




Vermont Center on Behavior & Health



Center on Rural Addiction
UNIVERSITY OF VERMONT

Stimulants 2021: Epidemiology, Effects and Treatments

Richard Rawson, PhD
Department of Psychiatry
Larner College of Medicine
University of Vermont



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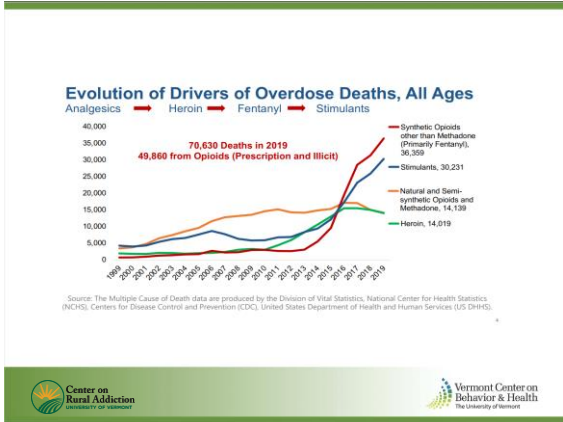


2

Epidemiology of Methamphetamine and Cocaine Use



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Hedegaard H, Miniño AM, Warner M. Drug Overdose Deaths in the United States, 1999-2018. NCHS Data Brief. 2020 Jan;(356):1-8. PMID: 32487285.

5

Stimulant Overdose Rates

From 2012 through 2018, the age-adjusted rate of drug overdose deaths involving cocaine more than tripled.

The rate of deaths involving psychostimulants (including methamphetamine) with abuse potential increased nearly 5-fold.

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Increase in Fatal Drug Overdoses Across the United States Driven by Synthetic Opioids Before and During the COVID-19 Pandemic Distributed via the CDC Health Alert Network December 17, 2020, CDCHAN-00438



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Synthetic Opioids and Overdose Deaths

- Increases in drug overdose deaths have accelerated during the Covid-19 pandemic.
- Synthetic opioids are the primary driver of the increases (38.4% increase from the 12 months ending June 2019, to the 12 months ending May 2020).
- Overdose deaths involving cocaine increased by 26.5%
- Cocaine-involved overdose deaths usually also involve illicit opioids.
- Overdose deaths involving psychostimulants (e.g., methamphetamine) are increasing at a rate (34.8%) higher than cocaine-involved.
- Psychostimulant overdose deaths are increasing with and without illicit opioids.



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Figure 76. Two Milligrams of Fentanyl - A Potential Lethal Dose



A lethal dose of carfentanyl 1/100th of the amount shown next to the penny

Source: Network Environmental Systems (NES)

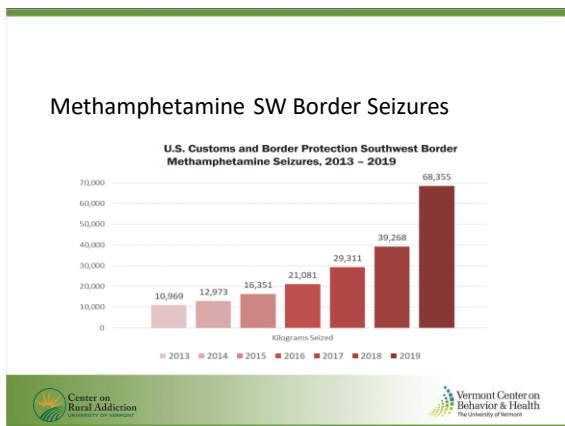
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Overdose-Related Cardiac Arrests Observed by Emergency Medical Services During the US COVID-19 Epidemic Friedman et al., 2020



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Overdose-Related Cardiac Arrests

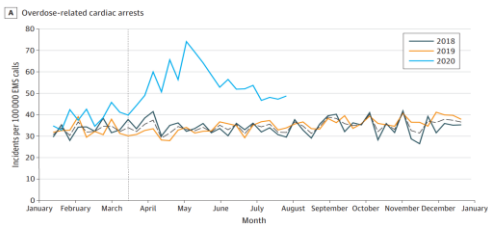
- State databases tracking overdose mortality have long lag times.
- Emergency medical services (EMS) provide near real-time information.
- This is a retrospective observational analysis using the National EMS Information System (NEMSIS).
- 10,000 EMS agencies in 47 states.



