Guidelines for Managing Stimulant Use Disorder

Applying a Pregnancy and Postpartum Lens

ASAM 56th Annual Conference Friday – April 25th 10:30 -11:45

- Niraj R. Chavan, MD, MPH, FACOG, FASAM
- Maria Manriquez, MD, FACOG, FASAM
- Cresta Jones, MD, FACOG, FASAM

Disclosures

- Niraj Chavan
  - No disclosures
- Maria Manriquez
  - No disclosures
- Cresta Jones
  - No disclosures

Learning Objectives

- Review ASAM/AAAP guidelines for management of stimulant use disorder in the context of perinatal populations
- Highlight key considerations and implications for maternal and neonatal wellbeing
- Provide evidence-informed treatment options for managing perinatal stimulant use disorder

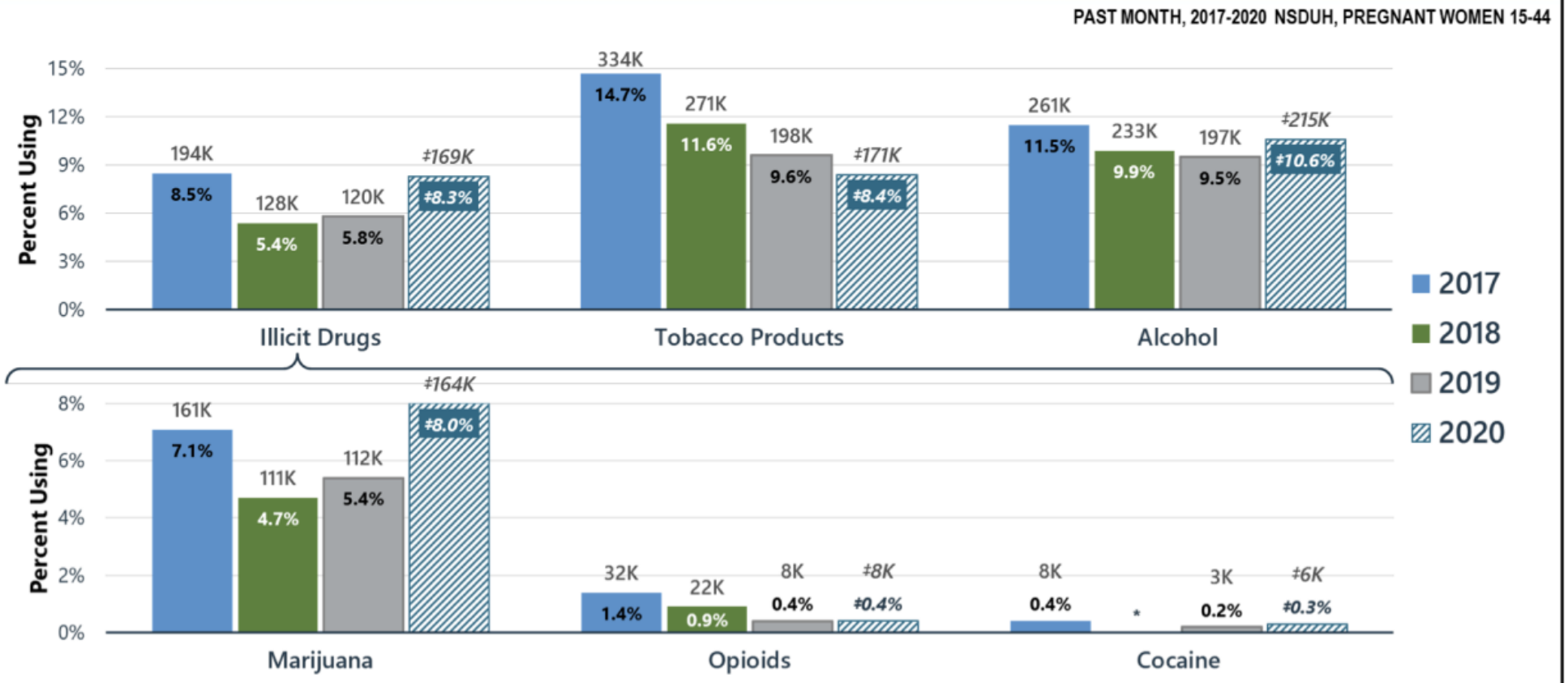
Perinatal MED talks

- Stimulant use and perinatal harm reduction
- Stimulant intoxication and withdrawal management in pregnancy
- Behavioral treatments for perinatal stimulant use disorder
- Medication management for perinatal stimulant use disorder

Stimulant Use and Perinatal Harm Reduction

Cresta W. Jones MD, FASAM, FACOG

Substance Use in Past Month: Among Pregnant Women Aged 15-44



* Estimate not shown due to low precision.

Tobacco products are defined as cigarettes, smokeless tobacco, cigars, and pipe tobacco.

‡ Estimates on the 2020 bars are italicized to indicate caution should be used when comparing estimates between 2020 and prior years because of methodological changes for 2020. Due to these changes, significance testing between 2020 and prior years was not performed. See the *2020 National Survey on Drug Use and Health: Methodological Summary and Definitions* for details.

SAMHSA
Substance Abuse and Mental Health Services Administration

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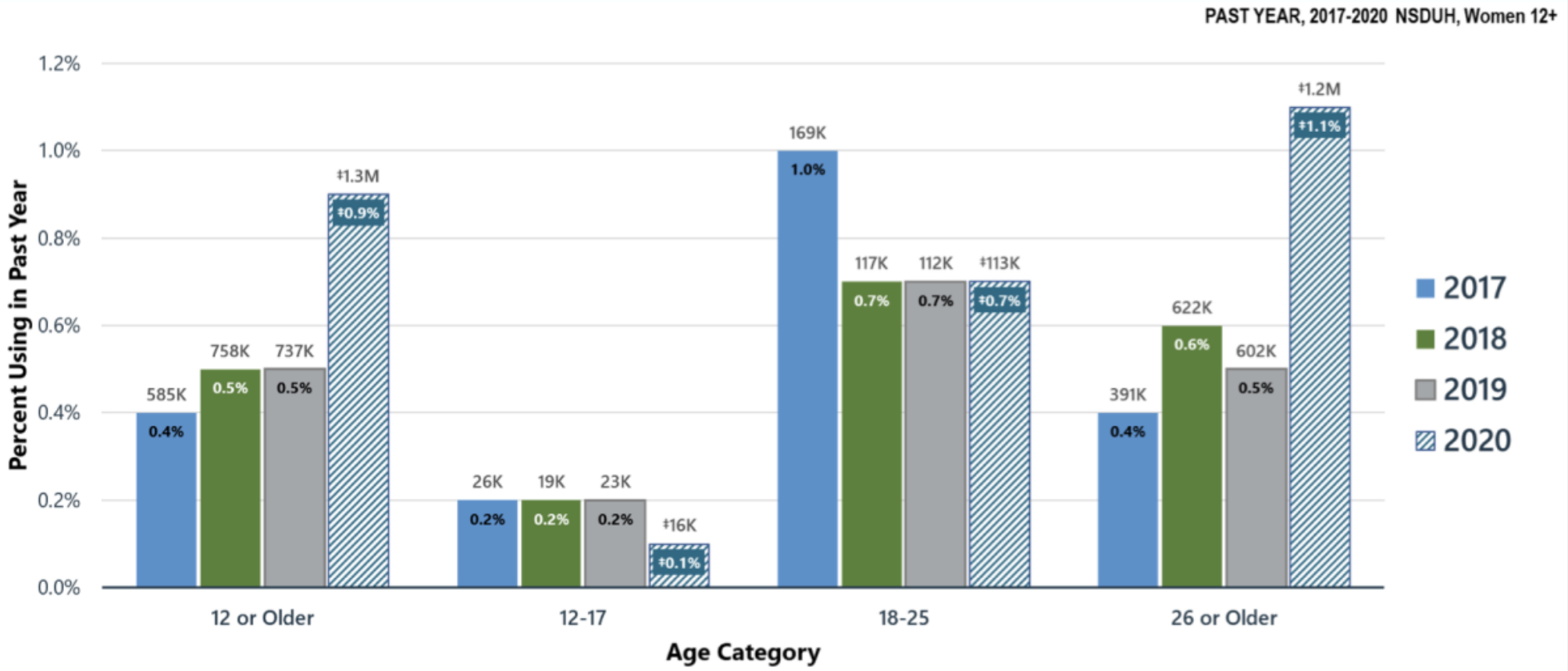
https://www.samhsa.gov/data/sites/default/files/reports/slides-2020-nsduh/2020NSDUHWomenSlides072522.pdf

Methamphetamine Use in Past Year: Among Women Aged 12+



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SAMHSA
Substance Abuse and Mental Health Services Administration

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https://www.samhsa.gov/data/sites/default/files/reports/slides-2020-nsduh/2020NSDUHWomenSlides072522.pdf

Start with a Case

A patient presents for initial obstetric care and is noted to be anxious with an elevated blood pressure

Routine substance use screening identifies frequent methamphetamine use

Potential pregnancy complications are reviewed with the patient through a brief intervention.

The patient is not interested in substance use disorder treatment at this time.

How do you optimize outcomes for this patient?

Harm Reduction:

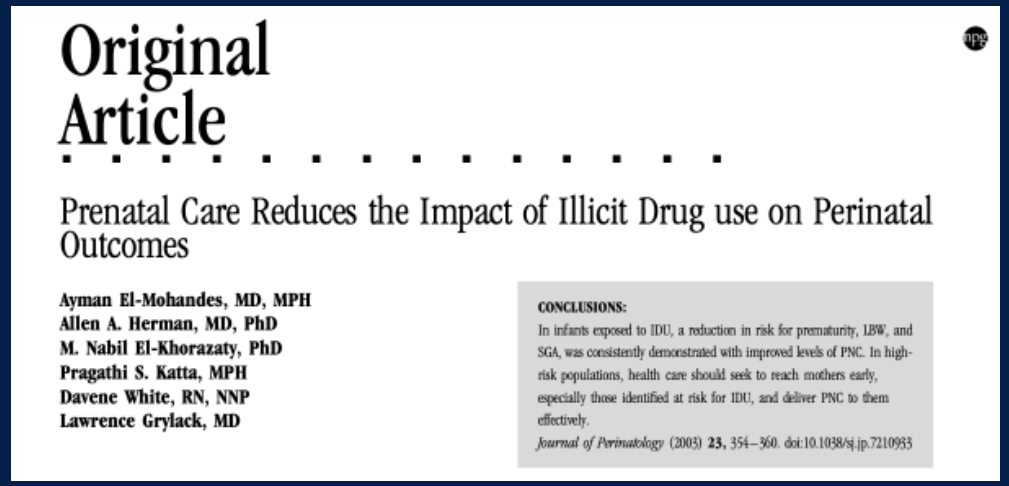
Attenuating the adverse effects of substance use through risk mitigation.

