The Pharmacotherapy of ALCOHOL DEPENDENCE

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Outline

1. Disulfiram
2. Naltrexone
3. Acamprosate
4. New Directions
5. Conclusions
6. Questions & Answers

1

DISULFIRAM

Introduced in 1954

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, chest pain).

Dosing and Safety

- 250-500 mg daily.
- Liver toxicity; monitor liver function.
- Increases dopamine levels centrally.
- Inhibits hepatic microsomal enzymes (CYP2E1) and increases drug levels (phenytoin, warfarin, isoniazid).

Physician's Desk Reference. www.PDR.net/druginformation. Accessed on March 23, 2010.

2

NALTREXONE

Oral - Introduced in 1954

Injectable – Introduced in 2006

Mechanism of Action

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

Dosing and Safety - Oral

- 50 mg daily.
- Liver toxicity; monitor liver function.
- Antagonizes opioid-containing agents, but:
  - No CYP450 metabolism, and
  - No other significant drug interactions.

http://ncadi.samhsa.gov/govpubs/BKD268/28c.aspx

Dosing and Safety - Injectable

- 380 mg a month.
- Long-acting naltrexone injection: 100 µm diameter microspheres composed of naltrexone and PLG polymeric matrix.
- Nausea, headache, injection site reactions, and fatigue are the prominent adverse effects.

Garbutt et al. *JAMA.* 2005;293:1617-1625.

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ACAMPROSATE

Introduced in 2005

Mechanism of Action

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

Dosing and Safety

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

Physician's Desk Reference. www.PDR.net/druginformation. Accessed on March 23, 2010.

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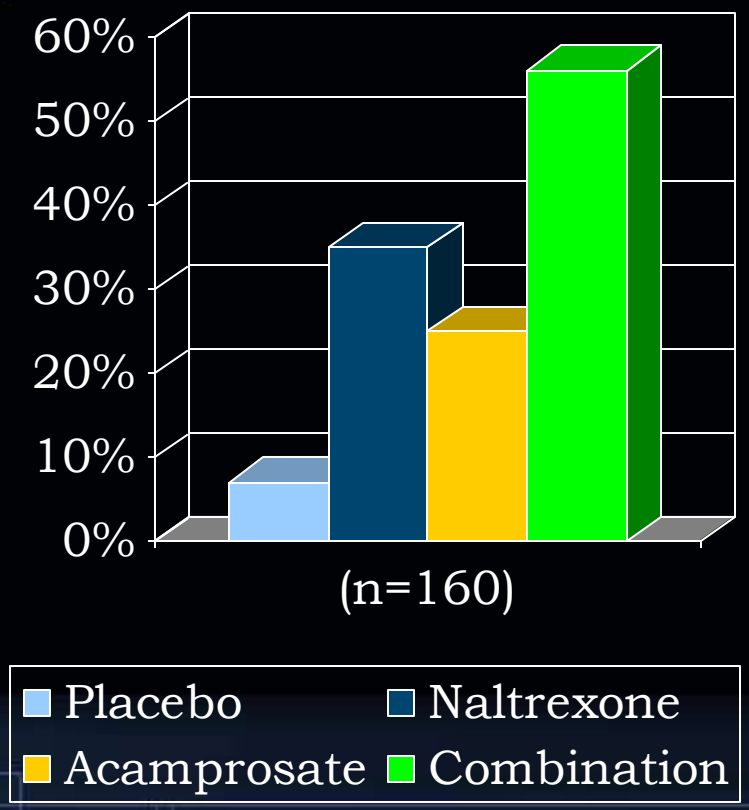
NEW DIRECTIONS