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Overdose-related cardiac arrests increased by about 50% in 2020 Friedman et al., 2020

Figure. Changes in Emergency Medical Services (EMS)-Observed Overdose Incidents, Cardiac Arrests, and Mobility During the US Coronavirus Disease 2019 (COVID-19) Epidemic



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Co-use of opioids and stimulants



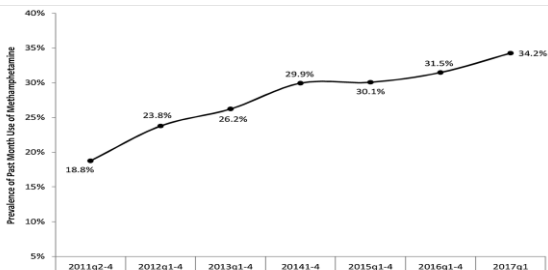
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Twin Epidemics: The surging rise of methamphetamine use in chronic opioid users.
 Ellis, M. Kasper, A., Cicero, T. (2018)
 Drug and Alcohol Dependence, 2018, 14-20



29

% of Respondents reporting use of meth in past 30 days Ellis et al 2018



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Vermont Opioid Use Harm Reduction Evaluation between June 2018 and November 2019

- Stimulant use is common among participants who are receiving Medication Assisted Treatment (MAT) for Opioid Use Disorder (N=44)
- Among those receiving MAT, 66% had used crack or cocaine within the past 30 days. •
- Among those receiving MAT, 75% had used any stimulant within the past 30 days. •
- Among those using any stimulants in the past 30 days (N=57), 65% were receiving MAT through a provider.



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Impacts of Methamphetamine Use



32

Paulus, M. P. and Stewart, J.L. , Neurobiology, Clinical Presentation and Treatment of Methamphetamine Use Disorder: A Review. JAMA Psychiatry, 77:959-966.
doi:10.1001/jamapsychiatry.2020.02462020



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Neurotoxicity

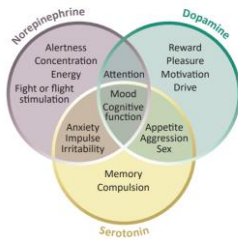
- Excessive dopamine resulting in damaged cell structures
- Cell death
- Activation of dopamine D3 receptors resulting in hyperthermia
- Disruption of the blood-brain barrier
- Overall, the altered brain state is consistent with degenerative central nervous system diseases.



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Behavioral Effects of Neurotransmitters

FIG. 1 Behavioral effects mediated by the three main neurotransmitters



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Cognitive effects

- Soon after cessation of methamphetamine use:
- Poor performance on motor and processing tasks
 - Poor performance on verbal fluency and attention

- After prolonged abstinence:
- Poor learning efficiency and comprehension
 - Poor visual-spatial processing
 - Slow processing and psychomotor speed



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Cognitive effects

It is estimated the more than 2/3 of those with methamphetamine use disorder show cognitive impairment.

Impairment is associated with older age, longer duration of use, injection route of administration and greater frequency of use.

Impairment may limit ability to follow through with treatment, comprehend advice and direction in treatment as well as generally achieve good treatment outcomes.



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Cerebrovascular and Cardiovascular Disease

Leading causes of death with methamphetamine use disorder

Strokes on rise, most often with young men

Strokes are primarily hemorrhagic

- Associated with methamphetamine use:
 - Pulmonary hypertension
 - Cardiac arrhythmia
 - Cardiomyopathy



38

Smid, M., Metz and Gorden. (2019). Stimulant Use in Pregnancy: An Under-Recognized Epidemic Among Pregnant Women, Clin Obstet Gynecol. 62(1), 168–184.



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Stimulant Use in Pregnancy

Smid et al., 2019

Meta-analysis of 31 studies found cocaine use during pregnancy increased risk of pre-term delivery, low birth weight, small for gestational age, earlier gestational age at delivery (Gouin, 2011).

Meta-analysis of 8 studies found methamphetamine use during pregnancy was associated with earlier gestational age at delivery, lower birth weight, and smaller head circumference (Kalaizopoulos, 2018).

Infants with prenatal exposure to methamphetamine exhibit jitteriness, drowsiness, and respiratory distress suggesting withdrawal. Cocaine and methamphetamine are excreted in breastmilk and contraindicate breastfeeding.



