Resources:

Efficacy of Disulfiram and Cognitive Behavior Therapy in Cocaine-Dependent Outpatients
A Randomized Placebo-Controlled Trial
Kathleen M. Carroll, PhD; Lisa R. Fenton, PsyD; Samuel A. Ball, PhD; et al
https://jamanetwork.com/journals/jamapsychiatry/article-abstract/481973

Levodopa pharmacotherapy for cocaine dependence: Choosing the optimal behavioral therapy platform
Joy M, Schmitz, Marc Mooney, F. Gerald Moeller, Angela L. Stotts, Charles Green, John Grabowski
https://doi.org/10.1016/j.drugalcdep.2007.11.004

C. Kenneth and Dianne Wright Center
for Clinical and Translational Research

Pharmacotherapy for Stimulant Use Disorder

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VCU School of Medicine

Disclosure

- Grant funding from Nektar and Indivior
- All medications to be discussed are off-label indications (***there is no FDA approved treatment for stimulant use disorder***).

The Current Pathway for Medication Development

- Discovery of novel compounds based on current theories
- Testing in animal models for safety/efficacy
- Human safety testing
- Clinical trials in patient populations

Challenges in Clinical Trials for Addictions

- Medication Compliance
- Treatment Retention

- Subject Heterogeneity
- Subject Recruitment

- Administer Medications in clinic
- Contingency Management
- Inclusion Criteria
- Subject Compensation

New Targets for Medication Development for Stimulant Use Disorder

- Focus initially was on reward systems
- Treatments focused solely on blocking reward have been disappointing (dopamine antagonists)
- More recently the model of medication development has examined other pathways to reduce cocaine use

Effects of Chronic Stimulant Use on the Brain that Could Increase Impulsivity/Cue reactivity

- Reduced dopamine D2 receptors
- Reduced presynaptic dopamine release
- Reduced serotonin function
- Can these effects be altered by medication?

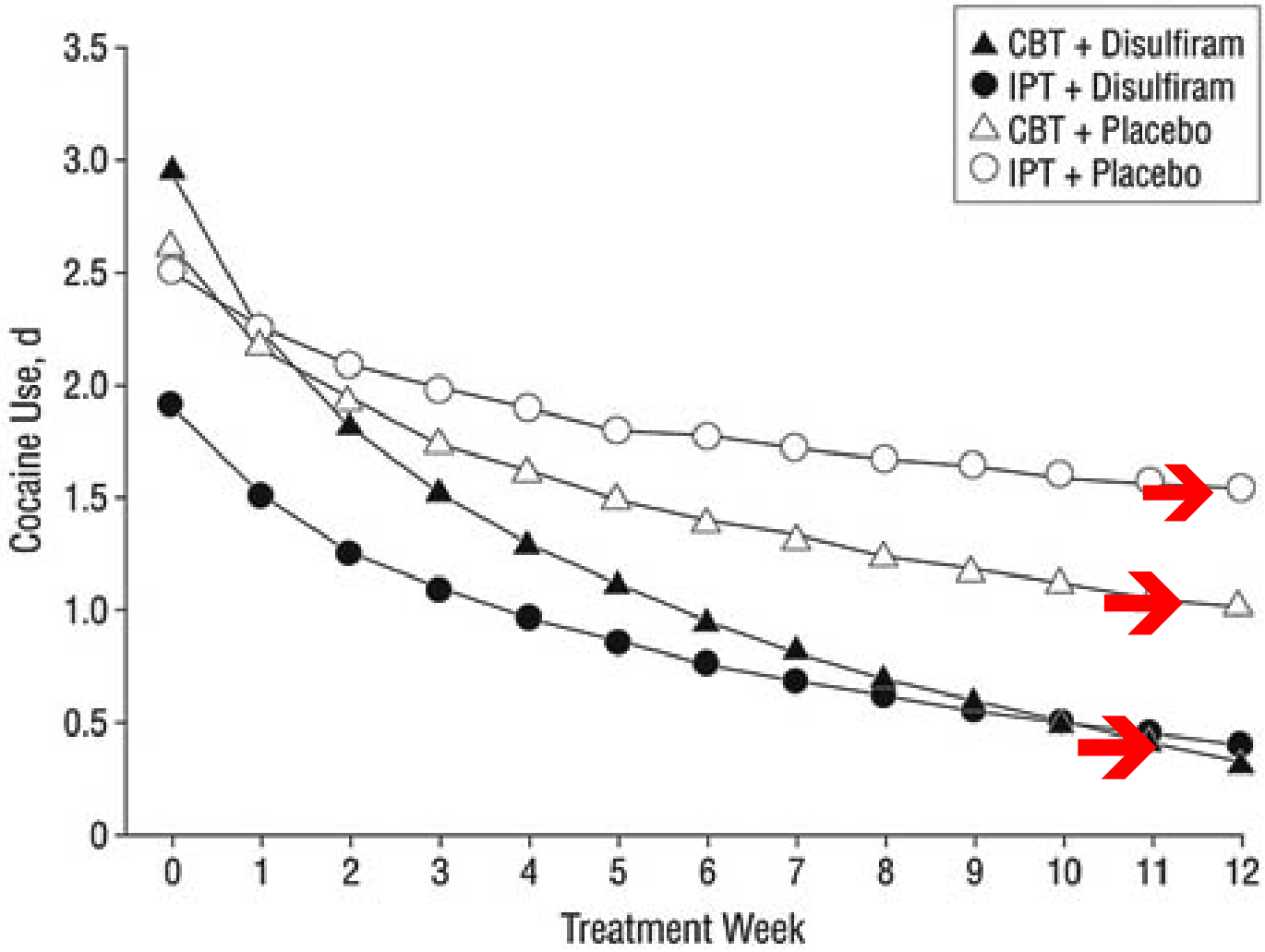
Medications For Cocaine Dependence

- Disulfiram (Antabuse)
  - Originally used to treat comorbid alcohol and cocaine dependence
  - Several studies show efficacy in single diagnosis cocaine users
  - Possibly mediated by disulfiram's effects as a dopamine beta hydroxylase inhibitor
  - Increases dopamine by blockade of dopamine breakdown