Wakeman, B., Kremer, M., & Schulkin, J. (2021). The application of harm reduction to methamphetamine use during pregnancy: a call to arms. *American journal of obstetrics & gynecology MFM*, *3*(5), 100418.

Prenatal Harm Reduction

- Reduce complications associated with non-prescribed substance use
- Decrease infectious burden for the birthing dyad
- Reduce overdose
- Identify pregnancy complications through engagement with care providers

Goal : Prenatal Care Engagement



Original Article

Prenatal Care Reduces the Impact of Illicit Drug use on Perinatal Outcomes

Ayman El-Mohandes, MD, MPH
Allen A. Herman, MD, PhD
M. Nabil El-Khorazaty, PhD
Pragathi S. Katta, MPH
Davene White, RN, NNP
Lawrence Grylack, MD

CONCLUSIONS:
In infants exposed to IDU, a reduction in risk for prematurity, LBW, and SGA, was consistently demonstrated with improved levels of PNC. In high-risk populations, health care should seek to reach mothers early, especially those identified at risk for IDU, and deliver PNC to them effectively.

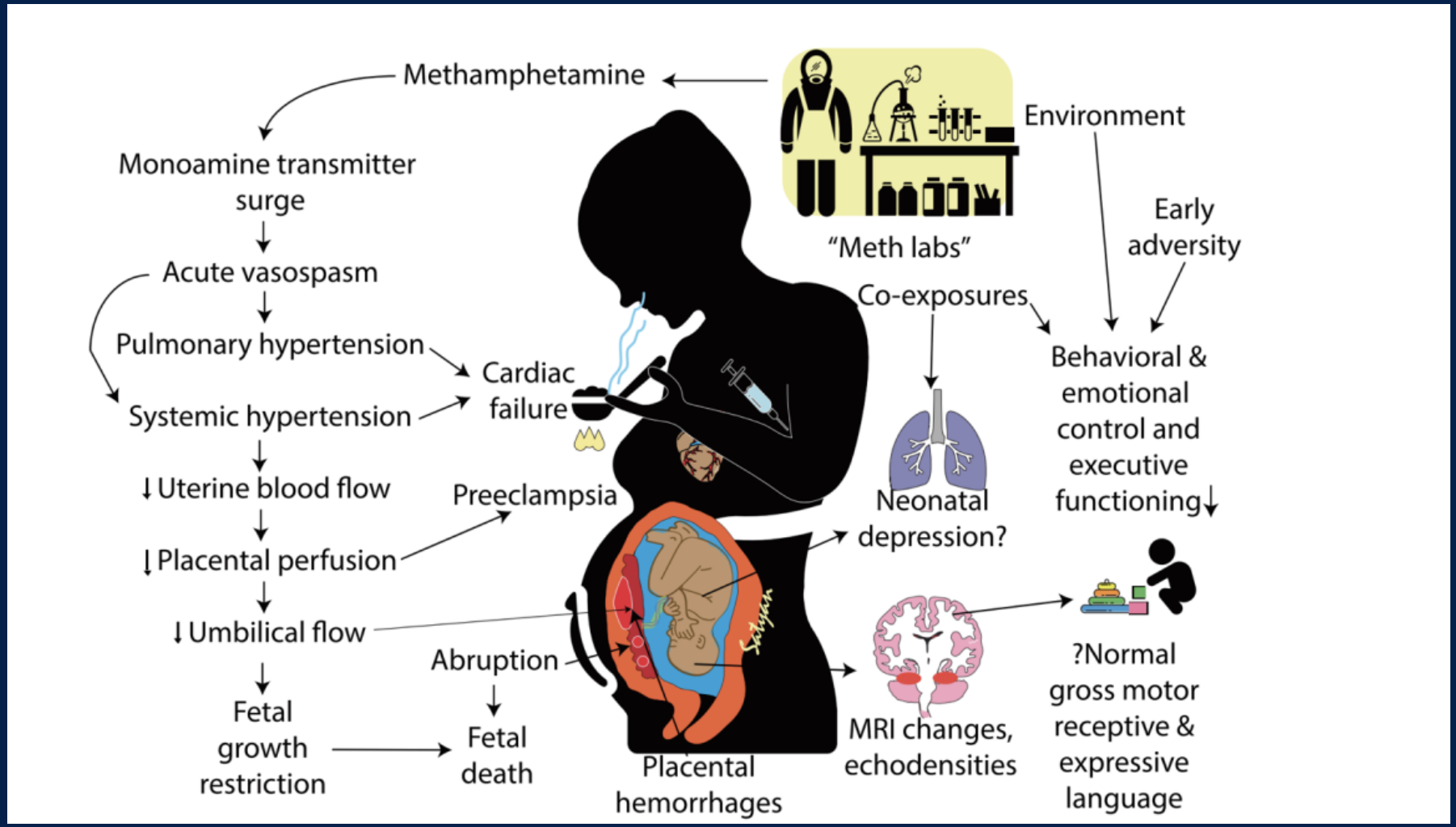
Journal of Perinatology (2003) **23**, 354–360. doi:10.1038/sj.jp.7210933

- Prenatal care reduces the risk of preterm birth, *even with* ongoing substance use.
- Prenatal care improves infant birth weight, *even with* ongoing substance use.

El-Mohandes, A., Herman, A. A., Nabil El-Khorazaty, M., Katta, P. S., White, D., & Grylack, L. (2003). Prenatal care reduces the impact of illicit drug use on perinatal outcomes. *Journal of perinatology : official journal of the California Perinatal Association*, *23*(5), 354–360.

Perinatal Harm Reduction and Stimulant Use

- Pregnancy
- Postpartum



Sankaran, D., Lakshminrusimha, S., & Manja, V. (2022). Methamphetamine: burden, mechanism and impact on pregnancy, the fetus, and newborn. *Journal of perinatology : official journal of the California Perinatal Association*, *42*(3), 293–299.

Pregnancy Complications

- Hypertensive crisis
- Fetal growth restriction
- Fetal distress
- Placental abruption
- Cardiomyopathy

Perinatal Harm Reduction

- Obstetric providers have experience in other use of harm reduction (pregnancy, STI prevention)
- Unfamiliar/uncomfortable with reducing the harms of drug use without changing the drug use itself
- Federal/state laws may complicate harm reduction in the perinatal space

Wakeman, B., Kremer, M., & Schulkin, J. (2021). The application of harm reduction to methamphetamine use during pregnancy: a call to arms. *American journal of obstetrics & gynecology MFM*, *3*(5), 100418.

Antepartum Harm Reduction - Wright 2012

- Transportation
- Child care
- Psychiatric and social services
- Group classes
- Healthy food access

→ Preterm rate similar to patients without substance exposure
→ Low birth weight also similar
→ Improved abstinence rates with increased prenatal care

Wakeman, B., Kremer, M., & Schulkin, J. (2021). The application of harm reduction to methamphetamine use during pregnancy: a call to arms. *American journal of obstetrics & gynecology MFM*, *3*(5), 100418. Wright, T. E., Schuetter, R., Fombonne, E., Stephenson, J., & Haning, W. F., 3rd (2012). Implementation and evaluation of a harm-reduction model for clinical care of substance using pregnant women. *Harm reduction journal*, *9*, 5. h

Antepartum Harm Reduction

- Safer use supplies
- Fentanyl test strips
- Naloxone
- STI testing and treatment (syphilis outbreak)
- Wound care

Rosenbaum M, Irwin K. Pregnancy, drugs and harm reduction. Harm reduction:national and international perspectives. Thousand Oaks, CA: SAGE Publications, Inc.;2000.p.89-110.

Antepartum Harm Reduction

- Patient - initiated harm reduction
  - Drug substitution for ‘less harmful’ substances
  - Remembering to eat and sleep
  - Lifestyle changes (relocation etc.)

Rosenbaum M, Irwin K. Pregnancy, drugs and harm reduction. Harm reduction:national and international perspectives. Thousand Oaks, CA: SAGE Publications, Inc.;2000.p.89-110.

Postpartum Harm Reduction

- Increased risk of return to use after birth
- Plan for return to use
- Access to supportive services
- Social support
- Peer recovery
- Discussion of fentanyl and other additives
- Naloxone

Wakeman, B., Kremer, M., & Schulkin, J. (2021). The application of harm reduction to methamphetamine use during pregnancy: a call to arms. *American journal of obstetrics & gynecology MFM*, *3*(5), 100418. https://doi-org.ezp3.lib.umn.edu/10.1016/j.ajogmf.2021.100418

Postpartum Mortality Reduction

Mental health and substance use disorders (SUDs) are the leading contributors to maternal mortality, accounting for approximately 30% of these outcomes.

Many are postpartum

Education of healthcare teams, patients and support networks is key

Follow up is necessary in the postpartum period

Hoskins IA, Brown HL. Preventable Maternal Mortality -Diagnosis and Management of Mental Health and Substance Use Disorders. *Obstet Gynecol Clin North Am*. 2025;52(1):33-41.

Advocacy and Research

- Ongoing investigation into perinatal harm reduction
- Advocacy for integration of harm reduction into care
  - Support services
  - Testing and use supplies
  - Safer use location
  - Protocols for care for obstetric care for patients with ongoing use

Funding, funding, funding!

