Methamphetamine Use & Complications

When to Treat Using Antipsychotic Medication

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Montana Primary Care Association
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Patient Case

HG is a 37-year-old man who presents to your clinic. He is currently unemployed and homeless, with a past psych hx of longstanding depressive symptoms, no prior hx of psychosis.

- Oftentimes feels extreme anxiety and has thoughts, “that scare me… I think a group of people are stalking me… I don’t know who they really are… but I’m starting to see them everywhere. I hear voices telling me awful things…”

- Uses >1g of methamphetamine daily, remarks: “I thought I had it under control, recently I starting injecting… now I just can’t stop.”

Patient Case *Continued*

- Currently off psychotropics: “only the meth really touches me.”

- Notes some potential interest in use reduction/cessation but voices overall ambivalence, remarks:

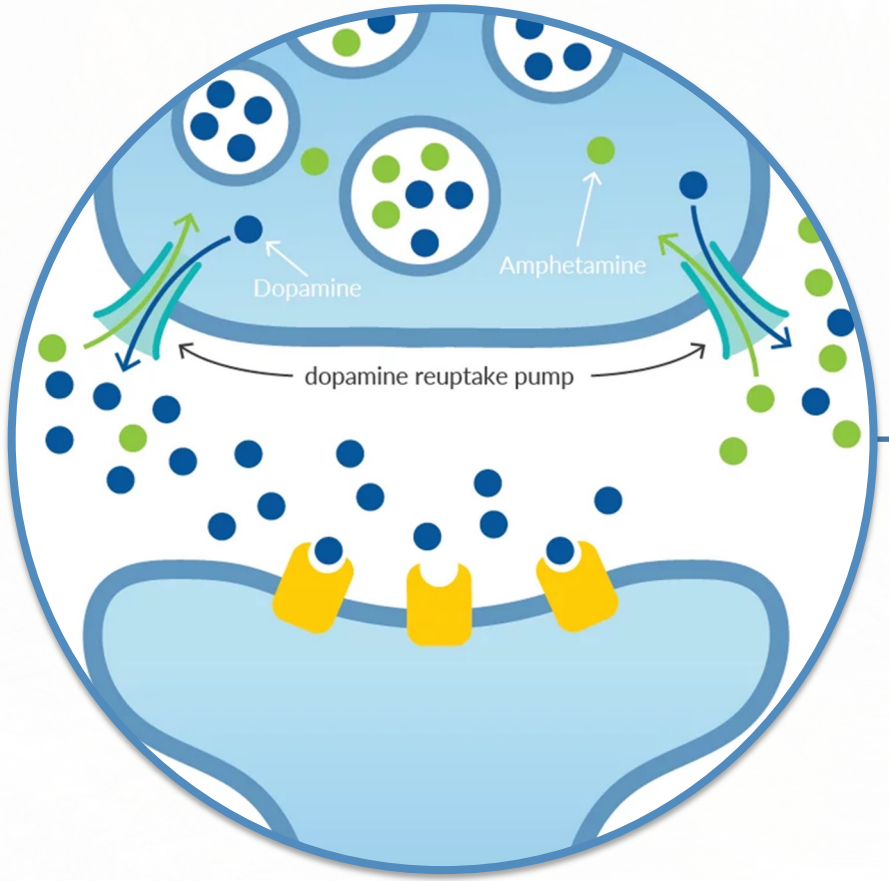
> *“I mean… it’s awesome… it makes the sex great, but I just got out of the hospital… I ended up there because of bad burns on my skin… I’m not sure how I got them… maybe I messed up putting bleach on my athlete’s foot.”*

Objectives

1. Review how methamphetamine works in the brain
2. Acknowledge substance-induced psychosis and the exceptionally high risk of psychosis in methamphetamine use
3. Characterize methamphetamine-induced psychosis (MIP) vs. methamphetamine use disorder (MUD)
4. Assess antipsychotic treatment for MIP vs. MUD

Methamphetamine

Mechanism of Action (MOA)



Highly potent psychostimulant that ↑ synaptic levels of **DA** >> **NE**, & **5HT** through ↑ release & blocked reuptake

- ↑ **DA** production
- ↑ availability of **DA** & **NE**
- Reversal of neurotransmitter transport through plasma membrane
- Blocking the activity & expression of transporters (especially for **DA**)
- Inhibiting enzymatic breakdown of neurotransmitters

