

# Pharmacotherapy for Alcohol Use Disorders

DEAN KRAHN, MD, MS  
ADDICTION PSYCHIATRIST, CHIEF MHSL VA-MADISON  
AND DIRECTOR, MHSL VISN 12  
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## Targets for Treatment

- **Drinking more than is healthy**
  - Screening, Brief Intervention, and Referral for Treatment (SBIRT)
    - × Becoming standard of care for primary care and probably reasonable skill for MH sites as well
- **Alcohol Abuse/Dependence: a distinction without importance? Likely to be gone in DSM-V**
  - Targets for Treatment in this (these) Syndrome(s)

## Targets for Treatment

- **Intoxication**
  - No new interventions
  - Remember dangerousness
  - Intoxication—the pathology multiplier
  - Multiple drugs are frequent
- **Withdrawal**
  - New approaches—gabapentin or other anticonvulsants
- **Relapse Prevention—The Most Important Target**

## Withdrawal

- **Characterized by lack of sufficient GABA function and excessive glutamatergic function**
- **Could treat by use of benzodiazepine as has been rule for 40 years in US**
  - Ongoing debates over lorazepam and short-acting benzos vs diazepam and long-acting benzos
    - × Short-acting leads to less sedation and build-up of delirium inducing metabolites; but diazepam and other long-actors have inborn taper

## Withdrawal

- **Valproic Acid, effective w/d treatment, Longo et al, Milwaukee!**
- **Myrick et al, 2009**
- **Gabapentin for alcohol withdrawal**
  - Modulator of gaba/glutamatergic balance
  - 1200 qd
  - Equally effective for w/d sx but most remarkable is better sleep, less craving, and less alcohol use a week after w/d treatment cessation
  - Huge advantages for outpt as no additive toxicity if drink on top of it; no addictive/abuse potential; no street value

## Relapse Prevention

- **Theory of Protracted Withdrawal**
  - Koob and colleagues have shown that brain adapts to repeated use of DA-releasing reinforcer by “turning down” the reinforcement/reward pathway so that when the addict abstains, “life is just less fun” unless they use their drug of choice. Shown in rats with experiments in which the voltage needed to result in reinforcement is much higher after a drug on which the rat is dependent is withheld.
  - Mediated by high CRH and glutamatergic overdrive
  - Might be the reason for stress-induced relapse and dysphoria of early abstinence
  - ? Prevent this type of relapse with acamprosate or anticonvulsants?

## Relapse Prevention

- Aside from stress-induced (? Anger-induced) relapse, there are also cue-induced and drug or alcohol-induced relapse
  - Alcohol-induced relapse could be interrupted by naltrexone
  - Cue-induced relapse (people, places, things) could be prevented by therapy or by substances that could stop DA-mediated trigger

## Medications for Relapse Prevention

- Until recently, best statement would have been that medications are always adjunctive
  - Still true in the more severe AD patients presenting for addiction treatment, but recently Project Combine, in which naltrexone, acamprosate, both, or placebo were combined with therapy or medication management in the treatment of alcohol dep pts found in primary care found that naltrexone plus medication management was best option.

## Medications for Relapse Prevention

- **Naltrexone: blocks mu opiate receptors**
  - Ingestion of alcohol as well as strong craving for alcohol releases endogenous opioid peptides that, in turn, cause dopamine release
  - Blockade of mu receptors results in alcohol ingestion being less pleasant in ingestion studies in lab
  - Naltrexone decreases alcohol cravings, decreases heavy drinking days/relapse in pts being treated with psychosocial therapies (NNT=7-13)

## Medications for Relapse Prevention

- Length of treatment: ? 3 months, ? Longer
- Dosage: 50 mg usual, some use 100 mg/d; ? Prn use?
- SE's: nausea, achy, flu-like state in about 10% but only enough to cause cessation of treatment in < 5%; worries about liver problems related to studies with markedly higher doses; need contract and wallet card or bracelet
- Biggest problem is lack of compliance/adherence
- Depot naltrexone??? Expensive but need good cost effectiveness study
- Soon, predict response via polymorphism near or at opiate receptor gene site: one polymorphism results in >80% response!

