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Session Date: Friday, July 19, 2024

Didactic Topic and Presenter:
Stimulant Use Disorder – Review of ASAM Management Guidelines

David Leinweber, MD
Content Experts: Sheila Weix and Joe Galey

- 12:15 PM: Attendance text-in – Introductions
- 12:25 PM: Case Presentation
    - Presenter: Thomas Hahn, MD – UW Health
- 1 PM: Didactic Presentation and Discussion
    - Presenter: David Leinweber, MD
- 1:15 PM End of Session

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Interprofessional Continuing Education Partnership
UNIVERSITY OF WISCONSIN-MADISON
School of Medicine and Public Health
School of Nursing
School of Pharmacy

Project ECHO
University of Wisconsin

ECHO ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics
2024-2025
Review of medications to treat stimulant use disorder
7/19/2024

Didactic Presenter: David Leinweber, MD
Case Presenter: Thomas Hahn, MD

Provided by the University of Wisconsin–Madison Interprofessional Continuing Education Partnership (ICEP)

Intended Audience:

Nurses, Nurse Practitioners, Pharmacists, Physicians, Physician Assistants, Pharmacy Technicians, Psychologists, Social Workers, Patient/Caregivers, Students

Objectives:

As a result of this educational regularly scheduled series, learners as members of the healthcare team will be able to:

1. Identify the difference in mechanism of action between methamphetamine and cocaine
2. Discuss off label medications which have shown benefit in the treatment of cocaine use disorder
3. Discuss the off label medications which have shown benefit in the treatment of methamphetamine use disorder

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Name	Role	Financial Relationship Disclosures	Discussion of Unlabeled/Unapproved uses of drugs/devices in presentation?	COI completion date
Randall Brown	RSS Chair	Usona Institute (Grant / Contract), multi-disciplinary association for psychedelic studies (Grant / Contract)	Yes	1/29/2024
Nada Rashid	RSS Coordinator	No relevant financial relationships to disclose	No	2/5/2024
Kathleen Maher	RSS Coordinator	No relevant financial relationships to disclose	No	2/6/2024
Ritu Bhatnagar	Planner	No relevant financial relationships to disclose	Yes	2/8/2024
Paul Hutson	Planner	No relevant financial relationships to disclose	Yes	1/29/2024
Susan Mindock	Planner	No relevant financial relationships to disclose	No	1/29/2024
Sheila Weix	Planner	No relevant financial relationships to disclose	No	2/9/2024
Kellene Eagen	Planner	No relevant financial relationships to disclose	No	1/29/2024
Joseph Galey	Planner	No relevant financial relationships to disclose	No	2/13/2024
David Leinweber	Planner	No relevant financial relationships to disclose	Yes	1/20/2024
Thomas Hahn	Presenter	No relevant financial relationships to disclose	No	7/7/2024
David Leinweber	Presenter	No relevant financial relationships to disclose	Yes	7/5/2024

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This session is designed to meet the requirements outlined in the Medication Access and Training Expansion (MATE) Act. (Click here for more information.) Number of hours: 1

Opioid Use Disorder: Role of Oral Naltrexone for Treatment and Impact of Buprenorphine on Commercial Drivers' Licenses in WI

Thomas Hahn, MD

UW Health

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For this educational activity there are no reported conflicts of interest

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Case Introduction

- One-liner (including age/sex): 31 year old male with history of opioid use disorder (OUD), alcohol use disorder, ADHD, and depression who presented for treatment for OUD.

- Primary question for discussion:
  - Primary question: Where does oral naltrexone fit into treatment of opioid use disorder?
  - Secondary question: What are rules in WI regarding buprenorphine use and commercial driver's licenses?