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Stimulant Use in Pregnancy

Smid et al., 2019

- Long-term follow-up of 204 methamphetamine exposed maternal-child pairs and 208 unexposed pairs (Derauf et al., 2007).
- At one month, 33% methamphetamine-exposed mothers did not have custody compared to 2% of unexposed.
- At age 3 years, heavy prenatal methamphetamine use (≥ 3 days per week) was associated with anxiety/depression and attention problems.
- At age 7.5 years, methamphetamine-exposed children had poorer cognitive function.
- UCLA Study of 4-5 year olds found impoverished vocabulary and poorer fluency with language



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Dental effects

- Rampant caries and tooth fracture most common (Shaner, 2002; 2006)
- Periodontal disease
- Mechanisms:
 - Poor oral hygiene
 - Xerostomia (dry mouth)
 - Alpha 2 receptor stimulation inhibits saliva
 - Dehydration from appetite suppression and increased psychomotor activity
 - Soft drink consumption
 - Bruxism
 - Acidic content of MA (controversial)
 - Corrosive contaminants of MA (smoking)



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Dermatological Effects

- Pruritis from vasoconstriction
- Cutaneous ulcers and excoriations from skin picking (formication, "meth bugs")
- Abscesses ("skin popping" confers greatest risk)
- Cellulitis
- Burn injuries



43

Foulds, JA, Boden, JM, McKetin, R. and Newton, Howes, G. 2020
 Methamphetamine use and violence: Findings from a longitudinal birth cohort. *Drug and Alcohol Dependence*, 207. 43-53.



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Methamphetamine and Violence

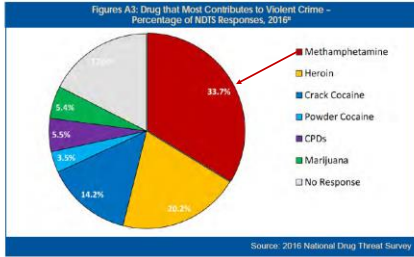
Foulds et al., 2020

- Compared to no use, amphetamines use was associated with a 2-fold increase in the odds of hostility or violence.
- Frequent and heavier/injection use increases the risk of violent behavior.
- Other risk factors included: psychotic symptoms, alcohol or other drug use, psychosocial problems, and impulsivity.
- A majority of violent episodes occurred during periods of psychosis



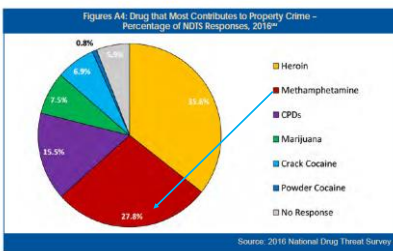
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Drugs and Violent Crime



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Drugs and Property Crime




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Rawson, R.A., Washton, A.M., Domier, C.P., & Reiber, C. (2002). Drugs and sexual effects: Role of drug type and gender. *Journal of Substance Abuse Treatment* 22(2), 103-108



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Clinical Challenges

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Clinical Challenges With Individuals with Stimulant Use Disorder



- Overdose death
- Limited understanding of stimulant addiction
- Ambivalence about need to stop use
- Impulsivity/Poor judgement
- Cognitive impairment and poor memory

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Clinical Challenges With Individuals with Stimulant Use Disorder

- Anhedonia
- Paranoia
- Hypersexuality
- Violence and psychosis
- Powerful Pavlovian trigger-craving response
- Elevated rates of psychiatric co-morbidity
- Very poor retention in outpatient treatment

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Interest in Reducing Methamphetamine and Opioid Use Among Syringe Services Program Participants in Washington State McMahan et al, 2020 Drug and Alcohol Dependence

- In a sample of 583 participants at a Washington state syringe exchange program (443 opioids; 140 methamphetamine), survey data were collected on their attitudes about stopping drug use.
- 82% of the individuals who reported opioids as their main drug expressed an interest in reducing/stopping opioid use.
- 46% of individuals who reported methamphetamine as their main drug expressed an interest in reducing/stopping their meth use.



52

Lappan SN, Brown AW, Hendricks PS. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. Addiction. 2020 Feb;115(2):201-217. doi: 10.1111/add.14793.



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Dropout rates of in-person psychosocial substance abuse treatment: a systematic review and meta-analysis (Lappan et al., Addiction, 2020)

- Meta-analysis of in-person psychosocial SUD treatment.
- Drop out rates in first 90 days of treatment
- 151 studies, with 26,243 participants.
- Results yielded overall average dropout rates, and predictors of dropout.



