

Alcohol Use Disorders - Pharmacotherapy and Treatment



State of Hawai'i

House Health Committee 26 Aug 2008

Informational Hearing

(Reps. Josh Green, M.D., and John Mizuno; hearing hosted
by Rep. Mizuno)

Presented by

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Introduction



- National trend to integrate medical management with treatment
- FDA approved medications are available
- Limited pharmacopoeia at this time, most agents restricted to use for alcohol dependence

Recommended Outcomes (preview – will review in detail at the conclusion)

- The approved medications warrant at least as much 3rd-party payer support as medications for other medical disorders.
- Approved medications have a place in the management of alcohol use disorders at several different stages, and in a variety of settings. Employment of these medications in treatment facilities and correctional facilities needs support.
- Mandated employment of medications is at least as controversial as mandated hospitalization/rehabilitation (the Lexington Hospital example). There is a need for more informed discussion on this, working towards a solution that motivates and encourages use of medications in the context of psychosocial rehabilitation.
- The same conversation needs to occur surrounding therapies for other drug use disorders (e.g., buprenorphine and methadone for opiate dependence).
- A similar conversation needs to occur regarding the type and duration of publicly-supported non-pharmacologic treatment (“rehab”).
- Multi-modality treatment (long-term or lifelong, medical, psychological, spiritual, social, behavioral) works and is cost-effective. Assistance to training programs is needed at the university and community college levels.

Summary



- Medications are useful in managing addictions, even some forms of substance abuse
- Medications are almost never enough
- Not all medications are useful for all patients
 - Use of medications for treatment of substance use disorders has to be in context
 - Not all addictions, nor even all alcohol dependencies, are alike
- Treatment presumes the principle of autonomy, and exceptions should be exceptional

Alcohol Use Disorder Prevalence

- **National Comorbidity Survey (NCS,1992), National Longitudinal Epidemiologic Survey (1992), Epidemiologic Catchment Area survey (1984).**
- **NCS is relatively consistent with the others: alcohol dependence lifetime prevalence for males was 20.1% and 8.2% for females; with alcohol abuse (no dependence) of 12.5% for males, 6.4% females. DSM3R criteria, and the 12-month prevalence was about half of those values.**
- **NLAES had similar, slightly higher numbers.**
- **ECA estimates tend to be higher, as the survey range was 18-45.**
- **State of Hawai'i Department of Health's survey for Hawai'i cites point prevalence 8% for treatable alcohol use disorders (2003), study limitations may yield considerable underestimate.**

Medications Enhance Treatment



- Medications not effective unless integrated with counseling
- Medication enhances treatment effectiveness but does not replace treatment
- Evidence-Based Practices (EBP)
 - Patient desire and counselor empathy most important

Medication Strategies

1. Agonist
Substitute effects of drug
2. Antagonist
Block the effects of drug
3. Deterrent Medications (aversive)
Pair noxious stimuli with drug intake
4. Reduce Craving: Modify Neuroadaptive changes due to drug use
5. Modify effects of drug to reduce reward from use

FDA vs. "Off Label"



- FDA-approved medications may be endorsed by NIDA and SAMHSA, are validated by research
- Treatment Providers use FDA approved medications
- Individual physicians may use off-label medications; while this is how many useful medications first reach professional awareness, blanket off-label use risks adverse consequences & liability without proven worth.
- The test: does a sick addict warrant less rigor in determination of product safety and efficacy than a diabetic, an arthritic, etc.?

Substances of Dependence (Drug classes)



- Alcohol
- Sedative-Hypnotics
- Opioids
- Stimulants
- Nicotine
- Dissociative agents & hallucinogens (THC, PCP, LSD, etc.)

FDA Approved Alcohol Medications



- Naltrexone (oral)
- Naltrexone depot injectable (Vivitrol)
- Acamprosate (Campral)
- Disulfiram (Antabuse)

Other agents (examples):

- Methadone (opioid dependence)
- Buprenorphine ("")
- Flumazenil (benzodiazepine intoxication)
- Varenicline (nicotine dependence)
- Nicotine (gum, patch, inhalant)

Costs

DRUG DOSAGE COST

- **Acamprosate**
- **Campral (Forest) 666 mg tid \$104.402**

- **Disulfiram**
- **average generic 500 mg max once/d 22.203**
- **x 1-2 wks, then**
- **125-500 mg once/d**
- **Antabuse (Odyssey) 47.363**

- **Naltrexone**
- **average generic 50 mg once/d 109.20**
- **ReVia (Barr) 138.30**

- **Depot Naltrexone – Vivitrol 380 mg. injection**
- **Avg Wholesale Price - AWP \$868.75**
- **Wholesale Acquisition Cost - WAC \$695**

