Stimulants and Approaches to the Management of Stimulant Use

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META:PHI
MENTORING, EDUCATION, AND CLINICAL TOOLS FOR ADDICTION
PARTNERS IN HEALTH INTEGRATION

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- Presenter: Tanya Hauck
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  - Fellowship funding: Bellwood Health Services

Mitigating Potential Bias

- We will discuss off-label pharmacotherapy treatments for stimulant use disorder and off-label treatments for stimulant-induced psychosis.

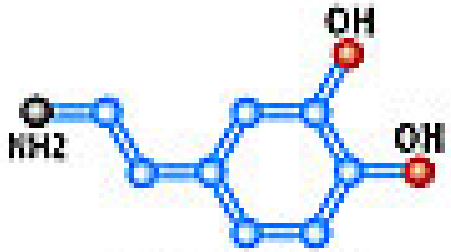
LEARNING OBJECTIVES

- Review stimulant pharmacology:
  - To understand the unique pharmacological properties of the various that contributes to its effects and risks.
- Psychosocial treatments:
  - To understand the evidence-based therapy options, their underpinnings, and appreciate their limitations
- Pharmacologic treatments:
  - To identify the limited evidence-based options and their limitations

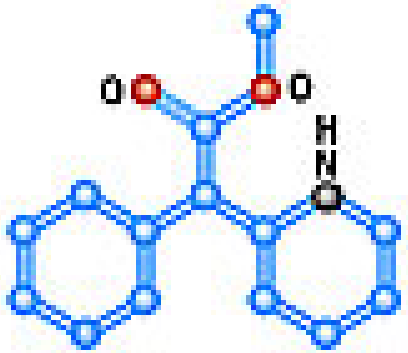
STIMULANT PHARMACOLOGY

EPIDEMIOLOGY & ISSUES

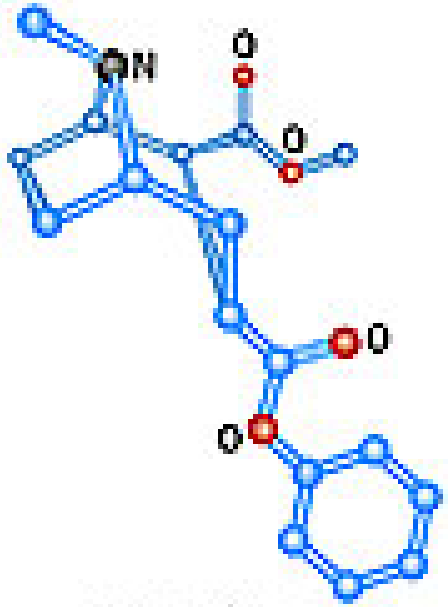
STRUCTURE OF DOPAMINE & STIMULANTS



Dopamine

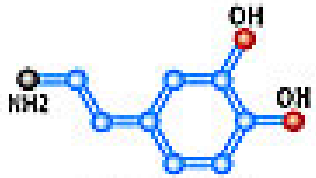


Ritalin

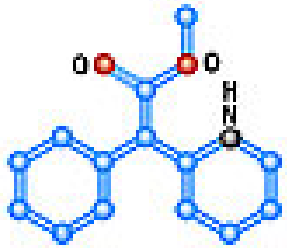


Cocaine

STRUCTURES OF AMPHETAMINES



Dopamine



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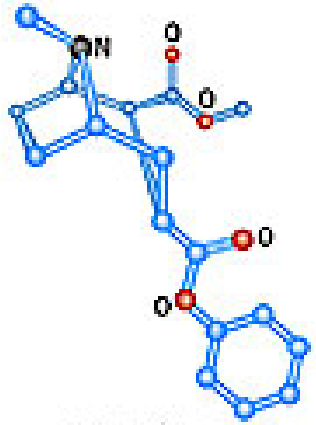
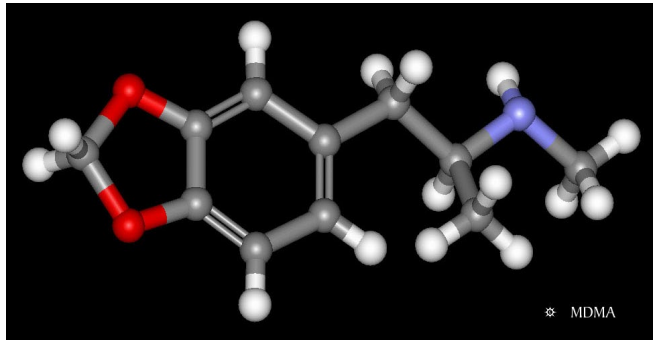
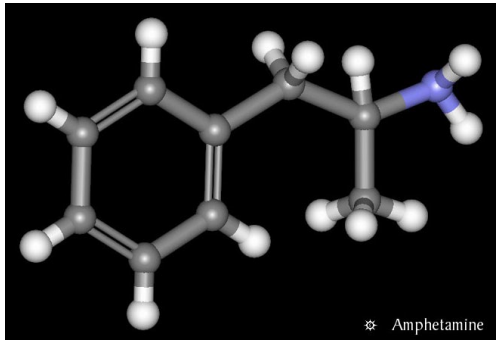
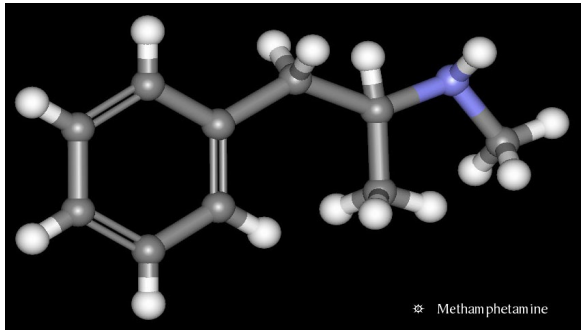
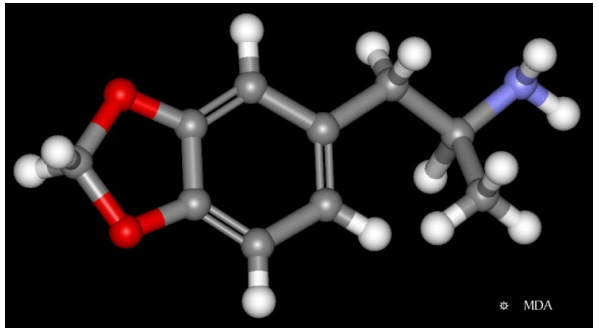