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Substance Targeted and Dropout

Treatment Target	Dropout Rate
Heroin	25.1
Tobacco	25.5%
Alcohol	26.1%
Cocaine	48.7%
Methamphetamine	53.5%



55

Judith I. Tsui, et al (2020) Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine. *Journal of Substance Abuse Treatment* 109:80–85



56

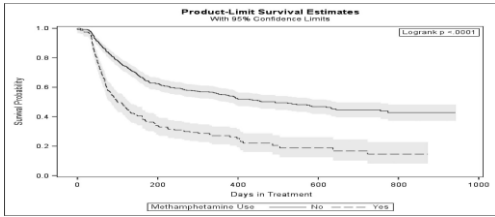
Association Between Methamphetamine Use and Retention Among Patients With Opioid Use Disorders Treated With Buprenorphine

- The study utilized data on adult patients receiving buprenorphine from Washington State Medication Assisted Treatment-Prescription Drug and Opioid Addiction program clinics between November 1, 2015, and April 31, 2018 (N=799). Past 30-day substance use data were collected at baseline, 6-months, and date of program discharge.
- 30% (n=237) of individuals reported meth use at admission. Baseline methamphetamine use was associated with more than twice the relative hazards for discharge in adjusted models (aHR=2.39; 95% CI: 1.94–2.93).



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Association Between Methamphetamine Use and Retention Among Patients With Opioid Use Disorders Treated With Buprenorphine



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Special Treatment Consideration Should Be Made for the Following Groups

- **People who inject stimulants.**
- **People who use stimulants daily or in very high doses.**
- Women (high rates of physical/sexual abuse).
- Homeless, chronically mentally ill, and/or individuals with high levels of psychiatric symptoms at admission.
- Men who have sex with men (MSM).
- Individuals in medication treatment for OUD.



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Clinical Interventions



60

Isoardi KZ, Ayles SF, Harris K, Finch CJ, Page CB. Methamphetamine presentations to an emergency department: Management and complications. Emerg Med Australas. 2019 Aug;31(4):593-599. doi: 10.1111/1742-6723.13219. Epub 2018 Dec 28.



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Methamphetamine Presentations to an Emergency Department: Management and Complications Isoardi et al., 2019

- 329 patients (378 presentations) in 2016
- ED in Brisbane, Australia
- Clinical effects:
 - Behavioral disturbance, 78%
 - Tachycardia, 56%
 - Hypertension, 42%
 - Hyperthermia, 5%



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Harm Reduction Strategies for Individuals who Use Stimulants

- Information about medical and psychiatric effects of meth
- Overdose education (fentanyl)
- Syringe exchanges
- Naloxone (for opioid overdose)
- Quiet rooms and wash up/shower rooms
- Condoms/safe sex education
- Topical antibiotic creams and ointments for injection sites
- Water (dehydration)
- Toothpaste/toothbrush



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Treatment for Individuals with Stimulant Use Disorder



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Systematic Reviews and Meta-analyses



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RESEARCH ARTICLE

Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis

Francesco De Crescenzo^{1,2,3}, Marco Ciabattini⁴, Gian Loreto D'Alò⁵, Riccardo De Giorgi^{6,7}, Cinzia Del Giovane⁸, Carolina Ciesan⁹, Luigi Janiri⁷, Nicolas Clark⁷, Michael Joshua Ostacher^{8,9}, Andrea Cipriani^{1,2,3*}

1 Department of Psychiatry, University of Oxford, Oxford, United Kingdom, **2** Oxford Health NHS Foundation Trust, Warfield Hospital, Oxford, United Kingdom, **3** Institute of Psychiatry and Clinical Psychology, Catholic University of the Sacred Heart, Rome, Italy, **4** School of Hygiene and Preventive Medicine, University of Rome Tor Vergata, Rome, Italy, **5** Institute of Primary Health Care (IPHC), University of Bern, Bern, Switzerland, **6** Department of Dynamic and Clinical Psychology, Sapienza University of Rome, Rome, Italy, **7** Mental Health and Substance Abuse, World Health Organization, Geneva, Switzerland, **8** Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, United States of America, **9** Department of Psychiatry, VA Palo Alto Health Care System, Palo Alto, California, United States of America



PLOS Medicine | December 26, 2018



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Meta-Analysis Findings

Network meta-analysis was used to analyze 50 clinical studies (6,943 participants) on 12 different psychosocial interventions for cocaine and/or amphetamine addiction.

The combination of contingency management and community reinforcement approach was the most efficacious and most acceptable treatment, both in the short and long term.