Disulfiram Clinical Trial

- Carroll et al., 2004
  - 121 Cocaine Dependent Subjects Randomized
  - Double blind placebo controlled trial
  - Four treatment groups
    - Disulfiram 250mg/Day plus Cognitive Behavioral Therapy
    - Disulfiram 250mg/Day plus Interpersonal Therapy
    - Placebo plus Cognitive Behavioral Therapy
    - Placebo plus Interpersonal Therapy

Results


CBT + Disulfiram
IPT + Disulfiram
CBT + Placebo
IPT + Placebo
Cocaine Use, d
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Treatment Week

Disulfiram Clinical Trial

- Carroll et al., 2004
  - Significant effect of drug and CBT on cocaine use
  - Effect present even in non-alcohol abusing cocaine users
  - In subjects without elevated LFTs side effects minimal, no serious adverse reactions
  - Risks of disulfiram include liver and interaction with alcohol in clinical use
  - Disulfiram can also increase cocaine levels

Clinical Trial Results of Other Medications that Increase Dopamine

Randomized controlled trial of levodopa-carbidopa and behavior therapy for cocaine-dependent outpatients

(Schmitz et al., Drug and Alcohol Dependence, 2008)

Study Design

Medication Condition

Therapy Condition	Placebo	L-Dopa
Clinical Management (CM)		
CM + Cognitive Behavior Therapy (CBT)		
CM + CBT + Contingency Management Procedures (CMP)		

Schmitz et al., 2008

Pharmacotherapy

- Levodopa 800 mg and Carbidopa 200 mg (Sinemet® CR) or Placebo
- Packed in capsules with riboflavin (100 mg) to monitor compliance, dispensed in Medication Event Monitoring (MEM) bottles
- 1-week dose run-up
- 12-week fixed dose (M-W-F clinic visits)

Schmitz et al., 2008

Therapy Conditions

Clinical Management (CM)

- Delivered by clinic nurse
- 10-15 minute sessions, once a week
- Ongoing assessment of patients' clinical status

Cognitive Behavioral Therapy (CBT)

- Delivered by master-level therapists
- 50-60 minute sessions, once a week
- Focus on coping skills training

Contingency Management Procedures (CMP)

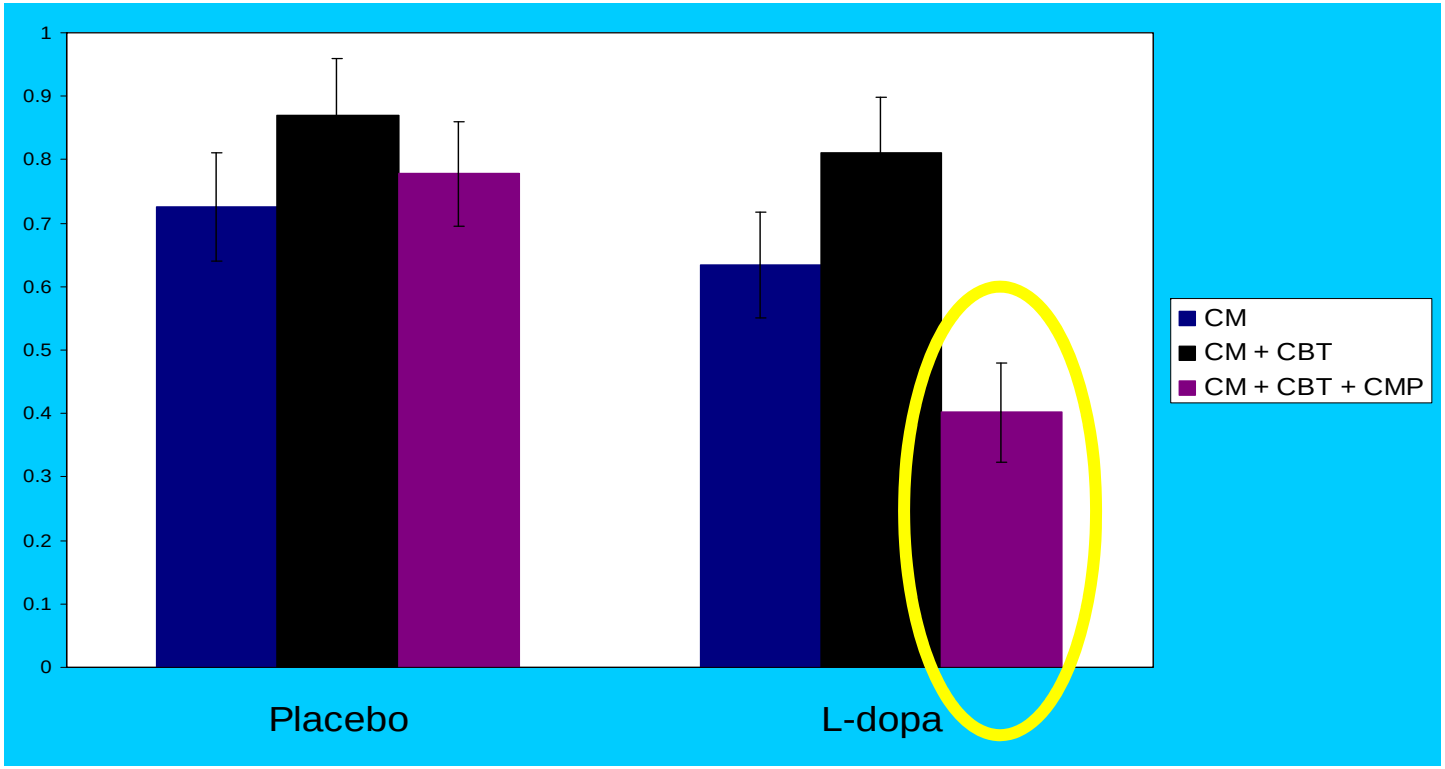
- Vouchers delivered contingent on cocaine-negative urines
- Incremental increases in voucher value with consecutive occurrences of the target behavior