Medical & Behavioral Health Diagnosis:	Current Medications:
• Opioid use disorder • Alcohol use disorder • Depression – suicide attempt at age 14 • ADHD – diagnosed in 2nd grade. On stimulants as a child but stopped at age 17. Interested in starting medication for ADHD. • Nicotine dependence – vape 5% nicotine	• Naltrexone PO 50 mg • Atomoxetine 40 mg

Substance Use

- History: 7 years of opioid use. Uses oxycodone and started after he was prescribed it for an injury. Most recently on 50-60 mg daily of oxycodone.
- Consequences of Substance Use:
  - Social/occupational/educational: Wife is concerned about his use.
  - Physical (including evidence of tolerance/withdrawal): No significant withdrawal
- Past treatments: Was on oral naltrexone and this helped him be off oxycodone for 1 year. Did intensive outpatient therapy in past 6 months. Has a therapist.

Social History:	Family History:
• Social Factors/History: Lives with wife and family • Education/Literacy: Unsure • Income source: Full time job in construction	• Father died of alcoholism when patient was 10

Patient strengths & protective factors:	Risk factors:
• Good family support with wife and child • Full time job in construction	• Access to people who sell oxycodone •

Labs

- None

Patient Goals & Motivations for Treatment

- Wants to be off opioids for his family
- Doesn't want to be dependent on an opioid (like buprenorphine)
- Wants to keep his job and CDL (concerned about impact of buprenorphine on CDL)
- Wants to avoid opioid cravings and notices this is worse if he misses PO naltrexone for a 2-3 days
- Wants to avoid high cost of med (worried about cost with IM naltrexone)

Proposed Diagnoses

- Opioid use disorder
- ADHD

Proposed Treatment Plan

- Started on PO naltrexone for dual benefit of OUD and alcohol use.
- After 5 months he had significantly decreased opioid use and had only used oxycodone 10 days in 5 months
- Not interested in buprenorphine due to dependence
- Interested in IM naltrexone due to avoid missing doses of PO naltrexone but worried about the cost

Discussion

- Primary question: What is the role of oral naltrexone in opioid use disorder?
- Secondary question: Buprenorphine and implications for commercial driver's license

DSM-5 Substance Use Disorder ("Addiction")

- Tolerance
- Withdrawal

} **Physical Dependence ≠ Use Disorder**

- Larger amts/longer periods than intended
- Persistent desire/failed attempts to quit/control use
- Much time obtaining/using/recovering
- Important activities sacrificed
- Continued use despite known adverse effects
- Failure to fulfill major obligations
- Recurrent hazardous use
- Craving
- Ongoing use despite interpersonal problems

2-3 = mild
4-5 = moderate
≥ 6 = severe

Stimulant Use Disorder – Review of ASAM Management Guidelines

David Leinweber, MD, MS

Disclosures

- David Leinweber has no relevant financial relationships with ineligible companies to disclose.

- The speaker does intend to discuss any unlabeled/unapproved uses of drugs/devices in the presentation.

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Types of stimulants

- Cocaine
  - Alkaloid that occurs in the leaves of coca bush may be processed to produce cocaine paste. Cocaine can be converted to a salt form (powder) by mixing with acid.
    - Effect duration ~20-30 minutes
- Methamphetamine – first synthesized from ephedrine in 1893
  - Effect duration ~2-7 hours
- 3,4-Methylenedioxymethamphetamine(MDMA)(aka ecstasy or molly) – first synthesized in 1912
- Prescription stimulants
  - Prescribed for attention deficit hyperactivity disorder, narcolepsy, weight loss
- Khat
  - Derived from Catha edulis plant which is native to East Africa.
- Ephedra
  - Ephedrine and pseudoephedrine are found in several Ephedraceae plant species

United Nations Office on Drugs and Crime. "Treatment of stimulant use disorders: current practices and promising perspectives." (2019).

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Neurobiology

- All stimulants act to enhance the extracellular concentrations of monoamine neurotransmitters (serotonin, catecholamines – dopamine, adrenaline and noradrenaline) [1]

TABLE 10-4 NEUROPHARMACOLOGIC ACTIONS OF SELECTED STIMULANTS

	CATECHOLAMINE		SEROTONIN			
	TRANSPORTER BLOCKER	TRANSPORTER SUBSTRATE (RELEASER)	TRANSPORTER BLOCKER	TRANSPORTER SUBSTRATE (RELEASER)	MAO INHIBITION	NA CHANNEL BLOCKER
Amphetamine	++	+++	0	+	+	0
Cocaine	+++	0	+++	0	0	+++
Ephedrine[a]	+	++	0	0	0	0
Mazindol	+++	0	+	0	0	0
Methamphetamine	++	+++	+	++	+	0
Methylphenidate	+++	0	+	0	0	0
Phentermine	+	++	0	0	+	0

[a]Also a direct agonist at adrenergic (norepinephrine) receptors.