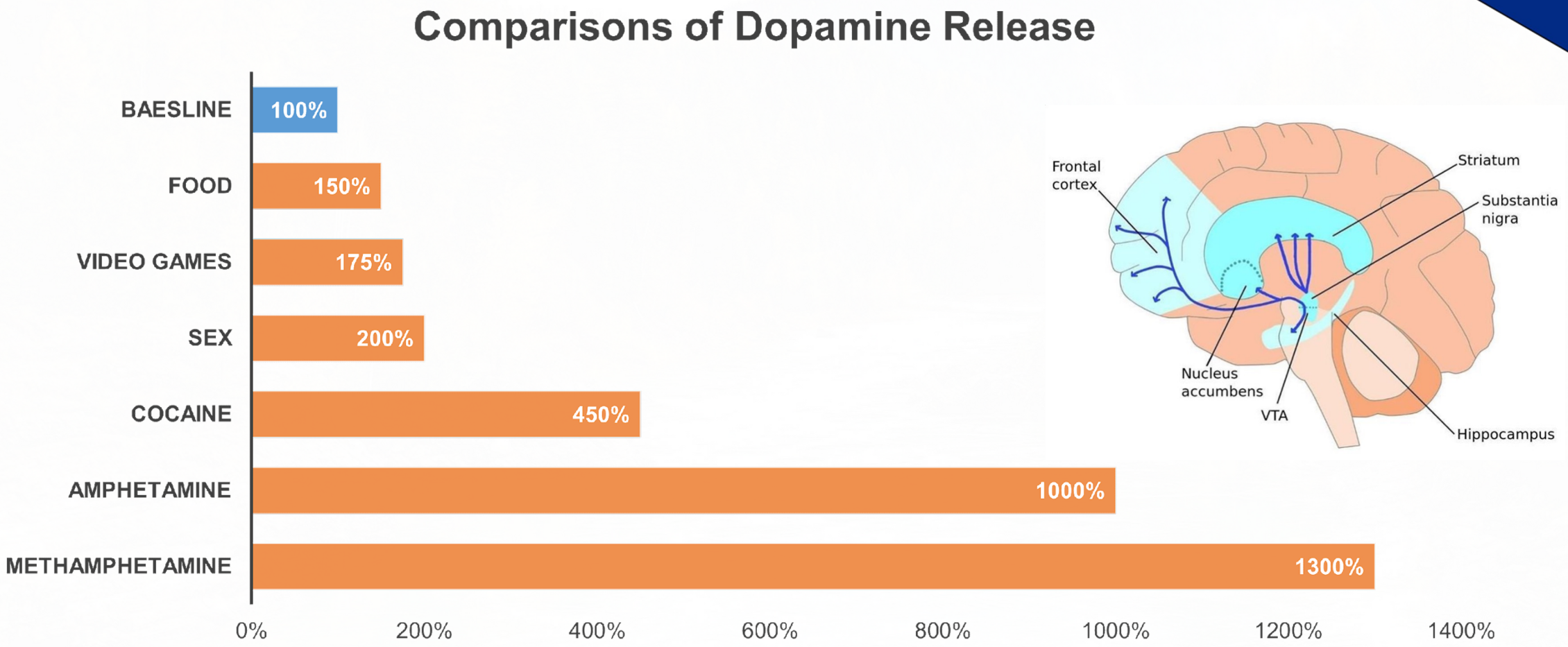
Net Effect: *¡Mucha Dopamina!*

DA: dopamine; NE: norepinephrine; 5HT: serotonin

Titus-Lay, E. Substance-Related Disorders. CPNP Psychiatric Pharmacotherapy Review. 2022.

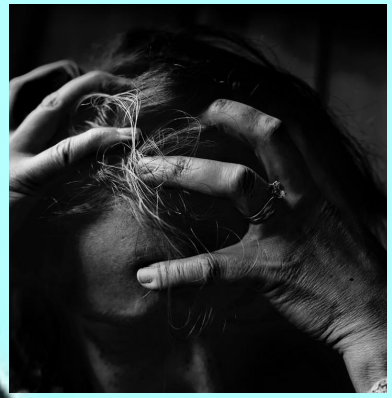
Meth= Dopamine Explosion

Dopamine Release from Natural Rewards vs Stimulants



Di Chiara et al., Neuroscience, 1999.; Fiorino and Phillips, J. Neuroscience, 1997.; Ferguson, 2018.