Schmitz et al., 2008

Cocaine Use:

Significant Therapy x Medication Effect

Cocaine-positive urine specimens (Proportion)



F(2, 126) = 3.44, p=.04.

Schmitz et al., 2008

L-Dopa/Carbidopa for Cocaine Dependence

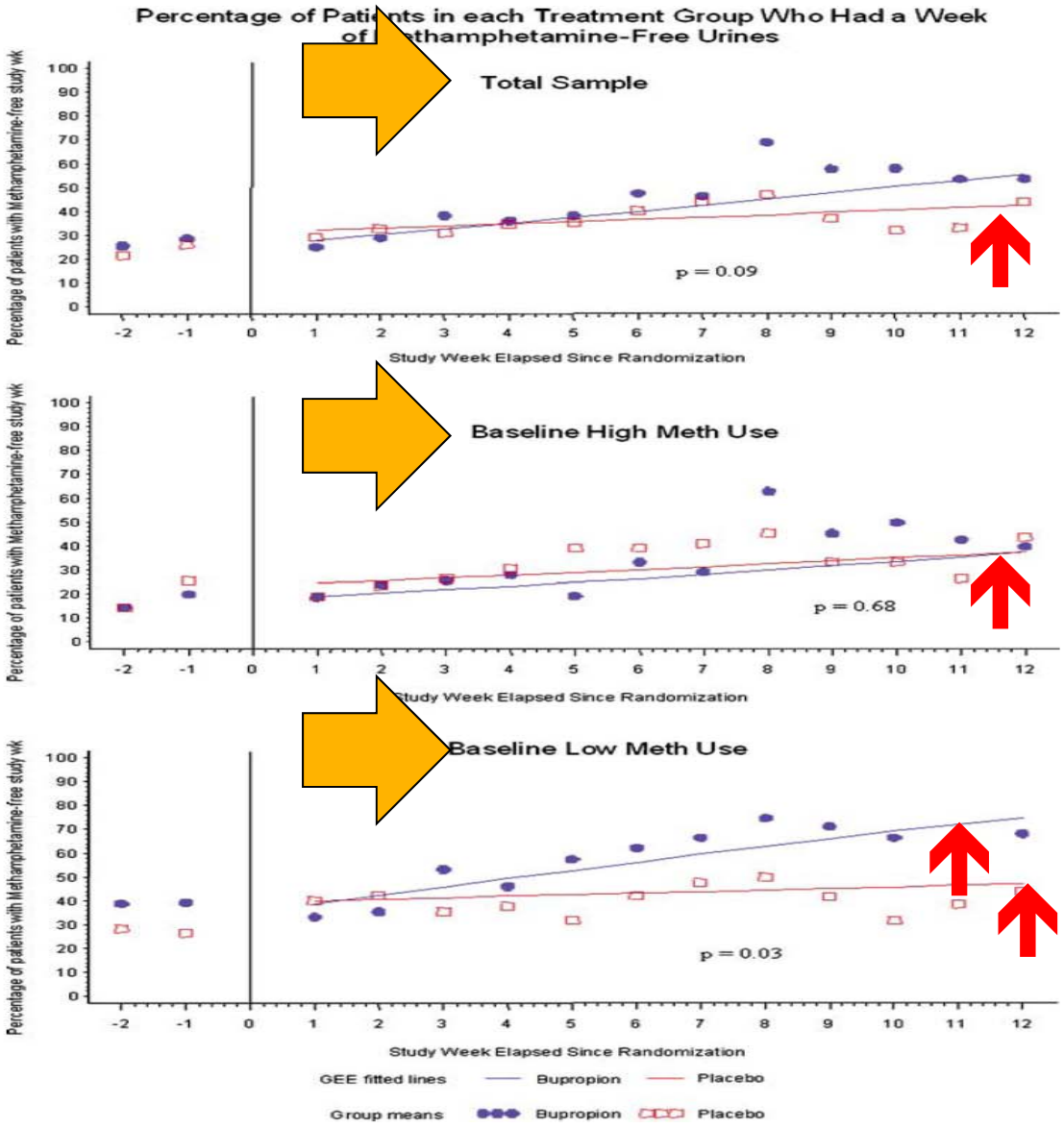
- Well tolerated
- Reduction in cocaine positive urines when combined with contingency management
- Unfortunately, second study not positive

Dopamine Enhancement Therapy for Cocaine Dependence

- Some evidence of reduction in cocaine use with several different medications
- Effect appears greatest when combined with contingency management
- Evidence for DA enhancement model in other stimulants?