Perinatal Harm Reduction and Methamphetamine Use

Harms Associated with Perinatal Use	***Harm Reduction Application***
Methamphetamine Use	Reduction in frequency/amount, planned use breaks
Adverse Childhood Experiences	Screening
Intimate Partner Violence	Periodic screening
Mental Health Needs	Periodic screening, referral to treatment
Polysubstance Use	Nicotine Replacement Therapy (NRT), MOUD, education alcohol consumption
Basic Social Needs and Social Support	Screen for SDOH, social services (including legal)
Social Stigma	Bias training for healthcare team
Infection Risk	Safe injection supplies, safe use routes
Unsafe Sexual Practices	Education, testing, condoms
Lack of Sleep	Education on sleep importance
Poor Nutrition	Education/access to nutritious food, water intake
Oral Health	Dental supplies, education

Adapted from - Wakeman, B., Kremer, M., & Schulkin, J. (2021). The application of harm reduction to methamphetamine use during pregnancy: a call to arms. *American journal of obstetrics & gynecology MFM*, *3*(5), 100418. https://doi-org.ezp3.lib.umn.edu/10.1016/j.ajogmf.2021.100418

Takeaways

- Harm reduction is a key component of perinatal stimulant use disorder, which has the potential to reduce obstetric complications
- Education of perinatal care professionals on their role in support is key
- It is important to address the need for more consistent follow up in the postpartum period, when the risk of substance overdose is highest

Stimulant Intoxication and Withdrawal in Pregnancy

Maria Manriquez, MD, FASAM, FACOG
University of Arizona College of Medicine Phoenix

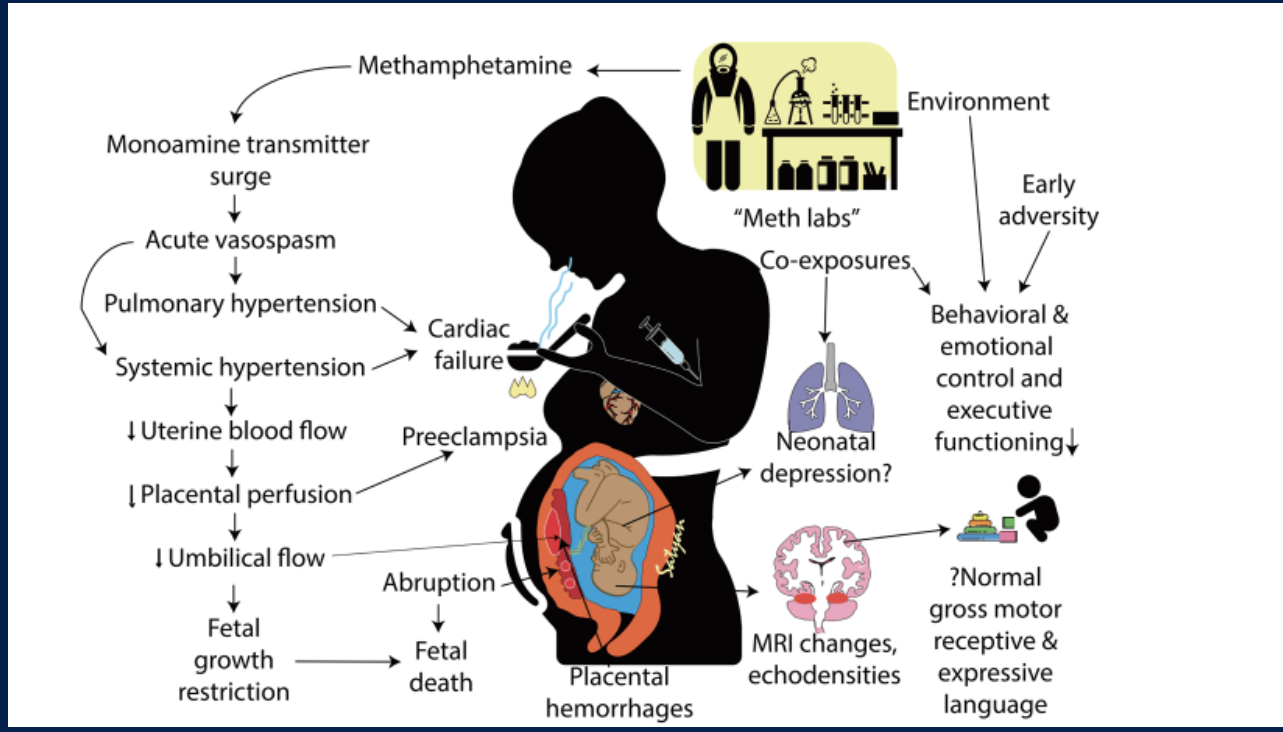
Stimulant Intoxication

Physical Effects

- Pupil dilation, headache and bruxism
- Hyperventilation, dyspnea, cough, chest pain, wheezing, hemoptysis, pulmonary edema
- Tachycardia, palpitations, increased blood pressure, myocardial ischemia, infarction, ruptured aneurysm, cardiogenic shock
- Headache, agitation, psychosis, tremor, hyperreflexia, small muscle twitching, myoclonus, seizure, cerebral hemorrhage or infarct, cerebral edema
- Nausea, vomiting, mesenteric ischemia, bowel infarction or perforation
- Diuresis, myoglobinuria, acute renal failure
- Fever, malignant hyperthermia

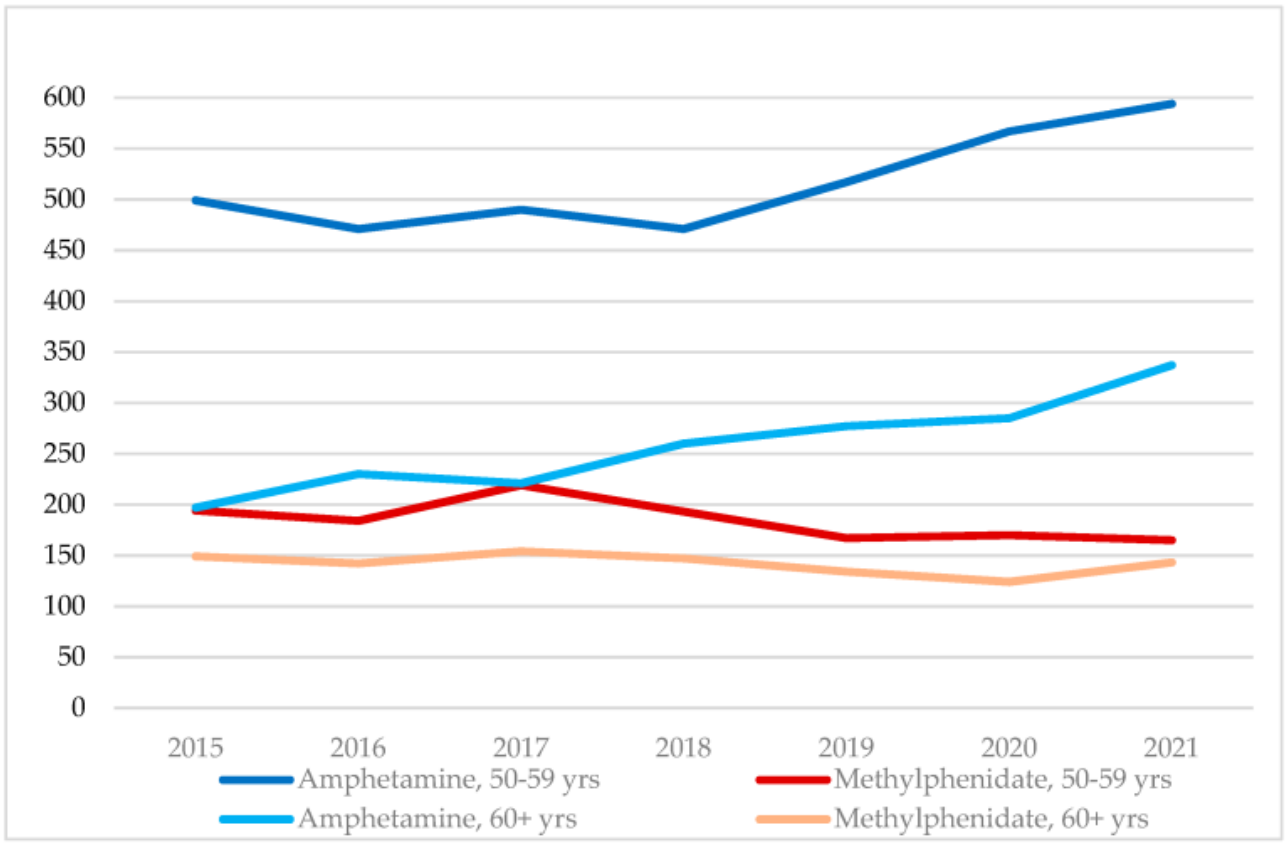
Stimulant Intoxication in Pregnancy

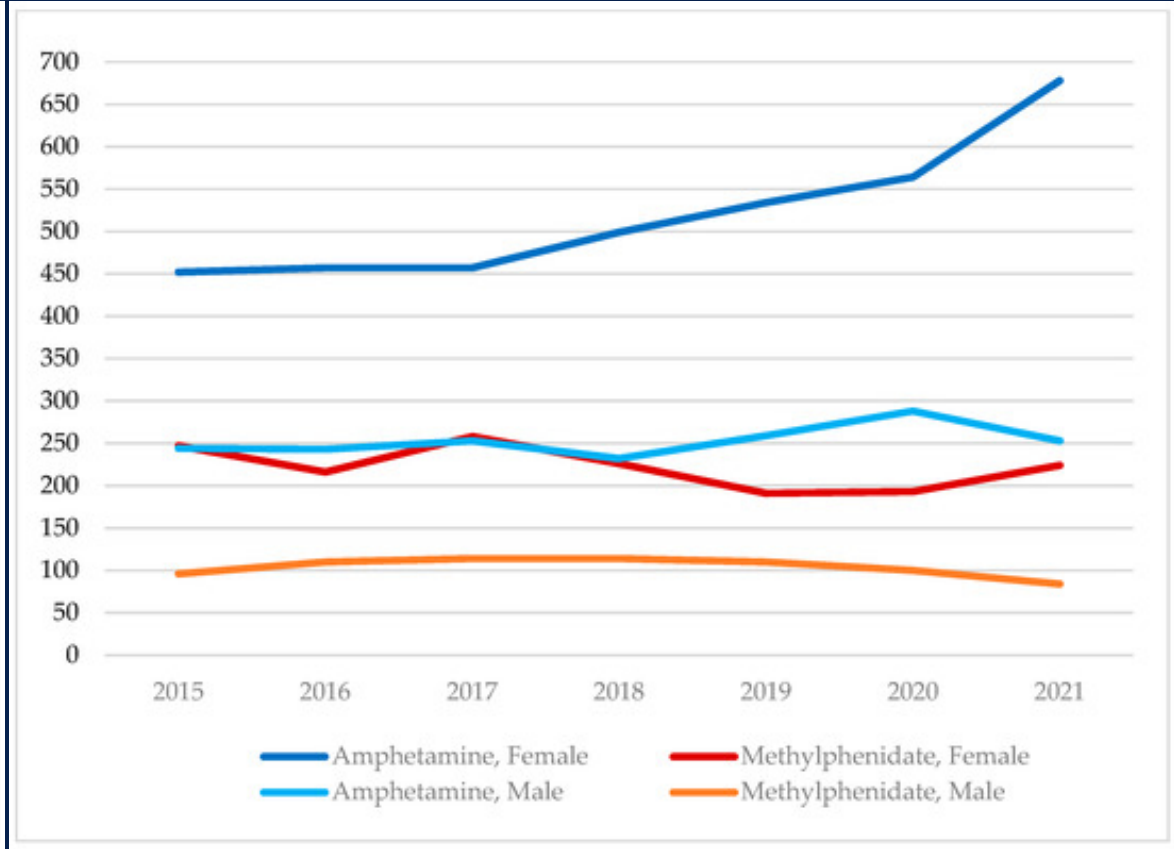
Stimulants, such as cocaine, methamphetamine, and prescription amphetamines (e.g., Adderall, Ritalin), affect the central nervous system by increasing dopamine, norepinephrine, and serotonin levels. This leads to **heightened alertness**, **euphoria**, increased heart rate and blood pressure.



