



METHAMPHETAMINE & PSYCHOSIS

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METHAMPHETAMINE BASICS



WHAT IS METH?

Meth, Crank, Speed, Blue, Ice, Crystal, Redneck Cocaine, LA Glass, Soap Dope

- N-methyl-1-phenylpropan-2-amine
- Man-made amphetamine that is potent CNS stimulant
- Most commonly a white, odorless crystalline powder

HISTORY

1887

Amphetamine Synthesized

Synthesized at the University of Berlin by chemist Lazar Edenleanu; later sold as Benzedrine, an inhaled version, to treat asthma

1893

Methamphetamine Synthesized

Synthesized from ephedrine by Japanese chemist Nagai Nagayoshi as an alternative to ephedra

1919

Crystal Meth

Synthesized methamphetamine hydrochloride from ephedrine using phosphorus and iodine
Produced a water-soluble, crystalline substance

1940

WWII

Pervitin given to German WWII soldiers & Japanese Kamikaze pilots for endurance & alertness, but also caused agitation & aggression

HISTORY

1950s

Japanese Epidemic & Increasing use in USA

OTC methamphetamine pills easily available in Japan due to post-WWII warehouse stockpiles

Non-medical use increasing in USA

Obetrol

FDA approved mixed amphetamine drug for obesity

Drug of choice for Andy Warhol

Intravenous use common

1960

Prescription Methamphetamine

Reaches peak of 31 million prescriptions in USA

1967

Controlled Substances Act

Classified methamphetamine as a schedule II controlled substance

Motorcycle gangs controlled most production & distribution in USA

1971

HISTORY

1980s

Endemic in California

Introduction of smokable form
Increased regulations around sale of ephedrine, a precursor to methamphetamine

1990s

Imported from Mexico

Increasing use, from 2% of population in 1994 to 5% by 2004

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2006

Most abused “hard drug” on earth

United Nations World Drug Report
Methamphetamine 2nd most abused illicit drug, only to cannabis, primarily due to high use in Asian countries