- **1. Cost of 30 days' treatment, based on the most recent data (October 31, 2004) from retail pharmacies nationwide available from NDCHealth, a healthcare information services company.**
- **2. Cost of 30 days' treatment, according to the manufacturer.**
- **3. Cost based on 500 mg/d x 1 wk, then 250 mg/d. Drug is available only in 250- and 500-mg tablets.**

Treatment Center Medication Limitations



- Fewer people receive medications than may be candidates, as treatment centers are target market and have not implemented yet
- Routes of administration/risks
 - Concern for counselors well-being (at-risk/recovering)
 - Need for nursing skill
- Administration (e.g., depot naltrexone requires injection; controlled substances require special licenses or assurances)
- Lack of reimbursement, stigma (willpower) and resistance by treatment professionals
- Medication is *indicated* for 30% to 60% of patients

Business Wire 07JUL08

- Based on the lackluster commercial performance of naltrexone and acamprosate, Pharma has erroneously underestimated the size of the alcoholism market. The lack of clear FDA guidance on trial design and resulting indications has stymied many pharmaceutical companies from entering this category. There is a stigma associated with alcoholism. Companies may have a few product champions but the general corporate attitude is that developing drugs for alcoholism carries the same kind of corporate image risks as developing contraceptives and other "morality drugs". There is also a tremendous fear of product liability litigation. The general corporate perception is that drugs for alcoholism won't be reimbursable, and many of the people who come in for treatment will be "down and out" and not able to afford medicine. An analogy would be to forecast the size of the antidepressant market before the availability of Prozac.

Substance Dependence - Therapies

- Interpersonal (individual)
 - Motivational Interviewing
- Cognitive-Behavioral Therapy (CBT)
- Motivational Enhancement Therapies (MET), Contingency Management (CM)
- Twelve-Step Facilitation (TSF)
- Others

Substance Dependence - Other Approaches

- Staged therapy using ASAM Criteria
 - Residential programs
 - Outpatient programs
 - ...Individual, group, milieu therapies
- Community-based mutual recovery programs (AA, NA, DRA)
- Miscellaneous controlled use or harm-reduction approaches (e.g., Rational Recovery, Alcoholics Victorious)

12-Step Groups (Community-Based Peer Therapy)

- Cluster of children crossing the road
- No driver/facilitator
- School = transitional destination (recovery)
- Students are peers
- Hazardous road
- Slow, conservative



Conventional Group Therapy

- The school bus
- Driver = facilitator
- Students = addicts under treatment
- School = transitional destination (recovery)
- Formal, does not generalize to community



Outcomes of Drug Abuse

2 million people die each year in the US

- 430,000 due to tobacco

- 100,000 due to alcohol

- 16,000 for illicit drugs

Cost of Drug Abuse

Economic costs of Alcohol and Drug Abuse
(NIDA 1992)

\$245 Billion Dollars

- Treatment (30%)
- Productivity losses (20%)
- Crime (40%)
- Deaths (10%)

Phases of Recovery (abstinence-based):

1. **Initiation of Abstinence**
 - Cf. "Stages of Change" model, Prochaska/Diclemente/Norcross
2. **Withdrawal and Detoxification**
3. **Relapse Prevention**

Goals of Medication Tx in Addictions

1. Abstinence (or Reduction)- make the patient less interested in using. Can be somewhat tricky- is a drug that reduces, but does not stop, drug use a useful intervention?
2. Treat or prevent withdrawal symptoms
3. Reduce urges/cravings
4. Diminish or block "the high" / make it less worthwhile
5. Minimize relapse time and intensity
6. Treat comorbid disorders that may interfere with recovery process

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Alcohol Withdrawal: Medication

Table 1. Medication Treatment for Alcohol Withdrawal.

Class	Examples	Effects
Benzodiazepines (preferably long-acting)*	Chlordiazepoxide, diazepam, oxazepam, lorazepam	Decreased severity of withdrawal symptoms; reduced risk of seizures and delirium tremens
Anticonvulsants	Carbamazepine	Decreased severity of withdrawal symptoms
Adjunctive agents		
Beta-blockers	Atenolol, propranolol	Improvement in vital signs; reduction in craving
Alpha-agonists	Clonidine	Decreased severity of withdrawal symptoms

Alcohol Dependence

1. Disulfiram (Antabuse)
2. Naltrexone (Revia)/ Nalmefene
3. Acamprosate (Campral)
4. Topiramate (Topamax)- Not FDA Approved
5. Combination Therapy

Antabuse

FDA Approved 1951

Mechanism: Inhibits aldehyde dehydrogenase, causing increased acetaldehyde and aversive reaction.

Evidence: Fairly good in European monitored therapy studies. Less impressive in unmonitored studies.

Probably underutilized in US

Most likely to benefit:

highly motivated patients, directly observed patients,

Due to danger of aversive reaction-not useful for initiation of abstinence or detoxification phase.