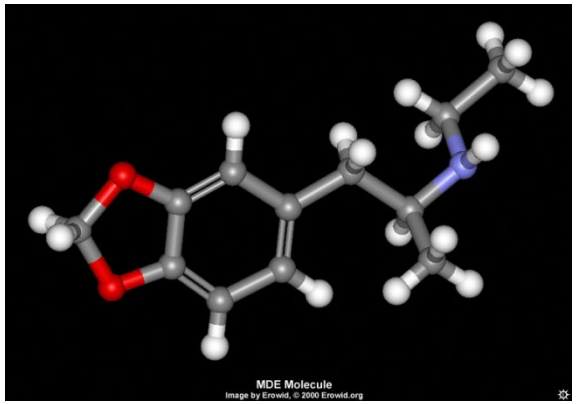
Cocaine



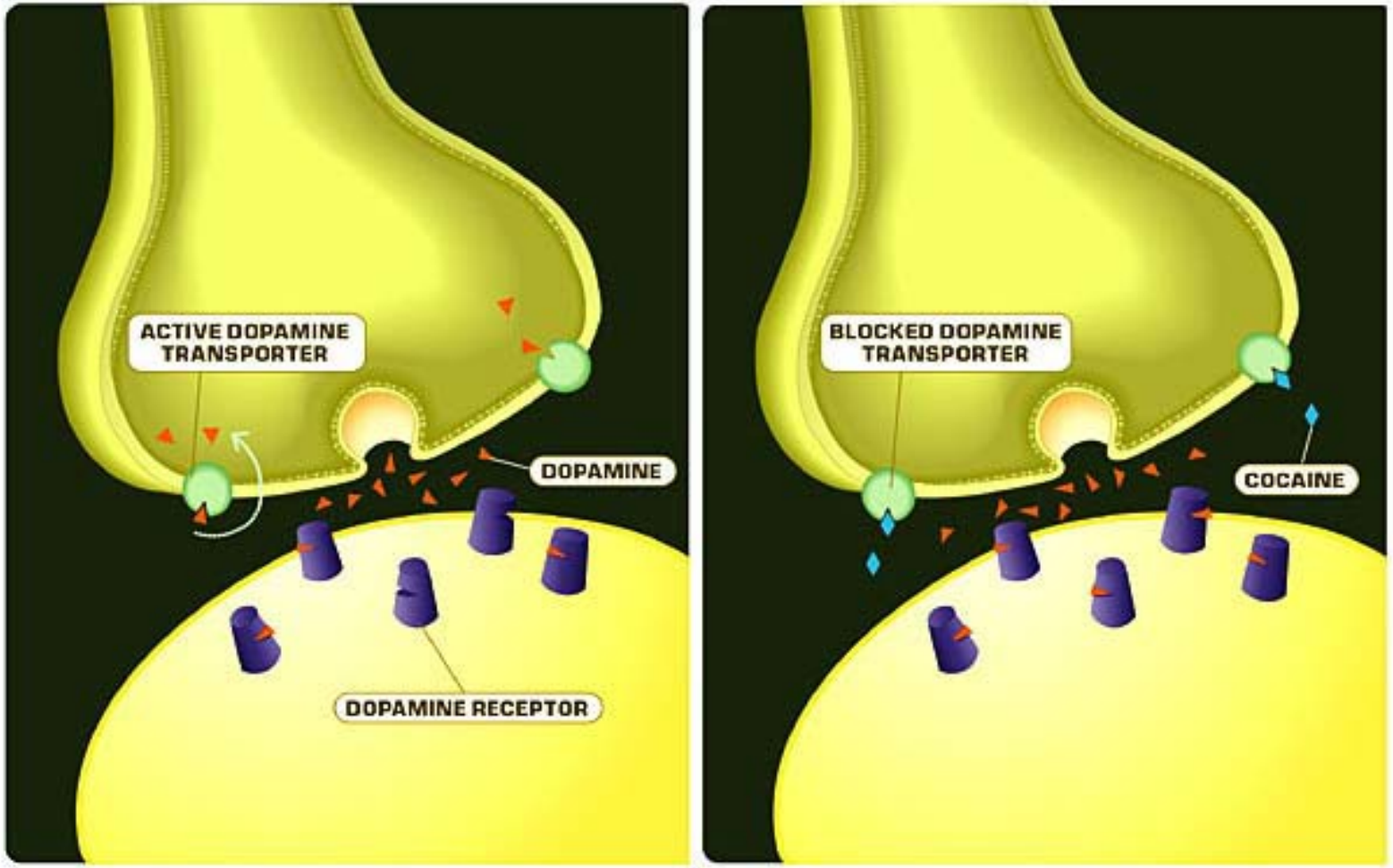








DOPAMINE TRANSPORTER



STIMULANTS

Cocaine: $t_{1/2}$ 45-90 minutes

- Blocks membrane sodium channels → anesthetic
- Blocks reuptake: dopamine, norepinephrine, serotonin

Amphetamine: $t_{1/2}$ 6-15 hours

- Blocks reuptake
- Causes RELEASE of additional dopamine

- Increased dopamine in nucleus accumbens leads to reinforcement
- Long term depletion of neurotransmitters leading to neurocognitive effects

7% of cocaine users develop dependence in the first year of use

ASAM Principles of Addiction Medicine, Figure 12-1, 2019
Lopez-Quintero et al, Drug Alcohol Depend. 2011 May 1; 115(1-2): 120–130.