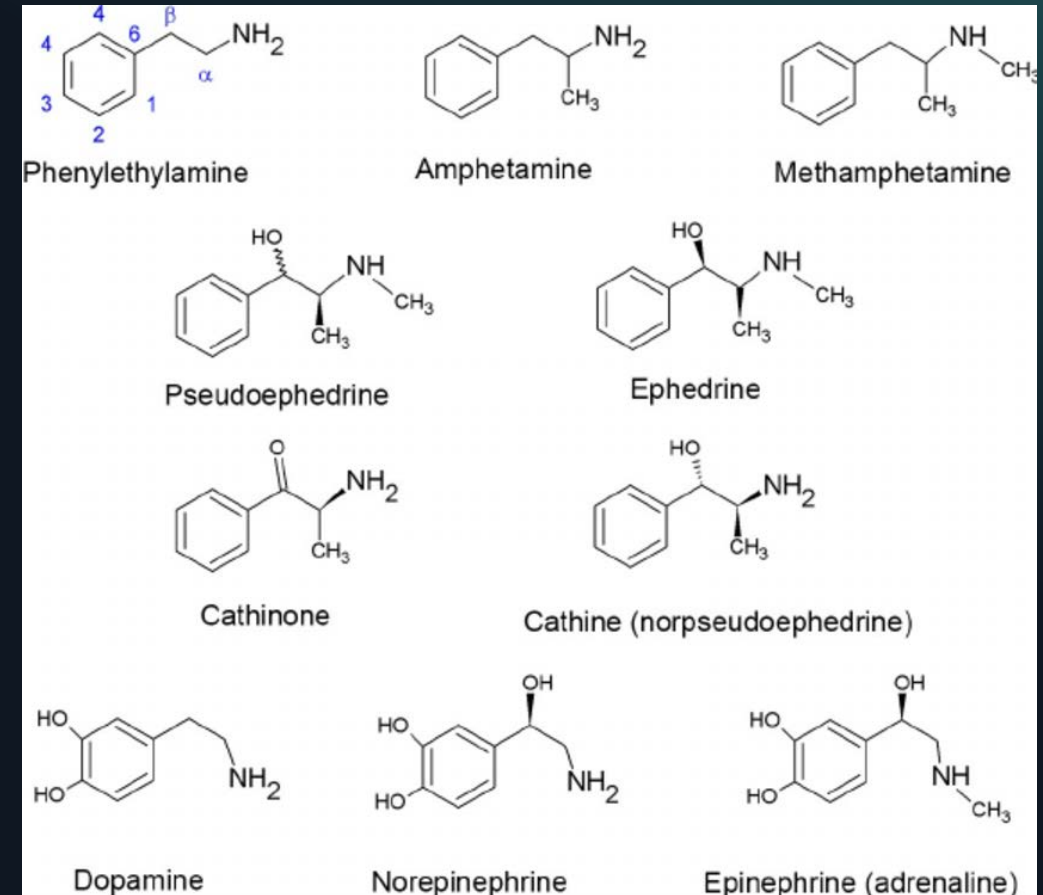
Methamphetamine in the USA

2017

- 1.6 million people (0.5%) used methamphetamine
- Involved in 15% of all overdose deaths
- 964,000 people had methamphetamine use disorder
- 0.5% of high schoolers used methamphetamine
- Highest use in Western & Midwestern USA
- Produced primarily in Mexico
 - Pure, potent and cheap
 - Limited domestic production due to restrictions on ephedrine & pseudoephedrine
- Geographic variability in method of use
 - injected, insufflated, smoked or ingested
- Binge and crash use pattern common
- Globally 35.7 million people use methamphetamine recreationally

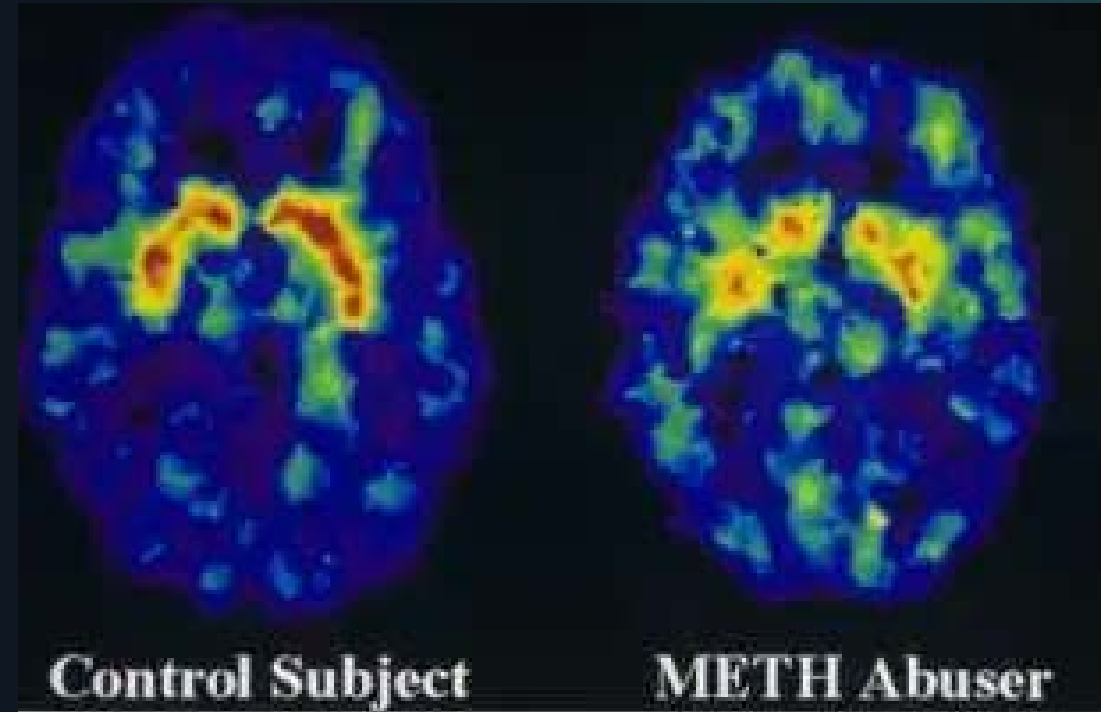
NEUROBIOLOGY BASICS

- Highly lipophilic due to methyl group
- Structurally similar to amphetamine and stimulating neurotransmitters
- Inhibits monoamine reuptake & increases release
- Euphorogenic effects wear off before drug is out of CNS; accumulates in CNS
- Reinforcement due to dopaminergic neurotransmission in mesocorticolimbic tract
- Increases dopamine by 4000% from baseline (v. 350% by cocaine)
- Methamphetamine induced neurotoxicity present with chronic use, leading to cognitive changes