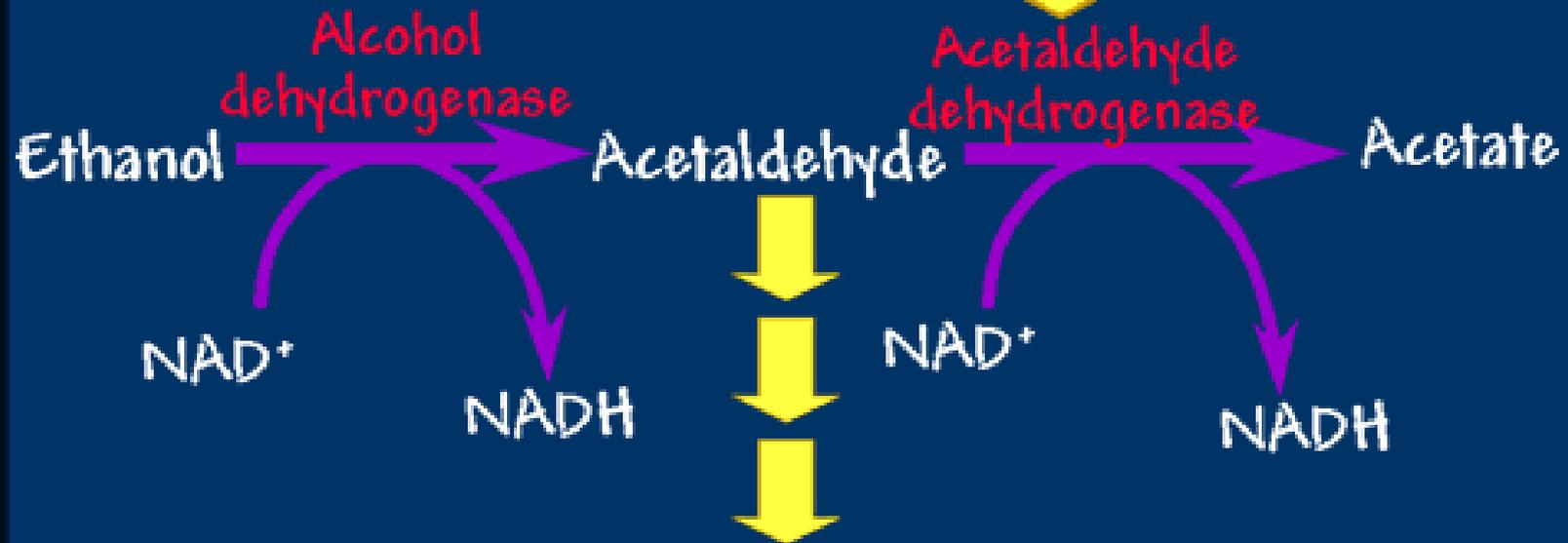
Clinical Experience- may be useful for short term management of relapse prevention with family support. (i.e first few months after leaving residential treatment)

Medication is available as generic and is very inexpensive

Liver toxicity has been reported but is much less likely than with continued alcohol abuse.

ANTABUSE EFFECT

Metronidazole



Hypotension, nausea, vomiting,
and discomfort

Antabuse

Dosing:

250 mg – 500 mg qd

Side effects:

Nausea, metallic taste, dysphoria,
fatigue, hepatitis, psychosis
(dopamine)

Effects can last 72 hours after last dose

Naltrexone (Revia)

FDA Approved For Treatment of Alcohol Dependence 1994.

Mechanism of Action: Opiate Antagonist

Blocks linkage between Alcohol and endogenous Opiate system and decreases positive, reinforcing effects of Alcohol

Can be used to initiate abstinence or decreases use as well as prevent relapse. Safe to take if patient relapses to Alcohol use.

Reduces Cue-Induced Craving for Alcohol

May be more effective in patients with early initiation of alcohol use and strong family history

Naltrexone-Dosing

Starting: (50 mg or 100 mg)

25 mg and increase by 25 mg week until
SE or target dose of 200 mg

Some Data showing efficacy at 300mg
3x weekly

SE: dysphoria, nausea, increased LFTs

Depot formulation coming (Vivitrex) . . .

Choice of Therapy with Naltrexone

Table 2. Naltrexone/Nalmefene Versus Placebo (>50 Patients) by CBT/Similar techniques or Supportive/12-Step Therapy

CBT/similar techniques (n = 947)			Supportive/12-step therapy (n = 1543)		
O'Malley	1992	+	O'Malley	1992	+
Heinälä	2001	+	Heinälä	2001	0
Ballidin	2003	+	Ballidin	2003	0
Volpicelli	1992	+	Chick	2000 ^a	0
Volpicelli	1997	(+)	Krystal	2001	0
Anton	1999	+	Morris	2001	+
Mason	1999	+	Latt	2002	+
Kranzler	2000	0	Gastpar	2002	0
Monti	2001	(+)	Rybakowski*	1997	0
Monterosso	2001	+	Auriacombe†	2000	0

CBT, cognitive behavioral therapy.