## Medications for Relapse Prevention

- **Acamprosate: modified amino acid developed to be a gaba agonist but actually a glutamatergic modulator**
  - Used in Europe for a number of years; studies in US not positive but probably not designed correctly—
  - Theory would be that acamprosate would prevent negative reinforcement-type of relapse that can only occur during protracted withdrawal state
  - Not expected to work to decrease heavy drinking or pleasure of drinking—European studies in abstinent pts

## Medications for Relapse Prevention

- Acamprosate has been effective at dose of 666 tid (usually use 333 tid for couple of days to let bowel get used to amino acid load)
  - Very few se's; diarrhea at times; no liver metabolism
- Head to head comparison with naltrexone tends to favor naltrexone
- Combination? (should work given different mechanisms)—one study with + results, one with trend?
- Big European study to match pts with ntx vs acamprosate pending

## Medications for Relapse Prevention

- **Topiramate: another glutamatergic modulator**
  - 3 studies now show positive results for topiramate
    - Remarkably, helpful even in subjects who do not want to abstain
    - By far the biggest effect size compared to ntx/acamprosate
    - Also the most se's—biggest problem is cognitive se's that can only be mitigated or minimized by very slow titration (25 mg/d increase each week)—too slow to help with w/d
    - Not FDA approved

## Medications for Relapse Prevention

- Ondansetron: effective in pts who are early onset alcohol dependent pts (ie Type 2)
- Differential effects of SSRI's: actually make Type 2 alcoholics work and Type 1 alcoholics better
- ? Gabapentin/Valproic Acid: do they help ongoing relapse prevention—both help short-term relapse

## Treatment of Alcohol Dependence in SMI Patients

- Atypical antipsychotics associated with decreased use of alcohol and other drugs in these pts.
- Need for co-occurring therapy, not sequential unless very tightly linked—good example: PTSD plus addiction treated with “Seeking Safety” by Najavits et al.—Perhaps prazosin helps both PTSD and alcohol dep as well??? (one abstract so far)

## Role of Disulfiram

- Disulfiram or Antabuse is one of the only medications doctors give to punish/hurt patient if they behave inappropriately
  - Makes education and informed consent very important
- Can't do a double-blind trial with this drug
- Network therapy involving spouse is very likely to be effective.
- Liver and psychosis problems
- Might be best for alcohol/cocaine dependent pts.

## Insomnia

- **Big problem**
  - Insomnia during early abstinence is associated with increased relapse—but no treatment shown to be effective
    - But alcohol dependent pts are more likely than others to abuse benzos; zolpidem and its relatives
    - Trazodone, in one study, possibly related to relapse
    - Need to use very good CBT for insomnia with good sleep hygiene recommendations

## Summary Statements

- NIAAA guidelines recommend that all alcohol dependent patients be offered naltrexone and acamprosate. These and other drugs are effective and really easy to use.
- But few use these drugs; why not? Even used effectively in primary care
  - 17 yrs from bench to bedside
  - Addiction programs are run by someone with less than a Master's degree in over 80% of cases and with less than 1.5 yrs on job the vast majority of time
  - Need for performance improvement!!! NIATX led by David Gustafson is doing excellent work.
  - Need for addiction-trained psychiatrists to lead!

## References That You Might Like

- **Efficacy of Naltrexone**
  - Volpicelli et al, 1992
  - O'Malley et al, 1992
- **Mechanism of Naltrexone**
  - Volpicelli et al, 1995
  - Swift et al, 1994
  - Monti et al, 1999
- **Adherence and Naltrexone**
  - Chick et al, 2000; Monti et al, 2001; Volpicelli et al, 1997
  - Injectable Naltrexone: Kranzler et al, 2004
- **Genetic polymorphism predicts efficacy**
  - Oslin et 2003
- **Project Combine and NTX in PC**
  - Anton et al, 2006

## References That You Might Like

- **Efficacy of Acamprosate**
  - Review by Swift, 2007; metaanalyses by Bouza et al, 2004 and Mann et al, 2004
- **Combining NTX and Acamprosate:**
  - Feeney et al, 2006 trend in + direction; Kiefer et al, 2003
- **Efficacy of Topiramate and anticonvulsants**
  - Johnson et al, 2003 and Johnson et al, 2007
  - Myrick et al, 2009 (gabapentin for detox)
- **Efficacy of atypical antipsychotics**
  - Hutchison et al, 2006; Kampman et al, 2007
- **Efficacy of ondansetron**
  - Johnson et al, 2000