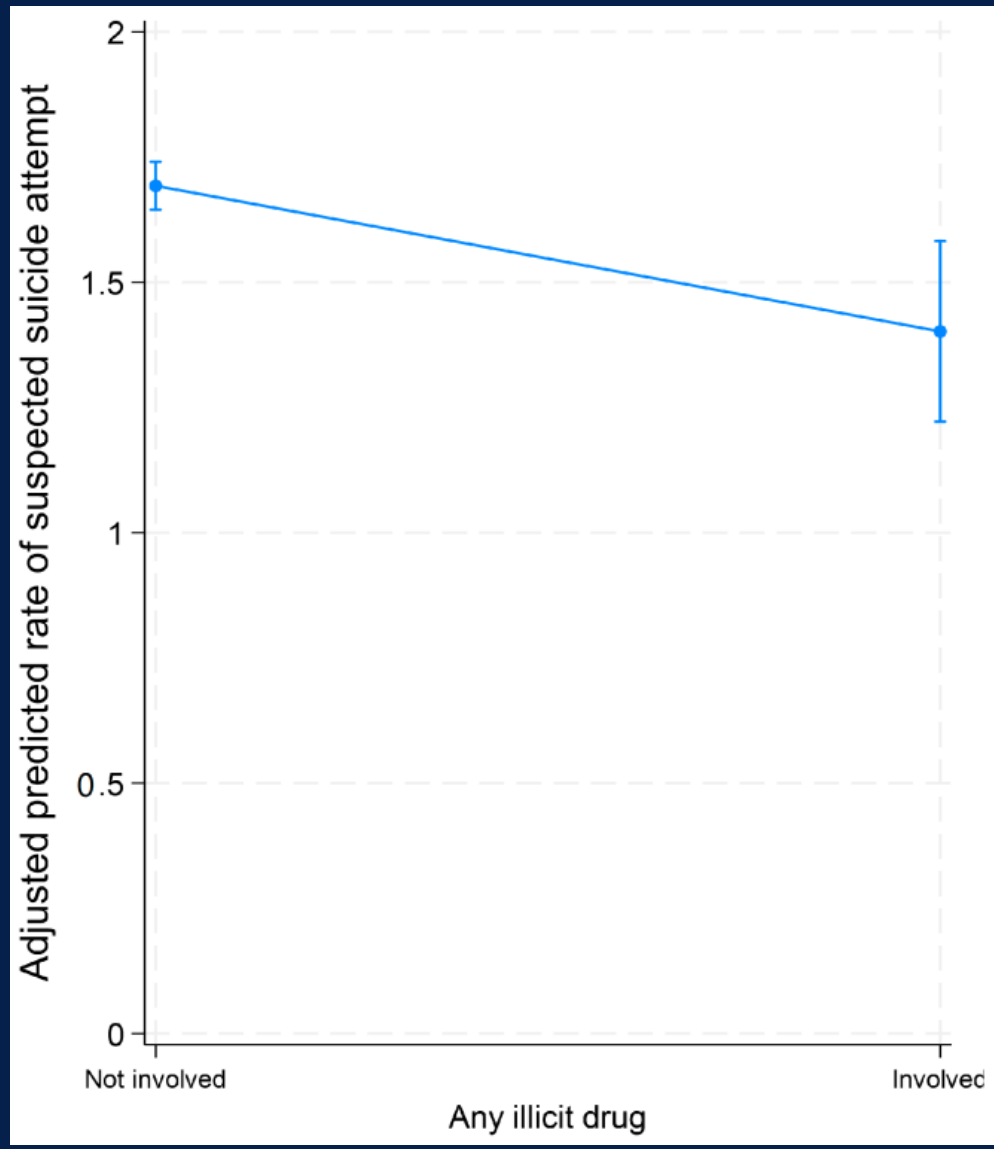
Sankaran, D., Lakshminrusimha, S., & Manja, V. (2022). Methamphetamine: burden, mechanism and impact on pregnancy, the fetus, and newborn. *Journal of perinatology : official journal of the California Perinatal Association*, *42*(3), 293–299.

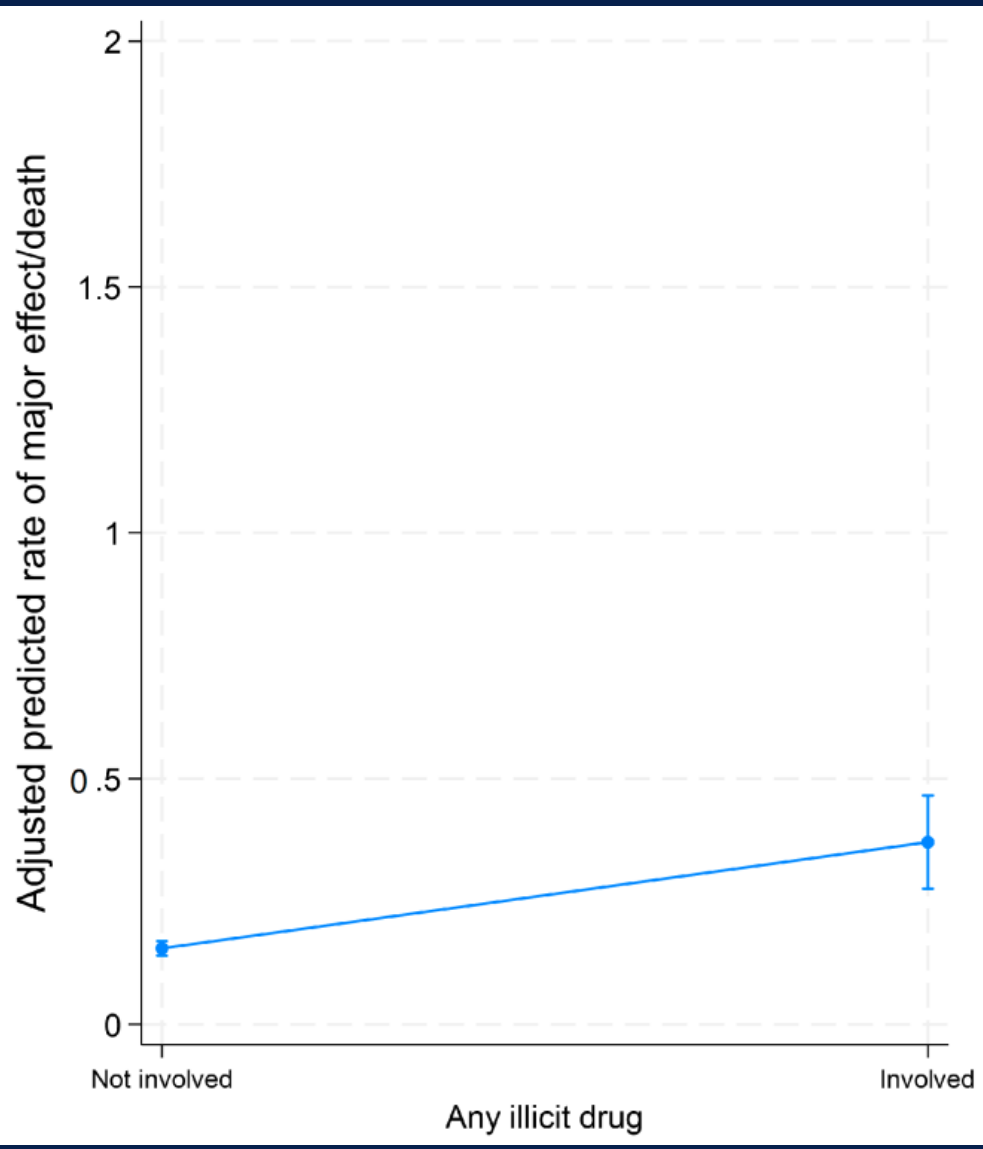
Number of exposure by age and gender





Suspected Suicide Attempt and Intentional Misuse Cases Aged 50+ Involving Amphetamine or Methylphenidate and Medical Outcomes: Associations with Co-Used Other Substances. Namkee G. Choi, Bryan Y. Choi 2 and S. David Baker





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Complications of Intoxication

Methamphetamine use is associated with increased risk of rhabdomyolysis which can lead to acute kidney injury and electrolyte imbalances

Mechanisms

- Hyperthermia
- Dehydration
- Direct Muscle Toxicity

DO NOT USE PHYSICAL RESTRAINTS

Clinical Evidence of Rhabdomyolysis

- Muscle Pain and Weakness (shoulders, thighs and lower back)
- Swelling
- Dark Urine - myoglobinuria is evidence of muscle breakdown
- Systemic Symptoms - fever, confusion or LOC
- Higher mean initial creatine phosphokinase in methamphetamine use compared to non-meth use.