METHAMPHETAMINE: ANYTHING YOU CAN DO I CAN DO BETTER

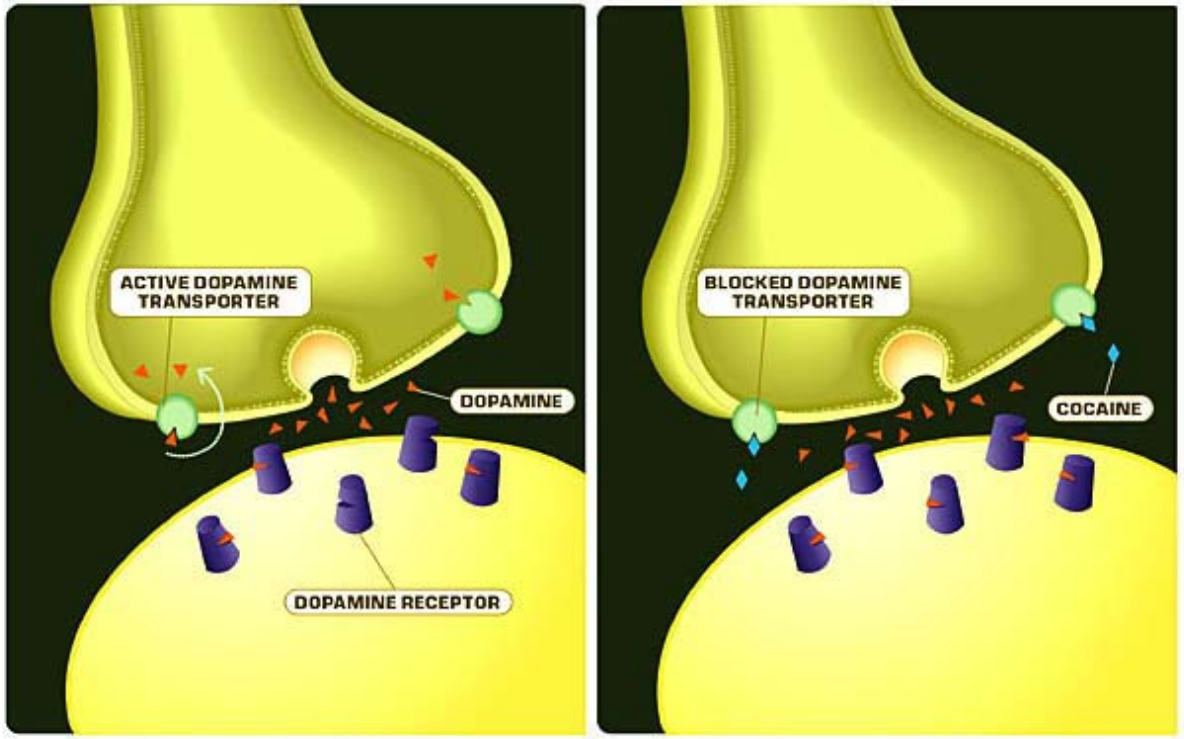
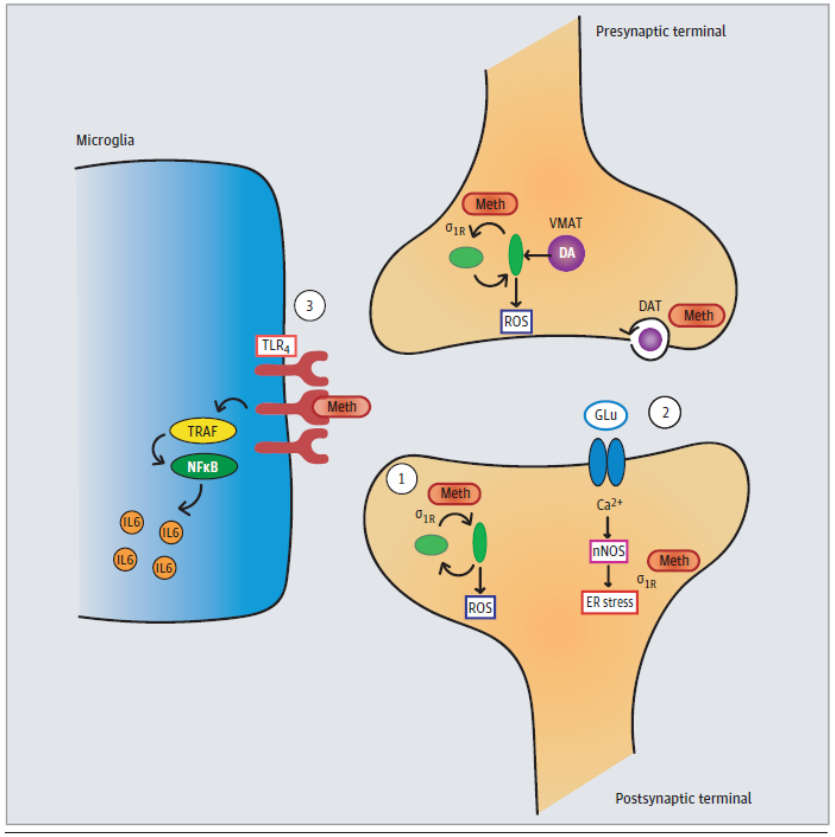


Figure 2. Methamphetamine-Induced Changes in Synaptic and Intracellular Pathways



Methamphetamine (Meth) increases dopamine in the synaptic cleft via its effect on the cell surface dopamine (DA) transporter (DAT) and increases DA in the the cell via its effect on the vesicular monoamine transporter (VMAT). Methamphetamine (1) directly alters mitochondrial fusion and fission via sigma-1 receptor (σ_{1R}) binding, leading to an increase in reactive oxygen species (ROS); (2) increases glutamatergic (GLu) transmission, which via increased intracellular calcium (Ca^{2+}) and nitric oxide synthase (nNOS) leads to endoplasmic reticulum (ER) stress; and (3) binds to the toll-like 4 (TLR_4) receptor to activate inflammatory pathways via nuclear factor κ-light-chain enhancer of activated B cells (NFκB) and tumor necrosis factor receptor–associated factors (TRAF) to produce proinflammatory cytokines (interleukin 6 [IL-6]).