Bupropion for Methamphetamine Dependence

- Bupropion antidepressant and weak dopamine reuptake inhibitor
- Depression significant problem in meth users
- Two studies have shown reduction in methamphetamine use in low to moderate users (Shoptaw et al., 2008, Elkashef et al., 2008).



(From Elkashef et al., 2009)

Bupropion for Methamphetamine

- Bupropion (150mg BID) showed reduction in meth use for low users (0-2 MA positive urines during 2- week screening, or < 19 days of use in last 30)
- Well tolerated without significant side effects
- There is a risk of seizures in patients treated with bupropion
- Results from secondary analysis, need to be confirmed in other studies

Controlled trials of Modafinil for Cocaine Dependence

A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence

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[1]University of Pennsylvania School of Medicine, Philadelphia, USA; [2]Department of Veterans Affairs Medical Center, Philadelphia, USA

Despite years of active research, there are still no approved medications for the treatment of cocaine dependence. Modafinil is a glutamate-enhancing agent that blunts cocaine euphoria under controlled conditions, and the current study assessed whether modafinil would improve clinical outcome in cocaine-dependent patients receiving standardized psychosocial treatment. This was a randomized, double-blind, placebo-controlled trial conducted at a university outpatient center (from 2002 to 2003) on a consecutive sample of 62 (predominantly African American) cocaine-dependent patients (aged 25–63) free of significant medical and psychiatric conditions. After screening, eligible patients were randomized to a single morning dose of modafinil (400 mg), or matching placebo tablets, for 8 weeks while receiving manual-guided, twice-weekly cognitive behavioral therapy. The primary efficacy measure was cocaine abstinence based on urine benzoylecgonine levels. Secondary measures were craving, cocaine withdrawal, retention, and adverse events. Modafinil-treated patients provided significantly more BE-negative urine samples ($p = 0.03$) over the 8-week trial when compared to placebos, and were more likely to achieve a protracted period ($\geqslant 3$ weeks) of cocaine abstinence ($p = 0.05$). There were no serious adverse events, and none of the patients failed to complete the study as a result of adverse events. This study provides preliminary evidence, which should be confirmed by a larger study, that modafinil improves clinical outcome when combined with psychosocial treatment for cocaine dependence.

Neuropsychopharmacology (2005) **30,** 205–211, advance online publication, 3 November 2004; doi:10.1038/sj.npp.1300600

Keywords: modafinil; cocaine; glutamate; pharmacotherapy; abstinence; addiction

Modafinil for Cocaine

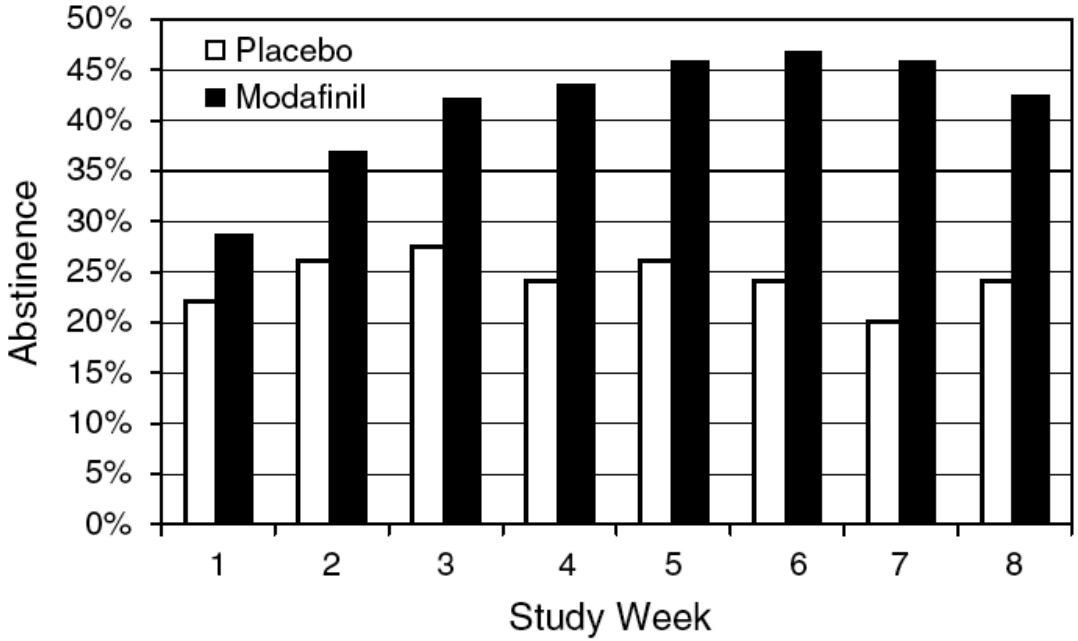

Figure 1 Weekly cocaine abstinence in modafinil and placebo groups, defined as the percentage of urine samples that were (1) submitted (requiring attendance), and (2) found to be BE-negative. Missing urines are therefore imputed as positive.

