Pharmacologic Interventions for Addictions

Eric C. Strain, M.D.
Johns Hopkins University School of Medicine, Baltimore, Maryland

Maryland Psychiatric Society
November 7, 2015

Objectives for This Talk

I. Identify at least two FDA-approved medications used for the treatment of alcohol use disorders

II. Identify at least three FDA-approved medication formulations used for the treatment of nicotine use disorders

III. Identify at least one new medication that is currently under development for the treatment of an addictive disorder

Outline for This Talk

I. Drug classes and medications currently approved for their treatment

II. Medications under development

III. Summary and conclusions

A Caveat

Focusing today on medications for the treatment of these disorders, but important to note that non-pharmacological interventions play a critical role in the treatment of these disorders. Just as we talk of “dose-related” efficacy of medications, there can also be a dose-related efficacy of non-pharmacological services.

Effect of Counseling in Methadone Treatment

Treatment	Treatment Retention	Urine (-) > 16 weeks
Methadone alone	31%	0%
Methadone + standard counseling	59%	28%
Methadone + enhanced counseling	81%	55%

(McLellan et al., 1993)

Outline for This Talk

I. Drug classes and medications currently approved for their treatment

II. Medications under development

III. Summary and conclusions

Drug Classes and Approved Medications

A. Alcohol

B. Nicotine

C. Opioids

Drug Classes and Approved Medications

Will focus on these three drug classes (approved medications):

A. Alcohol

B. Nicotine

C. Opioids

Alcohol pharmacological treatments

Disulfiram – 1950s

Naltrexone (oral, alcohol) – 1995

Acamprosate – Europe 1989; U.S. 2004

Naltrexone (extended release, alcohol) – 2006

Disulfiram

Trade name: Antabuse; FDA approved in 1951

Blocks aldehyde dehydrogenase; causes increase in acetaldehyde when person drinks (with subsequent disulfiram-alcohol reaction)

Reaction starts within 30 minutes of drink; can consist of flushing, sweating, throbbing, N/V, increased HR, weakness; can be severe in some cases

Disulfiram

Don’t start until at least 12 hours of abstinence

Dose range: 125-500 mg once per day (average, 250 mg/day)

Works best if compelling reason to take it

Disulfiram

Risk considerations:

- Can have a disulfiram-alcohol reaction (do not use in persons with cardiac disease)
- Most common side effects: skin reactions, headache, drowsiness/fatigue, impotence, garlic taste
- Rarely hepatic toxicity, neurologic reactions

Disulfiram

Risk considerations:

Can use in persons with liver disease if liver function tests okay (<5x ULN) – monitor LFTs

Need to watch for alcohol-containing products (mouthwash, sauces, lotions)

Disulfiram

Bottom line with disulfiram:

Generally a safe medication, biggest concerns are probably liver function tests/liver disease, risk of patient drinking while taking it, and compliance with taking it

Evolution of alcohol pharmacological treatments

Disulfiram – 1950s

Naltrexone (oral, alcohol) – 1995

Acamprosate – Europe 1989; U.S. 2004

Naltrexone (extended release, alcohol) – 2006

Naltrexone (oral)

Trade name: ReVia, Depade, others

Opioid antagonist

Mechanism of efficacy when used to treat alcoholism is not clear

Efficacy studies show better outcomes vs. placebo -- decreases craving; improves relapse rates (and longer time to relapse), lower percentage of drinking days and fewer drinks on days the person did drink

Naltrexone (oral)

Recommended 3-7 days abstinence before start

Typical dose: 50 mg per day (but, higher doses may be more effective -- up to 150 mg per day)

Naltrexone (oral)

Risk considerations:

Generally well tolerated medication with no significant side effects

In some cases can see some side effects: GI (nausea, vomiting), headache, fatigue, nervousness, headache, rash

Label warns regarding hepatotoxicity (black box) – an unfortunate situation, not really relevant

Naltrexone (oral)

Other considerations:

- Watch use if liver or renal impairment
- Need to stop if planning major surgery (possible need for opioid analgesics)
- Can have drug interactions

Naltrexone (oral)

Bottom line with naltrexone:

- Generally a safe medication and consistent evidence that it is effective
- Hepatoxicity not a substantial problem
- Nausea/GI effects can be seen
- Biggest drawback is cannot use if opioid agonists needed

Disulfiram

Disulfiram – 1950s

Naltrexone (oral, alcohol) – 1995

Acamprosate – Europe 1989; U.S. 2004

Naltrexone (extended release, alcohol) – 2006

Acamprosate

Trade name: Campral; FDA approved in 2004, but used for years in Europe

Mechanism of action not clear (glutamate?)

Not metabolized by the liver; do need to reduce dose if renal impairment

Use: 666 mg three times per day

Do not crush tablets

Acamprosate

Begin several days after last drink

Efficacy of some debate; two U.S. studies failed to show better results than placebo

May be useful in patients with higher motivation, possibly with more severe dependence

Acamprosate

Risk considerations:

- Safe medication
- No risk of abuse
- Virtually no overdose risk
- Minimal side effects (diarrhea)
- Few drug interactions (can increase naltrexone blood levels)

Acamprosate

Risk considerations:

- Can be used in patients with liver disease (not hepatic metabolism)
- Can be used with opioids (e.g., methadone, buprenorphine treated patients)

Acamprosate

Bottom line with acamprosate:

May be useful under certain circumstances, and risk profile is an advantage to this medication

Disulfiram

Disulfiram – 1950s

Naltrexone (oral, alcohol) – 1995

Acamprosate – Europe 1989; U.S. 2004

Naltrexone (extended release, alcohol) – 2006

Naltrexone (extended release)

Trade name: Vivitrol; FDA approved in 2006

Opioid antagonist

Similar features as oral naltrexone

Administered as gluteal injection given (380 mg) given once every four weeks

Naltrexone (extended release)

While similar profile as that seen with oral naltrexone, advantage in compliance (which has been shown to be an important factor in outcome for naltrexone treatment)

Naltrexone (extended release)

Risk considerations and bottom line:

Similar concerns as with oral naltrexone

Can see injection site reactions, infrequently depression

Important consideration is whether there is a need to use opioids in weeks after receiving an injection