Paulus MP, Stewart JL. Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder: A review. JAMA Psychiatry. 2020;77(9):959-966. doi:10.1001/jamapsychiatry.2020.0246

METHAMPHETAMINE

- Methamphetamine appeared as a recreational drug in early 1940's
- Can be ingested, smoked or used intranasally or intravenously
  - Dependence is related to speed of onset of effects with most drugs
- Half life is ~12 hrs in serum (range 9-13 hours)
- CNS stimulation for 6 to 24 hours
- Two isomers – the d-methamphetamine is more potent

Urbina, A and Jones K. HIV/AIDS 38 (2004) 890-894

EPIDEMIOLOGY

- Methamphetamine use was declining into the mid-2000s, but is increasing again.
- Amphetamine-type stimulants were prescribed widely in the 1950s and 1960s for mood and weight loss, and they were reclassified as scheduled drugs in the 1970s.
- Genetic component to use disorder, but multifactorial risk factors, polymorphisms in dopamine receptor and transporter https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021NSDUHFFRRev010323.pdf

Current users:

Methamphetamine: 0.3% of population (USA) in 2015 → 0.9% in 2021

Cocaine: 0.7% of population (USA) in 2015 → 1.7% in 2021 (past year use)

The "twindemic": between 2015 and 2017, methamphetamine use tripled among people using heroin (**9.0% to 30.2%**). (Strickland, 2019)

https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf
https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021NSDUHFFRRev010323.pdf

METHAMPHETAMINE AND WOMEN

- While most drugs effect men and women similarly, stimulants are an exception
- Mood impacts have interactions between meth and menstrual hormonal fluctuations
- In pregnancy, there are additional risks:
  - Pre-eclampsia 9.3% vs 4.4% with opioids vs. 4.8% general
  - Placental abruption 4.3% vs. 3.1% vs. 1.0%
  - Preterm delivery (<37 weeks) 16.7% vs. 12.6% vs. 5.5%
- Placental vasoconstriction decreases oxygen and nutrients to foetus, increases mother's blood pressure

Credit to Dr. Suzanne Turner at McMaster for these points – references available

METHAMPHETAMINE AND WOMEN

- No fetal anomalies
- The appetite suppression effects can lead to small for age babies, also shorter which is not made up over time
- Pregnant moms who are using may be less likely to come for prenatal care
- There seem to be some behavioural consequences in babies at 1 year
- Methamphetamine is in the breast milk of using mom's and so it is not safe to breast feed until at least 48 hours after use (based on case studies)

Credit to Dr. Suzanne Turner at McMaster for these points – references available

DOPAMINE IS THE NEUROCHEMICAL OF SALIENCE (NOT REWARD)

STIMULANT USE DISORDER (DSM5)

1. Larger amounts/longer period
2. Persistent desire/unsuccessful attempt to cut down
3. Significant time spent obtaining/using/recovering
4. Cravings/strong desire to use
5. Failure to fulfill role obligations (work, school, home)
6. Use despite social/interpersonal problems
7. Social/occupational/recreational activities given up
8. Recurrent use in hazardous situations
9. Use despite physical/psychological problems caused/exacerbated by alcohol
10. Tolerance
11. Withdrawal

>12 months

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

STIMULANT WITHDRAWAL

DSM 5 criteria

- Dysphoric mood
- Fatigue
- Vivid and unpleasant dreams
- Insomnia or hypersomnia
- Increased appetite
- Psychomotor agitation or retardation

Other observations

- Suicidal ideation and nihilistic thinking can be prominent 2-3 days after cessation of use
- Immediately after cessation of use most users have a “crash” where they sleep more
- Some may manage sleep-wake cycles by alternating between stimulants and benzodiazepines/alcohol or other sedating drugs – this can layer different withdrawal syndromes

PHASES OF STIMULANT WITHDRAWAL

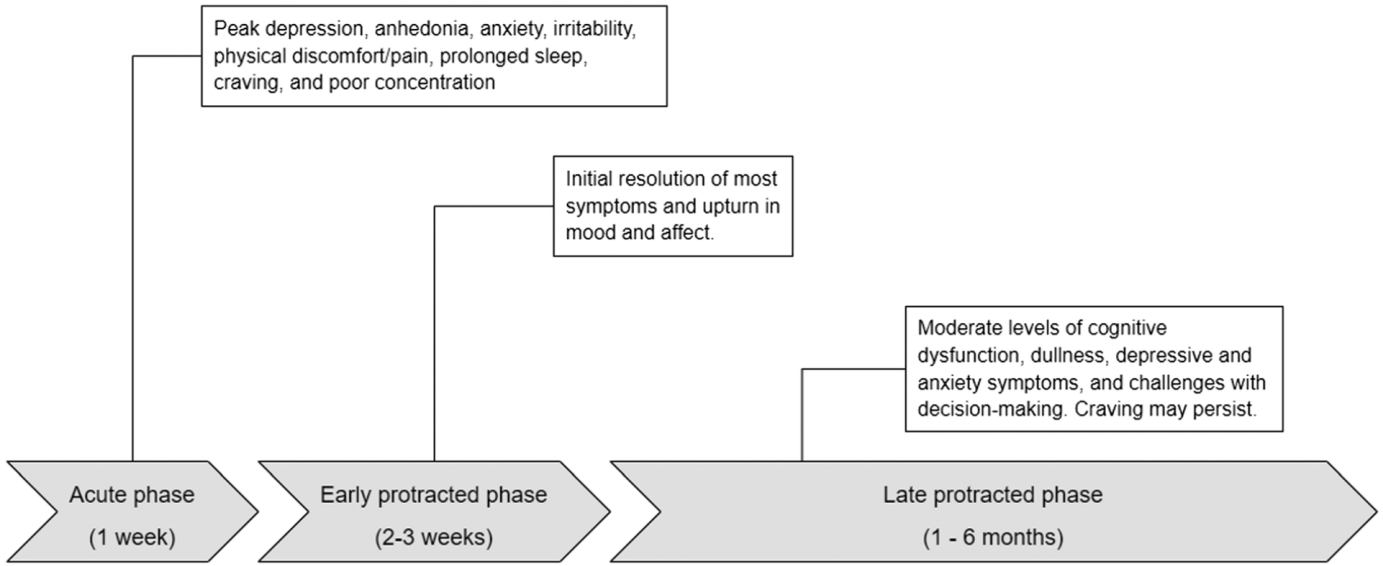


FIGURE 1 Summary of stimulant withdrawal symptoms across different phases (with time-frame following abstinence)