MAO, monoamine oxidase; 0, no effect; +, marginal effect; + +, substantial effect; + + +, predominant effect.

Based on data from Rothman RB, Baumann MH, Dersch CM, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 2001;39:32–41 (256); Howell LL, Kimmel HL. Monoamine transporters and psychostimulant addiction. *Biochem Pharmacol* 2008;75:196–217 (219).

Transport Blockers – aka reuptake inhibitors

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1. Ries, Richard K., et al. *The ASAM principles of addiction medicine*. Lippincott Williams & Wilkins, 2014.

Treatment for stimulant use disorder

- No FDA approved medication for stimulant use disorder [1]
- Limitation of meta-analysis of studies [1]
  - Lack of standardized outcomes
  - Majority of literature is focused on cocaine use disorder
  - Primary outcomes tend to be abstinence
  - Length of study time period
- Further research still needs to be conducted

1. Ronsley, Claire, et al. "Treatment of stimulant use disorder: a systematic review of reviews." *PloS one* 15.6 (2020): e0234809.
2. Chan, Brian, et al. "Pharmacotherapy for cocaine use disorder—a systematic review and meta-analysis." *Journal of general internal medicine* 34.12 (2019): 2858-2873.

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Treatment for Cocaine Use Disorder

- Topiramate
  - 13 week, double-blind, placebo-controlled trail with 170 participants with cocaine and alcohol use who received either topiramate 300 mg daily or placebo. [1]
    - Patients were more likely to be retained in treatment and more likely to be abstinent from cocaine during the last 3 weeks of the trial (20% topiramate group vs 7% placebo group). [1]
  - Data is still limited and further study of topiramate is needed to determine benefit [3]
  - ASAM statement – may consider use to reduce cocaine use, consider in patients with co-occurring alcohol use disorder.

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1. Kampman, Kyle M., et al. "A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence." *Drug and alcohol dependence* 133.1 (2013): 94-99.
2. Ronsley, Claire, et al. "Treatment of stimulant use disorder: a systematic review of reviews." *PloS one* 15.6 (2020): e0234809.
3. Chan, Brian, et al. "Pharmacotherapy for cocaine use disorder—a systematic review and meta-analysis." *Journal of general internal medicine* 34.12 (2019): 2858-2873
4. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

Treatment for Cocaine Use Disorder

- Bupropion
  - 16 week, Double-blind, placebo controlled randomized trial of CBT with bupropion vs placebo among 70 participants with chronic cocaine use [2]
    - There was no statistically significant differences between bupropion and placebo at the end of treatment or on treatment retention [2]
  - 25 week, Double-Blind, placebo controlled RCT of contingency management (CM) and placebo vs CM and bupropion vs voucher control and placebo vs voucher control and bupropion among 106 participants with opioid use disorder tx with methadone and cocaine use
    - Contingency management and bupropion group cocaine-positive urine samples decreased during weeks 3 to 13 ($P<0.001$)
  - ASAM statement - "potential benefits of bupropion outweigh the potential risks"
    - Consider in patients with co-occurring tobacco use to reduce tobacco use s
    - Consider in patients with co-occurring depression

1. Shoptaw, Steven, et al. "Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence." *Drug and alcohol dependence* 96.3 (2008): 222-232.
2. Shoptaw, Steve, et al. "Bupropion hydrochloride versus placebo, in combination with cognitive behavioral therapy, for the treatment of cocaine abuse/dependence." *Journal of Addictive Diseases* 27.1 (2008): 13-23.
3. Poling, James, et al. "Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population." *Archives of general psychiatry* 63.2 (2006): 219-228.
4. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

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Treatment for Amphetamine Use Disorder