Drug Classes and Approved Medications

A. Alcohol

B. Nicotine

C. Opioids

Nicotine pharmacological treatments

Nicotine -- gum ‘84; patch ‘92; nasal spray ‘96; inhaler ’97

Bupropion – 1997

Varenicline -- 2006

Nicotine

Nicotine gum initially approved as a prescription product (1984); made available over the counter (OTC) in 1996

Followed by other nicotine delivery systems (patch [by prescription, 1992; OTC 1996], nasal spray [prescription only, 1996], inhaler [prescription only, 1997])

Nicotine

NRT = nicotine replacement therapy

NRT products generally safe, more effective than placebo (multiple studies have shown, conclusion of Cochrane review), using 6 months sustained/prolonged abstinence after start of treatment

OR of 1.84 (1.71-1.99)

Combinations of NRT outperform NRT alone

Nicotine

Overall safety profile good – can see some minor concerns (for example, skin reactions with patch, hiccups with gum)

Nicotine pharmacological treatments

Nicotine -- gum ‘84; patch ‘92; nasal spray ‘96; inhaler ’97

Bupropion – 1997

Varenicline -- 2006

Bupropion

Bupropion initially marketed in U.S. as an antidepressant (Wellbutrin products)

Approved for smoking cessation (by prescription) in U.S. in 1997 (intriguing alternate mechanism of action -- not another nicotine-based product; grew out of clinical observation)

Bupropion

- Functions as a weak dopamine and norepinephrine reuptake inhibitor, and also appears to have some effects on nicotinic receptors
- Efficacy is not related to its antidepressant effects
- Marketed as Zyban (and need to ensure double dosing does not occur through prescribing of it for smoking cessation and for depression)

Bupropion

Like NRT, more effective than placebo (OR 1.60, 95% 1.60-2.06 – similar to NRT, and not significantly different on head-to-head comparison)

Typically start dosing similar to use as an antidepressant (150 mg/d for several days, then increase to 300 mg/d), and set quit date after stabilized on medication (e.g., a week after dosing)

Bupropion

- Primary concern with risk of seizures, which is dose related, and can occur if other risk factors for seizures
- Other effects possible (GI, headache)

Nicotine pharmacological treatments

Nicotine -- gum ‘84; patch ‘92; nasal spray ‘96; inhaler ’97

Bupropion – 1997

Varenicline -- 2006

Varenicline

Varenicline (Chantix, Champix) approved in U.S., 2006

Yet another mechanism of action (partial nicotinic agonist, vs. nicotine replacement products and antidepressant)

Varenicline

Efficacy superior to NRT, bupropion

Compared to placebo: OR 2.88 (95%, 2.40-3.47)

Initial concerns of neuropsychiatric effects (depression, suicidal ideation) – these do not appear to be as great a concern as initially noted

Varenicline

- Dosing relatively simple (0.5 mg a day for 3 days, 0.5 mg twice a day; no more than 2 mg total per day)
- Set quit date a week or so after start use

Drug Classes and Approved Medications

A. Alcohol

B. Nicotine

C. Opioids

Evolution of pharmacologic treatments

Methadone – 1960s

Naltrexone (oral, opioids) – 1984

LAAM – 1993

Buprenorphine – France 1996; U.S. 2002

Naltrexone (extended release, opioids) – 2010

Opioid treatments

Essentially two primary approaches:

Opioid agonist or partial agonists: have main therapeutic effect on mu receptor (activate it)

(Buprenorphine, LAAM, methadone)

Opioid antagonists: occupy opioid receptors (primary therapeutic target is mu receptor), but don't activate the receptor

(Naltrexone)

Opioid treatments

Essentially two delivery systems:

Opioid Treatment Programs (OTPs – what we would have called methadone clinics in the past)

(Buprenorphine, LAAM, methadone)

Office Based Opioid Treatment (OBOT)

(Buprenorphine, Naltrexone)

Opioid treatments

All of these treatments are effective, safe

Substantial database supporting use of these medications

Outline for This Talk

I. Drug classes and medications currently approved for their treatment

II. Medications under development

III. Summary and conclusions

Potential new medications

Alcohol

Opioids

Cocaine/stimulants

Cannabis

Medications studied for alcoholism

Ondansetron

Topiramate

Rimonabant

Quetiapine

Levetiracetam

Varenicline

Medications studied for alcoholism

Ondansetron: approved for treatment of nausea; low doses useful for alcoholism, especially early-onset?

Topiramate

Rimonabant

Quetiapine

Levetiracetam

Varenicline

Medications studied for alcoholism

Ondansetron

Topiramate: anticonvulsant, migraine treatment; clinical trials showing efficacy for alcoholism, but side effects may limit development

Rimonabant

Quetiapine

Levetiracetam

Varenicline

Medications studied for alcoholism

Ondansetron

Topiramate

Rimonabant: cannabinoid antagonist briefly marketed outside U.S. for obesity but withdrawn (side effects); cannabinoid system remains of interest