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Responding to Global Stimulant Use: Challenges and Opportunities Lancet (Farrell et al., 2019)

Psychosocial **interventions other than contingency management have weak and non-specific effects** on stimulant problems, and there are no effective pharmacotherapies. Substantial research investment is needed to develop more effective, innovative, and impactful prevention and treatment.



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Non-Pharmacological Interventions for Methamphetamine Use Disorder: A Systematic Review Drug and Alcohol Dependence, AshaRani, PV, et al. 2020



- 44 Studies reviewed.
- Conclusions: While Contingency Management (CM) interventions showed the strongest evidence favoring the outcomes assessed, tailored CBT alone or with CM was also effective in the target population.



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Current Status of Treatment Approaches for Stimulant Use Disorder

- **Contingency management unanimously** (5 systematic reviews and meta-analyses) found to have best evidence of effectiveness.
- Other approaches with less but clear evidence of support: Cognitive Behavioral Therapy (CBT) and Community Reinforcement Approach (CRA).
- Approach with evidence for treatment of a broad variety of SUD: Motivational Interviewing (MI).
- Approach with recent studies showing benefit to methamphetamine users: Physical Exercise (PE) (e.g., Rawson et al., 2015).






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Contingency Management for the Treatment of Methamphetamine Use Disorder: A Systematic Review

Brown and DeFulio, 2020



- A review of 27 studies.
- All included a contingency management intervention for individuals with methamphetamine use disorder.
- Outcomes:
 - Drug abstinence
 - Retention in treatment
 - Attendance/treatment engagement
 - Sexual risk behavior
 - Mood/affect
 - Treatment response predictors

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Results of CM Treatments

- Reduced methamphetamine use in 26 of 27 studies.
- Longer retention in treatment.
- More therapy sessions attended; higher use of other services and medical services.
- Reductions in risky sexual behavior.
- Increases in positive affect and decreases in negative affect.

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Three Major Challenges to using CM

- Staff resistance to the idea of incentives
 - Patients should not have to be "paid" or "bribed"; recovery is the reward
 - Motivation needs to come from within, etc.....
- Where does the funding for incentives come from?
- Medicaid regulations that restrict the amount of incentives that can be given to patients to \$75 per patient per year.



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Office of Inspector General (OIG), Department of Health and Human Services (HHS). ACTION: Final rule

- Medicare and State Health Care Programs: Fraud and Abuse; Revisions to Safe Harbors Under the Anti-Kickback Statute, and Civil Monetary Penalty Rules Regarding Beneficiary Inducements
- 77684 Federal Register / Vol. 85, No. 232 / Wednesday, December 2, 2020 / Rules and Regulations
- rawson@uvm.edu Will send PDF



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One view on Final Rule

- Per the Final Rule, there is no OIG ban on CM within a Medicaid environment, nor \$75 limit on the incentive total used.
- **Health systems should consider implementing pilot projects using CM with evidence-supported incentive amounts.**
- HOWEVER, per the Final Rule, careful attention should be given to making sure that:
 - Programs do not advertise the use of CM (incentives) in their marketing, patient recruitment materials.
 - Use of CM requires the development and use of a clear protocol and methodology for CM.
 - A clear and documented plan for the oversight and supervision of this protocol and documentation of adherence to the protocol is required.
 - A rigorous accounting system is required to ensure the security and accountability of funds used for incentives and to prevent any fraud or other diversion of funds.
- At the present time, standards acceptable to the OIG for addressing #5 a-d have not been established.



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Medications






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Medications for Cocaine Use Disorder

Medications with positive studies and under consideration.

- topiramate*
- modafinil*
- bupropion*
- amphetamine salts
- disulfiram (mixed, worse retention)
- propranolol (WD)
- buprenorphine+naltrexone






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Medications for Methamphetamine Use Disorder

Medications with positive studies and under consideration

- Bupropion/naltrexone
- mirtazapine
- bupropion
- naltrexone
- methylphenidate
- d-amphetamine
- topiramate

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TRUST: Treatment of Individuals who Use Stimulants: TRUST

An Integrated Behavioral Model



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TRUST: The Components

TRUST is an integrated, evidence-based, multi-component program for the treatment of individuals with stimulant use disorders. The contents include:

1. Motivational incentives (based on contingency management research),
2. Elements of cognitive behavioral therapy
3. Elements of community reinforcement approach,
4. Motivational interviewing skills,
5. Physical exercise

Participation in recovery support programs encouraged (eg. 12-Step; Moderation management).

Appendix includes other EBPs to augment the core program at the discretion of each organization.



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