Methamphetamine-Induced Psychosis (MIP)



Methamphetamine Use Disorder (MUD)

Substance-Induced Psychosis

- Withdrawal from substances
  - Alcohol, benzodiazepines
- Intoxication
  - Methamphetamine, cocaine, hallucinogens, PCP, inhalants, cannabis, bath salts

Methamphetamine-induced psychosis occurs in 15-23% of individuals with recreational use

- May be up to 60% in dependent users in treatment settings

- Implicated pathophysiology is similar to that of primary psychosis: → **overactivation of dopamine pathway**

Psychosis

→Gross impairment of reality testing

Core symptoms

- Hallucinations
- Delusions
- Disorganized thinking and speech
- Disorganized behavior
- Negative symptoms
- Cognitive deficits

•Functional impairments

- Relationships, work, education, activities of daily living

Substance-Induced Psychosis (SIP) per DSM5

"Substance/medication-induced psychotic disorder" has:

- The presence of **delusions** and/or **hallucinations** during or soon after **intoxication/exposure** or **withdrawal**
- Disturbance **not better explained** by another type of **psychotic disorder**
- The disturbance cannot **"occur exclusively during the course of a delirium"**
- Must cause **significant distress** or impairment in function

Primary vs. Meth-Induced Psychosis (MIP)

Often there is a distinct presentation

- Visual hallucinations (e.g., Meth intoxication)
- Positive symptoms often predominate
  - Often there is lack of negative symptoms.
  - Chronic use may shift presentation:

    → Psychosis in chronic meth use appears similar to schizophrenia (though normally there is a lack of negative symptoms)

How MIP Stands Out vs. Other Forms of SIP

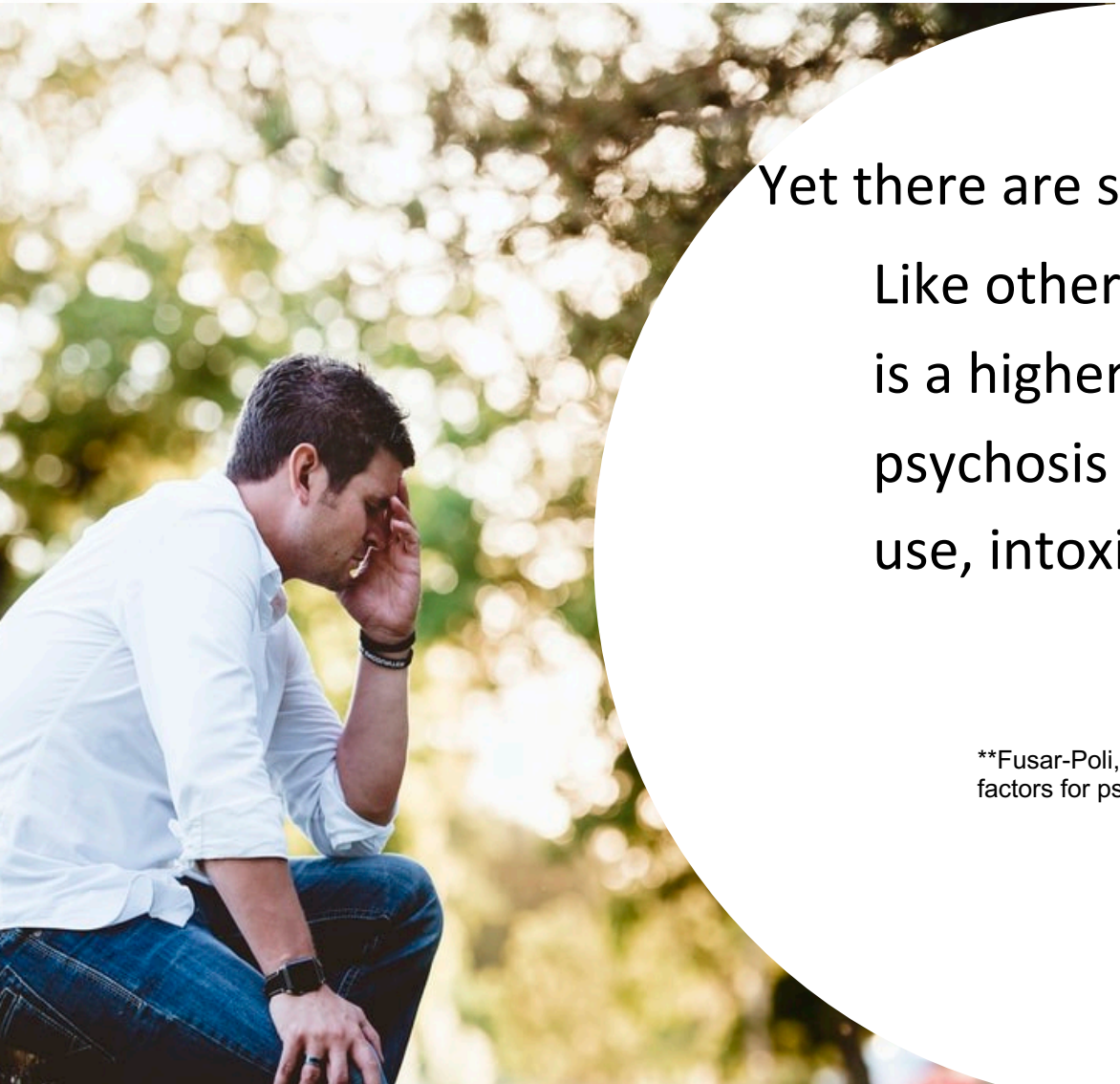
Diagnostic criteria for DSM5 substance-induced criteria fall short for meth-induced psychosis

