Systematic Review of Treatment for Alcohol Dependence

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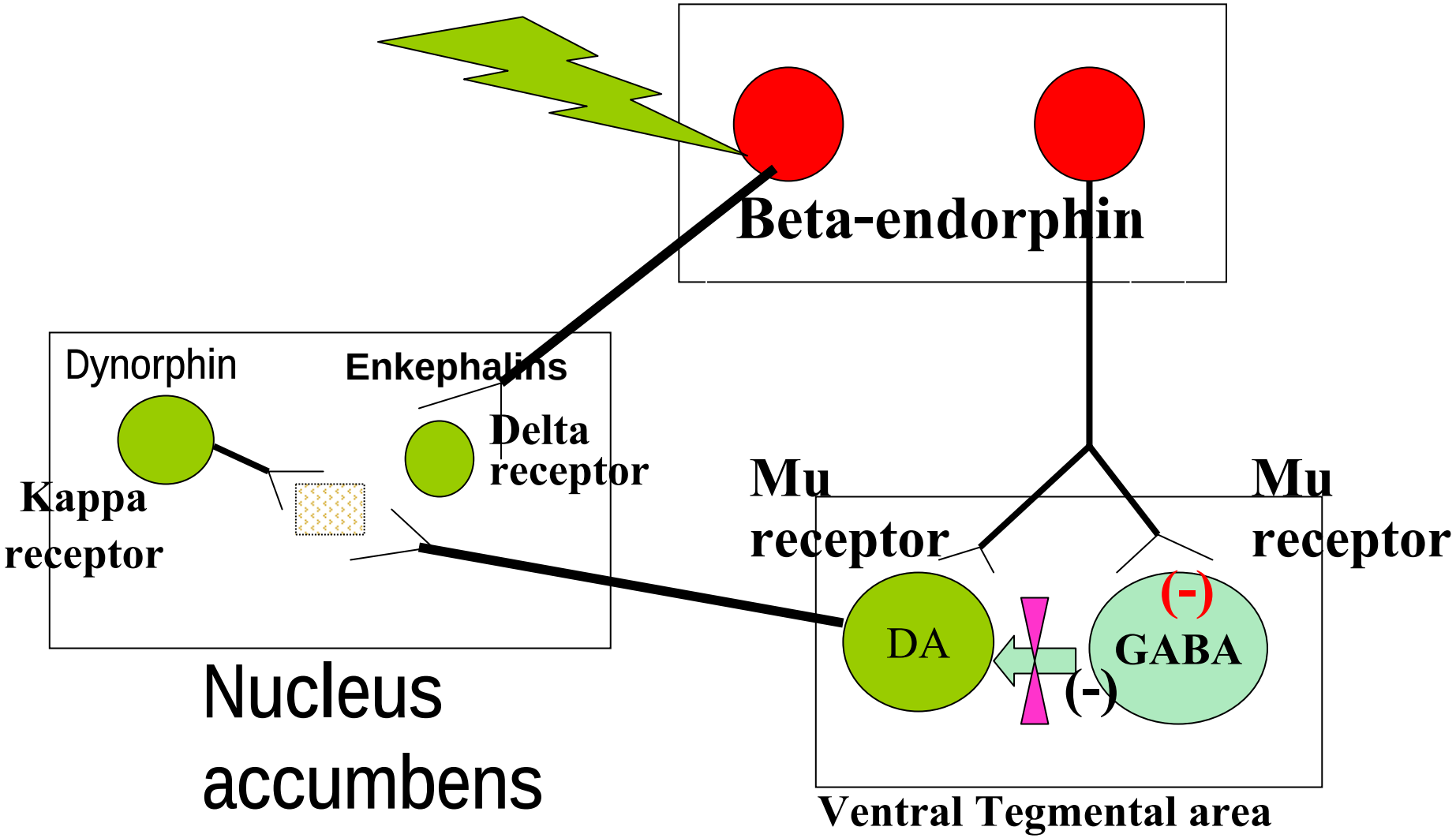
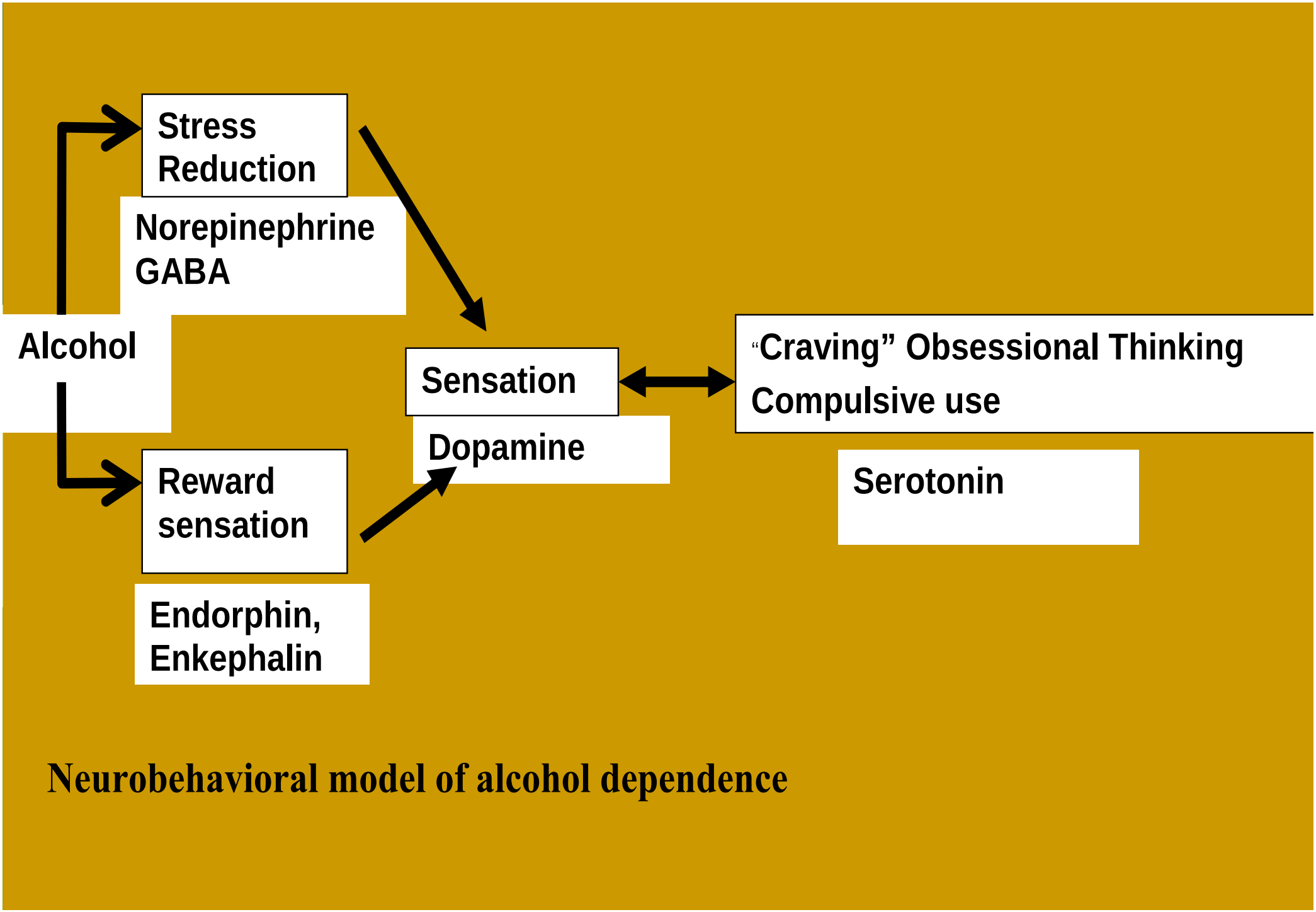
ARCUATE NUCLEUS in