- Rare Methamphetamine Triad: Compartment Syndrome, Rhabdomyolysis and Severe Renal Failure

A Rare Methamphetamine Triad: Compartment Syndrome, Rhabdomyolysis, and Severe Renal Failure. Matthew Fry, DO, Emana Sheikh-Kapadia, DO,

Management of Rhabdomyolysis

- Early Recognition
- Aggressive Hydration
- Monitoring and Correction of Electrolyte Imbalances
- Avoidance of Nephrotoxic Agents
- Dialysis may be necessary in cases of severe acute kidney injury

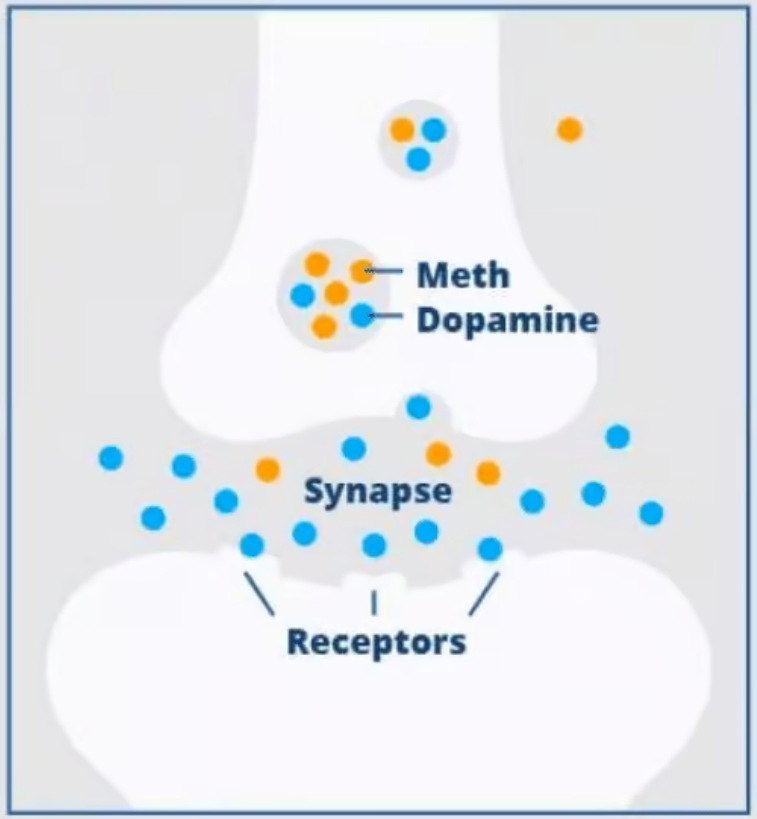
If surgery is required important to know that succinylcholine can potentiate rhabdomyolysis and is a relative contraindication

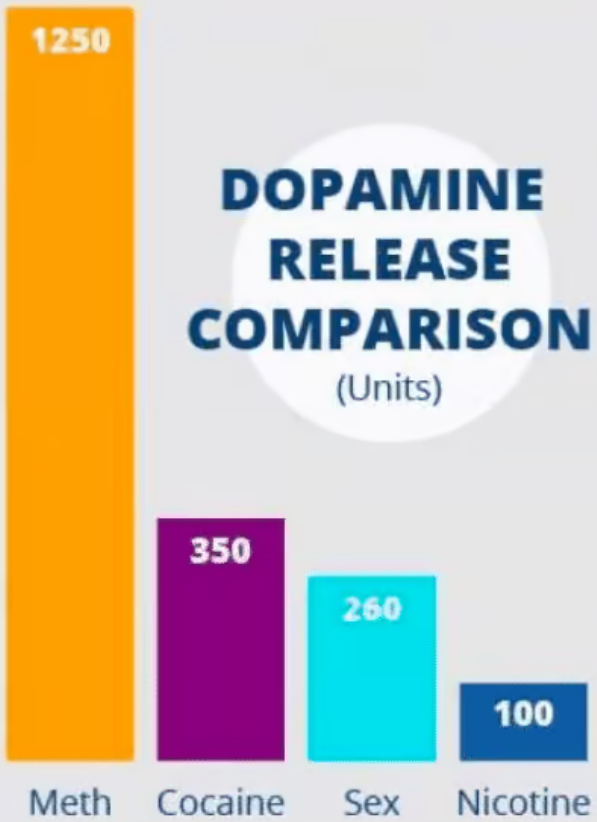
Clinical problem	Moderate syndrome	Severe syndrome
Anxiety; agitation	Provide reassurance; place in a quiet, nonthreatening environment	Diazepam (10-30 mg PO, 2-10 mg IM, IV) or lorazepam (2-4 mg PO, IM, IV); may repeat every 1-3 h
Paranoia; psychosis	Place in a quiet, nonthreatening environment; benzodiazepines for sedation	High-potency antipsychotic (eg, haloperidol) or second-generation antipsychotic
Hyperthermia	Monitor body temperature; place in a cool room	If temperature is >102 °F (oral), use external cooling with cold water, ice packs, hypothermic blanket; if >106 °F, use internal cooling; epigastric lavage with iced saline
Seizures	Diazepam (2-20 mg IV, <5 mg/min) or lorazepam (2-8 mg)	For status epilepticus: IV diazepam or phenytoin (15-20 mg/kg IV, <150 mg/min) or phenobarbital (25-50 mg IV)
Hypertension	Monitor blood pressure closely; benzodiazepines for sedation. Generally avoid beta-adrenergic antagonists (ie, "beta-blockers")	If diastolic is >120 for 15 min, give phentolamine (2-10 mg IV over 10 min)
Cardiac arrhythmia	Monitor electrocardiogram, vital signs; benzodiazepines for sedation	As appropriate for specific rhythm, based on advanced cardiac life-support criteria
Myocardial infarction	Benzodiazepines for sedation; supplemental oxygen; sublingual nitroglycerin for vasodilation; aspirin for anticlotting; morphine for pain	Give nitrates IV for coronary artery dilation; phentolamine (2-10 mg IV) to control blood pressure; thrombolysis, angioplasty (if clot is confirmed and no hemorrhage)
Rhabdomyolysis	IV hydration to maintain urine output >2 mL/kg/h	Force diuresis with aggressive intravenous hydration
Increased urinary drug excretion	Cranberry juice (8 oz tid) or ammonium chloride (500 mg PO every 3-4 h) until urine pH is <6.6 (if renal and hepatic function are normal)	Same as for moderate intoxication
Recent (few hours) oral drug ingestion	Activated charcoal orally or gastric lavage via nasogastric tube (if patient is awake and cooperative)	Gastric lavage via nasogastric tube after endotracheal intubation (if patient is unconscious)

Withdrawal Management

- Physical Effects
  - Headache, muscle pain, dental pain, tremor and chills
- Management
  - Immediate
    - Mirtazapine (Remeron) - reduced heavy use methamphetamine
    - Trazodone - for insomnia and agitation
    - Antipsychotics - quetiapine, olanzapine
    - Propranolol - anxiety and hypertension
  - Lisdexamfetamine
  - TrMS repetitive transcranial magnetic stimulation(10hz directed at the left dorsolateral prefrontal cortex)
  - Supportive therapy, cognitive-behavioral therapy, relapse prevention therapy and contingency management

WHY IS METH SO ADDICTIVE?





DOPAMINE RELEASE COMPARISON

(Units)

Medication	Outcome measure	Type of evidence
Low-quality evidence		
Buprenorphine (history of opioid use disorder)[67]	↓ use	1 RCT
Disulfiram (men with specific genotypes)[36-40]	↓ use	5 RCTs
Doxazosin[89,90]	↓ use, cont abst ≥ 2 weeks	2 RCTs
Naltrexone[65,66]	↓ use	2 RCTs
Ondansetron (specific genotypes)[51,52]	↓ use, ↑ retention in tx	2 RCTs
Moderate-quality evidence		
Amphetamines—long-acting formulations[8,17,72]	↓ use, cont abst ≥ 3 weeks	5 RCTs
Bupropion[17]	cont abst ≥ 3 weeks	2 RCTs
Desipramine (mild CUD)[16,17]	cont abst ≥ 3 weeks	5 RCTs
Modafinil[73]	Achieve abstinence	6 U.S. RCTs
SSRIs—citalopram[24,25] Sertraline[17]	↓ use 2 consecutive cocaine-negative urine samples	2 RCTs 2 RCTs
Topiramate[17]	cont abst ≥ 3 weeks	2 RCTs

Takeaways

- Methamphetamine has a high addictive burden secondary to the high release of dopamine and reuptake inhibition
- Rhabdomyolysis is a severe consequence of methamphetamine use
  - Avoid physical restraining of patients
  - Recognize and Treat
- No FDA approved Treatment
- Multiple severe consequences to pregnant patients and their fetus

Behavioral Treatments - Perinatal Stimulant Use Disorder

Cresta Jones MD, FASAM, FACOG

Start with a Case

First OB visit at 12 weeks

Patient with stimulant use disorder, no current treatment

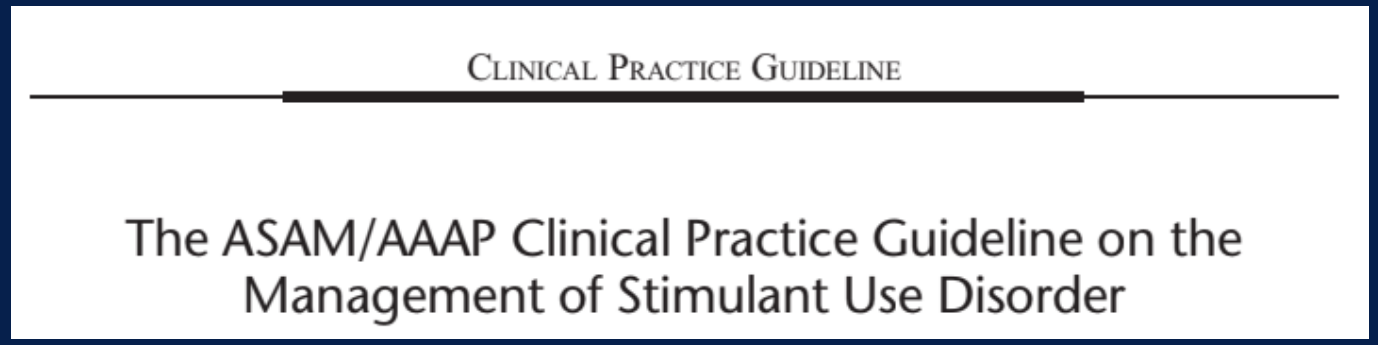
Stress of pregnancy increasing craving but has not returned to use

Inquiring about treatment options that don't involve medication.