Quetiapine

Levetiracetam

Varenicline

Medications studied for alcoholism

Ondansetron

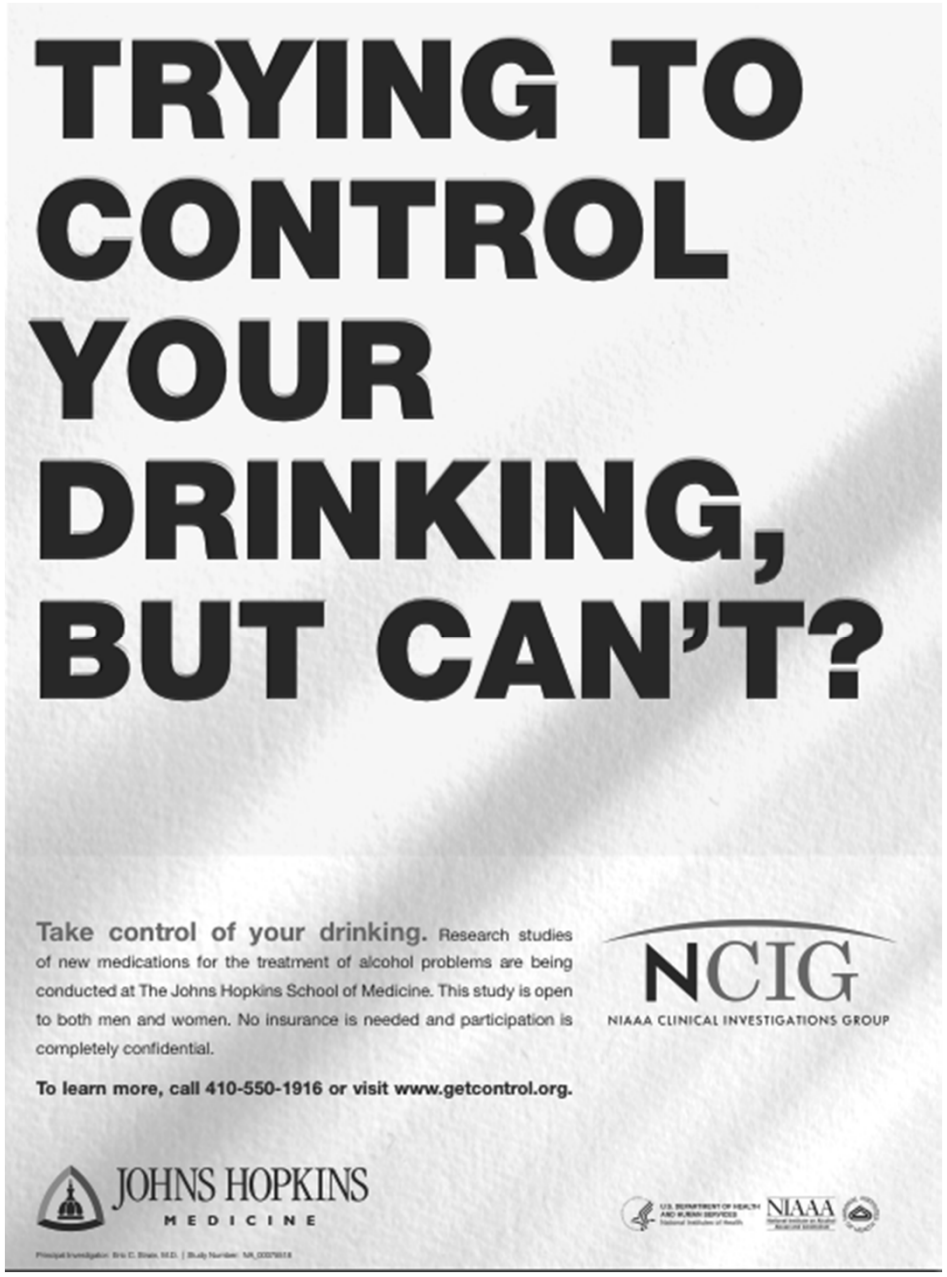
Topiramate

Rimonabant

Quetiapine: first medication studied by NIAAA's clincial trial program (NCIG, "Get Control")

Levetiracetam

Varenicline



NCIG

NCIG (NIAAA Clinical Investigations Group)

Multi-site program for studying new medications for alcohol dependence (Hopkins, Penn, UVA, Boston U, Dartmouth)

Medications studied for alcoholism

Ondansetron

Topiramate

Rimonabant

Quetiapine: no efficacy found for alcohol dependence

Levetiracetam

Varenicline

Medications studied for alcoholism

Ondansetron

Topiramate

Rimonabant

Quetiapine

Levetiracetam: approved anticonvulsant; second medication studied in NCIG, and again no efficacy found for alcoholism

Varenicline

Medications studied for alcoholism

Ondansetron

Topiramate

Rimonabant

Quetiapine

Levetiracetam

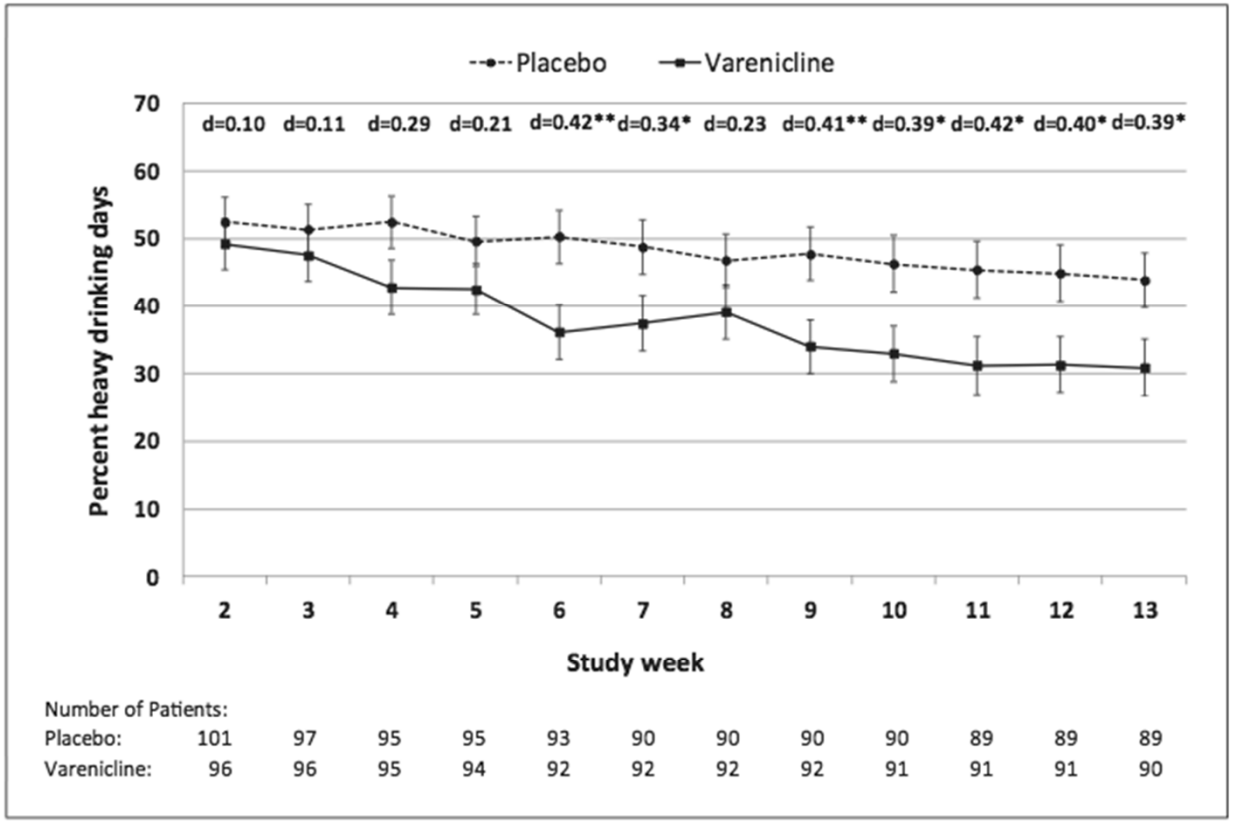
Varenicline: partial nicotinic agonist; approved for the treatment of nicotine dependence; recent NCIG study showing efficacy for alcoholism