Dackis et al., 2005

Follow-up study with Modafinil

Modafinil for the treatment of cocaine dependence☆

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ABSTRACT

Aim: Modafinil was tested for efficacy in facilitating abstinence in cocaine-dependent patients, compared to placebo.
Methods: This was a double-blind placebo-controlled study, with 12 weeks of treatment and a 4-week follow-up. Six outpatient substance abuse treatment clinics participated in the study. There were 210 treatment-seekers randomized, having a diagnosis of cocaine dependence; 72 participants were randomized to placebo, 69 to modafinil 200 mg, and 69 to modafinil 400 mg, taken once daily on awakening. Participants came to the clinic three times per week for assessments and urine drug screens, and had one hour of individual psychotherapy weekly. The primary outcome measure was the weekly percentage of cocaine non-use days.
Results: The GEE regression analysis showed that for the total sample, there was no significant difference between either modafinil group and placebo in the change in average weekly percent of cocaine non-use days over the 12-week treatment period ($p > 0.79$). However, two secondary outcomes showed significant effects by modafinil 200 mg: the maximum number of consecutive non-use days for cocaine ($p = 0.02$), and a reduction in craving ($p = 0.04$). Also, a *post hoc* analysis showed a significant effect of modafinil that increased the weekly percentage of non-use days in the subgroup of those cocaine patients who did *not* have a history of alcohol dependence ($p < 0.02$).
Conclusions: These data suggest that modafinil, in combination with individual behavioral therapy, was effective for increasing cocaine non-use days in participants without co-morbid alcohol dependence, and in reducing cocaine craving.

Published by Elsevier Ireland Ltd.

Anderson et al., 2009

Modafinil for Cocaine Dependence

- Initial study showed reduction in cocaine positive urines
- Follow-up larger study negative overall
- Secondary analysis showed reduced cocaine use in single diagnosis cocaine users, not in dual diagnosis cocaine-alcohol users (needs to be confirmed)

Serotonin Reuptake Inhibitors and other Antidepressants for Cocaine Dependence

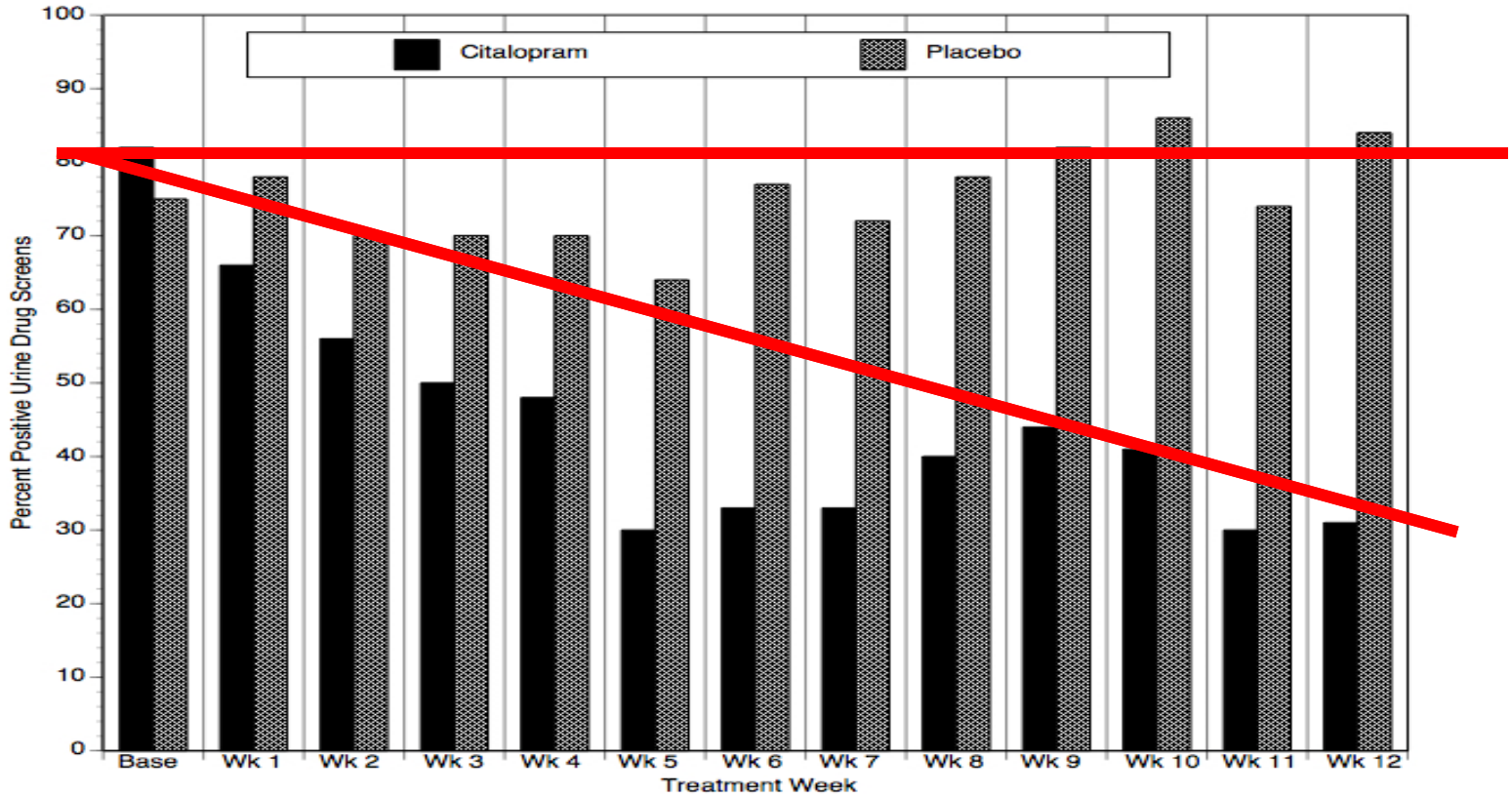
- Initial positive open label studies in 1990s
- Later double blind studies less successful
- SSRIs not generally effective
- Citalopram combined with behavioral therapy has been shown to reduce cocaine use