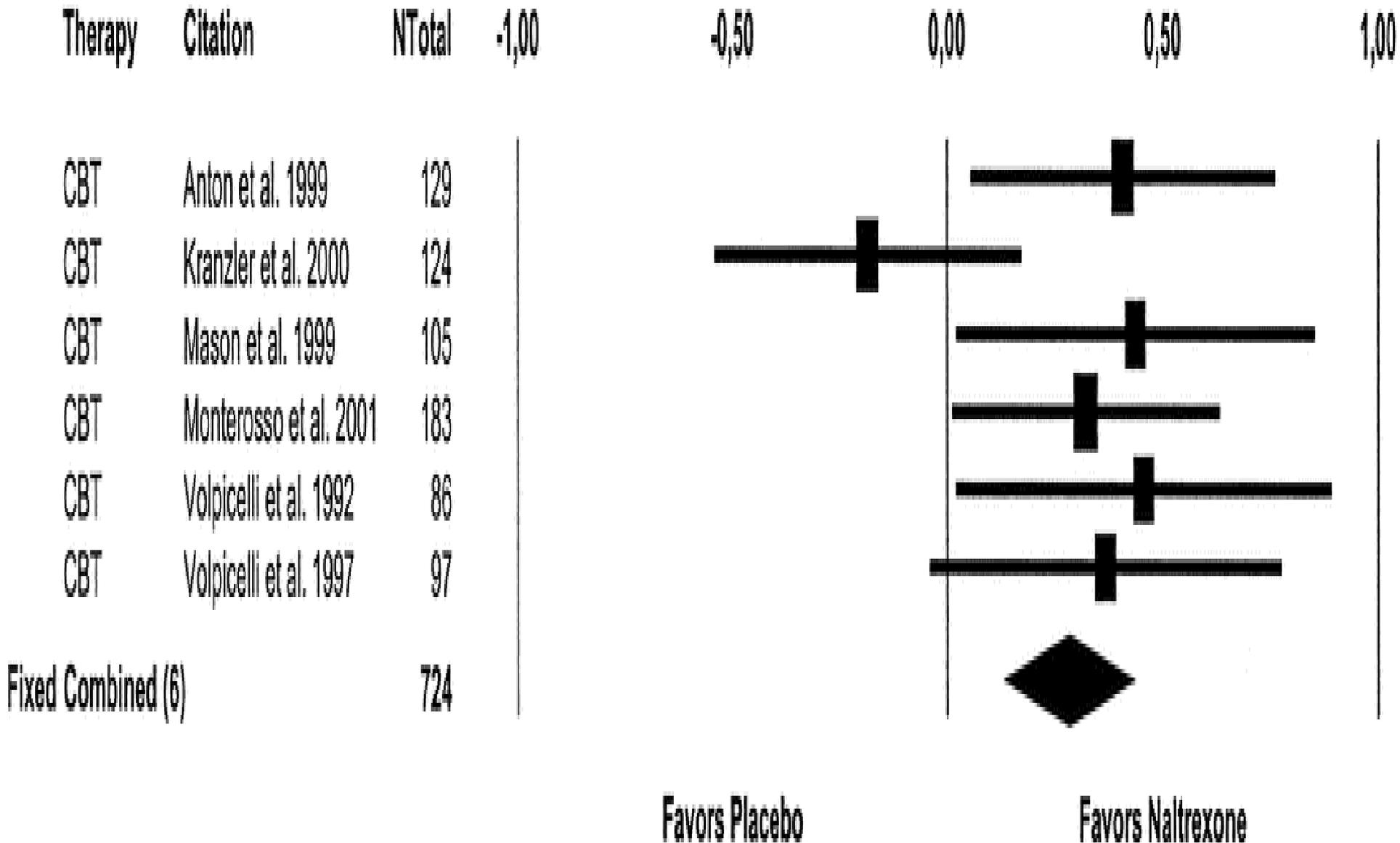
There was a significant difference ($p < 0.05$) between drug and placebo.

+, ITT; (+), completers.

* Rybakowski JK, Ziolkowski M, Volpicelli JR (1997) A study of lithium, carbamazepine and naltrexone in male patients with alcohol dependence—results of four months of treatment. Abstract ESBRA.