COGNITIVE EFFECTS

- Methamphetamine induced neurotoxicity present with chronic use, leading to cognitive changes
- Low dose use causes damage to serotonergic pathways of frontal cortex, hippocampus
- High dose use causes damage to the striatum, parietal cortex
 - Decreases density of D2 receptors
 - Decreases serotonin, dopamine, norepinephrine with chronic use
- Impairment in
 - Episodic memory
 - Executive functioning
 - Processing speed
 - Motor skills
 - Language
 - Visuoconstructional abilities



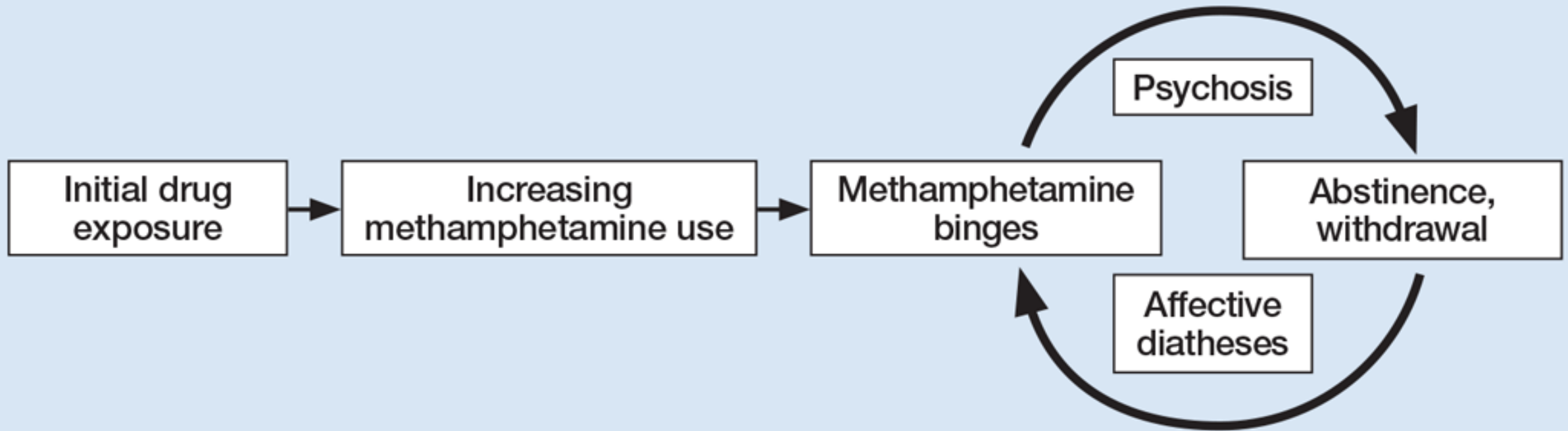
PHYSIOLOGIC EFFECTS

- Increased wakefulness
- Increased physical activity
- Decreased appetite
- Tachycardia
- Hypertension
- Arrhythmias
- Hyperthermia
- Rhabdomyolysis
- Seizure



METHAMPHETAMINE & PSYCHIATRIC SYMPTOMS

CYCLE OF USE



ACUTE INTOXICATION

- Insomnia
- Euphoria
- Hyperactivity
- Irritability
- Anxiety
- Auditory hallucinations
- Visual hallucinations
- Tactile hallucinations
- Paranoia
- Persecutory delusions
- Ideas of reference
- Hypersexuality
- Aggressive or violent behavior



Transient psychotic symptoms occur in up to 40% of those who use

WITHDRAWAL & ABSTINENCE SYNDROME

- May develop in hours, peaks at ~48 hours, lasts up to 2 weeks
- Acute withdrawal or “crash”
 - Dysphoria
 - Irritability
 - Anhedonia
 - Fatigue
 - Hypersomnia or insomnia
 - Drug craving
 - Increased appetite & hyperphagia
- Post-Acute Withdrawal Syndrome may persist for 1+ months
 - Sleep disturbance
 - Appetite changes
 - Depressed mood

METHAMPHETAMINE PSYCHOSIS

- Prevalence rate ~44% in those with methamphetamine use disorder
- Recreational users 2-3x more likely to develop psychotic sx v. general population
- Regular users 11x more likely v. general population
- Average time between first use & psychotic sx is
 - 1.7 years when smoking
 - 4.4 years when injecting

WHEN IS IT PRIMARY PSYCHOSIS?