Medications studied for alcoholism

Varenicline

- 200 subjects randomized (198 analyzed); alcohol dependent, but not needing medically supervised withdrawal
- 13 week trial
- Target varenicline dose of 1 mg bid
- Concurrent computer-based treatment

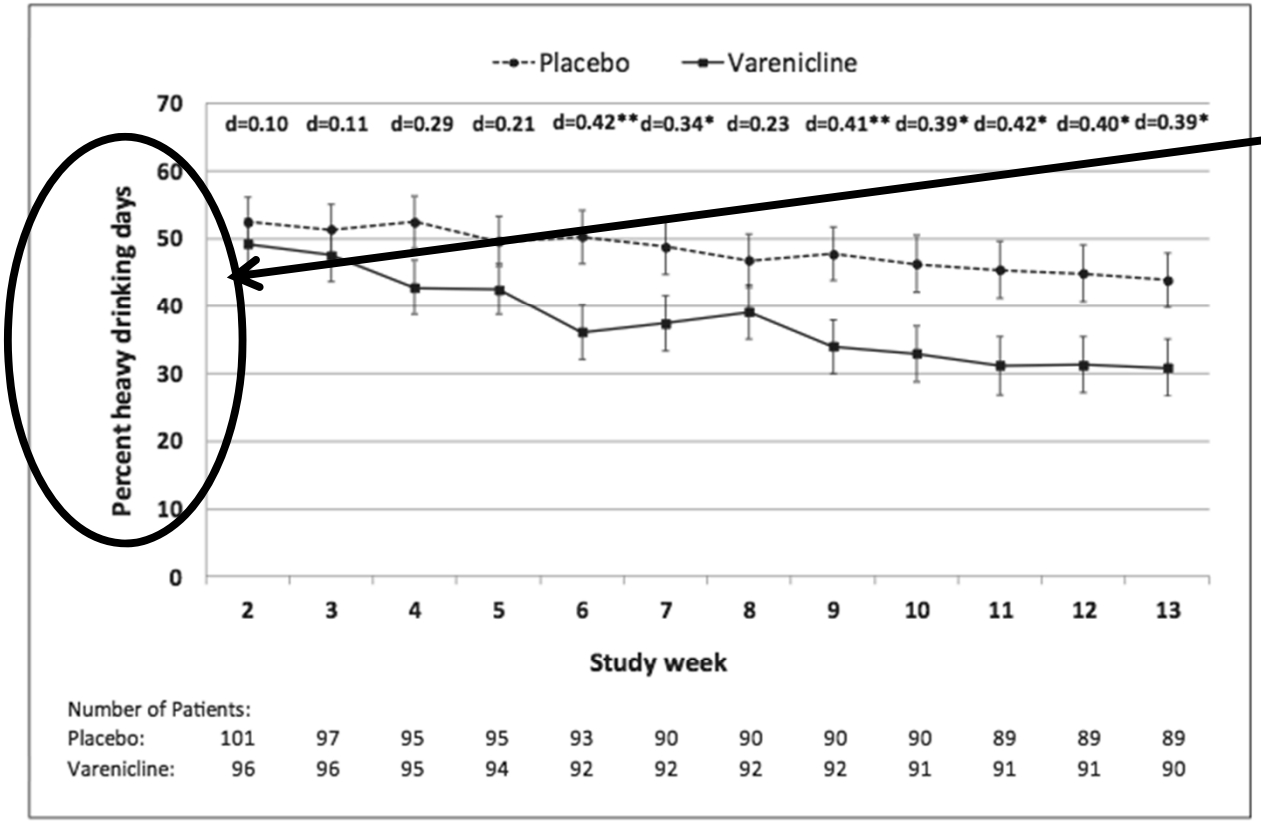
Varenicline for alcohol dependence



Litten et al., JAM, 2013)

FIGURE 2. Weekly differences between placebo and varenicline on the primary outcome measure and percent heavy drinking days during study maintenance phase (weeks 2-13).
*$P < 0.05$; **$P < 0.01$. Means are least-square means obtained during the maintenance period (weeks 2-13) from a mixed model that includes treatment group, week, site, treatment goal, craving, baseline percent heavy drinking days, and treatment group by week interaction. Error bars are standard errors. The treatment group by week interaction is statistically significant ($P = 0.011$).