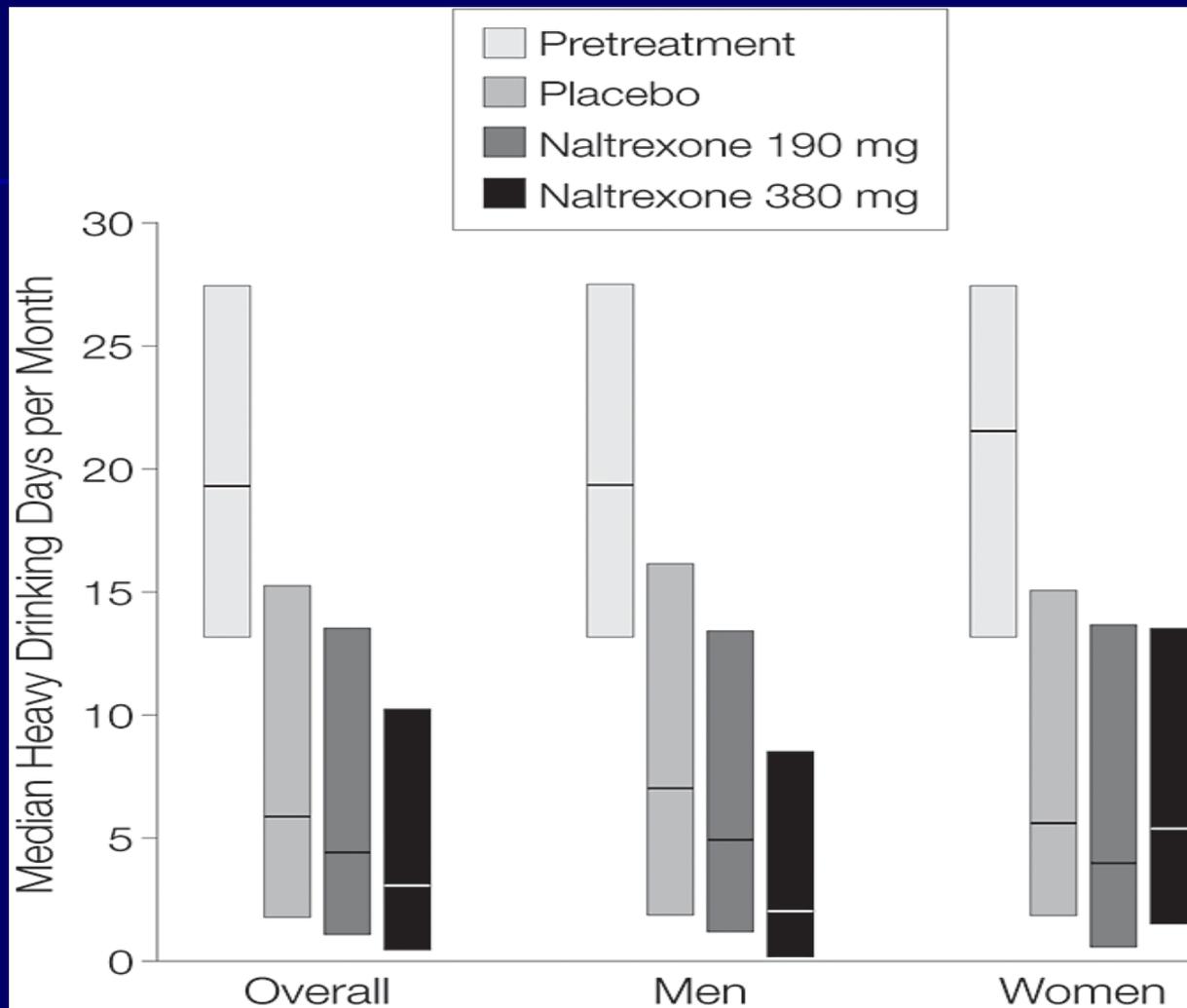
† Auriacombe M, Robinson M, Grabot D, Tignol J (2000) Naltrexone is ineffective to prevent relapse to alcohol in a realistic out-patient setting. A double blind one-year controlled study. CPDD abstract.

Naltrexone + CBT: Effect Size



DEPOT NALTREXONE

Median Heavy Drinking Days per Month for Each Treatment Group Overall and by Sex



Garbutt, J. C. et al. JAMA 2005;293:1617-1625.

Acamprosate (Campral)

MOA: Made from taurine (Red Bull); NMDA receptors in the glutamate system – generally inhibitory

Not much action on GABA

Dose: 333mg bid – 333mg tid (1,998 mg)

Notes:

European data – 4500 patients,

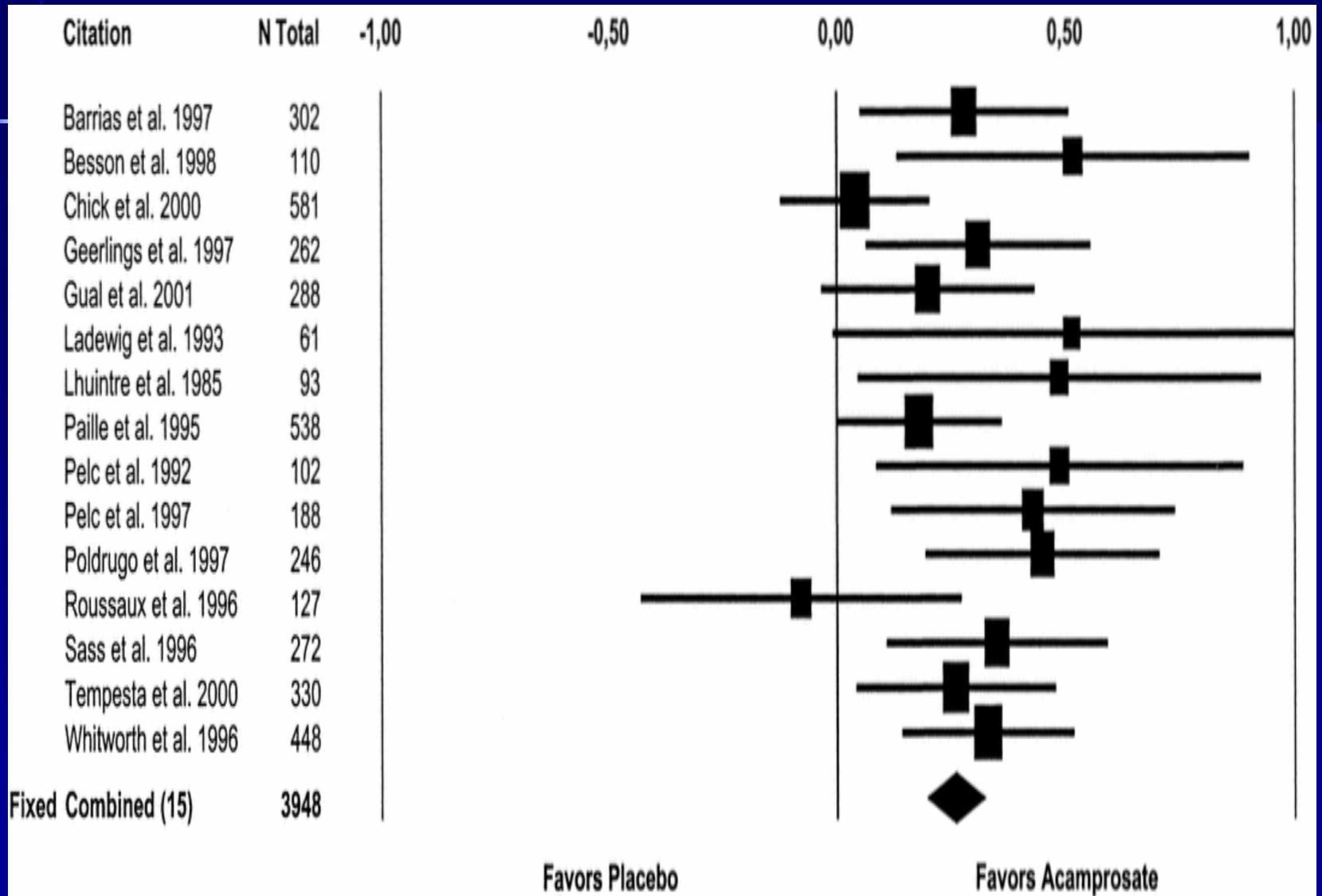
FDA approved Sept 2004

Relapse Prevention,

targets “negative reinforcement”

SE: Diarrhea, rash.

Acamprosate-Effect Size



Combination Treatment: Acamprosate + Naltrexone

- Several Randomized Controlled Trials comparing combined Acamprosate and Naltrexone to monotherapy and placebo.
- Data suggests additive efficacy and little increase in side effects
- Studies done with oral Naltrexone.

Review-Alcohol Pharmacotherapy

1. There are several well-proven medication treatments available for treatment of alcohol dependence
2. Combination treatment with naltrexone and acamprosate should be strongly considered
3. Psychosocial treatment continues to be the primary method of treatment and all patients should be in psychosocial treatment as well as pharmacotherapy.