- ICD-10: An episode of psychosis that occurs in the context of substance use can be considered a primary psychotic disorder if:
 - 1) Symptoms are substantially in excess of expected based on type/amount/duration of substance used
 - 2) History of psychotic episodes that are not substance-related
 - 3) Psychotic symptom onset pre-dates substance use
 - 4) Psychotic symptoms persist for at least one month after cessation of substance, withdrawal
- DSM-5 criteria specify substance-induced psychotic disorders as occurring for <1 month after acute intoxication/withdrawal

METHAMPHETAMINE PSYCHOSIS

- Significant variability in duration of psychotic symptoms after use
 - Days to months
 - Years of lifetime use may contribute to variability
 - Type A: <1 month of psychotic sx associated with <5 years of use
 - Type B: 1+ months of sx associated with 5+ years of use
 - Role of chronic amphetamine effects on dopaminergic and serotonergic activity, and neurotoxicity
 - 30% have sx for >6 months following abstinence
- Moderate variability in dose-response relationship between methamphetamine use and psychotic symptoms
 - Binge use associated with psychosis
- High rates of recurrence with decreased periods of latency
 - Methamphetamine "sensitization" or "reverse-tolerance"

METHAMPHETAMINE-INDUCED PSYCHOSIS

- May be a genetic vulnerability to persistent psychosis
- Family members of persons with methamphetamine induced psychosis are 5x more likely to develop schizophrenia
- 7 candidate genes associated with susceptibility to methamphetamine psychosis & confer poorer clinical course
- Overlap between genetic markers for methamphetamine psychosis & schizophrenia
- In study of >1000 methamphetamine users in Thailand who experienced 1+ episodes of psychosis, within 6 years, 40% had been diagnosed with schizophrenia

METHAMPHETAMINE-INDUCED PSYCHOSIS

- Can exacerbate psychosis in pts with underlying psychotic disorders
 - Schizophrenia
 - Schizoaffective Disorder
 - Schizotypal personality
- Other risk factors:
 - Poly drug use
 - Affective disorders
 - Antisocial personality disorder
 - Family psychiatric history (schizophrenia)
 - Childhood & adolescence
 - Method of administration: higher in smoking v. injecting

METHAMPHETAMINE-INDUCED PSYCHOSIS

- Methamphetamine-induced psychosis (v. schizophrenia)
 - Higher prevalence of visual and tactile hallucinations
 - Fewer negative symptoms (withdrawal, blunted affect, poverty of speech)
 - Less disorganized
 - Presence of movement disorders (orofacial dyskinesia, choreoathetoid movements)

METHAMPHETAMINE-INDUCED PSYCHOSIS

- Is pre-existing schizophrenia being unmasked?
- Is there a stress-diathesis process, such that methamphetamine use is a triggering event for schizophrenia?
- Does methamphetamine psychosis simply share a similar clinical course to schizophrenia?
- Are methamphetamine psychosis and schizophrenia simply a continuum of psychosis rather than distinct entities?