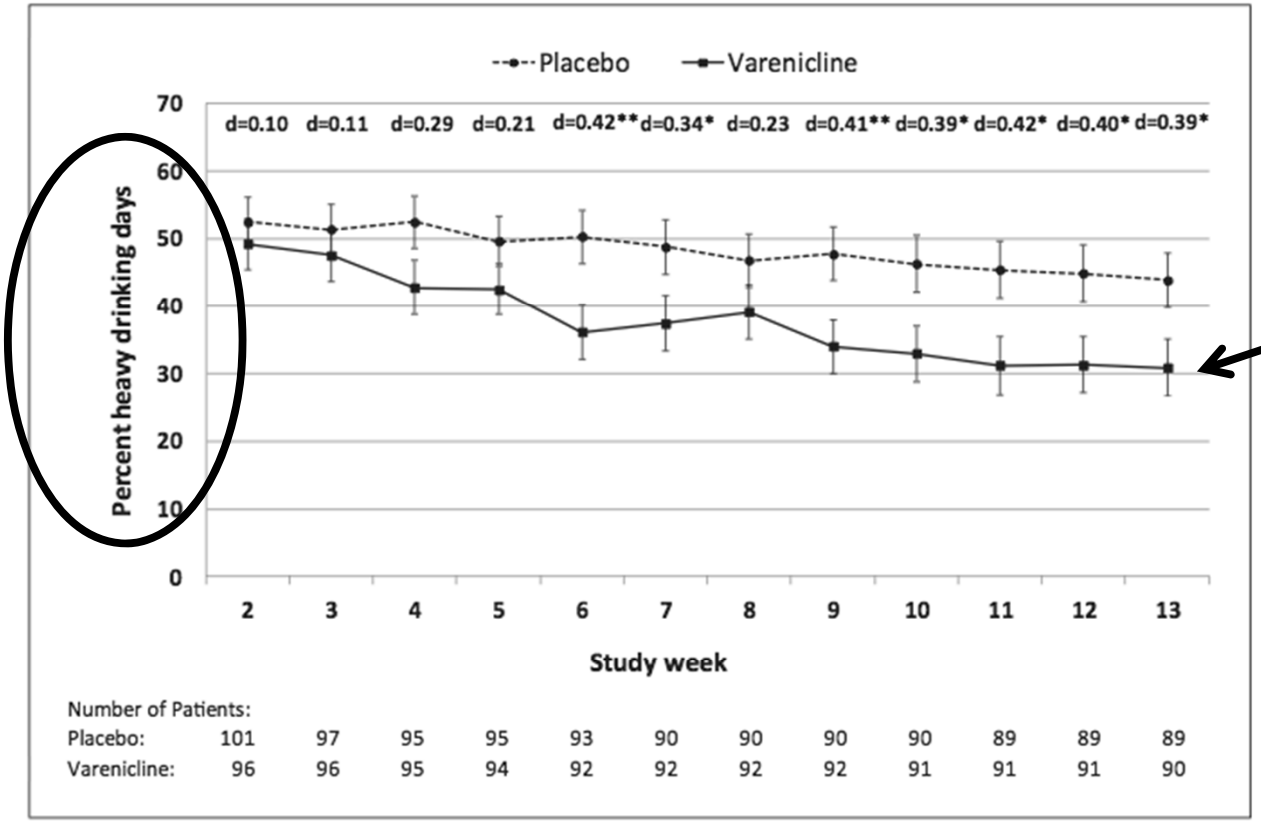
Varenicline for alcohol dependence



Primary outcome: Percent Heavy Drinking Days (HDD)

FIGURE 2. Weekly differences between placebo and varenicline on the primary outcome measure and percent heavy drinking days during study maintenance phase (weeks 2-13).
*$P < 0.05$; **$P < 0.01$. Means are least-square means obtained during the maintenance period (weeks 2-13) from a mixed model that includes treatment group, week, site, treatment goal, craving, baseline percent heavy drinking days, and treatment group by week interaction. Error bars are standard errors. The treatment group by week interaction is statistically significant ($P = 0.011$).

Varenicline for alcohol dependence



Varenicline

FIGURE 2. Weekly differences between placebo and varenicline on the primary outcome measure and percent heavy drinking days during study maintenance phase (weeks 2-13).
*$P < 0.05$; **$P < 0.01$. Means are least-square means obtained during the maintenance period (weeks 2-13) from a mixed model that includes treatment group, week, site, treatment goal, craving, baseline percent heavy drinking days, and treatment group by week interaction. Error bars are standard errors. The treatment group by week interaction is statistically significant ($P = 0.011$).

Medications studied for alcoholism

Varenicline

- Intriguing results

Potential new medications

Alcohol

Opioids

Cocaine/stimulants

Cannabis

Medications studied for opioid dependence

- Lofexidine
- Buprenorphine rods
- Buprenorphine injections
- Other buprenorphine products
- Tramadol

Potential new medications

Alcohol

Opioids

Cocaine/stimulants

Cannabis

Medications studied for cocaine/stimulants

- Naltrexone: opioid antagonist; no evidence of efficacy for cocaine or methamphetamine, but interesting results for amphetamine dependence
- Cocaine vaccine
- Modafinil
- Disulfiram
- Amphetamine products

Medications studied for cocaine/stimulants

FIGURE 2. Percentage of Negative Urine Samples in the Naltrexone and Placebo Groups During the 12-Week Trial (Intention-to-Treat Analysis)

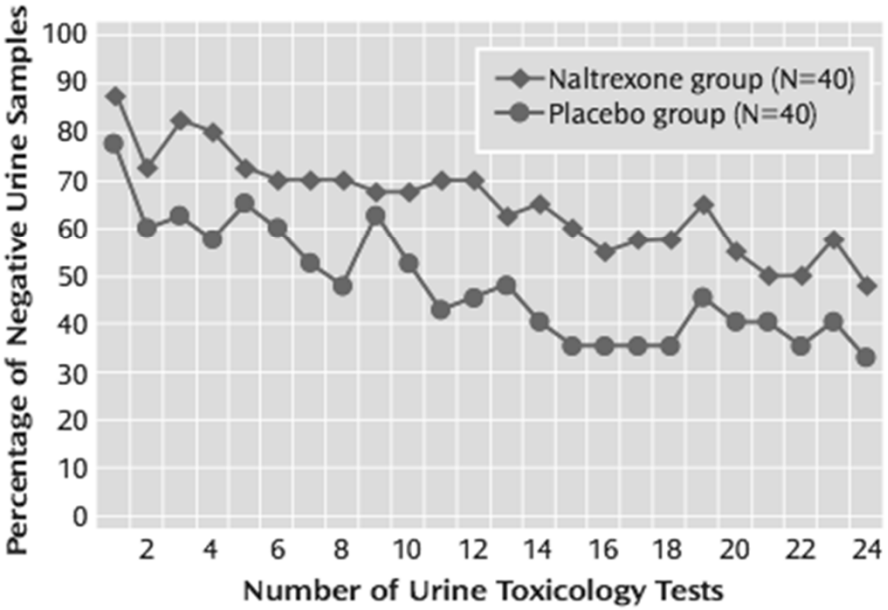
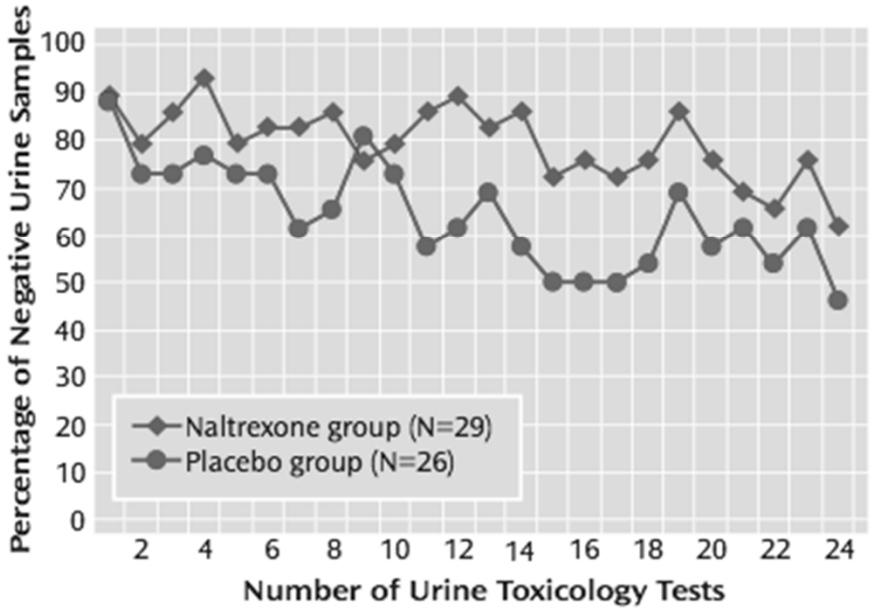