Other Benefits of Medications



- Help patient commit to change
- Reduce relapse to increase nondrinking time
- Better chance to maximize skill development in psychological therapy
- Still need patient participation to achieve sustained recovery and self-efficacy

Naltrexone



- “Anti-craving” drug blocks opioid receptors reducing euphoric effects
- Initially deployed for management of opioid (e.g., heroin) dependence, as an antagonist
- Reduces craving for alcohol, increases satiety
- Naltrexone qua “ReVia” (oral form) released 12 years ago but without counseling not sufficient therapy

Depot Naltrexone



- Vivitrol = Extended-release injectable form of naltrexone
- Marketed to addiction professionals
- Costly and new, but more positive results with multiple relapses and extensive cravings
- Enhances client medication compliance

Depot Naltrexone Uses



- Patients with alcohol use, multiple relapses, multiple treatment episodes, heavy cravings
- Lasts for 30 days
- Mild side effects though nausea, headaches, shaking decrease with each injection
- Not recommended for opioid dependency - severe withdrawal

ACAMPROSATE (Campral)



- Anti-craving medication for alcoholics
- Lengthens abstinence and reduces relapses
- Reduces negative emotional effect, irritability, and other withdrawal symptoms; may diminish these also as an expression of craving
- Helps diminish protracted withdrawal symptoms

Acamprosate

- Multicenter studies, Europe, principally focusing on females, *Sass et al. 1996*. 3000+ pts. 1st large-scale trial
- Structural analogue of homocysteic acid which interacts with excitatory amino acid neurotransmitters (glutamate)
- Significant increase in abstinence days (20+% vs. 11% abstinent at one year), but type-specific: Alcoholism, exclusive of those with organicity and those with "self-medication" profiles

Disulfiram (Antabuse)



- First medication but no longer popular
- Negative reinforcer – causes nausea, flushing if patient drinks alcohol
- Best used after treatment at high risk situations for relapse
- Seek assistance from treatment provider

Alcohol Relapse

Prevention

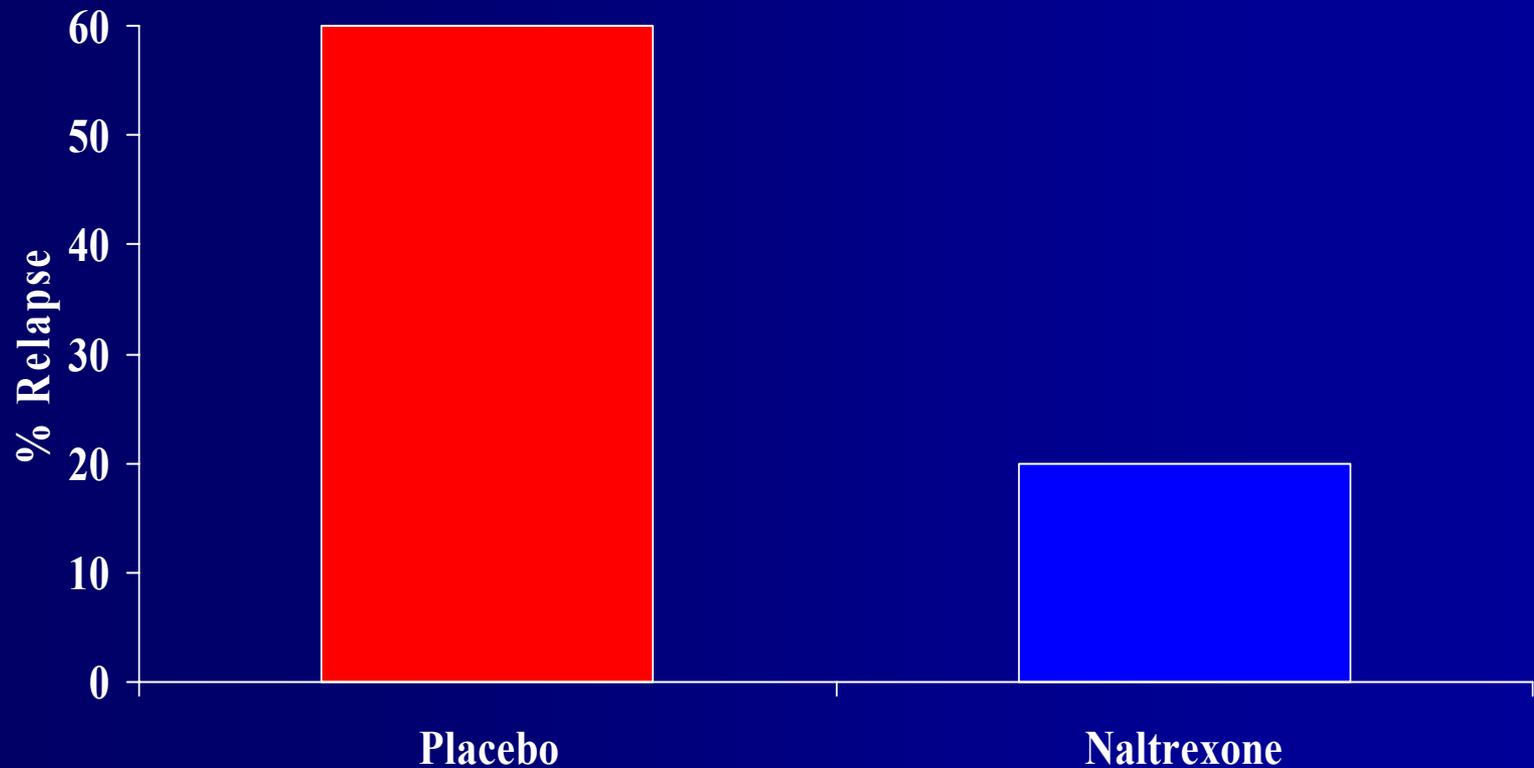
Disulfiram

- Aversive with alcohol use: vomit, hypotension
- Inhibit acetaldehyde breakdown
- Problems with compliance
- Contraindications: liver failure, psychosis