Citalopram plus Contingency Management for Cocaine Dependence

- 76 cocaine dependent subjects randomized to Citalopram 20 mg/day or placebo
- 12 Week double-blind trial
- All subjects receive contingency management in addition to pharmacotherapy
- Percentage of positive urine drug screens for benzoylecgonine and craving outcome measures

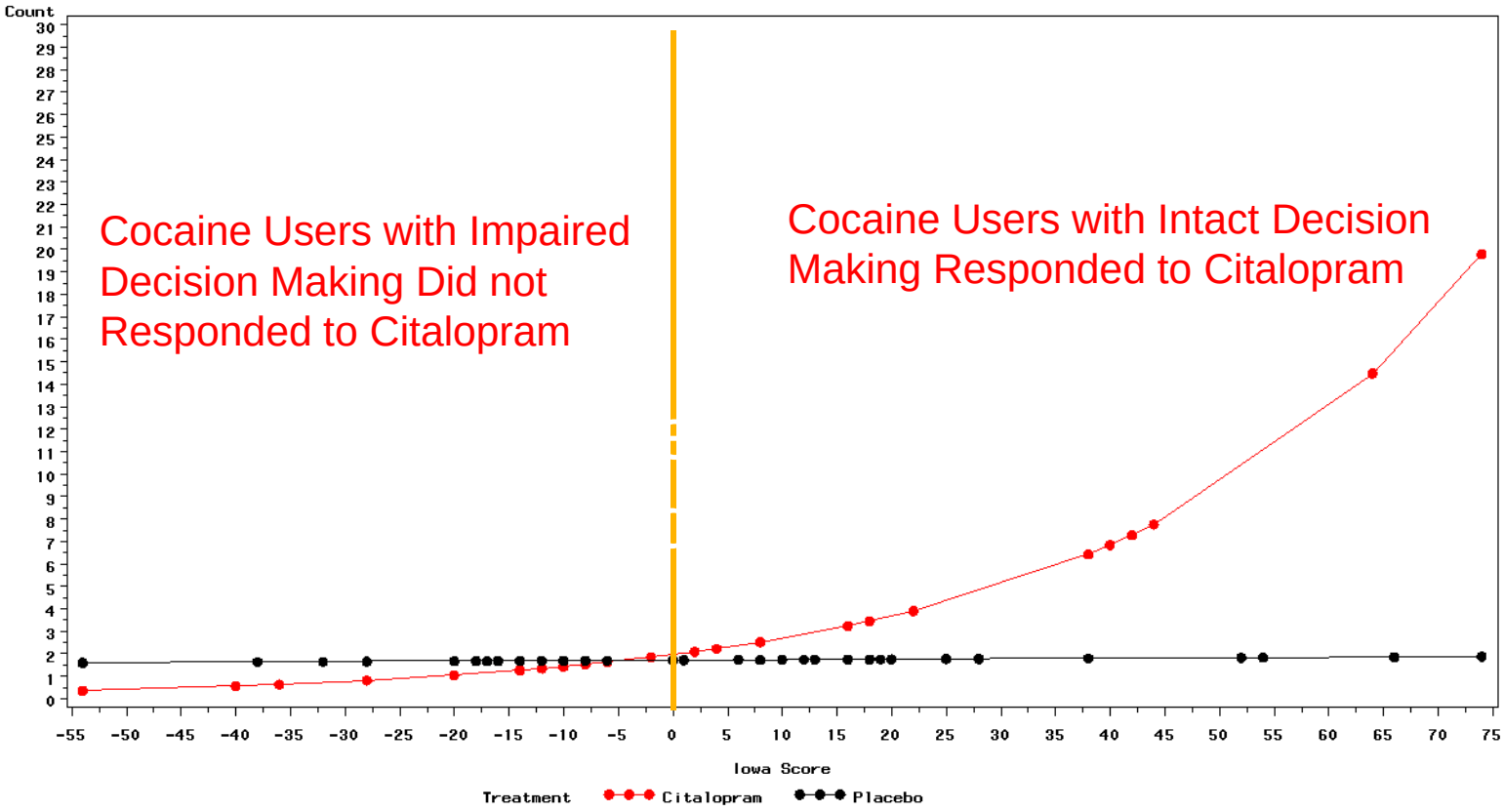
(Moeller et al., 2007)

Citalopram plus CM Significantly Reduced Cocaine Positive Urines



Percent Positive UDS By Week (Moeller et al., 2007)

Longest Estimated Consecutive Cocaine–Free Urines as Function of Baseline Iowa Scores



Simple Effects

Label	Risk Ratios	Standard Error	Alpha	Confidence Limits		Chi-Square	Pr > ChiSq
Iowa Score Under Placebo	1.0012	0.0097	0.05	0.9825	1.0205	0.02	0.8987
Iowa Score Under Citalopram	1.0317	0.0053	0.05	1.0213	1.0422	36.42	<.0001

(Green et al., 2009)