Hypothalamus, pituitary

ALCOHOL





Neurobehavioral model of alcohol dependence

Medications for treating Alcohol dependence

- Naltrexone
- Nalmefene
- Disulfiram
- Acamprosate
- SSRIs
- Topiramate
- Lithium
- Buspirone
- Dopamine neuroleptics

Clinical recommendation	Evidence rating	References
Naltrexone and Acamprosate FDA approved (conjunction with behavior therapy)	**A**	**Srisurapanont M., 2005**
Disulfiram FDA approved (does not increase abstinence rates or decrease relapse rates or craving compared with placebo, not recommended for routine use in PCU)	**B**	**West et al,1999**

Clinical recommendation	Evidence rating	References
Fluoxetine and other SSRIs recommended for patients with comorbid depressive disorders	**B**	**Cornelius et al,1997** **Naranjo et al,2001**
Topiramate and Ondansetron recommended to reduce drinking frequency and increase abstinence	**B**	**Johnson et al,2000** **Johnson et al,2003**

http://www.aafp.org/afpsort.xml.

Naltrexone

- Opioid-receptor antagonist
- blockage of μ-opioid receptors
- reduces reinforcing effects of alcohol
- decreased feeling of intoxication and fewer craving.

Naltrexone

- In systematic review by Srisurapanont M.,2005
  - 29 RCTs compared natrexone with placebo, a short-term treatment of naltrexone
    - Significantly decreased the relapse for 36% (RR 0.64, 95%CI=0.51-0.82) ; NNT=7
    - Decreased the return to drinking for 13% (RR 0.87, 95%CI=0.76-1.00) :NNT =12
    - Diminished withdrawal from treatment for 18% (RR 0.82, 95%CI=0.70-0.97); NNT=13

Naltrexone

- A medium-term treatment of naltrexone
  - No benefit for relapse prevention
  - Beneficial on increasing time to first drink and diminishing craving
  - Superior to acamprosate in reducing relapse FOR 29% (NNT=5), standard drinks and craving.
  - Natrexone + intensive psychosocial treatment was superior to Natrexone + simple psychosocial treatment in increasing time to first drink and decreasing craving.

Naltrexone

- Long-term treatment of naltrexone reported mixed results
  - In systematic review by West et al, 1999 : from 3 RCTs found no difference between naltrexone and placebo.
  - In large RCT (Krystal et al,2001) 12 months of naltrexone therapy found no significant differences in numbers of days to relapse, numbers of drinking days, or numbers of drinks per drinking day

Naltrexone

- Recommended dosage is 50 mg/d in single dose
- Contraindication for chronic pain with opioid therapy, heroin dependence, hepatitis or liver failure
- Dose-related hepatotoxicity
- Should have checked hepatic transaminase levels monthly for the first 3 months and every 3 months thereafter.
- Nausea is the most common adverse effect (~10%) followed by headache, anxiety, and sedation.
- FDA pregnancy category C

Nalmefene

- Opioid-receptor antagonist
- Without FDA approval for treatment of alcohol dependence
- Dosage of 20-80 mg/d show in 1 RCT (Mason et al,1999) to significantly reduce relapse to heavy drinking in outpatients with alcohol dependence.
  - Relapse rate in nalmefene was 37% (placebo was 59%) NNT=5
  - No differ significantly in the percentage of day abstinent, in the mean number of drinks in drinking day, or in self-reported craving ratings.

Disulfiram

- Inhibits acetaldehyde dehydrogenase.
- It has been used to treat alcohol dependence for > 40 years
- The evidence for its effectiveness is weak. (serious methodologic weakness, and 4RCTs reported mixed results: high drop out rate=46%)
- Dosage of 250 mg/d – 500 mg/d
- Severe alcohol-disulfiram reaction included myocardial infarction, congestive heart failure, respiratory depression, and death.

Disulfiram

- Contraindication in
  - patients received metronidazole
  - ingested alcohol
  - have psychosis
  - have cardiovascular disease.
- Not recommended for patients with
  - severe pulmonary disease
  - chronic renal failure
  - diabetes
  - elderly
  - peripheral neuropathy
  - seizures
  - cirrhosis with portal hypertension

Disulfiram

- Recommended baseline LFT and repeat testing at 2 weeks, 3 months, 6 months thereafter.
- Not recommended for treating alcohol dependence in primary care setting.
- FDA pregnancy category C

Acamprosate (calcium homotaurinate)

- Block GABA receptors and Glutamate receptors
- And activate GABA-A receptors
- Recently approved by FDA for treatment of alcohol dependence
- Dosing by weights (dosage 333 mg/ enteric coated tablets)
  - ≥ 132 lbs (60 kg) : 2 tab. 3 times per day
  - < 132 lbs : 2 tab with morning meal, 1 tab with the midday meal, and 1 tab with the evening meal

Acamprosate (calcium homotaurinate)

- A systematic review by Mason BJ,2001 of 15 studies showed
  - Acamprosate reduced short term and long term (> 6 months) relapse rates when combined with psychosocial treatments
  - Fewer patients returning to drinking (68% vs 80%, NNT =8)
  - Higher percentage of days of total abstinence (54% vs 38%, NNT=7)
  - Most common side effects are diarrhea (~10%) followed by headache, flatulence, nausea, vomiting, and dyspepsia.

Acamprosate (calcium homotaurinate)

- A systematic review by Bouza et al,2004 of 33 studies showed
  - Acamprosate was significantly
    - improved abstinence rate (OR 1.98, 95%CI=1.57-2.25, p <0.001) NNT = 10 (7-15)
    - increase days of cumulative abstinence (WMD: 26.55, 95%CI=17.56-36.54).