Li M and Shoptaw S. Clinical management of psychostimulant withdrawal: review of the evidence. Addiction (2023) 118: 750-762. * review is based on 30 studies – 11 on MA, 12 on cocaine, 4 amphetamines, 3 mixed

PSYCHOSOCIAL TREATMENTS

REVIEW OF THE APPROACHES

PSYCHOSOCIAL TREATMENTS

- Abstinence
  - Matrix Model (16 week model)
    - CBT + family education + self-help participation
    - Focused on relapse prevention, drug avoidance, identification of triggers and drug refusal
  - Contingency management
  - Community Reinforcement?
  - Cognitive behavioural therapy?
- Reduction in use (and/or abstinence)
  - CBT
  - CRA
- Symptom management
  - Anti-psychotic medication
  - Benzodiazepines

Courtney KE, Ray LA. Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology , and treatment literature. Drug and Alcohol Dependence (2014) 143:11-21.

A NOTE ABOUT STIMULANT-INDUCED NEUROCOGNITIVE EFFECTS

"Chronic cocaine or amphetamine use is associated with cognitive impairment that may persist for **at least several months of abstinence**. Most affected are **visuomotor performance**, **attention**, **inhibitory control**, and **verbal memory**. Several studies have found abnormalities of behavioral regulation and risk-reward decision-making. This type of impairment is associated with lesions of the **frontal cortex**, a brain area that shows decreased regional blood flow and metabolic activity in abstinent cocaine users." (ASAM 2019)

- High levels of dopamine lead to reactive oxygen species, oxidative stress and neurotoxicity
- Improvements after prolonged abstinence (9-12 months) (Courtney and Ray, 2014)
- Methamphetamine-related changes to executive function likely reduce the effectiveness of cognitive-based treatments

COMMUNITY REINFORCEMENT APPROACH

Triggers				
External	Internal	Behaviour	Short-Term Positive Consequences	Long-Term Negative Consequences
1. Whom are you usually with when you use?	1. What are you usually thinking about right before you use?	1. What do you usually use?	1. What do you like about using with _____? (whom)	1.What are the negative results of _____ (behaviour/activity) Regarding each of these areas:
2. Where do you usually use?	2. What are you usually feeling physically right before you use?	2. How much do you usually use?	2. what do you like about using _____? (where)	a. Family members b. Friends c. Physical feelings
3. When do you usually use?	3. What are you usually feeling emotionally right before you use?	3. Over how long a period do you usually use?	3. What you like about using _____? (when)	d. Emotional feelings e. Legal situations f. School situations
			4. What are some of the pleasant thoughts you have while you are using?	g. Job situations h. Financial situations i. Other situations
			5. What are some of the pleasant physical feelings you have while you are using?	
			6. What are some of the pleasant emotional feelings you have while you are using?	

FUNCTION OF USE

Physical effects

- Increased sensory acuity
- Increased energy
- Decreased appetite
- Decreased sleep
- Decreased reaction time

Psychological Effects

- Increased confidence/decreased timidity
- Increased alertness and attention
- Improved mood
- Increased sex drive
- Decreased boredom
- Decreased loneliness

Ciccarone D, Shoptaw S. Understanding stimulant use and use disorders in the new era. Medical Clinics of North America (2022) 106:81-97.

METHAMPHETAMINE AND SEX

Reasons people may have sex on meth

- It feels good
- Certain contexts include methamphetamine:
  - Gay men
  - Sex trade
- Managing impact of sexual abuse or guilt/shame associated with sex

TIPS IN REDUCTION/RECOVERY WHEN SEX OVERLAPS WITH METHAMPHETAMINE USE

Sex therapy principles are key:

- Reductions or abstinence from methamphetamine may need reduction and abstinence from some sex acts
  - Cast this as a holiday, a rest, a vacation
- Changing to new associations, changing sexual activities and or settings, re-programming our sexual pleasure
  - Explore new activities without meth
- Understand the connections – do a functional analysis (what is the drug doing, when are you using it, what prompts it, what extends it)
- Avoid triggering situations initially, learn alternate ways to get needs met
  - Avoid usual places and types of sex

CONTINGENCY MANAGEMENT

Evolved from these principles of behaviour theory and reinforcement (ASAM, 2019):

1. “Identification of a target behavior that is **measurable and important** (e.g., abstinence from drugs as indicated by urine toxicology; attendance at counseling sessions).
2. Provision of **concrete reinforcement** (e.g., money, goods, “prizes,” access to privileges or to work opportunities) contingent upon producing the target behavior.”

CONTINGENCY MANAGEMENT

Basic principles (Petry, 2012):

1. Frequently monitor the behaviour that you are trying to change.
2. Provide tangible, immediate positive reinforcers each time that the behaviour occurs, such as:
   - vouchers, that increase with each target behaviour
   - drawing for prizes, with increasing draws.
3. When the behaviour does not occur, withhold the positive reinforcers.

We are already doing this in opioid agonist treatment

Many businesses do this all the time

CONTINGENCY MANAGEMENT: THE EVIDENCE

This is an evidence-based treatment and many studies have shown it is effective!

"Among psychotherapeutic and behavioral treatments for SUDs, CM **has shown the most consistent and strongest evidence of efficacy compared to control conditions**" (ASAM Principles, 2019)

Contingent reinforcement is effective (versus non-contingent) (Silverman et al, 1996):

- Patients receiving methadone who also used cocaine
- Random assignment of contingent or non-contingent vouchers
- Same rewards used in both groups
- 6% abstinence in non-contingent group (and only for two weeks) versus 42% in contingent group (for 7-12 weeks)

EVIDENCE: PATIENT POPULATIONS

- Studies have **demonstrated effectiveness** in patients with comorbid mental illness, including schizophrenia.
- "Patients with **trauma-induced symptomology may be particularly responsive** to CM interventions with respect to long-term drug abstinence outcomes" (Pertry, 2012).
- However, our experience is that patients have many complex mental health needs. CM does **not** provide treatment for depression or suicidal ideation, and patients may need other treatment of check-ins. Counselling should be available if patients are distressed.
- CM has been very effective in populations experiencing homelessness, for example in an enhanced day treatment program.
- CM is not as effective in forensic populations, and this is believed to be related to the strong contingencies already in place in the judicial system.

