Prescription Stimulants and Stimulant Use Disorder (StUD)

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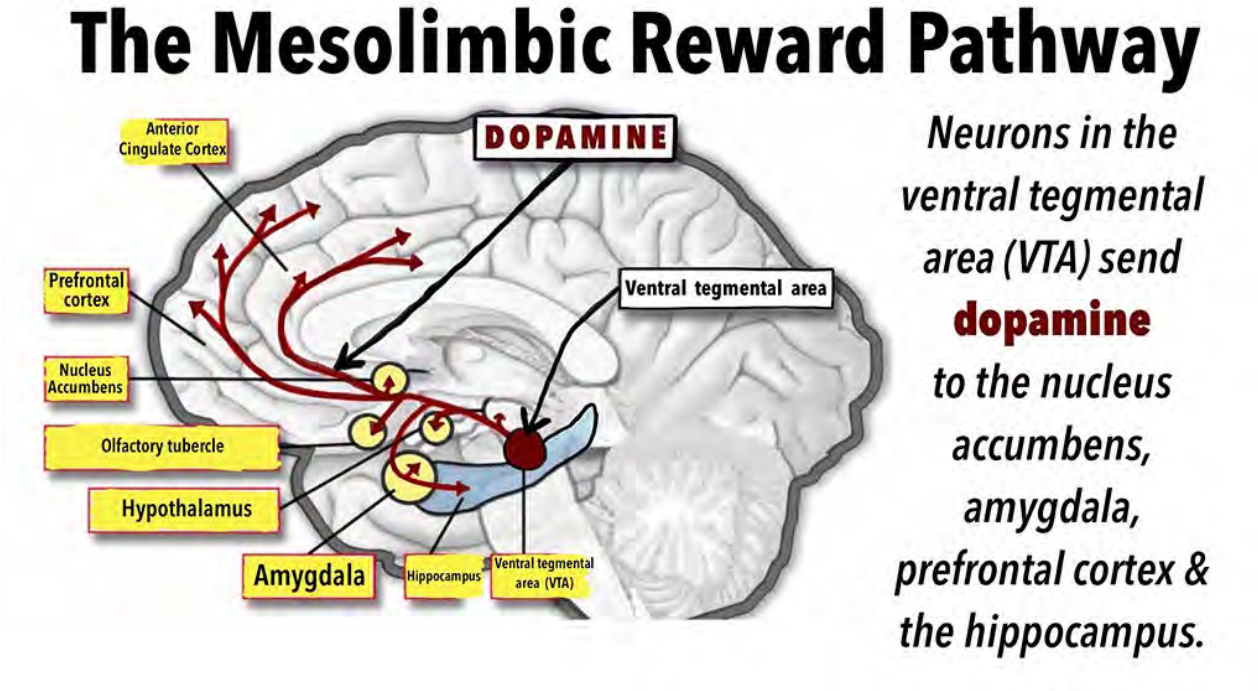
Learning Objectives

- Briefly review the pharmacology and neurobiology of stimulants
- Discuss the epidemiology of stimulant use and StUD in the U.S.
- Review pharmacological interventions studied for the treatment of StUD

Neural Pathways



Why is that pathway important ?

How much dopamine does an activity release?

Various activities cause the brain to release more dopamine than usual. Enjoying food brings a 50 percent boost to dopamine levels in the brain, for instance. Video games and sex also increase dopamine, and drug use does so significantly. It's not reasonable to equate the brain response to drug use with that of video games.