Acamprosate (calcium homotaurinate)

- Short-term of naltrexone
  - reduced relapse rate significantly (OR 0.62, 95%CI=0.52-0.75, p <0.001)
  - but not associated with a significant modification in abstinence rate (OR 1.26, 95%CI=0.97-1.64, p =0.08)
  - Insufficient data to ascertain naltrexone's efficacy over more prolonged periods.

Acamprosate (calcium homotaurinate)

- had a good safety pattern with significant in treatment compliance (OR 1.29, 95%CI=1.13-1.47, p <0.001)
- higher than Naltrexone (OR 0.94, 95%CI=0.80-1.10, p =0.5)

Acamprosate (calcium homotaurinate)

- No interaction with use of
  - Alcohol
  - Diazepam
  - Disulfiram
  - Imipramine
- Patients can continue acamprosate during a relapse.
- Contraindication in patients with
  - Renal insufficiency (creatinine clearance < 30 mL/min(0.5 mL/sec)
  - Advanced cirrhosis.
- FDA pregnancy category C

SSRIs

- SSRI studies has used small samples and inconsistent outcome measures.
- Kranzler et al,1995 had studied RCT of 101 alcoholic patients without major depression showed that
  - Fluoxetine 60 mg/d had no significant effect on alcohol consumption.

SSRIs

- Cornelius et al,1997 had studied RCT of alcoholic patients with major depression showed that
  - Fluoxetine 20-40 mg/d over 12 weeks had fewer drinks, fewer drinking days and fewer heavy drinking days.
- More severe alcohol dependence (type B) showed no benefit and some worse outcomes with SSRI.

SSRIs

- Ondansetron study (Johnson et al,2000) was shown to significantly reduce self-reported drinking. Patients with early-onset alcoholism received Ondansetron 4 mcg/kg twice per day. All patients also received weekly group CBT
  - Fewer drinks/day
  - Greater percentage of days of abstinence (70% vs 50% with placebo)
  - Greater total number of days abstinence/week (6.7 vs 5.9 with placebo)

SSRIs

- Most common side effects are
  - Nausea
  - Headache
  - Sedation
  - Anxiety
  - Sexual dysfunction
- Contraindications in patients received MAOI, mesoridazine, or thioridazine

SSRIs

- Drug interactions for SSRIs :
  - MAOI
  - Warfarin
  - Antipsychotics
  - Tetracyclic antidepressants
  - Benzodiazepines
  - S.John’s wort
  - Phenytoin

Topiramate

- Topiramate stimulates GABA-A receptor and inhibits glutamate AMPA/Kainate receptors➔ inhibits mesocorticolimbic dopamine release➔ reduce alcohol craving
  - Johnson et al,2003 had studied 12-week DB-RCT of actively drinking patients with alcohol dependence found that
    - 26% more abstinent days with topiramate
    - Reducing self-reported drinks per day, drinks per drinking day, and heavy drinking days
    - Reduced craving as measured on obsessive-compulsive-drinking scale
    - Dosage of 25-300 mg/d

Topiramate

- Hypersensitivity is the only known contraindication.
- Adverse effects include
  - Dizziness
  - Somnolence
  - Ataxia
  - Confusion
  - Impaired concentration
  - Fatigue
  - Paresthesia
  - Speech difficulties
  - Diplopia
  - Nausea
- Drug interaction with phenytoin, valproic acid, and carbamazepine.

Summary

- Naltrexone, Disulfiram and Acamprosate are currently the treatment approved for the management of alcohol dependence.
- The best choices for relapse prevention are Naltrexone and Acamprosate with concurrent counseling through professional or self-help programs.

Summary

- Short term treatment of Naltrexone
  - decreases alcohol relapses 36%
  - reduce returning to drinking 13%
  - lower the risk of treatment withdrawal 28%(NNT=13)
  - nausea is reported ~10%
- Acamprosate are beneficial on increasing abstinence rates in short term treatment (OR 1.88,95%CI=1.57-2.25,p<0.001)
  - significant improvement in treatment compliance (OR 1.29, 95%CI=1.13-1.47, p<0.001)
  - diarrhea is the most frequent adverse effect

Summary

- Disulfiram still has no unequivocal evidence from RCT to improves abstinence rates over the long term, so Disulfiram is not recommended in the primary care setting.
- SSRI may indirectly improve outcome by treating underlying depression rather than affecting drinking behavior
- Evidence is lacking for combination pharmacotherapy, but research is under way.

Summary

- Topiramate and Ondansetron show promise as treatments to increase abstinence.
- Buspirone, Lithium, Dopamine neuroleptic and Benzodiazepines have not yet demonstrated evidence of activity in large RCTs
- Pharmacotherapy should be used with appropriate psychosocial support and specific treatment for comorbidities.

Thank you for your attention