FIGURE 3. Percentage of Negative Urine Samples in the Naltrexone and Placebo Groups During the 12-Week Trial (Completer Analysis)



80 amphetamine-dependent patients; double-blind, RCT

(Jayaram-Lindstrom et al., AJP, 2008)

Medications studied for cocaine/stimulants

Naltrexone

Cocaine vaccine: cocaine bound with protein (cholera toxin), creates antibodies -- prevents cocaine from then crossing blood brain barrier

Modafinil

Disulfiram

Amphetamine products

Medications studied for cocaine/stimulants

- Naltrexone
- Cocaine vaccine
- Modafinil: treatment for narcolepsy, excessive sleepiness; clincial trials for cocaine have been equivocal (some positive, but not all), and some suggestion that persons with higher levels of methamphetamine dependence may respond
- Disulfiram
- Amphetamine products

Medications studied for cocaine/stimulants

Naltrexone

Cocaine vaccine

Modafinil

Disulfiram: initially studied for dual alcohol/cocaine users (10+ years ago), but then studies found effective without alcohol use; results for positive effect less consistent over time; may need a champion to push it forward

Amphetamine products

Medications studied for cocaine/stimulants

Naltrexone

Cocaine vaccine

Modafinil

Disulfiram

Amphetamine products: studies as a proof of concept (for cocaine), have shown can work

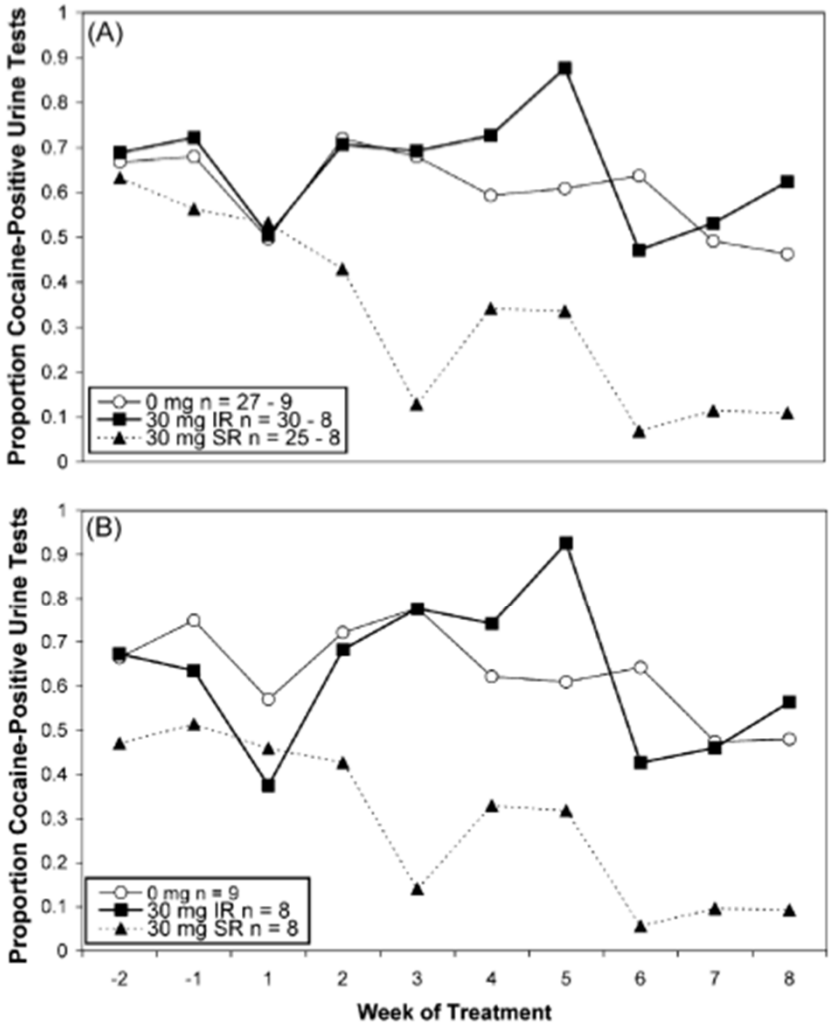


Fig. 3. (A) Cocaine-use proportion in the intention-to-treat sample. Beginning (week 1 of treatment) and ending (week 8 of treatment) sample sizes are shown in the legend. The SR group had significantly fewer BE-positive urine tests than the placebo (0 mg) or IR conditions. (B) Cocaine-use proportion in those completing treatment. Samples sizes are shown in the legend. The SR group had significantly fewer BE-positive urine tests than the placebo (0 mg) or IR conditions.