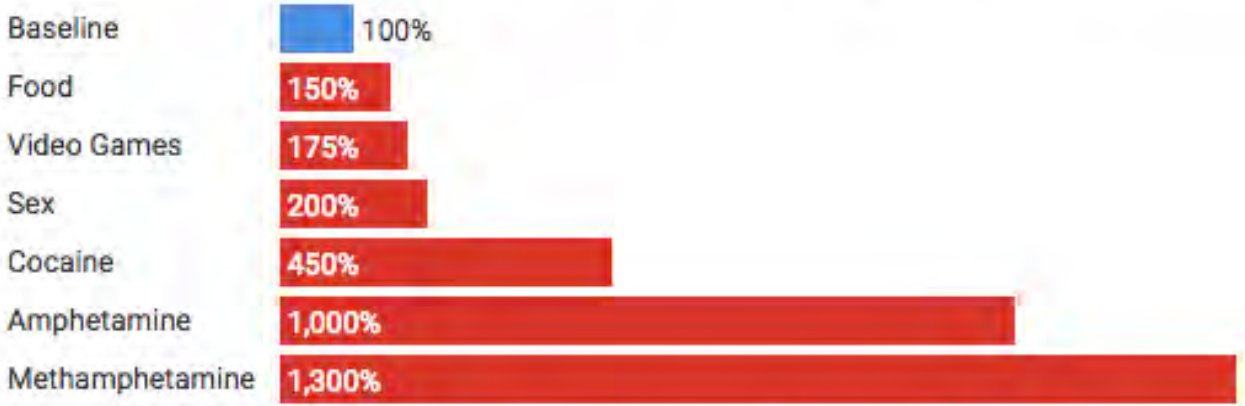
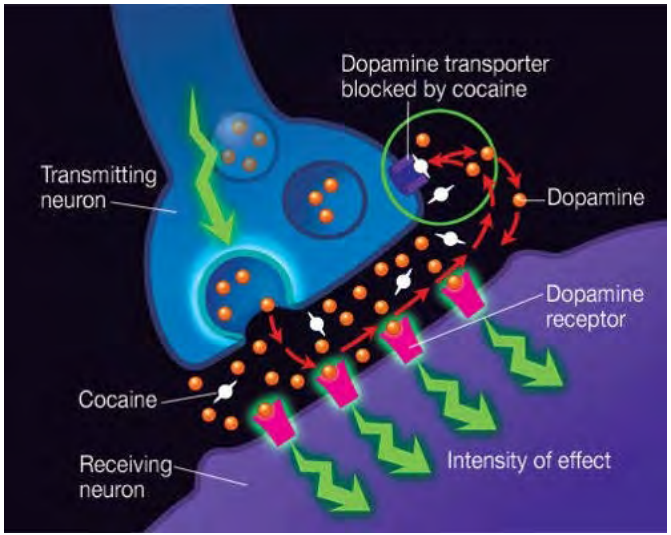


Chart: The Conversation, CC-BY-ND • Source: National Institute on Drug Abuse • Get the data