- Bupropion
  - 12 week, Double-blind, placebo controlled randomized trial of 150 mg bupropion sustained release BID vs placebo among 73 treatment seeking methamphetamine dependent participants. Urine drug screens were performed 3 times per weeks. [1]
    - No statistically significant findings for bupropion compared to placebo for reduction of methamphetamine cravings, reducing severity of depressive symptoms, or positive urine drug screens. [1]
    - Post hoc analysis demonstrated reduced methamphetamine use among light users (0-2 methamphetamine positive urines at baseline) compared to heavy users (3-6 methamphetamine positive urines at baseline) ($p<0.001$, 95% CI 1.61-4.93)[1]
  - ASAM statement– consider in amphetamine use disorder with low to moderate frequency of use or if co-occurring tobacco use disorder

1. Shoptaw, Steven, et al. "Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence." *Drug and alcohol dependence* 96.3 (2008): 222-232.
2. Shoptaw, Steve, et al. "Bupropion hydrochloride versus placebo, in combination with cognitive behavioral therapy, for the treatment of cocaine abuse/dependence." *Journal of Addictive Diseases* 27.1 (2008): 13-23.
3. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

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Treatment for Amphetamine Use Disorder

- Naltrexone and Bupropion [1]
  - Multisite, double blind, two stage, placebo-controlled trial of extended-release naltrexone (380 mg q3weeks) and oral extended-release bupropion (450 mg daily), length of trial 12 weeks
  - 403 participants with moderate or severe methamphetamine use disorder
  - Primary outcome was at least 3 methamphetamine-negative urine samples out of 4 samples obtained in last 2 weeks of each stage
  - Overall weighted response was 13.6% in treatment group compared to 2.5% in placebo group
    - Stage 1 (week 5-6): 16.5% (treatment group) vs 3.4% (placebo group) had a response
    - Stage 2 (weeks 11-12): 11.4% (treatment group) vs 1.8% (placebo group) had a response
  - Number needed to treat was 9
- ASAM statement – consider prescribing together to reduce use. May consider as well in patients with co-occurring alcohol use disorder and/or tobacco use disorder.

1. Trivedi, Madhukar H., et al. "Bupropion and naltrexone in methamphetamine use disorder." *New England Journal of Medicine* 384.2 (2021): 140-153.
2. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

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Treatment for Amphetamine Use Disorder

- Mirtazapine
  - 12 week, Double-blind, placebo controlled randomized trial of mirtazapine (30 mg once daily) or placebo among 60 men who have sex with men with methamphetamine use disorder demonstrated reduction in use[1][4]
    - Participants receiving mirtazapine had fewer methamphetamine-positive urine samples at 12 weeks (RR = 0.55 (95% CI, 0.35-0.93), P=0.02) [4]
      - Urine positivity decreased from 73% to 44% in mirtazapine arm and 67% to 63% in placebo arm at 12 weeks
  - 24 week, Double-blind, placebo controlled randomized trial of mirtazapine (30 mg once daily) or placebo among 120 cisgender men and transgender women who have sex with men with methamphetamine use disorder demonstrated reduction in use [3]
    - Participants receiving mirtazapine had fewer methamphetamine-positive urine samples at 24 weeks (RR=0.75,P=0.05) and 36 weeks (RR = 0.73,(95% CI, 0.57=-.96), P=0.02) [3]
      - Urine positivity decreased from 85% to 63% in mirtazapine arm and 75% to 74% in placebo arm at 24 weeks
      - Urine positivity decreased from 85% to 71% in mirtazapine arm and 75% to 88% in placebo arm at 36 week
- ASAM statement – consider in patients with co-occurring depression.