Alcohol Relapse Prevention Naltrexone

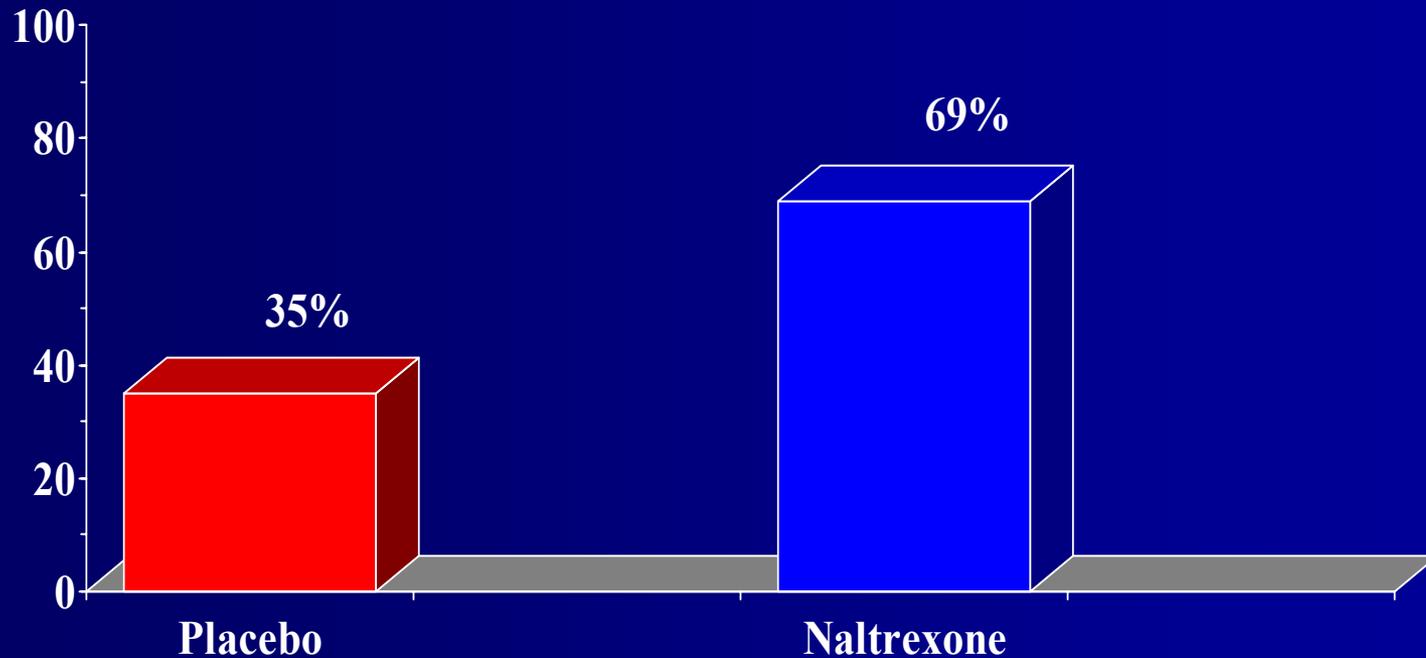
- Mechanism: anti-craving, block priming effect
- Decrease positive effect
- No aversive effect if alcohol used
- Daily oral dose of 50 mg
- Duration - 6 to 12 months
- Contraindications: opioid dependence
severe liver disease
- Side effects (5-10%): nausea, headache

Early Studies: Reduction in Relapse to Alcohol Abuse with Naltrexone (10 Week Trial) (O'Malley et al., 1992)



Early Studies: Subjects Who Did Not Meet Criteria for Alcohol Abuse or Dependence at 6-Month Follow-up ($P < .01$) - (O'Malley et al., 1992)

Subjects, %



Risks vs. Benefits for Naltrexone in Alcoholism

Risks

- ✓ 6-10% initial dropout due to vomiting, nausea, and anxiety, which does not persist after discontinuation

Benefits

- ✓ Approximately 30-40% reduction of relapse risk
- ✓ Improved ratings of employment problems
- ✓ Benefits for preventing relapse persist for six months after discontinuation
- ✓ Improved abstinence rates at endpoint and follow-up

Recommended Outcomes

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Acknowledgments

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