Conventionally, primary psychosis is considered likely if symptoms persist at after at least one month of abstinence from substances

→ Yet long-term psychotic sx can persist months into sustained abstinence from heavy meth use*

*Wearne, Travis A., and Jennifer L. Cornish. "A comparison of methamphetamine-induced psychosis and schizophrenia: a review of positive, negative, and cognitive symptomatology." *Frontiers in psychiatry* 9 (2018): 491.

How MIP Stands Out vs. Other Forms of SIP



Yet there are still similarities:

Like other forms of substance-induced psychosis: there is a higher suspicion for meth-induced vs. primary psychosis if onset of symptoms coincide with substance use, intoxication or withdrawal**

**Fusar-Poli, Paolo, et al. "Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk." *European Psychiatry* 40 (2017): 65-75.

Meth-Induced Psychosis (MIP) Risk Factors

Usage Patterns:

- Higher risk with frequent use (more than weekly) and recent use
- Increased risk with larger doses (dose-responsive relationship)

Demographic Factors:

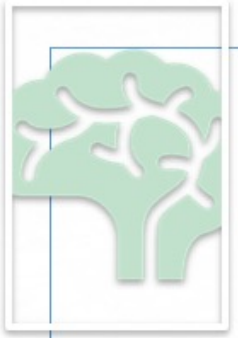
- Higher prevalence among individuals who are unhoused (mutual influence between homelessness and drug use)

Adverse Childhood Experiences:

- Childhood adversities significantly increase the
- 4.5 times higher lifetime risk of psychosis*

Age of First Use:

- Younger age at initial methamphetamine use



Methamphetamine-induced psychosis occurs in 15-23% of individuals with recreational use

- May be up to 60% in dependent users in treatment settings

*Ding, Lin, et al. "Early adversity and later use of methamphetamine among adolescents in Shanghai, China." Drug and Alcohol Dependence, vol. 134, 2014, pp. 31-34.

Meth-Induced Psychosis (MIP) Risk Factors

Genetic Predisposition:

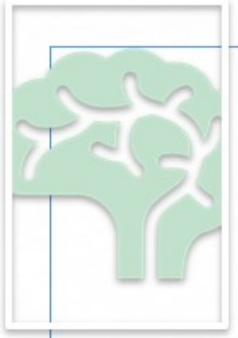
- Higher genetic loading for schizophrenia increases the likelihood and duration of methamphetamine-induced psychosis*
- Family history of psychotic disorders

Co-Substance Use:

- Concurrent use of marijuana
- Any use of ketamine (even occasionally)
- Alcohol Use Disorder (AUD)

Impact of Non-SUD Co-Occurring Disorders

- Major Depressive Disorder (MDD)
- Antisocial Personality Disorder (ASPD) (unclear if association is causal)