(Petry, 2012)

PHARMACOLOGICAL TREATMENTS

REVIEW OF THE APPROACHES

METHAMPHETAMINE/AMPHETAMINE TREATMENTS 1

Drug	# Studies (sample sizes)	Results
Amineptine (removed from market)	1 (29)	Less depressed in withdrawal
Mirtazapine	3 (20,31,60[MSM])	+,-,+
Bupropion	6 (204,156,19,84,73,583)	No statistically significant results on primary outcomes (2 post-hoc analyses found positive results for light users)
Sertraline	1 (229)	Less likely to achieve abstinence and increased + UDS
Imipramine	1 (183)	Enhanced retention, NS changes in use
Atomoxetine	1 (69[also OUD])	Proportion of + UDS less; no difference in days abstinent
Aripiprazole	2 (90,37,53)	-,- (better retention), increased use (study stopped)
Topirimate	2 (140,62)	NS (reduction secondary), at interim better but NS at final

Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A systematic review. CNS Drugs (2020) 34:337-365.

METHAMPHETAMINE/AMPHETAMINE TREATMENTS 2

Drug	# Studies (n)	Results
Dexamphetamine	2 (60,49)	No differences on planned analyses, reduced cravings[1]
Methylphenidate	3 (110,79,56)	No differences in first 2, last – less craving, less use by UDS
Modafinil	4 (210,71, 20, 80)	No differences
Baclofen vs gabapentin	1 (88 [3-arm])	No differences
Buprenorphine	1 (40 [inpatients])	Reduced initially, trending to no difference at follow-up
Buprenorphine vs. methadone	1 (40 [inpatients])	Reduced cravings in buprenorphine arm
Naltrexone	5 (100,80,52,100,100[2])	NS, + by UDS, + by self report only, no diff, no diff UDS
Ondansetron	1 (150)	No differences in any outcome measure; 3 dose levels

1 – Outpatients who continued MA use, 2 – Opiate use plus amphetamines – reduction in overall substance use, no difference in amphetamine use

Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A systematic review. CNS Drugs (2020) 34:337-365.

METHAMPHETAMINE/AMPHETAMINE TREATMENTS 3

Drug	# Studies (n)	Results
Varenicline	1 (52)	No differences (reduced cigarette smoking)
NAC	1 (32)	Reduced cravings (optional Matrix model)
NAC & naltrexone	1 (31)	No differences
Riluzole (glutamatergic)	1 (86)	Higher retention and abstinence at end of treatment
Pexacerfont (CRF1 antagonist	1 (51)	Less cravings, no difference in use
Flumazenil, gabapentin & hydroxyzine	2 (120,135)	1 – improved cravings, no difference in use 2 – no differences in cravings or use

Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A systematic review. CNS Drugs (2020) 34:337-365.

LIMITATIONS TO THE RESEARCH

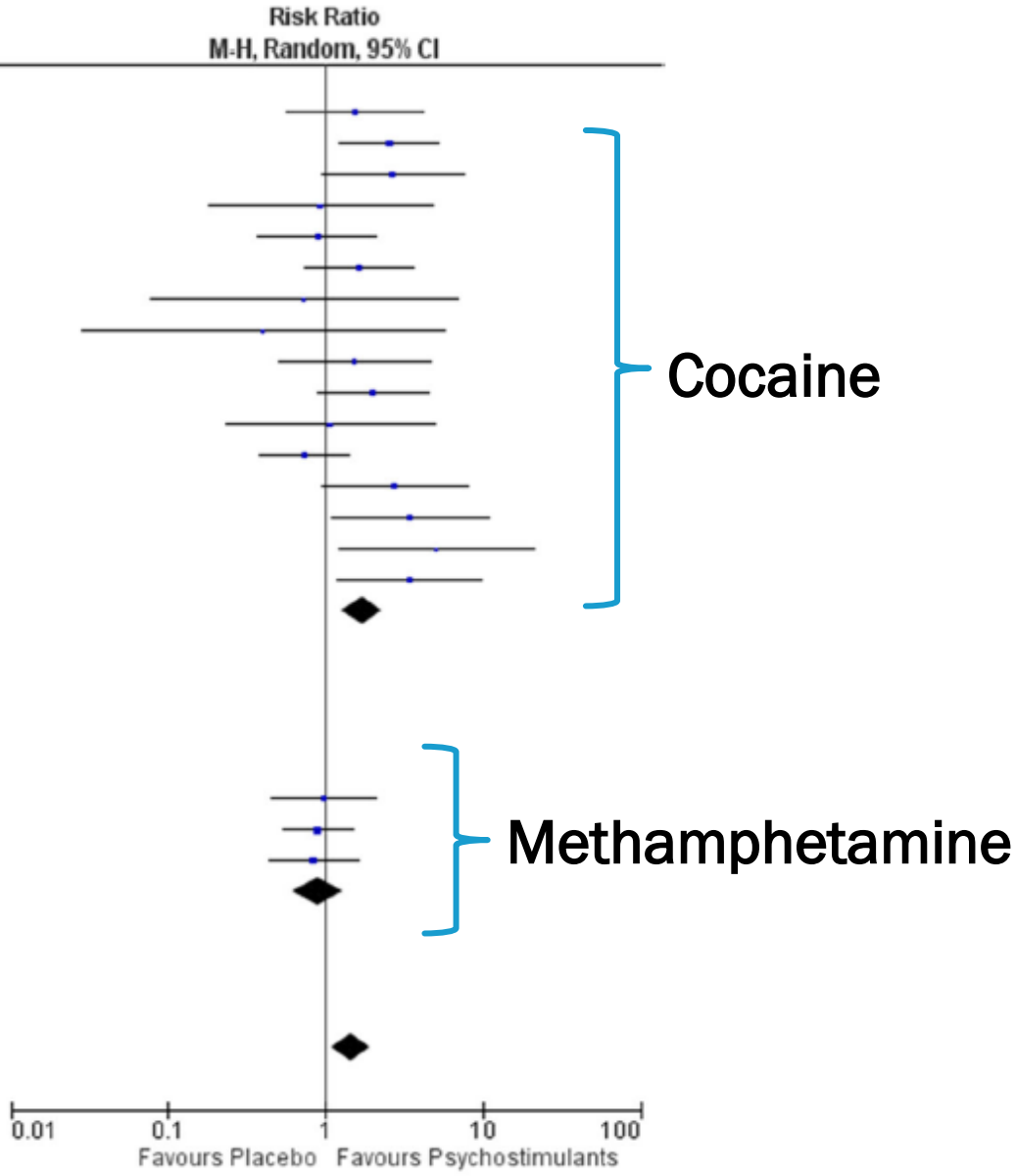
- “Seventy-nine percent of the reviewed studies excluded participants with comorbid mental health diagnoses or concomitant medications prescribed for comorbid mental health diagnoses. Research suggests that transient psychotic symptoms are observed in up to 40% of MA-using populations and possibly more amongst treatment seekers.”
- This severely limits the generalizability of any findings.