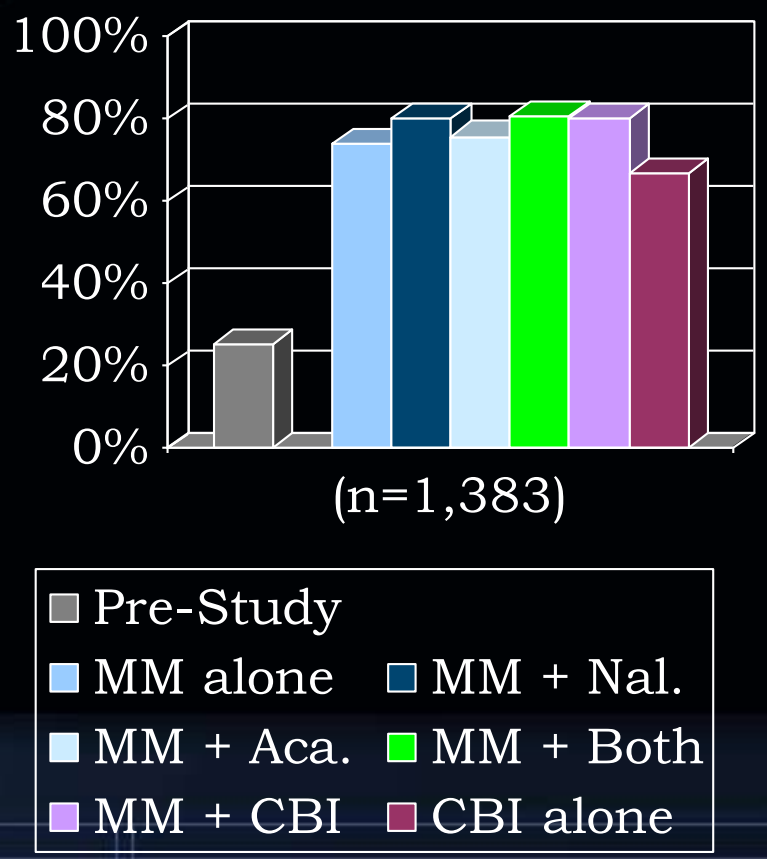
Naltrexone/Acamprosate



- Abstinence rates during a 12-week trial with:
  - Naltrexone 50 mg QD,
  - Acamprosate 666 mg TID.
- The **combination** of the two medications helped alcoholics stay abstinent (*P*=0.002) better than each drug alone.

Adapted from Kiefer F et al. *Arch Gen Psychiatry.* 2003;60:96.

The COMBINE Study



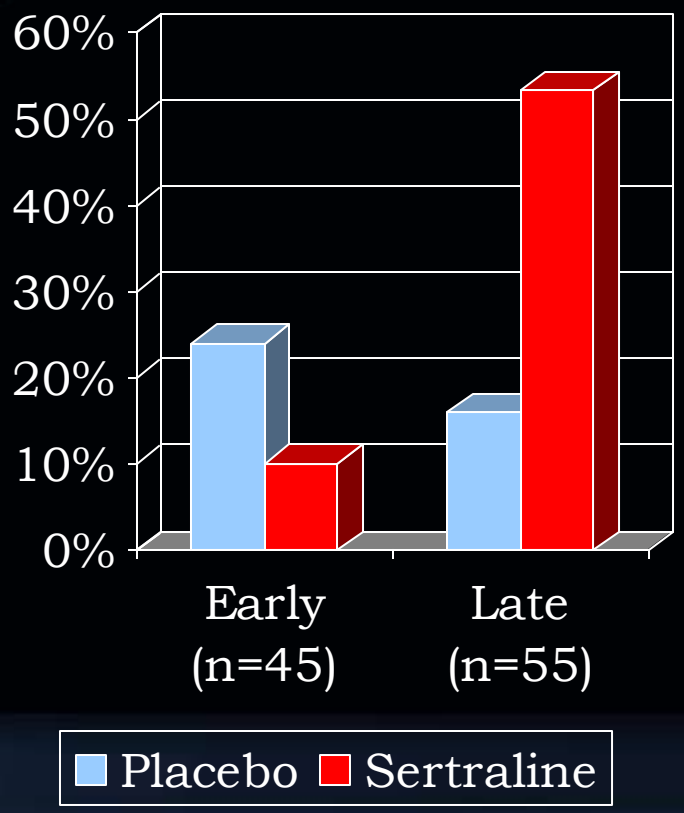
- Percentage of abstinent days per month during a 16-week treatment trial with:
  - Naltrexone 100 mg QD,
  - Acamprosate 1 g TID.
- **All** treatment groups had an increase in % days abstinent. Overall effect was from 25% to 73%.

Adapted from Anton et al. *JAMA*. 2006;295:2003-2017.

New Pharmacological Agents

- Anticonvulsants
  - Topiramate
  - Carbamazepine
  - Valproate (Valproic Acid)
- Antipsychotics
  - Quetiapine
- GABA agonists
  - Baclofen
- Serotonin (5-HT_3) antagonists
  - Ondansetron
- Selective Serotonin Reuptake Inhibitors

Sertraline



- Abstinence rates during a 14-week treatment trial with sertraline 200 mg QD.
- Sertraline helped **Late-Onset** alcoholics stay abstinent (*P*=0.004), but not Early-Onset.

Adapted from Pettinati et al. *Alcohol Clin Exp Res.* 2000;24:1041-1049.

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CONCLUSIONS

1. Medications for the treatment of alcohol dependence are relatively safe but modestly effective.
2. Naltrexone is best for “cutting down.”
3. Acamprosate is best during the protracted withdrawal syndrome.
4. Early-onset and late-onset alcoholism may require different pharmacological approaches.

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QUESTIONS & ANSWERS