Limitations to diagnostic certainty

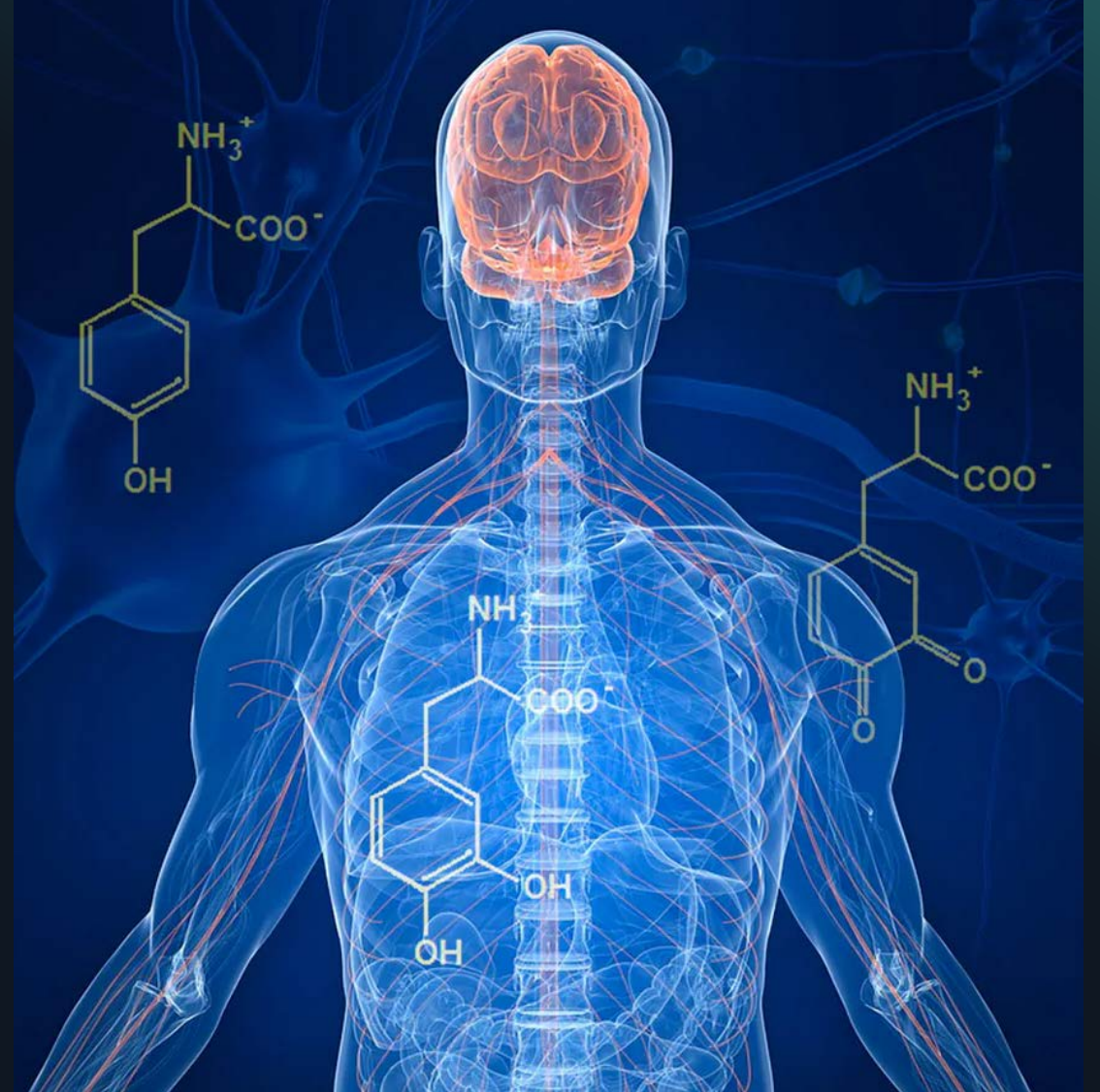


METHAMPHETAMINE- INDUCED PSYCHOTIC DISORDERS

APPROACH TO TREATMENT

TREATMENT CONSIDERATIONS

- Persistence of symptoms
- Degree of impairment
- Chronicity of course
- Extent to which symptoms are temporally related to methamphetamine use



ACUTE PSYCHOSIS

- Benzodiazepines for acute agitation, insomnia
 - Blunt hyperadrenergic effects of methamphetamine
 - Can give every 10 minutes based on patient response; higher doses based on severity of agitation
 - Lorazepam 1 – 4 mg IM/IV
 - Diazepam 10 – 20 mg IV
 - Midazolam 2.5 – 5 mg IM or IV
- Physical restraints should be avoided if possible due to risk of isometric muscle contractions against restraint associated with lactic acidosis, hyperthermia, etc.
 - Should always be accompanied by benzodiazepines
- Minimize environmental stimulus
- Neuroleptics?
 - Potential interaction between methamphetamine and haloperidol resulting in GABAergic cell death, increasing risk of seizure & movement disorders
 - Risk of QT prolongation
 - Most have resolution of sx in ~1 week without pharmacological intervention
 - Antipsychotic blockade may increase anhedonia and increase vulnerability to relapse
- Psychosocial interventions for relapse prevention
 - Cognitive behavioral therapy: drug avoidance, identification of triggers, drug refusal
 - Family Education

CHRONIC PSYCHOSIS

- Antipsychotic medication
 - But should it be discontinued? And when?
- Comprehensive care management
 - Relapse prevention
 - Vocational rehabilitation
 - Psychotherapy
 - Family Interventions

WITHDRAWAL

- Primarily supportive care
- Mirtazapine (off-label) has been demonstrated in small studies to help withdrawal symptoms
 - Blocks alpha-2, 5-HT₂, 5-HT₃ receptors, raises levels of synaptic NE and dopamine
 - May be benefit in decreasing future methamphetamine use based on small study



SUMMARY

Methamphetamine psychosis is complicated and not fully understood.

- Acute psychosis is common and requires supportive care & benzodiazepines
- Withdrawal can be prolonged, mirtazapine may help
- Chronic psychotic symptoms difficult to distinguish from other psychotic disorders, like schizophrenia, and may be on a spectrum
- Chronic methamphetamine induced psychosis warrants treatment with antipsychotics and psychosocial support



THANK YOU!

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