SUBSTITUTION THERAPY WITH PRESCRIPTION STIMULANTS

- May be helpful in withdrawal (Härtel-Petri et al, 2017), but not recommended in this review unless part of a trial
- **Castells, 2016 Cochrane review:**
  - 26 studies with 2366 participants
  - Bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, mixed amphetamine salts and selegiline were included
  - "Very low quality evidence that psychostimulants improved sustained cocaine abstinence (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.05 to 1.77, P = 0.02), but they did not reduce cocaine use (standardised mean difference (SMD) 0.16, 95% CI −0.02 to 0.33) among participants who continued to use it."
  - "Psychostimulants did not improve retention in treatment (RR 1.00, 95% CI 0.93 to 1.06)."
  - Studies were generally small (Schmitz, 2012), with approximately 20 participants in each arm, and while they were blinded, it is not clear if that was successful in comparing amphetamine to placebo. In addition, it is not clear if these were observed or take-home doses
- **Tardelli, 2020 systematic review:**
  - Prescription amphetamines, in higher doses, may help cocaine use (in particular)
  - Prescription amphetamines do not improve retention in treatment
  - Extended-release formulations, under direct observation and daily dispensing, are recommended

Tardelli, 2020

Study or Subgroup	Psychostimulants Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Cocaine							
Shearer 2003	7	16	4	14	5.2%	1.53 [0.56, 4.15]	2003
Grabowski 2004	24	54	7	40	7.4%	2.54 [1.22, 5.30]	2004
Dackis 2005	10	30	4	32	4.9%	2.67 [0.94, 7.60]	2005
Levin 2006	3	21	2	13	2.4%	0.93 [0.18, 4.84]	2006
Levin 2007	8	53	9	53	6.1%	0.89 [0.37, 2.13]	2007
Anderson 2009	22	138	7	72	6.8%	1.64 [0.74, 3.65]	2009
Schmitz 2012	2	22	1	8	1.4%	0.73 [0.08, 6.97]	2012
Schmitz 2012	1	20	1	8	1.0%	0.40 [0.03, 5.65]	2012
Dackis 2012	11	135	4	75	4.5%	1.53 [0.50, 4.63]	2012
Mariani 2012	13	39	7	42	6.7%	2.00 [0.89, 4.49]	2012
Dürsteler-MacFarland 2013	3	30	3	32	2.8%	1.07 [0.23, 4.88]	2013
Schmitz 2014	9	22	10	18	8.4%	0.74 [0.38, 1.41]	2014
Kampman 2015	11	47	4	47	4.7%	2.75 [0.94, 8.02]	2015
Levin 2015	20	83	3	43	4.2%	3.45 [1.09, 10.98]	2015
Nuijten 2016	11	38	2	35	3.0%	5.07 [1.21, 21.27]	2016
Levin 2019	14	64	4	63	4.8%	3.45 [1.20, 9.90]	2018
Subtotal (95% CI)		**812**		**595**	**74.4%**	**1.70 [1.26, 2.31]**	
Total events	169		72				
Heterogeneity: Tau² = 0.09; Chi² = 19.85, df = 15 (P = 0.18); I² = 24%							
Test for overall effect: Z = 3.44 (P = 0.0006)							
1.1.2 Meth							
Heinzerling 2010	9	34	10	37	7.1%	0.98 [0.45, 2.12]	2010
Konstenius 2010	8	12	9	12	10.1%	0.89 [0.53, 1.49]	2010
Anderson 2012	21	142	12	68	8.4%	0.84 [0.44, 1.60]	2012
Subtotal (95% CI)		**188**		**117**	**25.6%**	**0.89 [0.62, 1.27]**	
Total events	38		31				
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.95); I² = 0%							
Test for overall effect: Z = 0.63 (P = 0.53)							
Total (95% CI)		**1000**		**712**	**100.0%**	**1.45 [1.10, 1.92]**	
Total events	207		103				
Heterogeneity: Tau² = 0.13; Chi² = 28.77, df = 18 (P = 0.05); I² = 37%							
Test for overall effect: Z = 2.61 (P = 0.009)							
Test for subgroup differences: Chi² = 7.32, df = 1 (P = 0.007), I² = 86.3%							



SUBSTITUTION THERAPY WITH PRESCRIPTION STIMULANTS

Nuijten, 2016:

Study population: “population of patients currently receiving oral methadone plus inhalable or injectable diacetylmorphine for their concurrent heroin dependence in supervised heroin-assisted treatment programmes in two treatment centres in Amsterdam, one in Rotterdam, and one in The Hague”

- Target substance was crack **cocaine**
- 60 mg/day oral sustained-release **dexamfetamine**
- Randomization and blinding described
- Doses were supervised
- 29% of dexamphetamine group, compared to 6% of placebo, had consecutive cocaine abstinence in final 21 days of the trial
- Patients were excluded in case of (1) severe medical problems (eg, electrocardiography or blood abnormalities) or severe psychiatric problems (eg, **acute psychosis** or suicidality);