Medications studied for cocaine/stimulants

82 cocaine-dependent patients; double-blind, RCT

Tested methamphetamine (immediate release and sustained release)

(Mooney et al., DAD, 2009)

Medications studied for cocaine/stimulants

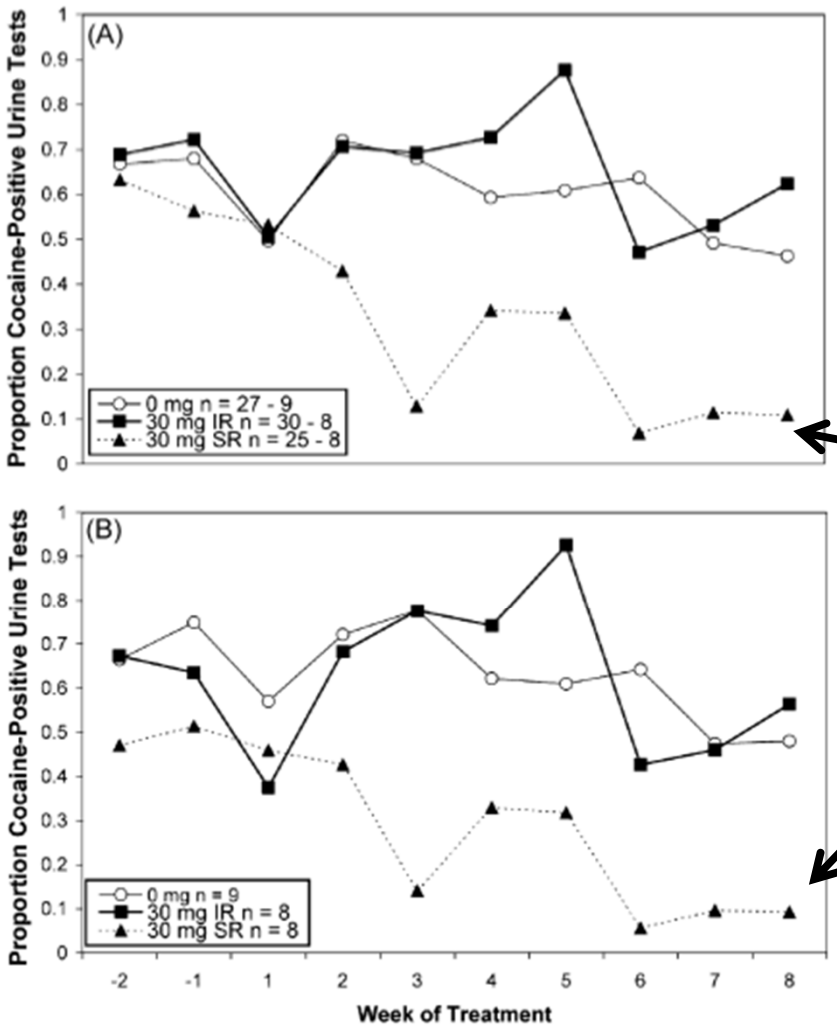


Fig. 3. (A) Cocaine-use proportion in the intention-to-treat sample. Beginning (week 1 of treatment) and ending (week 8 of treatment) sample sizes are shown in the legend. The SR group had significantly fewer BE-positive urine tests than the placebo (0 mg) or IR conditions. (B) Cocaine-use proportion in those completing treatment. Samples sizes are shown in the legend. The SR group had significantly fewer BE-positive urine tests than the placebo (0 mg) or IR conditions.

SR methamphetamine group (30 mg once a day) – lowest rates of cocaine + urine samples over time

Potential new medications

Alcohol

Opioids

Cocaine/stimulants

Cannabis

Medications studied for cannabis

Dronabinol: approved form of delta-9-THC (nausea, vomiting, weight gain); CB-1 agonist, and use follows logic of other agonist treatments; evidence from clinical pharmacology studies that may be effective in treating cannabis withdrawal

Zolpidem

(Rimonabant)

Medications studied for cannabis

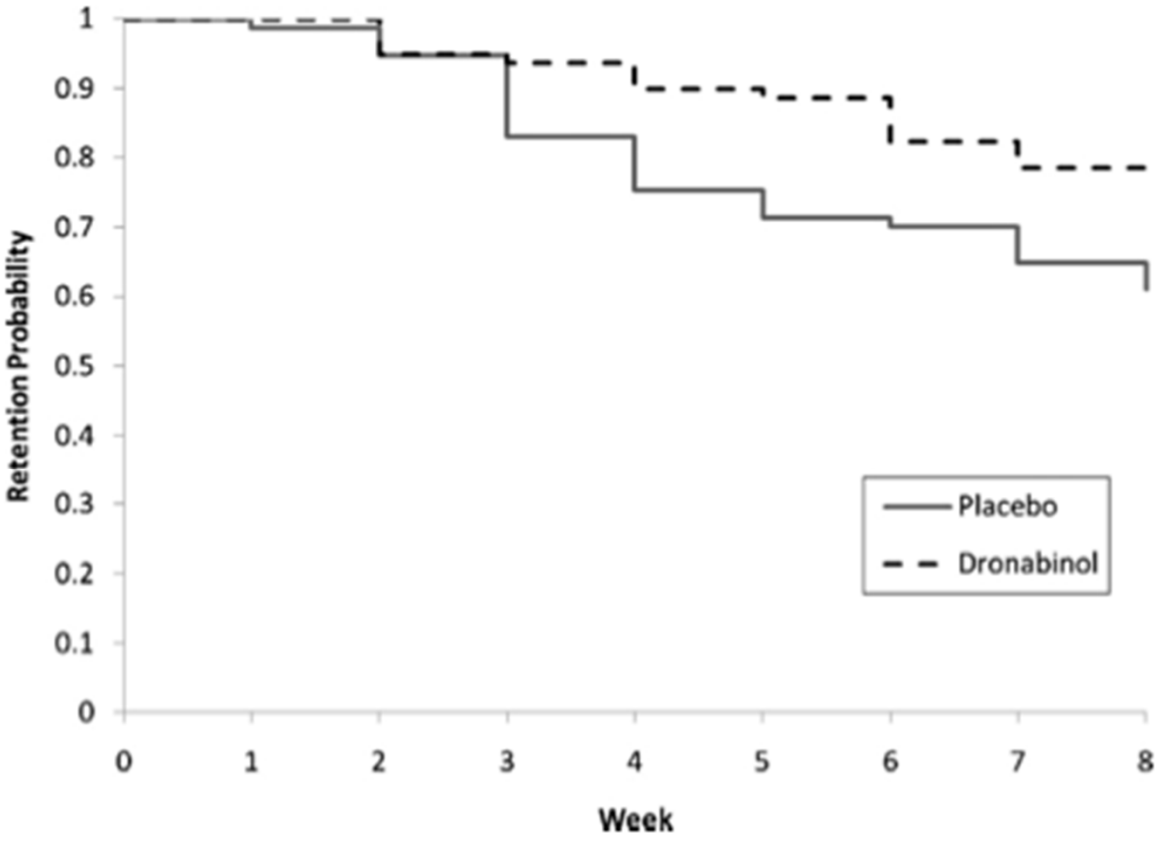


Fig. 2. Retention rates were found significantly different between the treatment groups based on log-rank statistics ($P = .02$).