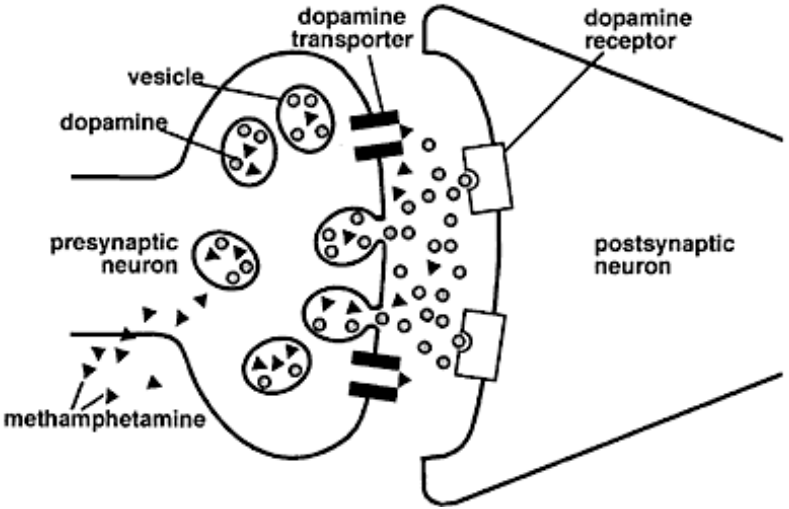
Cocaine vs. Amphetamines

Cocaine



Dopamine (and NE) Reuptake Inhibitor

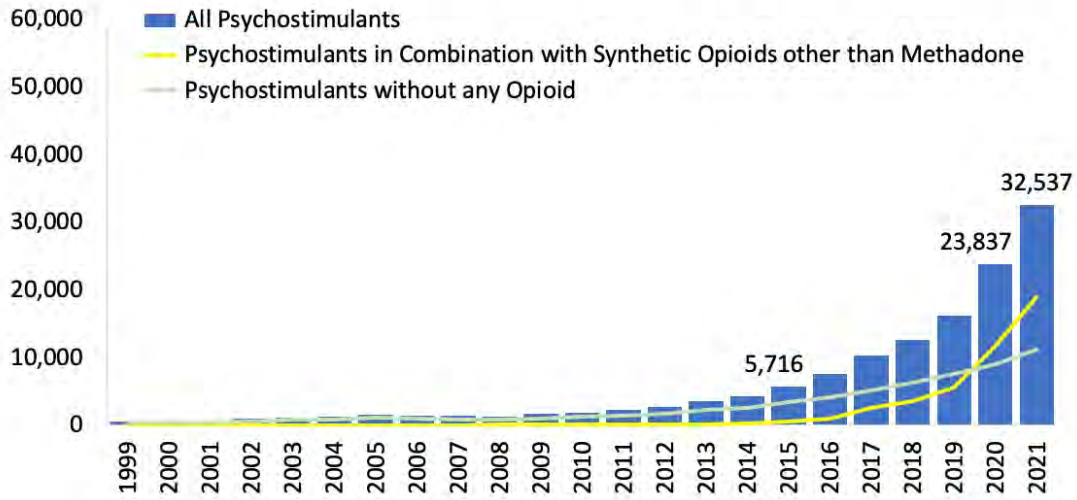
Amphetamines



Dopamine Excess

Mortality

Figure 7. National Overdose Deaths Involving Psychostimulants with Abuse Potential (Primarily Methamphetamine)*, by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

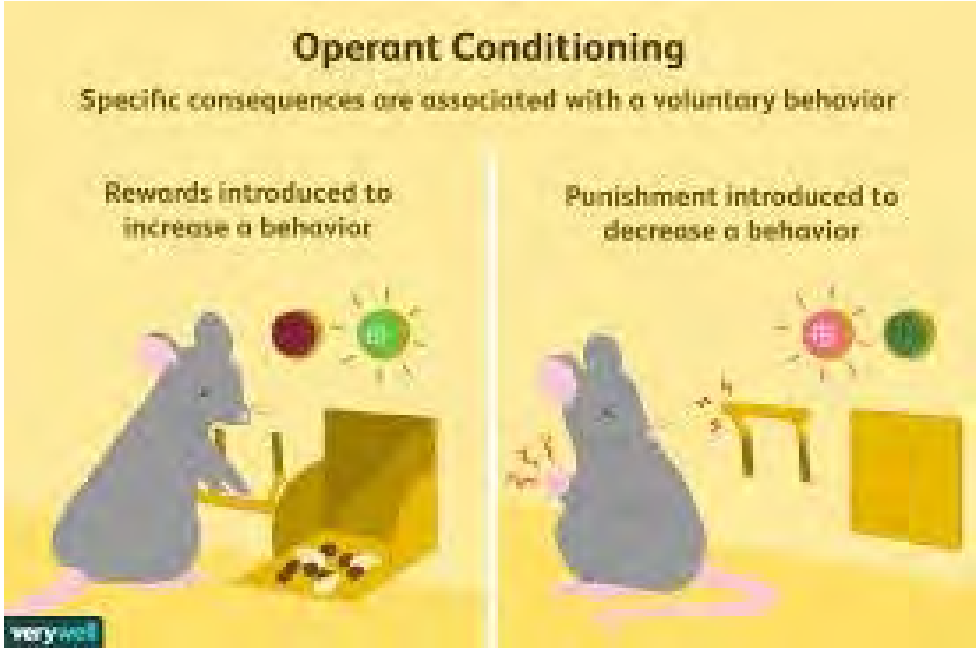
- Overdose
  - ~20x increase since 2001
  - Inflection point in 2011
- Cause of Overdose
  - With and without opioid approaching even split
  - Difficult treatment