SUBSTITUTION THERAPY WITH PRESCRIPTION STIMULANTS

Heikkinen, 2023:

Study population: cohort study from Sweden, ages 16-64, diagnosed with amphetamine or methamphetamine use disorder **"and without previous diagnoses of schizophrenia or bipolar disorder"**

- Various medications were studied as exposures
- Included ADHD medications, mood stabilizers, antidepressants, benzodiazepines, antipsychotics
- Vyvanse (lisdexamphetamine) was associated with a decrease in hospitalizations due to SUD, any hospitalization or death:

0.82; 95%CI, 0.72-0.94 for SUD hospitalization;

0.86; 95%CI, 0.78-0.95 for any hospitalization or death

0.43; 95%CI, 0.24-0.77 for all-cause mortality

- Benzodiazepine use was associated with worse outcomes
- Psychiatric hospitalization was not included as a covariate

TREATMENT UPDATES

- No medications have been demonstrated as useful for all people, psychotherapy is the current best option (Siefried et al., 2020)
- Bottom line: medications alone are not helpful, in some situations adding a medication to psychotherapy may be tried but this is ‘off-label’

- Exception: For gay and bi men, the medication mirtazapine (antidepressant) has now been shown in 2 randomized control trials to assist with abstinence, second study had 120 participants randomized (Coffin et al., 2020)

Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A systematic review. CNS Drugs (2020) 34:337-365.
Coffin PO, Santos GM, Hern J, Vittinghoff E, Walker JE, Matheson T, et al. Effects of mirtazapine for methamphetamine use disorder amongst cisgender men and transgender women who have sex with men: a placebo-controlled randomized clinical trial. JAMA Psychiatry (2020) 77(3):246-255.

WHAT ABOUT COMBINATION TREATMENT?

- Gains from all treatment are relatively small in stimulant use disorder
- CM has an effect size of 0.56 (Petry, 2017) however, while it doubles the period of abstinence (4.4 weeks CM, versus 2.6 standard treatment) the overall duration of treatment is low
- Similarly, the benefit in medication trials is small, and over a brief period of study (weeks), e.g. Trivedi, 2021 with 13.6% response in treatment, compared to 2.5% with placebo
- Recent review of combination therapy involving CM and pharmacology (Tardelli, 2018) found that 10 out of 21 relevant publications found CM + medication was superior to either treatment alone
- Given the lack of available treatments in stimulant use disorder, comprehensive wrap-around treatment is likely critical, although more evidence is needed
- This may also address the bimodal distribution often seen in CM studies

STIMULANT-INDUCED PSYCHOSIS

- The general definition of a substance-induced mental disorder means that the symptoms are not better explained by a non-substance induced disorder, such that (DSM-5):
- symptoms do not precede the onset of substance use
- symptoms do not persist for a substantial period of time (**"about one month"**) after withdrawal/intoxication
- there is not other evidence that there is an independent non-substance induced disorder, such as recurrent episodes

(DSM-5)

***this relates to the importance of urinalysis (broad spectrum)**

(there is a similar definition for substance-induced anxiety, depression, and so on)

The complexity, in clinical practice, is how to proceed if a clear history of the period prior to substance use is unavailable, and if abstinence cannot be achieved.

STIMULANT-INDUCED PSYCHOSIS

- The most common symptoms of methamphetamine-associated psychosis are:
- **persecutory** and referential delusions
- **auditory** and visual hallucinations
- conceptual disorganization, hyperactivity, inappropriate affect, depression also common

Negative symptoms such as flat affect, social withdrawal, poverty of speech, avolition, reduced movement are less common (compared to schizophrenia).

Voce et al., 2019 (20–30% of participants were female in these studies)

STIMULANT-INDUCED PSYCHOSIS

- “The overall median prevalence of persistent symptoms across these studies was **25%**” after >1 month of abstinence.
- **Longitudinal studies reported persistence in 40% of participants.**
- Studies have shown transition to a diagnosis of schizophrenia to be 33-38% at 6-7 years, or 16% at 16 years.
- →psychotomimetic properties of the drug precipitating psychosis in anyone
- →methamphetamine precipitating primary psychosis in predisposed individuals
- →…a combination of both forming a heterogenous population among methamphetamine users

- Voce et al, 2019

TREATMENT OF STIMULANT-INDUCED PSYCHOSIS: ACCESSING CARE

- Urbanoski, 2018:
- OR 0.250 (0.206 to 0.304) of seeing a psychiatrist, 30 days after an ED visit, for individuals who visited an emergency department 5+ times in a year for substance use disorder.
- “Controlling for sociodemographic characteristics, comorbidities and past-year service use, those with 1–4 ED visits for SUD and those with 5+ ED visits for SUD had **reduced odds of being hospitalised or visiting a psychiatrist** in the 30 days following their index ED visit, relative to those with no ED visits for SUD”.

TREATMENT OF STIMULANT-INDUCED PSYCHOSIS

- Generally, second-generation antipsychotics are recommended and a tapering attempt at 6 months to determine if they are necessary. (Wodarz, 2017)
- There are concerns that neuroleptics can promote cravings due to dopamine blockade (Härtel-Petri, 2017)
- ***In general, if there are significant symptoms, and particularly if there is possibly an underlying primary psychotic disorder (schizophrenia) consider treating with an atypical antipsychotic.***

- **Things to consider from our RAAM experience:**
- is it possible to obtain further history about the onset of symptoms?
- is abstinence reasonably likely or desired from the patient's perspective?
- is there good insight into the symptoms?
- even with reasonably good insight, are the symptoms leading to significant functional impairment, such as inability to remain in a safe housing environment or participate in medical tests?

HARM REDUCTION

- Route of administration based:
  - Instructions on safer injection and inhalation practices
  - Sterile syringes, one's own pipe
- Converting to a route with slower onset may help with dependency forming risk (swallowing, snorting or hooping)
- Testing drugs
- Planning use, enforcing a sleep/rest schedule
- Ottawa group has tried a safer supply project

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