What are our next steps?

Behavioral Treatments - Perinatal Stimulant Use Disorder

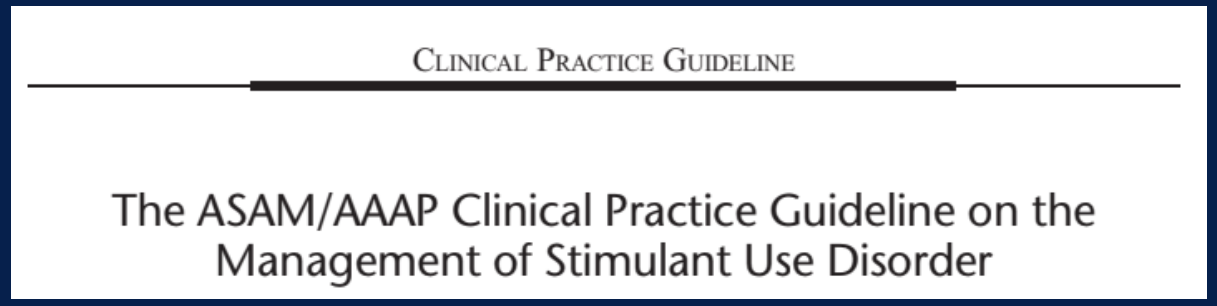
- Pharmacologic treatment for StUD has been lacking
- Limited awareness of ASAM/AAAP Clinical Practice Guideline
- Important to review current data on behavioral treatment for StUD in pregnancy



- Contingency management (CM) has demonstrated the best effectiveness in the treatment of StUDs compared to any other intervention studied and represents the current standard of care.

- Can be combined with other psychosocial interventions and behavioral therapies

Clinical Guideline Committee (CGC) Members , ASAM Team , AAAP Team , & IRETA Team (2024). The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder. *Journal of addiction medicine*, *18*(1S Suppl 1), 1–56.



- **Contingency Management (CM)** - primary component of the treatment plan

- Interventions are preferred alongside CM:
  - a. **Community Reinforcement Approach (CRA)** (Conditional Recommendation),
  - b. **Cognitive Behavioral Therapy (CBT)** (Strong Recommendation), and
  - c. **The Matrix Model** (Conditional Recommendation).

- **Technology-Based Interventions**

  Consider offering evidence-based behavioral interventions via digital therapeutics or web-based platforms as add-on components but they should not be used as standalone treatment (Strong Recommendation).
  - Consider using telemedicine to deliver behavioral treatment for patients who may face challenges accessing in-person care (Strong Recommendation).

Clinical Guideline Committee (CGC) Members , ASAM Team , AAAP Team , & IRETA Team (2024). The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder. *Journal of addiction medicine*, *18*(1S Suppl 1), 1–56.

Contingency Management and Pregnancy

- Highly effective in reducing tobacco smoking
  - Abstinence contingent 36-46%
  - Standard care 10-18%
- Typically employ validation (biochemical, attendance at OB visits)
  - Often escalating and resetting with use
- Can reduce illicit substance use
- Limited studies in pregnancy, limited examination of use to benefit maternal and infant health outcomes

Hand, D. J., Ellis, J. D., Carr, M. M., Abatemarco, D. J., & Ledgerwood, D. M. (2017). Contingency management interventions for tobacco and other substance use disorders in pregnancy. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors*, *31*(8), 907–921. https://doi-org.ezp2.lib.umn.edu/10.1037/adb0000291

Community Reinforcement Approach and Pregnancy

- Limited data in pregnancy
- Cocaine - decreased frequency of use with community reinforcement, but less effective than contingency management
- Synergistic effects with contingency management
- Limited effect with cannabis use

Schottenfeld, R. S., Moore, B., & Pantalon, M. V. (2011). Contingency management with community reinforcement approach or twelve-step facilitation drug counseling for cocaine dependent pregnant women or women with young children. *Drug and alcohol dependence*, *118*(1), 48–55.

Cognitive Behavioral Therapy and Pregnancy

- Well established as effective for depression and anxiety in pregnancy and postpartum
- Easily accessible in many perinatal behavioral health programs
- Absence of data on reducing substance use in pregnancy

Okatsau, A., Aoyama, S., Yamaji, N., & Kataoka, Y. (2022). Cognitive behavioral therapy in perinatal mental health: An overview of systematic reviews. *Japan journal of nursing science : JJNS*, *19*(4), e12501. https://doi-org.ezp2.lib.umn.edu/10.1111/jjns.12501

The Matrix Model and Pregnancy

- Developed in response to cocaine use in 1980s
  - Also validated for cocaine use
- Relapse prevention groups, education groups, social support groups, individual counseling and toxicology testing over 16 weeks
- Outpatient treatment of stimulant use disorder
- Limited data on outcomes in pregnancy
- Can be challenging commitment for parenting people
- Needs coordination with obstetric care

Obert, J. L., McCann, M. J., Marinelli-Casey, P., Weiner, A., Minsky, S., Brethen, P., & Rawson, R. (2000). The matrix model of outpatient stimulant abuse treatment: history and description. *Journal of psychoactive drugs*, *32*(2), 157–164.

Technology Based Interventions

- Mobile Health (mHealth)
  - Preliminary support for efficacy with perinatal mood and anxiety disorders
  - Wearable technology, internet based CBT, VR including for periprocedural anxiety, eConsult, machine learning
  - Limited evidence-based recommendations for use
  - Absent evidence for perinatal SUD support

Novick, A. M., Kwitowski, M., Dempsey, J., Cooke, D. L., & Dempsey, A. G. (2022). Technology-Based Approaches for Supporting Perinatal Mental Health. *Current psychiatry reports*, *24*(9), 419–429. https://doi-org.ezp2.lib.umn.edu/10.1007/s11920-022-01349-w

Obstetric Collaboration

- Limited perinatal behavioral health access
- Look for structured contingency management - can it be expanded to include stimulant use?
- Advocate for increased access, programming, and reimbursement!

Takeaways

- Behavioral treatments are an important component of perinatal stimulant use disorder treatment
- Contingency management is well supported for management of perinatal SUDs and should be a primary component of perinatal stimulant use disorder
- Additional behavioral supports should be considered and studied

Medication Management for Perinatal Stimulant Use Disorder

Niraj R. Chavan, MD, MPH, FACOG, FASAM

Associate Professor, Div. of Maternal Fetal Medicine,
Program Director, Maternal Fetal Medicine Fellowship,
Medical Director, Women and Infant Substance Help (WISH Center),
Dept. of Obstetrics, Gynecology & Women's Health,
Saint Louis University / SSM Health

Methamphetamine Use Disorder (MUD) Pharmacotherapy

Medications for Methamphetamine Use Disorder (MUD)

- Bupropion (may have benefit for lower intensity MUD)
  - Also beneficial for treating tobacco use disorder, depression.
- XR-naltrexone injection + high dose bupropion XL (largest RCT)
- Mirtazapine (two small studies + meta analysis)
  - Additional benefit for management of depression
- Topiramate (low intensity MUD)
  - May have additional benefit for treating AUD
- Methylphenidate – ER
    - Additional considerations for ADHD

None are FDA-approved

Bupropion

- Atypical antidepressant medication that has FDA approval for the treatment of depression and for smoking cessation.
- Mechanism: Inhibits dopamine and norepinephrine transporters (DAT and NET), reducing the reuptake of these neurotransmitters.
- Bupropion supports smoking cessation by providing anti-craving and anti-withdrawal benefits by disrupting the reward pathways linked to nicotine addiction.
- Dosing: Wellbutrin XL (bupropion XL):
  - 150 mg starting dose – once daily
  - Dose range: 150 – 450 mg daily

Bupropion for MA: adherence considerations

Randomized trial of bupropion SR 150mg twice daily versus placebo for 12 weeks in individuals with MUD and less than daily MA use.

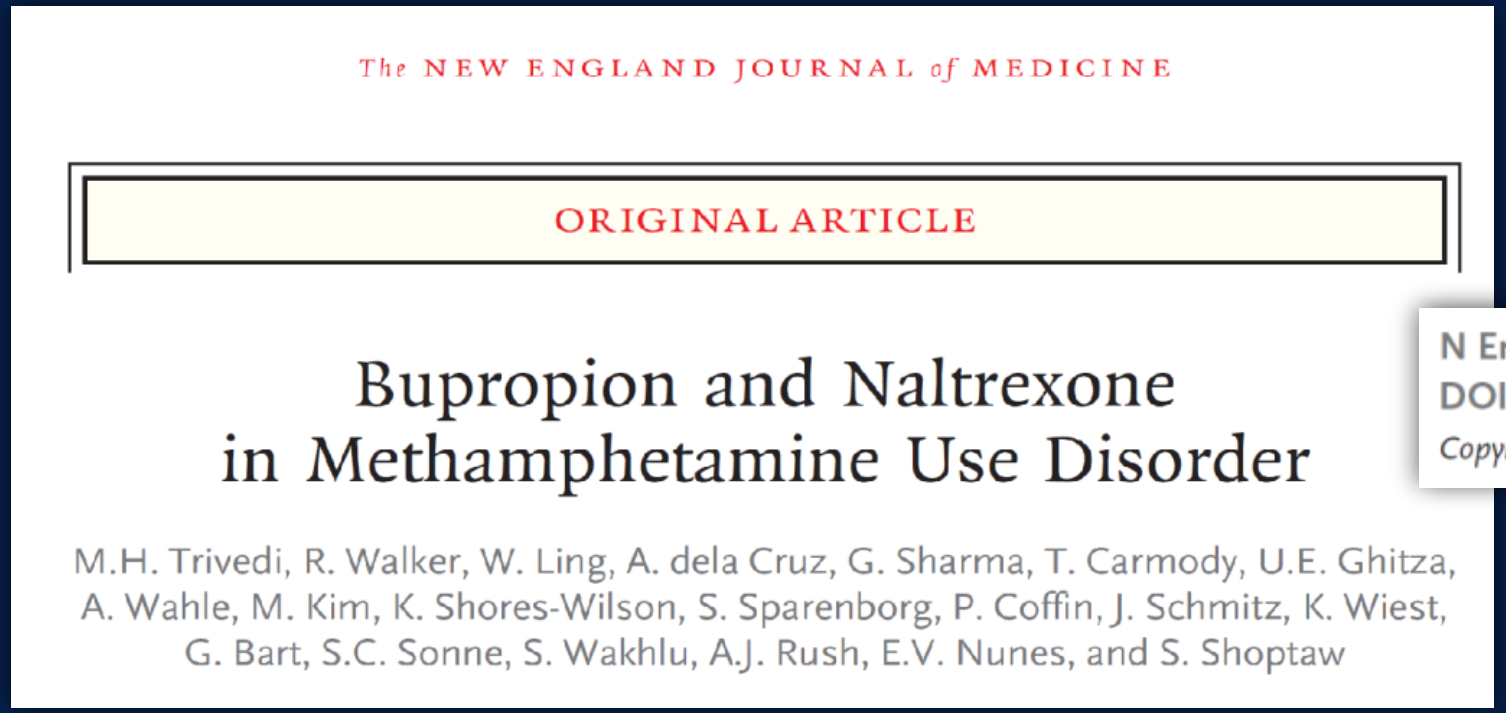
Total Sample	Bupropion (N = 41)	Placebo (N = 43)	P value
End of treatment abstinence	29% (12)	14% (6)	0.087

Only 32% (13/41) of bupropion participants were deemed medication adherent via week six plasma bupropion level. Adherence was strongly associated with end-of-treatment methamphetamine abstinence.