1. Ronsley, Claire, et al. "Treatment of stimulant use disorder: a systematic review of reviews." *PloS one* 15.6 (2020): e0234809.
2. Chan, Brian, et al. "Pharmacotherapy for cocaine use disorder—a systematic review and meta-analysis." *Journal of general internal medicine* 34.12 (2019): 2858-2873
3. Coffin, Phillip O., et al. "Effects of mirtazapine for methamphetamine use disorder among cisgender men and transgender women who have sex with men: a placebo-controlled randomized clinical trial." *JAMA psychiatry* 77.3 (2020): 246-255.
4. Colfax, Grant N., et al. "Mirtazapine to reduce methamphetamine use: a randomized controlled trial." *Archives of general psychiatry* 68.11 (2011): 1168-1175.
5. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

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Treatment for Amphetamine Use Disorder

- Topiramate
  - Two RCTs demonstrated reduction in use of methamphetamine via urine drug testing with topiramate compared to placebo
    - 10 week, double-blind, placebo controlled RCT of topiramate (200 mg once daily) or placebo among 62 subjects with methamphetamine use disorder. [1]
      - At 6 weeks topiramate group showed significantly lower proportion of methamphetamine-positive urine in comparison with placebo (P=0.01). [1]
    - 13 week, double-blind, placebo controlled RCT of topiramate (200 mg once daily) or placebo among 140 subjects with methamphetamine use disorder [2]
      - Decrease in methamphetamine use between weeks 6-12. [2]
      - No difference between topiramate and placebo in abstinence from methamphetamine use [2]
  - ASAM Statement – Consider in patients with co-occurring alcohol use disorder

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1. Rezaei, Farzin, et al. "Topiramate for the management of methamphetamine dependence: a pilot randomized, double-blind, placebo-controlled trial." *Fundamental & clinical pharmacology* 30.3 (2016): 282-289.
2. Elkashef, Ahmed, et al. "Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial." *Addiction* 107.7 (2012): 1297-1306.
3. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

Treatment for stimulant use disorder

- Psychostimulants
  - Review of 14 RCT for cocaine use disorder showed improve abstinence versus placebo [1]
  - Review of 26 studies for cocaine use disorder (N=2366 participants) found low quality of evidence that psychostimulants improved sustained cocaine abstinence (RR =1.36, 95% CI 1.05-1.77, P=0.02). Also found that it did not reduce cocaine use among participants who continued to use. [3]
  - Review of 38 trials for stimulant use disorder showed increased rate of sustained abstinence of 2-3 weeks (RR=1.45, 95% CI 1.10-1.92, NNT=16) [2]

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1. Ronsley, Claire, et al. "Treatment of stimulant use disorder: a systematic review of reviews." *PloS one* 15.6 (2020): e0234809
2. Tardelli, Vitor S., et al. "Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis." *Psychopharmacology* 237.8 (2020): 2233-2255.
3. Castells, Xavier, et al. "Psychostimulant drugs for cocaine dependence." *Cochrane Database of Systematic Reviews* 9 (2016).

Treatment for stimulant use disorder

- ASAM Statement
  - Modafinil - consider in patients with cocaine use disorder and without co-occurring AUD (may reduce cocaine use and improve treatment retention) [1]
  - Methylphenidate - consider in patients with amphetamine use disorder. Consider using long-acting methylphenidate formulation to promote reduce use of amphetamines. Consider in patients with co-occurring ADHD. [1]

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1. https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

Treatment for stimulant use disorder

- Behavioral treatments
  - Matrix Model – behavioral therapy, family education, individual counseling, 12-step support, drug testing, and encouraging non-drug related activities [1][2]
  - Cognitive behavioral therapy (CBT) [1][2]
  - Contingency management – tangible incentives (vouchers, rewards, prizes) in exchange for engaging in treatment, reduction in use, management of other health concerns. [1][2]
    - Cost effective – 1.46 dollars per participant per day [2]
    - Number Needed to Treat 3-5 [3]
    - May be performed individually, group setting, outpatient or inpatient
- Stabilizing other medical and psychiatric comorbidities[1]

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1. Ries, Richard K., et al. *The ASAM principles of addiction medicine*. Lippincott Williams & Wilkins, 2014.
2. Ronsley, Claire, et al. "Treatment of stimulant use disorder: a systematic review of reviews." *PloS one* 15.6 (2020): e0234809.
3. De Crescenzo, Franco, et al. "Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis." *PLoS medicine* 15.12 (2018): e1002715.

Questions?