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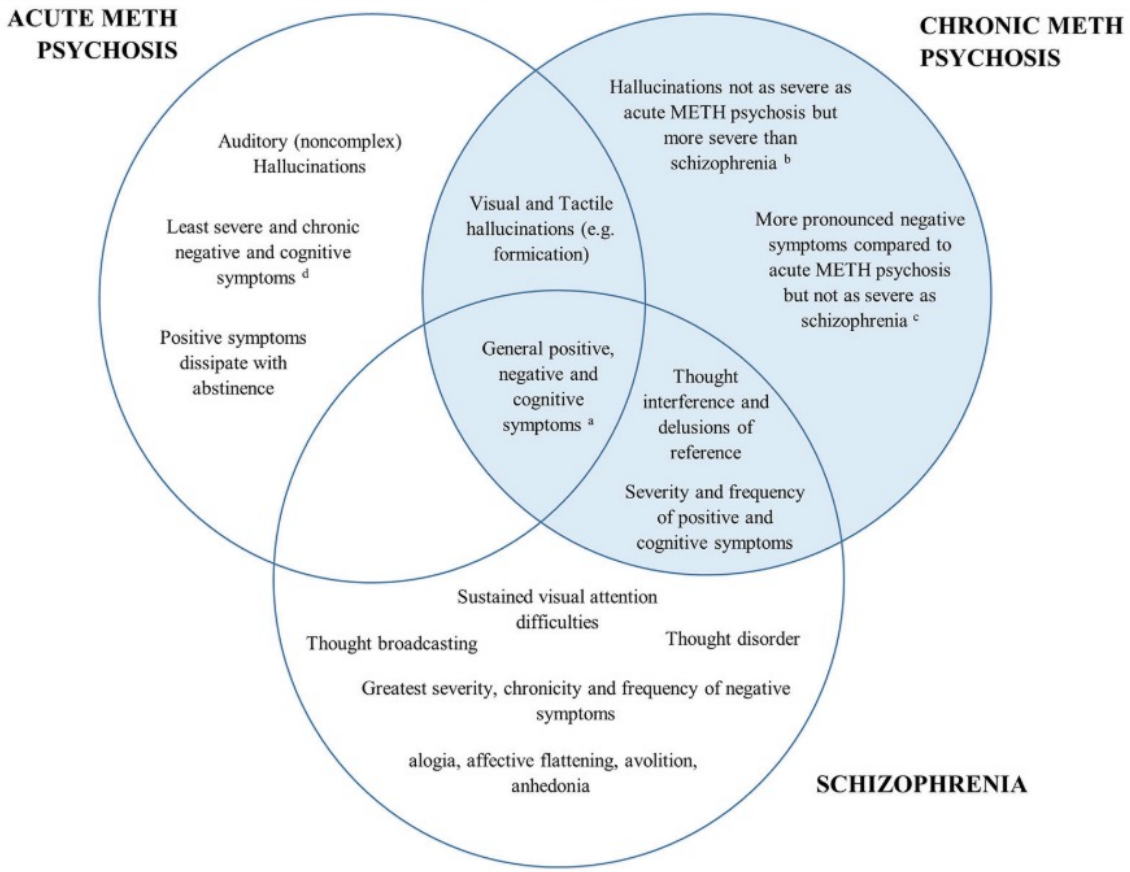
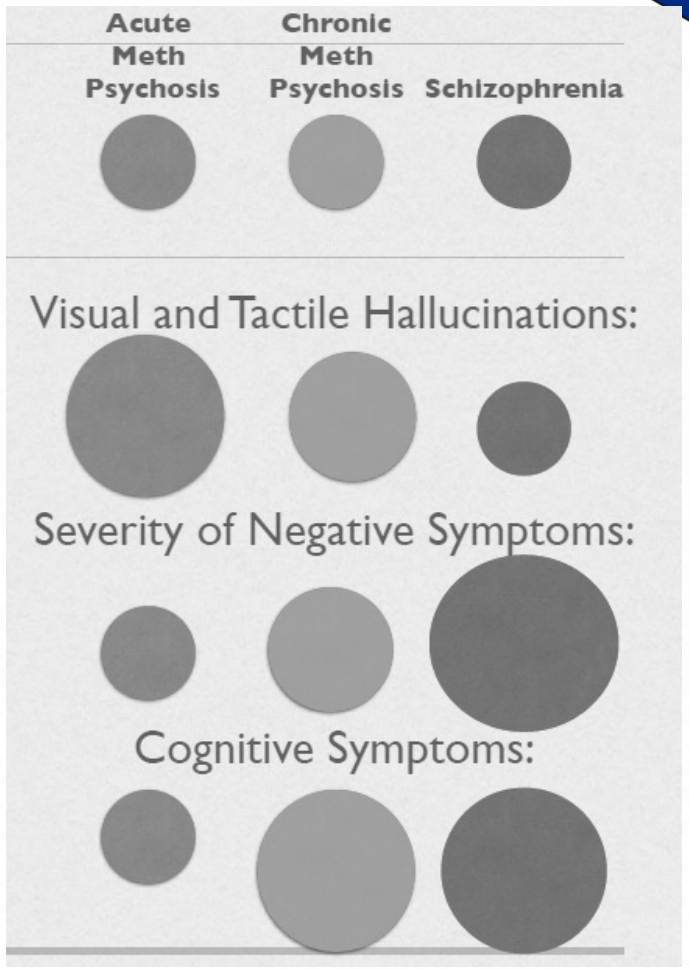
*Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh, E. W., Hsiao, C. C., Chiang, Y. L., Ree, S. C., Lee, C. H., & Murray, R. M. "Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis." Psychological Medicine, vol. 35, no. 4, 2005, pp. 701-710.