156 cannabis dependent patients (RCT)

Dronabinol associated with better treatment retention

(Levin et al., DAD, 2011)

Medications studied for cannabis

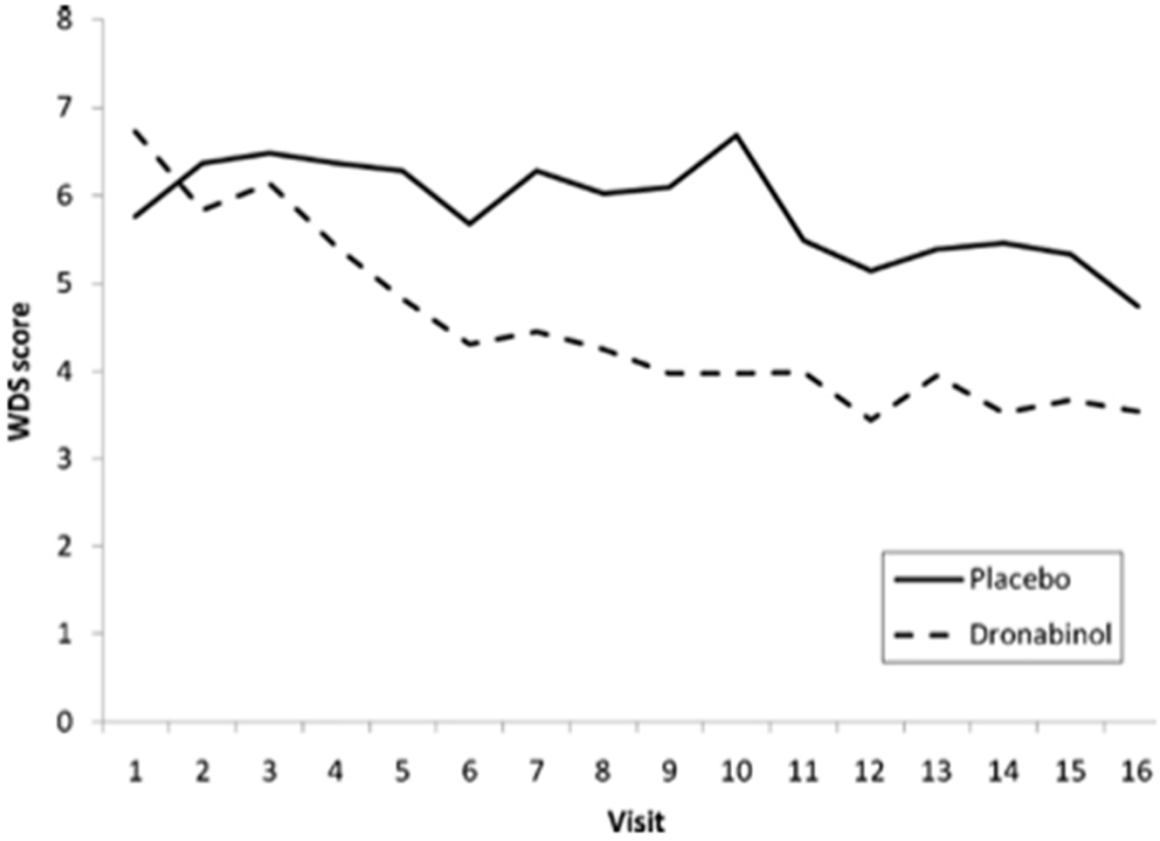


Fig. 3. Modeled withdrawal discomfort scores (WDSs) between the treatment groups over time display a significant two-way interaction between time and treatment ($P = .02$). Results shown are based on an analysis using a mixed effect model.

Dronabinol decreased cannabis withdrawal

(Levin et al., DAD, 2011)

Medications studied for cannabis

Dronabinol

Zolpidem: approved medication for insomnia; logic of it is to treat a prominent symptom of cannabis withdrawal (sleep difficulties)

(Rimonabant)

Cannabis withdrawal (DSM-5)

Three or more of the following:

1. Irritability, anger, or aggression
2. Nervousness or anxiety
3. Sleep difficulty (e.g., insomnia, disturbing dreams)
4. Decreased appetite or weight loss
5. Restlessness
6. Depressed mood
7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache

Medications studied for cannabis

Dronabinol

Zolpidem: evidence that there are increasing numbers of persons seeking treatment for cannabis dependence, and who report difficulty stopping cannabis use (related, in part, to sleep problems associated with withdrawal)

(Rimonabant)

Medications studied for cannabis

Cannabis

Zolpidem

(Rimonabant: cannabinoid antagonist, and such antagonists are theoretically interesting as possible therapeutic options for treating cannabis dependence)

Outline for This Talk

I. Drug classes and medications currently approved for their treatment

II. Medications under development

III. Summary and conclusions

Summary of potential new medications

The primary driver behind medication development for substance use disorders has been (and will probably continued to be) NIH; the pharmaceutical companies have picked up interest in addictions, but primarily in forms of buprenorphine

Summary/conclusions

Progress in the development of medications for treatment drug use disorders, although after a burst of work in late 1990s/early 2000s, seems there has been some decrease in the pace of novel pharmacotherapies

Summary/conclusions

While emphasis here is on medications, want to stress that efficacy of these medications is enhanced when combined with effective non-pharmacologic treatments

True advances may require the identification of new mechanisms for medications actions (such as vaccines or facilitation of learning) – it may be that the current pharmacological approaches are less fruitful (the agonist models of therapies)

Summary/conclusions

In addition to the development of medications, we are witnessing considerable change in the organization and reimbursement of substance abuse treatment, and this has the potential to lead to need for expanded treatment capacity

Finally, we are also witnessing a social experiment with respect to cannabis – some might say an ironic twist to the current cultural disdain for smoking tobacco

Thank you

Acknowledgements

Support of the National Institute on Drug Abuse (K24 DA023186)