Health Implications

- Cardiovascular disease
- Chronic vasoconstriction
  - Part of “meth mouth” paradigm
  - Also frequent cause of ED in men (“crystal di**)
- Malnutrition and miscarriage in pregnancy
- Increased risk of:
  - Cigarette smoking
  - Psychiatric disorders (induced or underlying)
  - Acquiring and transmission of sexually transmitted infections
- All the usual complications of IV Use
  - Note: IV complications are not inherent to IV use; it’s *lack of sterile equipment*

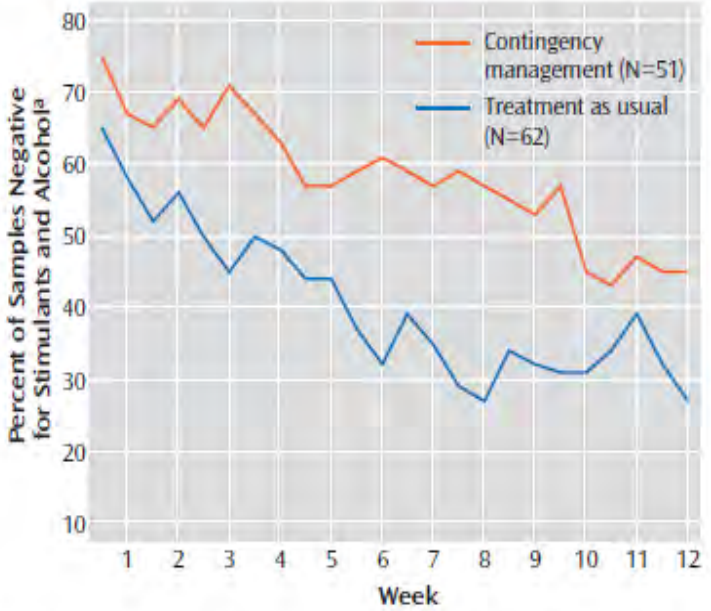
Contingency Management

- Works on the theory that Drug use is an **operant** behavior.



Contingency Management

FIGURE 2. Negative Drug Samples[a] Over 12 Weeks for Patients With Methamphetamine Use Disorders Receiving Usual Treatment With or Without Contingency Management



[a] Urine samples were tested for cocaine, amphetamine, and methamphetamine. Alcohol was sampled by breath tests.

Roll et al, Am J Psychiatry, 2006

Treatment (Cocaine)

- 2016 Cochrane Review (*Castellanos et alia)*[18]
  - Psychostimulants showed benefit in terms of sustained abstinence (RR=1.36)
  - **Bupropion** alone (RR=1.63)

Analysis 2.2. Comparison 2 Subgroup analysis: type of drug, Outcome 2 Sustained cocaine abstinence.

Review: Psychostimulant drugs for cocaine dependence

Comparison: 2 Subgroup analysis type of drug

Outcome: 2 Sustained cocaine abstinence

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Bupropion					
Poling 2006	13/30	6/24		7.3 %	1.73 [0.78, 3.88]
Poling 2006	15/27	9/25		10.2 %	1.54 [0.83, 2.87]
Shoptaw 2008	6/37	3/33		3.4 %	1.78 [0.48, 6.57]
Subtotal (95% CI)	**94**	**82**		**20.8 %**	**1.63 [1.03, 2.59]**
Total events: 34 (Psychostimulants), 18 (Placebo)					

Agonist Treatment (Cocaine)[20]

Randomized Controlled Trial > Drug Alcohol Depend. 2009 Apr 1;101(1-2):34-41.
doi: 10.1016/j.drugalcdep.2008.10.016. Epub 2008 Dec 5.