Meth-Induced Psychosis vs. Schizophrenia





Wearne TA, Cornish JL. A Comparison of Methamphetamine-Induced Psychosis and Schizophrenia: A Review of Positive, Negative, and Cognitive Symptomatology. Front Psychiatry. 2018 Oct 10;9:491. doi: 10.3389/fpsyt.2018.00491. PMID: 30364176; PMCID: PMC6191498.

Antipsychotic Medication Doses for Methamphetamine-Induced Psychosis

MEDICATION	DOSE	SIDE EFFECTS
Olanzapine	5-20mg qHS (can divide BID)	Sedating, metabolic effects
Quetiapine	100-300mg qHS (can divide BID)*	Sedating, metabolic effects, slight increase in QTc prolongation
Risperidone	1.5mg-3mg daily (max 6mg, can divide BID)*	Less sedating and metabolic effects; hyperprolactinemia, higher risk for EPS
Aripiprazole	5-20 mg daily	Anxiety, agitation, akathisia, tremor

**Note: can uptitrate to significantly higher dose*

Treatment of MIP

- No consistent dosing and treatment time frames across studies*
- No clear evidence favoring one agent*
- Antipsychotics with evidence supporting their use include:
  - ***Aripiprazole, haloperidol, quetiapine, olanzapine, and risperidone****
- Side effect profile can help guide tx*
- Ensure appropriate level of care setting depending on level of severity
- For severe positive symptoms/agitation: first (e.g., Haldol) vs. second generation antipsychotics (e.g., Olanzapine)

Beware of hemodynamic instability in meth-induced psychosis

*Fiorentini A, Cantù F, Crisanti C, Cereda G, Oldani L, Brambilla P. Substance-Induced Psychoses: An Updated Literature Review. Front Psychiatry. 2021 Dec 23;12:694863. doi: 10.3389/fpsyt.2021.694863. PMID: 35002789; PMCID: PMC8732862.

DSM 5 Diagnostic Criteria

Stimulant Use Disorder

A problematic pattern of amphetamine-type substance, cocaine, or other stimulant use leading to clinically significant impairment or distress, as manifested by ≥2 of the following, occurring within a 12-month period:

1. Stimulants are often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control stimulant use
3. A great deal of time is spent in activities necessary to obtain, use or recover from the stimulant
4. Craving, or a strong desire or urge to use the stimulant
5. Recurrent stimulant use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the stimulant
7. Important social, occupational, or recreational activities are given up or reduced because of stimulant use
8. Recurrent stimulant use in situations in which it is physically hazardous
9. Use is continued despite having a persistent/recurrent physical/psychological problem that is caused/exacerbated by the stimulant
10. Tolerance, as defined by either of the following:
    a. A need for markedly ↑ amounts of the stimulant to achieve intoxication or desired effect
    b. A markedly diminished effect with continued use of the same amount of the stimulant
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the stimulant
    b. The stimulant is taken to relieve or avoid withdrawal symptoms

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

Oral antipsychotics as treatment of MUD?