Bupropion only	Adherent (N = 13)	Non-adherent (N = 28)	P value
End of treatment abstinence	54% (7)	18% (5)	0.018

Heinzerling KG et al., 2014, Addiction

Medication for Methamphetamine Use Disorder



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

M.H. Trivedi, R. Walker, W. Ling, A. dela Cruz, G. Sharma, T. Carmody, U.E. Ghitza, A. Wahle, M. Kim, K. Shores-Wilson, S. Sparenborg, P. Coffin, J. Schmitz, K. Wiest, G. Bart, S.C. Sonne, S. Wakhlu, A.J. Rush, E.V. Nunes, and S. Shoptaw

N Engl J Med 2021;384:140-53.
DOI: 10.1056/NEJMoa2020214

- Multisite, double-blind, two-stage, placebo-controlled trial to evaluate the efficacy and safety of extended-release injectable **naltrexone** (380 mg every 3 weeks) plus oral extended-release **bupropion** (450 mg per day) in adults with moderate or severe methamphetamine use disorder

- **Evidence informed =>** NOT evidence based for pregnant and postpartum individuals

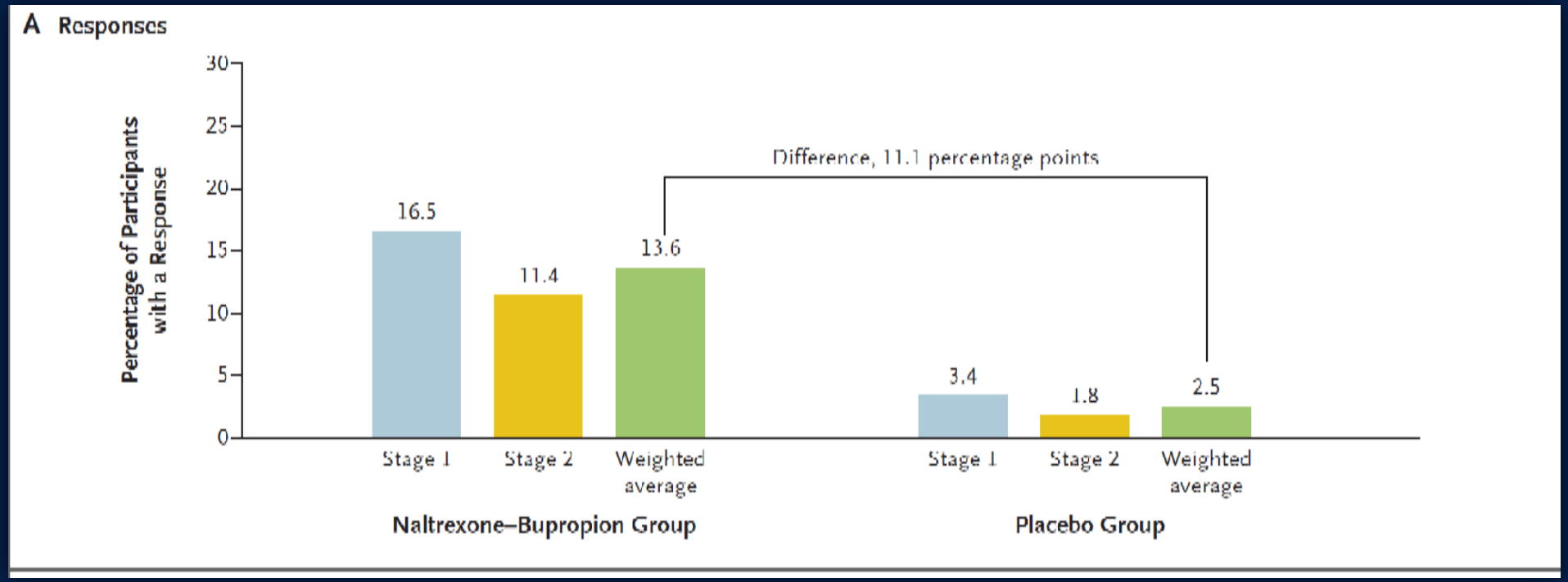
XR-Naltrexone Injection Plus Bupropion XL

- Medications: XR-NTX 380mg via intramuscular injection every three weeks in combination with bupropion XL titrated up to 450 mg daily.
- 12-week, 2 stage trial (N=403 Stage 1, N = 225 Stage 2)
- Response defined as at least three methamphetamine negative urine samples out of four during the final two weeks; urine collected twice weekly.
- Percentage response calculated for each stage => and used to calculated the weighted average response across both stages
- Treatment effect – defined as the between group difference in overall weighted response
- NNT = 9 - to have 1 patient respond to NTX + bupropion XL combination treatment

Trivedi et al., 2021, NEJM

Key Findings

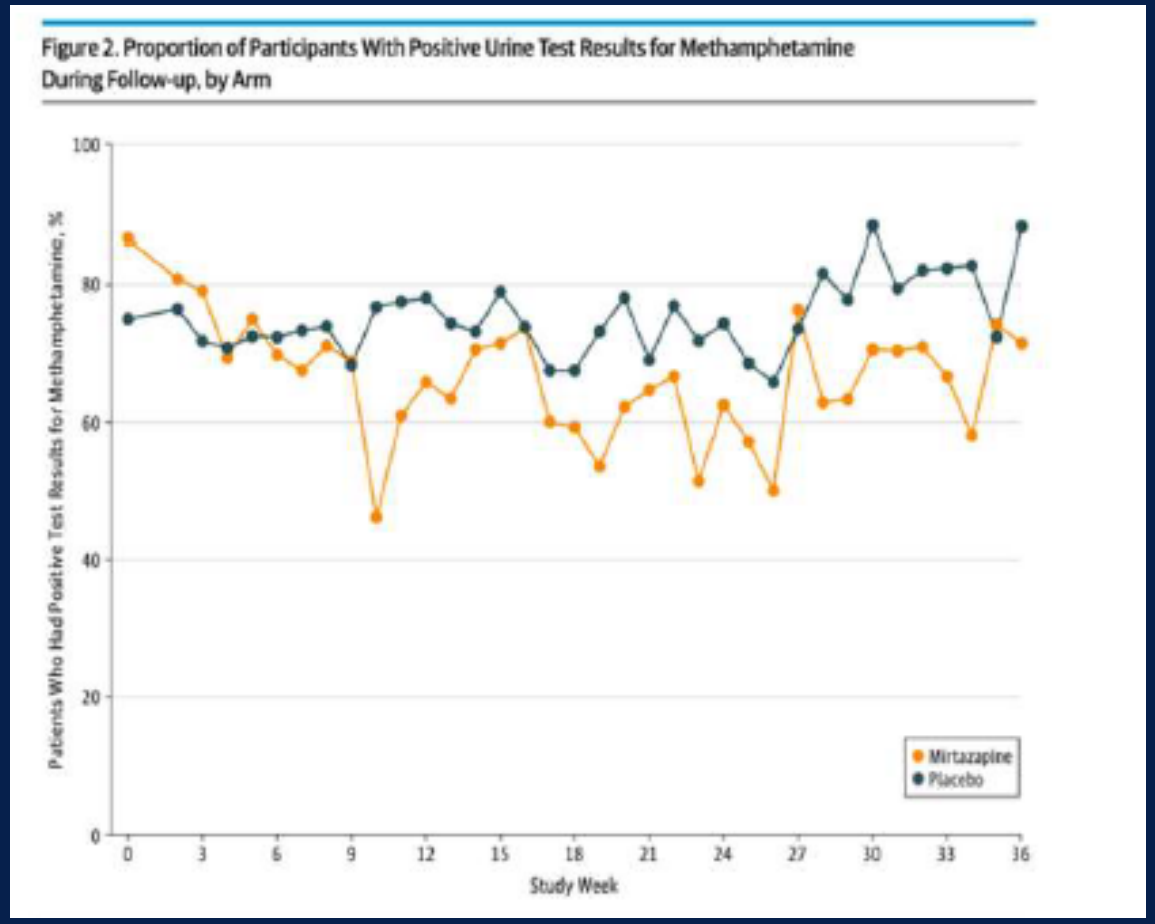
- 403 participants were enrolled in stage 1, and 225 participants in stage 2
- Average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo
- Overall treatment effect of 11.1% across a 12-week treatment period



Mirtazapine

- Atypical antidepressant: used primarily for the treatment of a major depressive disorder.
- Pharmacology: Belongs to a group of tetracyclic antidepressants (TeCA).
- Mechanism: Mirtazapine inhibits the central presynaptic alpha-2-adrenergic receptors, which causes an increased release of serotonin and norepinephrine.
- Starting dose 15 mg per day – preferentially at night (can make you sleepy)
- Dose range – 15 – 45 mg per day

Mirtazapine for Methamphetamine Use Disorder



Summary

- Double blind, RCT, n=120 cis men, transgender men, transgender women, who have sex with men and MA use disorder, actively using methamphetamine.
- Mirtazapine 30 mg vs placebo, plus counseling, for 24 weeks and 12 weeks of follow up
- ~40% adherence in both groups
- Significant reductions in methamphetamine positive UDS in the mirtazapine group at all time points.