Citalopram for Cocaine Dependence

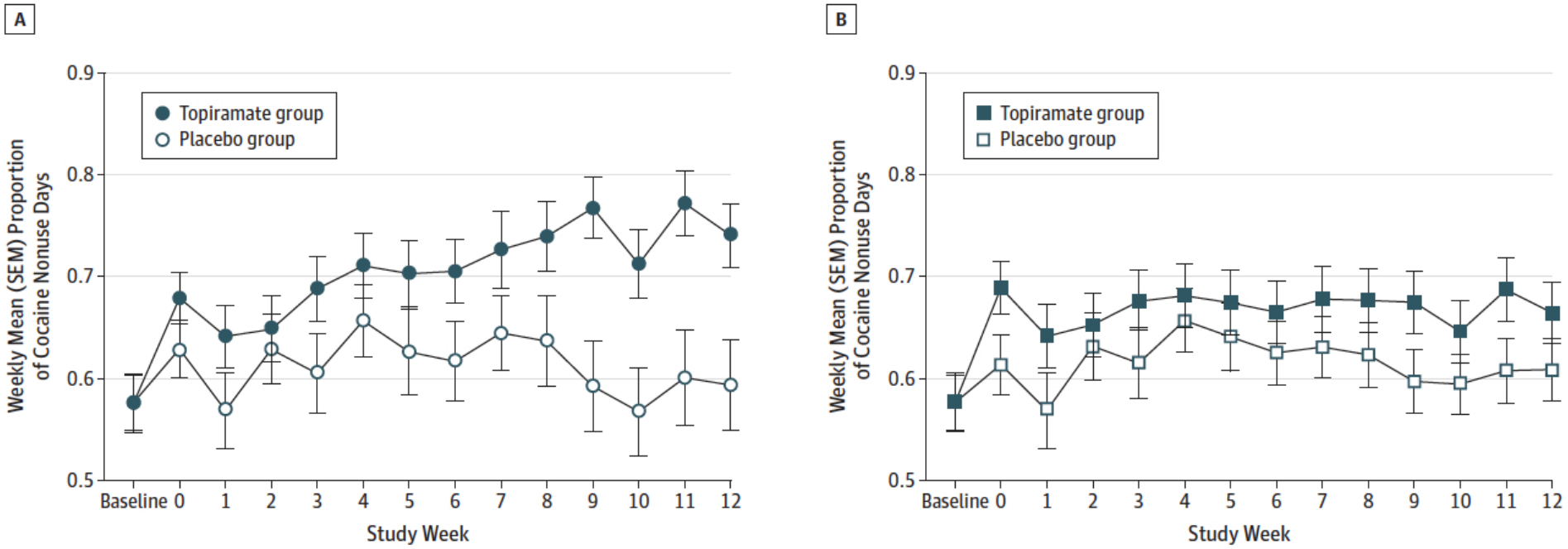
- Single site study positive for 20mg daily
- No significant adverse events
- Intact decision making as measured by Iowa Gambling Task predicts good response to citalopram
- Larger study negative

Topiramate

- Johnson et al., 2013 JAMA Psychiatry
- 12 week trial of topiramate 300mg vs. placebo plus CBT in 142 cocaine dependent subjects
- Titration of topiramate over 5 weeks

Topiramate

Figure 2. Weekly Mean Proportion of Cocaine Nonuse Days From Baseline Through Study Week 12



Without imputing missing data

With imputing missing data

From Johnson et al., 2013

Other studies not entirely positive with topiramate

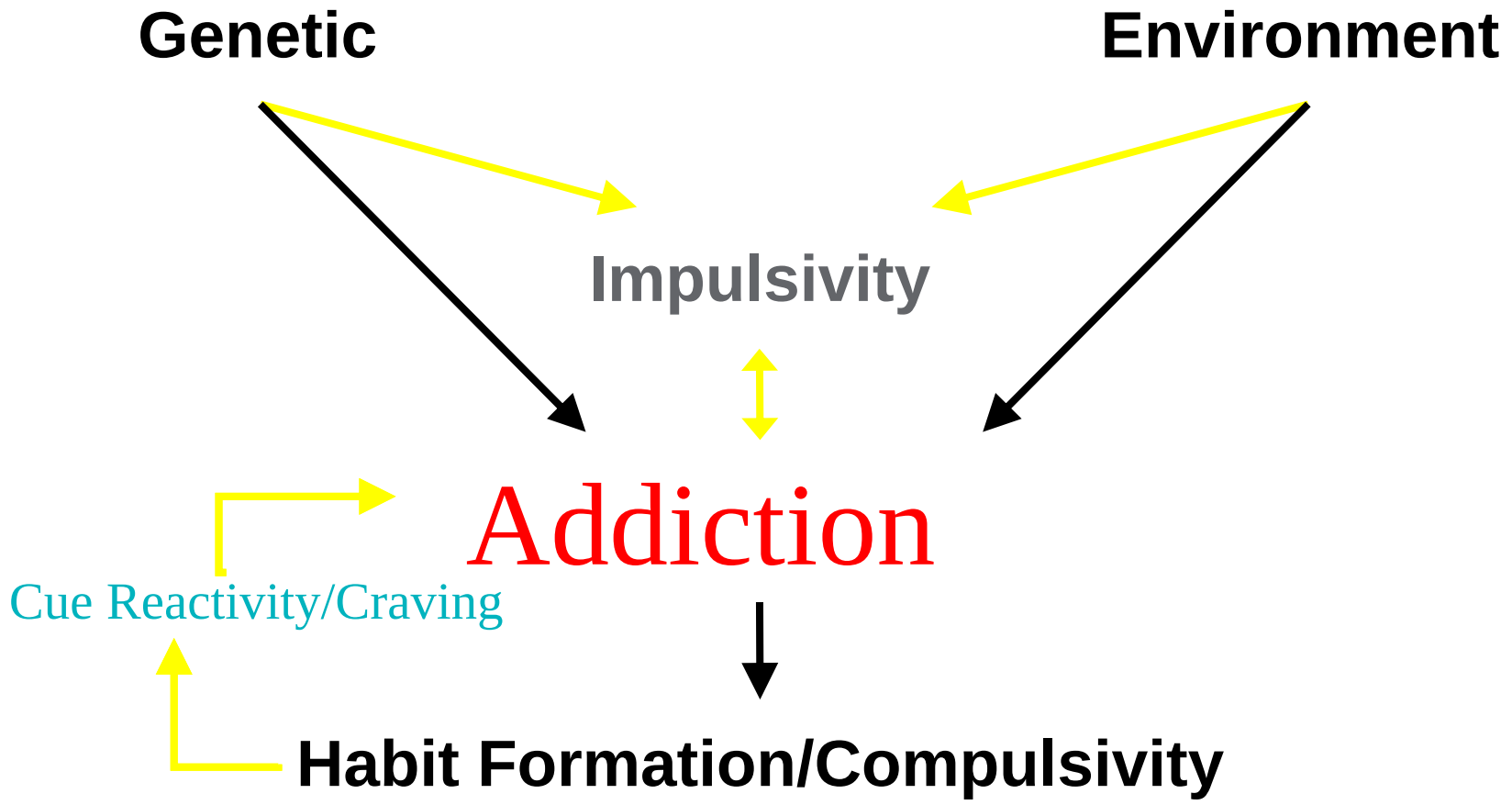
Kampman et al., 2013:

- Topiramate was not significantly better than placebo in preventing relapse (planned primary cocaine outcome),
- Significantly more topiramate than placebo-treated subjects achieved three weeks of continuous abstinence from cocaine at the end of the trial (20% vs. 7%)
- Subgroup analyses showed topiramate appeared to be more effective in patients with more severe cocaine withdrawal symptoms

Other Behavioral Targets Related to Drug Use

- Impulsivity and Drug Cue reactivity

The Cycle of Impulsivity/ Cue Reactivity and Addiction

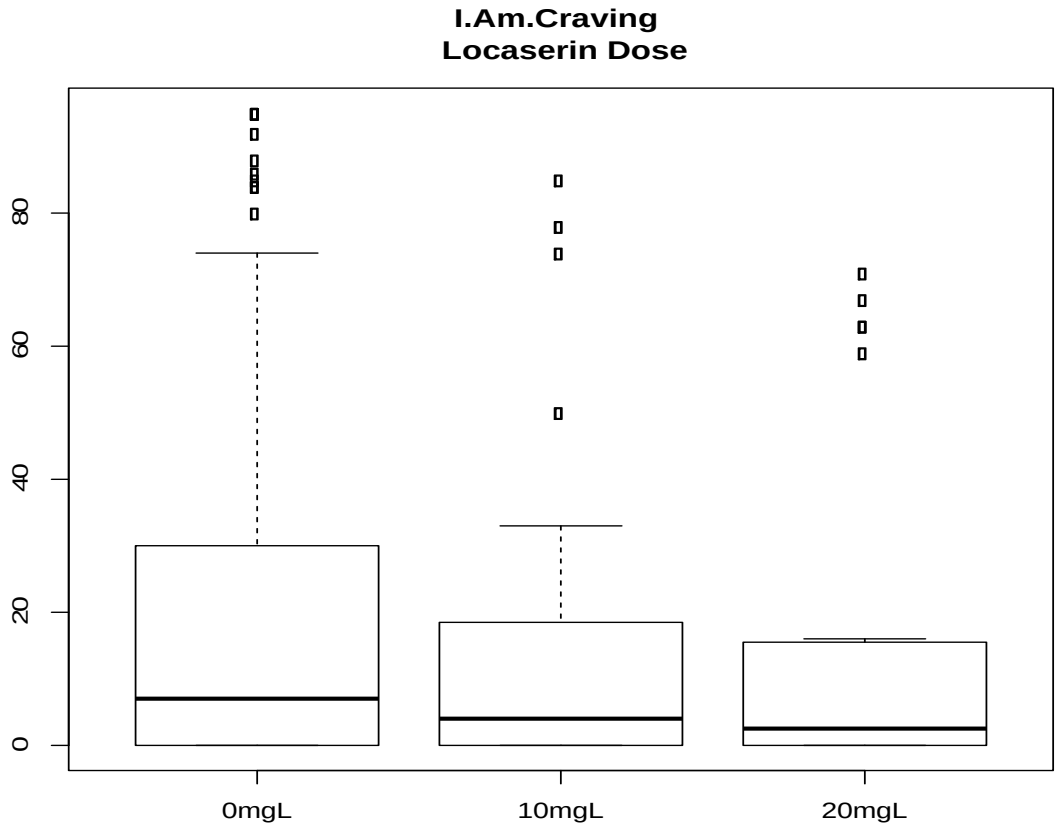


5-HT_{2C}R Agonists and Antagonists Effects on Impulsivity and Cocaine Self-Administration Preclinical Studies

5-HT Manipulation	Action	Impulsive Action	Cocaine Self-Administration		
			Reward	Reinstatement	
				Cue	Cocaine
Ro60-0175 WAY163909 MK 212	5-HT_{2C}R agonist	↓	↓	↓	↓
SB242084	5-HT_{2C}R antagonist	↑		↑/NE	↑
---	*5-HT_{2C}R knockdown in mPFC*	↑		↑	

From Cunningham and Anastasio, 2014

Preliminary Data Effect of Lorcaserin on Craving in Cocaine Users in Phase I study



Summary

- As of now, there are no FDA approved medications for stimulant use disorder
- Some medications have produced reductions in stimulant positive urines in subsets of patients with stimulant use disorder
- Larger trials have failed with most of these medications

Summary

- While medications may be of some benefit in some patients,
- Risks and benefits of medications for stimulant use disorder should be discussed with patients before starting medications
- Medication alone (without behavioral therapy) unlikely to be effective
- Since not FDA approved, some insurance companies may not cover costs of medications