- Mesolimbic dopamine system is substantially dysregulated in MUD
- Antipsychotics can help restore relative homeostasis within the mesolimbic dopamine system.
- Aripiprazole functions as a partial agonist at dopamine D2 receptors, modulating dopamine activity more subtly than traditional antipsychotics:
  - -acting as a functional antagonist in hyperdopaminergic states
  - -acting an agonist in hypodopaminergic states*
- This balancing effect was hypothesized to mitigate the reinforcing effects of meth without causing the dopamine blockade side effects typical of traditional antipsychotics.*

*Tiihonen J, Kuoppasalmi K, Föhr J, Tuomola P, Kuikanmäki O, Vorma H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry. 2007 Jan;164(1):160-2. doi: 10.1176/ajp.2007.164.1.160. PMID: 17202560.

Oral antipsychotics as treatment of MUD?

- Yet Tiihonen et. al 2007's study on **amphetamine** use disorder with observed dosing (aripiprazole vs. methylphenidate vs. placebo) demonstrated Abilify actually had the worst outcomes: higher meth use rates than placebo*
- May be due to failed Dopaminergic Modulation:
  - → Inadequate Dopamine Suppression: Aripiprazole's partial agonist activity at D2 receptors may not have sufficiently counteracted amphetamine's dopaminergic effect
    Facilitating a state that continued to support amphetamine use?
  - → Potential for Partial Agonism to Increase Use: Partial agonists can act as agonists if the endogenous dopamine levels are low and don't suppress the dopaminergic stimulation caused by amphetamines.
    Potentially encouraging continued use?

*Tiihonen J, Kuoppasalmi K, Föhr J, Tuomola P, Kuikanmäki O, Vorma H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry. 2007 Jan;164(1):160-2. doi: 10.1176/ajp.2007.164.1.160. PMID: 17202560.

Injectable Antipsychotic: LAI Risperidone as Treatment

- **Reduction in Methamphetamine Use:** Participants reported a significant decrease in methamphetamine use from an average of 4.1 days per week to 1.0 day per week.
- **Improvement in Neurocognitive Function:** Verbal memory showed significant improvement at week 4 compared to baseline.
- **Decrease in Psychiatric Symptoms:** Reductions in psychiatric symptomatology were noted, particularly in areas of thought disturbance and anxiety/depression.

ORIGINAL ARTICLE

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Key Words: methamphetamine, risperidone, injection, neuropsychological function, psychiatric symptoms, addiction severity

(*J Addict Med* 2009;3: 55–65)

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Until recently, antidepressants have not been shown to be effective in treating MA dependence. Imipramine 150 mg per day kept MA abusers in treatment longer than did 10 mg per day but led to no measurable reduction in MA use,[4,5] whereas the addition of despiramine to standardized behavioral treatment for MA dependence did not improve outcomes.[6] Fluoxetine failed to decrease subjective reports of MA use or frequency of positive urine toxicology screens,[7] whereas sertraline seems to worsen outcomes in MA dependence.[8] However, bupropion has recently been shown to decrease MA use in male individuals with lower levels of MA use at baseline.[9]

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From the Mental Health Service (CWM, JPR, CAM, EVY, AK, LCF, AMT, and AJS), Center of Excellence in Substance Abuse Treatment and Education (CAM, LCF, and AJS), VA Puget Sound Health Care System; and Department of Psychiatry and Behavioral Sciences (CWM, CJ, MC, LCF, AMT, and AJS), University of Washington, Seattle, WA.
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The other authors have nothing to disclose and no conflicts of interest.
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e-mail: Charles.meredith@va.gov

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Source: Meredith, Charles W., et al. "Open Trial of Injectable Risperidone for Methamphetamine Dependence." Journal of Addiction Medicine, vol. 3, no. 2, 2009, pp. 55-65.

Injectable Antipsychotic: LAI Risperidone as Treatment

- **No Serious Adverse Events:** No participants experienced serious adverse events.
- **Common Side Effects:** Mild akathisia, increased prolactin levels, increased cholesterol, and increased BMI were observed.
- **Overall Tolerability:** Injectable risperidone was well-tolerated, with a significant proportion of participants completing the study.

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Study Limitations:

- Open-label, uncontrolled design limits the ability to draw firm conclusions.
- High dropout rate reduces the strength of the findings.
- Small sample size may affect the generalizability of the results.

Areas for Further Research:

- Larger, placebo-controlled double-blinded studies to confirm efficacy.
- Exploration of optimal dosing strategies to enhance treatment outcomes.
- Long-term studies to assess the sustainability of cognitive and psychiatric improvements.