Effects of oral methamphetamine on cocaine use: a randomized, double-blind, placebo-controlled trial

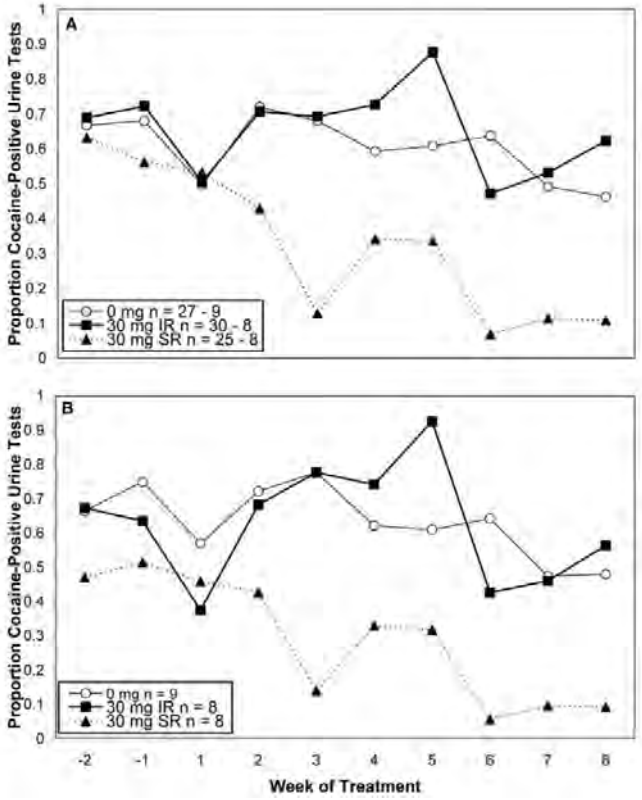
Marc E Mooney [1], David V Herin, Joy M Schmitz, Nidal Moukaddam, Charles E Green, John Grabowski

Affiliations + expand

PMID: 19058926 PMCID: PMC2742691 DOI: 10.1016/j.drugalcdep.2008.10.016
Free PMC article

Results: Both preparation forms of methamphetamine were well-tolerated, with similar retention to placebo (0mg, 33%; 30 mg IR, 30%, 30 mg SR, 32%). Methamphetamine SR was associated with decreased sleep and increased weight loss. Medication adherence rates were high for the first dose of the day (95%), while adherence for subsequent capsules was lower. Those in the SR condition exhibited consistently lower rates of cocaine-positive urine samples (0mg, 60%; 30 mg IR, 66%; 30 mg SR, 29%), $p<0.0001$, and reported the greatest reduction in craving for cocaine, $p<0.05$.

Conclusions: SR methamphetamine significantly reduced cocaine use and craving. Additional research is warranted to develop and evaluate agonist-like medications that may effectively treat cocaine dependence.



Agonist Treatment (Cocaine)[21]

Randomized Controlled Trial > JAMA Psychiatry. 2015 Jun;72(6):593-602.
doi: 10.1001/jamapsychiatry.2015.41.

Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial

Frances R Levin [1], John J Mariani [1], Sheila Specker [2], Marc Mooney [2], Amy Mahony [3], Daniel J Brooks [3], David Babb [2], Yun Bai [4], Lynn E Eberly [4], Edward V Nunes [1], John Grabowski [2]

Affiliations + expand

PMID: 25887096 PMCID: PMC4456227 DOI: 10.1001/jamapsychiatry.2015.41

- Cocaine Use Disorder + ADHD
- Outcomes
  - 30% or greater ADHD symptom reduction
  - Consistent urine toxicology
- MAS-XR group outperformed placebo

Conclusions and relevance: Extended-release mixed amphetamine salts in robust doses along with cognitive behavioral therapy are effective for treatment of co-occurring ADHD and cocaine use disorder, both improving ADHD symptoms and reducing cocaine use. The data suggest the importance of screening and treatment of ADHD in adults presenting with cocaine use disorder.

