, Levounis, LaRose, *Office-Based Buprenorphine Treatment of Opioid Use Disorder*, APA Publishing, 2018.

Effectiveness

- Best for people who:
  - also suffer from severe pain syndromes.
  - respond to highly structured environments, i.e., opioid treatment programs (OTPs).

Dosing and Safety

- 80 - 120+ mg po daily.
- Overdose, QT interval prolongation.
- Sedation, nausea, constipation, decreased libido.
- Synergistic effect with other CNS depressants, such as other opioids, alcohol, and benzodiazepines.

Blanco-Gandía MC, *European Journal of Pharmacology*, 2018.

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Naltrexone

Mechanism of Action

Mu receptor ← **Antagonist binding …**

1. occupies without activating
2. is not reinforcing
3. blocks abused agonist opioid types
4. includes naloxone and naltrexone

Renner, Levounis, LaRose, *Office-Based Buprenorphine Treatment of Opioid Use Disorder*, APA Publishing, 2018.

Effectiveness

- Best for people:
  - who prefer no opioid agonism.
  - in correctional settings.

Dosing and Safety

- Same as with alcohol use disorders.

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Buprenorphine

Mechanism of Action

Mu receptor ← Partial agonist binding …

1. activates the receptor at lower levels
2. is relatively less reinforcing
3. is a less abused opioid type
4. includes buprenorphine

Renner, Levounis, LaRose, *Office-Based Buprenorphine Treatment of Opioid Use Disorder*, APA Publishing, 2018.

Effectiveness

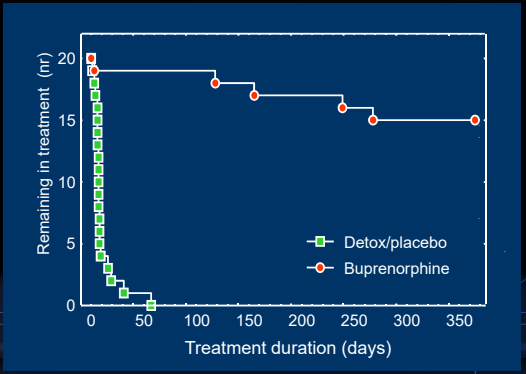
- Best for most patients.

Dosing and Safety

- 8 - 24 mg sublingually daily.
- Minimal overdose risk, no QT prolongation.
- Sedation, nausea, constipation, decreased libido, but less severe than methadone.
- Partially antagonizes opioid-containing agents, but no other significant drug-drug interactions.

Blanco-Gandía MC, *European Journal of Pharmacology*, 2018.

Maintenance v. Detoxification 1



Adapted from Kakko J, *Lancet*, 2003.

Maintenance v. Detoxification 2

	Detox	Bup	Cox regression
Dead	4/20 (20%)	0/20 (0%)	χ^2=5.9; p=0.015

Adapted from Kakko J, *Lancet*, 2003.

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New Directions

Pregnancy and NAS

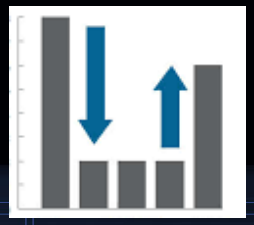
See Jones H, *New England Journal of Medicine*, 2010.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3073631/figure/F2/

Physician Management

See Fiellin, *The American Journal of Medicine*, 2013.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3621718/figure/F2/

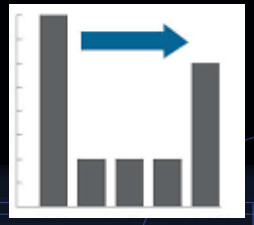
Different Expectations

Hypertension Treatment



Before During After

Addiction Treatment



Before During After

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Conclusions

1. Medications for alcohol are modestly effective, but medications for opioids turn people's lives around.
2. Alcohol: Naltrexone is probably best for "cutting down."
3. Alcohol: Acamprosate is probably best for preventing "the first drink."
4. Opioids: Buprenorphine maintenance is the first-line treatment of opioid use disorder.