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Methamphetamine (MA) dependence has increased to epidemic proportions across the United States. Amphetamines have become the second most abused substances in the world,[1] affecting 25 million people.[2] Although data on pharmacological treatment options for MA dependence are emerging, there remain no FDA-approved medication options for treatment of this serious public health problem. Although they are the mainstay of treatment, behavioral treatments remain imperfect and can have high relapse rates.[3]

Until recently, antidepressants have not been shown to be effective in treating MA dependence. Imipramine 150 mg per day kept MA abusers in treatment longer than did 10 mg per day but led to no measurable reduction in MA use,[4,5] whereas the addition of despiramine to standardized behavioral treatment for MA dependence did not improve outcomes.[6] Fluoxetine failed to decrease subjective reports of MA use or frequency of positive urine toxicology screens,[7] whereas sertraline seems to worsen outcomes in MA dependence.[8] However, bupropion has recently been shown to decrease MA use in male individuals with lower levels of MA use at baseline.[9]

Other psychotropic agents have shown limited promise. Neither ondansetron[10] nor gabapentin[11] have shown efficacy in MA dependence although emerging pilot data of baclofen,[11] methylphenidate,[12] and D-amphetamine[13] suggest they may have some potential efficacy in limiting MA use. Use of flumazenil, hydroxyzine, and gabapentin in combination seems to be associated with reductions in MA use in an open-label paradigm but double-blinded placebo-controlled data on this treatment are not yet available.[14] The anticonvulsant vigabatrin has been evaluated for MA dependence in an open-label study but is not clinically available in the United States due to an association with ocular field problems.[15]

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Patient Case

HG is a 37-year-old man who presents to your clinic. He is currently unemployed and homeless, with a past psych hx of longstanding depressive symptoms, no prior hx of psychosis.

- Oftentimes feels extreme anxiety and has thoughts, “that scare me… I think a group of people are stalking me… I don’t know who they really are… but I’m starting to see them everywhere. I hear voices telling me awful things…”

- Uses >1g of methamphetamine daily, remarks: “I thought I had it under control, recently I starting injecting… now I just can’t stop.”

Patient Case *Continued*

- Currently off psychotropics: “only the meth really touches me.”

- Notes some potential interest in use reduction/cessation but voices overall ambivalence, remarks:

> *“I mean… it’s awesome… it makes the sex great, but I just got out of the hospital… I ended up there because of bad burns on my skin… I’m not sure how I got them… maybe I messed up putting bleach on my athlete’s foot.”*

How do you proceed?

Select all that apply:

1. Insist on abstinence from meth prior to prescribing any medication
2. Tolerate meth use so long as he is only using < 1 g daily
3. Prescribe bupropion and IM naltrexone as medication-assisted treatment (MAT) for meth use disorder
4. Start methylphenidate as MAT for meth use d/o
5. Engage in motivational interviewing targeting meth use reduction/cessation
6. Proceed to treat psychosis and depression with evidence-based pharmacological treatment
7. Provide contingency management

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Select all that apply:

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4. Start methylphenidate as MAT for meth use d/o
5. **Engage in motivational interviewing targeting meth use reduction/cessation**
6. **Proceed to treat psychosis and depression with evidence-based pharmacological treatment**
7. **Provide contingency management**

How do you proceed?

Discharge Med Regimen

1. **Abilify** 20 mg PO qHS (following **Olanzapine** 10 mg PO qHS during first few days of hospitalization)
2. Sertraline 50 mg PO qday with plan to likely increase to 100 mg PO qday in the near future

F/U:

Referred to EMCMHC to establish care via their TRUST program's SUD counseling initiative that features **contingency management**

Objectives → *Takeaways*

1. Review how methamphetamine works in the brain

   Dopamine explosion: alters mood/cognition & often provokes psychosis

2. Acknowledge substance-induced psychosis and the exceptionally high risk of psychosis in methamphetamine use

   MIP is one of the most common types of SIP and can be long lasting

3. Characterize methamphetamine-induced psychosis (MIP) vs. methamphetamine use disorder (MUD)

   MIP= common meth use complication

   MUD= physiologic methamphetamine dependence + impaired function

4. Assess antipsychotic treatment for MIP vs. MUD

   → *Effective, evidence-based treatment for MIP*

   → *Appears to hold some potential to treat MUD, meriting further research*

Questions?

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