Treatment (Methamphetamine)[24]

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

Madhukar H. Trivedi, M.D., Robrina Walker, Ph.D., Walter Ling, M.D., Adriane dela Cruz, M.D., Ph.D., Gaurav Sharma, Ph.D., Thomas Carmody, Ph.D., Udi E. Ghitza, Ph.D., Aimee Wahle, M.S., Mora Kim, M.P.H., Kathy Shores-Wilson, Ph.D., Steven Sparenborg, Ph.D., Phillip Coffin, M.D., M.I.A., et al.

Article Figures/Media Metrics

January 14, 2021
N Engl J Med 2021; 384:140-153
DOI: 10.1056/NEJMoa2020214

29 References 10 Citing Articles

RESULTS

A total of 403 participants were enrolled in stage 1, and 225 in stage 2. In the first stage, 18 of 109 participants (16.5%) in the naltrexone–bupropion group and 10 of 294 (3.4%) in the placebo group had a response. In the second stage, 13 of 114 (11.4%) in the naltrexone–bupropion group and 2 of 111 (1.8%) in the placebo group had a response. The weighted average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1 percentage points (Wald z-test statistic, 4.53; P<0.001). Adverse events with naltrexone–bupropion included gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia. Serious adverse events occurred in 8 of 223 participants (3.6%) who received naltrexone–bupropion during the trial.

CONCLUSIONS

Among adults with methamphetamine use disorder, the response over a period of 12 weeks among participants who received extended-release injectable naltrexone plus oral extended-release bupropion was low but was higher than that among participants who received placebo. (Funded by the National Institute on Drug Abuse and others; ADAPT-2 ClinicalTrials.gov number, NCT03078075.)

Pharmacotherapy Systematic Review (*Siefried et alia 2020*)[26]

Meta-Analysis > CNS Drugs. 2020 Apr;34(4):337-365. doi: 10.1007/s40263-020-00711-x.

Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review

Krista J Siefried [1 2 3], Liam S Acheson [4], Nicholas Lintzeris [5 6 7], Nadine Ezard [8 4 9 7]

Affiliations + expand

PMID: 32185696 PMCID: PMC7125061 DOI: 10.1007/s40263-020-00711-x

Free PMC article

- 43 studies with 23 medication/med combinations
- Could not perform meta-analysis due to heterogeneity of studies

- Most consistently effective:
  - **stimulant agonist treatment (dexamphetamine and methylphenidate), naltrexone and topiramate**
- Less consistent:
  - Bupropion
  - Mirtazapine
  - Riluzole (glutamatergic)
  - Pexacerfont (CRF-1 antagonist)
- Not effective:
  - SSRI/SNRI
  - TCA

Summary/ How to use in Pregnancy

- **What generally *doesn't* work**
  - Antidepressants
  - Anticonvulsants
  - Antipsychotics
  - Monoamine agonists
- **What has *promise***
  - Bupropion
  - Topiramate
  - Modafanil
  - Psychostimulants

What can we do *today* with (relatively) low barriers?

Bupropion
- Screen for seizure history

LAI naltrexone
- Not w/ agonist OUD therapy

Topiramate
- Previously Cat. D in pregnancy

Contingency Management
- availability

CBT

- **Disclaimers in Pregnancy:**
  - **The evidence for StUD presented here was not adequately studied in pregnant patients.**
  - **Any medication above, particularly topiramate or modafinil, would require serious risk discussions as first trimester malformations are associated with these medications, while the harm reduction of stopping illicit stimulants is beneficial.**
  - **Breast feeding safety for these medications should also be discussed with patients.**

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