Coffin PO et al. (2019) JAMA Psychiatry

Drug and Alcohol Dependence 232 (2022) 109295

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journal homepage: www.elsevier.com/locate/drugalcdep

Review

Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis

Leen Naji [a,b,*], Brittany Dennis [c], Tea Rosic [b,d], Wojtek Wiercioch [e], James Paul [f], Andrew Worster [b,c], Lehana Thabane [b,g], Zainab Samaan [b,d]

- Evidence informed => Not entirely evidence-based for pregnant and parenting persons
- Meta-analysis of 2 RCTs of mirtazapine => Both studies were double blinded placebo-controlled RCTs including a total of 180 cisgender men and transgender women
- Small reduction in MA use after 12 weeks => RR = 0.81, 95% CI: 0.63, 1.03; approximately 14 fewer individuals will test positive for methamphetamines in their urine at 12-weeks per 100 individuals receiving mirtazapine compared to placebo.
- No difference in treatment retention or clinical depression.

Key Findings

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Coffin et al 2019	25	38	32	41	76.8%	0.84 [0.64, 1.12]
Colfax et al 2011	12	27	17	27	23.2%	0.71 [0.42, 1.18]
Total (95% CI)		**65**		**68**	**100.0%**	**0.81 [0.63, 1.03]**
Total events	37		49			

Heterogeneity: $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 1.69 (P = 0.09)

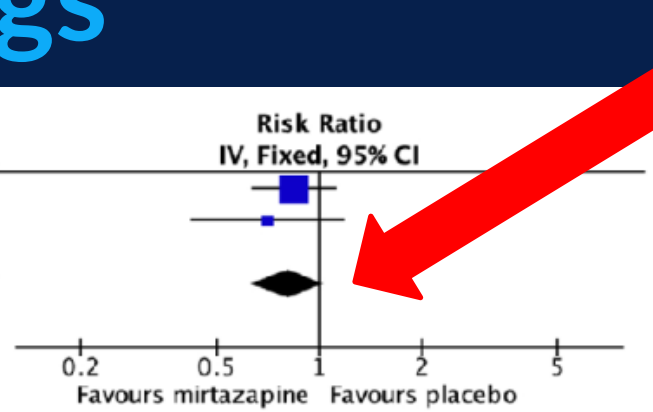


Fig. 2. : Forest plot and meta-analysis of reduction in methamphetamine positive urine toxicology screens at 12 weeks.

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Coffin et al 2019	49	60	48	60	37.6%	1.02 [0.86, 1.22]
Colfax et al 2011	28	30	28	30	62.4%	1.00 [0.87, 1.14]
Total (95% CI)		**90**		**90**	**100.0%**	**1.01 [0.91, 1.12]**
Total events	77		76			

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.85); $I^2 = 0\%$
Test for overall effect: Z = 0.14 (P = 0.89)

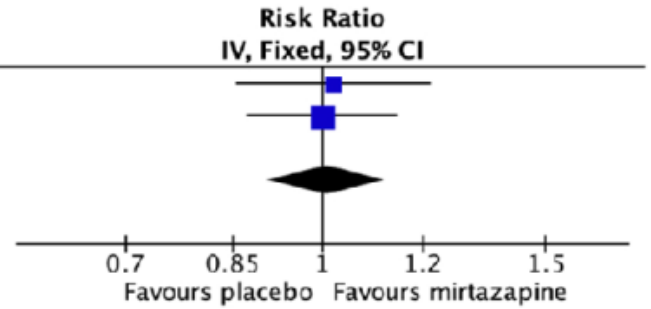


Fig. 3. : Forest plot and meta-analysis of retention in treatment at 12 weeks.

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Coffin et al 2019	-0.28	2.2143	58.9%	-0.28 [-4.62, 4.06]
Colfax et al 2011	1.5	2.6531	41.1%	1.50 [-3.70, 6.70]
Total (95% CI)			**100.0%**	**0.45 [-2.88, 3.78]**

Heterogeneity: $Chi^2 = 0.27$, df = 1 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 0.27 (P = 0.79)

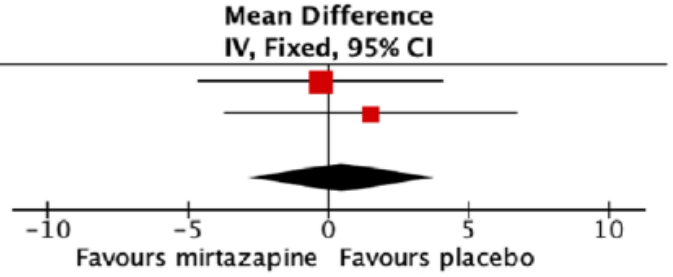


Fig. 4. : Forest plot and meta-analysis of reduction in depression symptom severity as measured by the CES-D scale at 12 weeks.

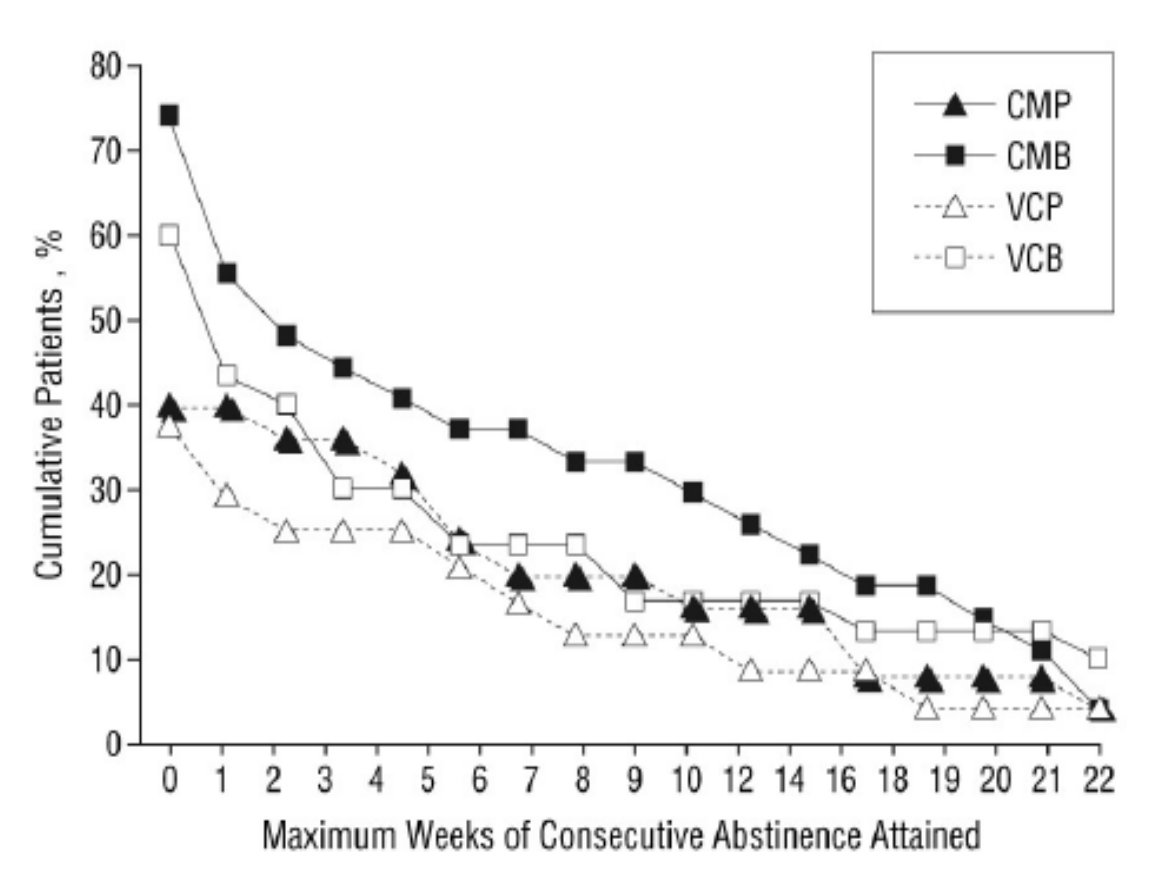
Cocaine Use Disorder (CUD) Pharmacotherapy

Medications for Cocaine Use Disorder (CUD)

- Modafinil (may have benefit without co-occurring AUD)
- Topiramate (lower intensity CUD)
  - *Additional consideration for AUD*
- Mixed Amphetamine Salts-ER + Topiramate
  - *Additional consideration for AUD, ADHD*
- Bupropion (best when combined with CM)

None are FDA-approved

Bupropion for Cocaine Use Disorder



- Methadone-maintained population (N = 106)
- Dosing: titrated to 300 mg daily
- Effect on consecutive abstinence weeks when combined with contingency management (CM)
- The average maximum numbers of consecutive weeks of cocaine abstinence was highest for **CM + bupropion**

Poling J, et al. Arch Gen Psychiatry. 2006

PROMPT

Prevention of Methamphetamine Use Among Postpartum Women Trial

- Postpartum treatment with progesterone
- **Duration:** Up to 12 weeks postpartum
- **Intervention**: Micronized progesterone (200 mg twice daily) versus placebo.
- **Feasibility study**: 40 women.
- **Safety**: maternal and neonatal outcomes.
- **Primary efficacy outcome**: return to methamphetamine use.

PROMPT: Pilot RCT – The How

- Double-blind, RCT of people with MUD within 12 weeks postpartum comparing oral micronized progesterone to placebo
- Excluded those with recent MA use within 4 weeks of enrollment.
- Primary outcome was feasibility, defined as enrollment of 80% planned sample (n = 32/40)
- Preliminary estimate of efficacy was determined by MU and craving scores

Smid et al; 2025; Pregnancy

PROMPT: Pilot RCT – Key findings

- Demographics and craving scores were similar between arms
- AEs did not differ by arm.
- Craving reduced for both arms, with a larger, but not significant, decrease in progesterone group
- Noted a significant interaction by OUD or MOUD, with:
  - Progesterone increasing cravings for those without OUD and with OUD taking buprenorphine
  - Reducing cravings for those with OUD taking methadone

Smid et al; 2025; Pregnancy

Takeaways

- Pharmacotherapy options are evidence informed at best, with lack of clinical trial data specifically in the context of pregnancy
- Reasonable considerations in pregnancy: bupropion with or without naltrexone (not FDA approved) and mirtazapine
- Non pharmacologic approaches currently remain first line and mainstay of treatment

Questions?

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