Western Canada Addiction Forum
May 26, 2023
Kelowna, BC

METHAMPHETAMINE-INDUCED PSYCHOSIS

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I acknowledge that we are gathered today on the traditional, ancestral, unceded territory of the Syilx/Okanagan People

DISCLOSURES AND BIAS MITIGATION

I have previously received funding from Vancouver Coastal Health, the BC Centre for Substance Use, and the University of British Columbia for substance use-related educational materials and presentations

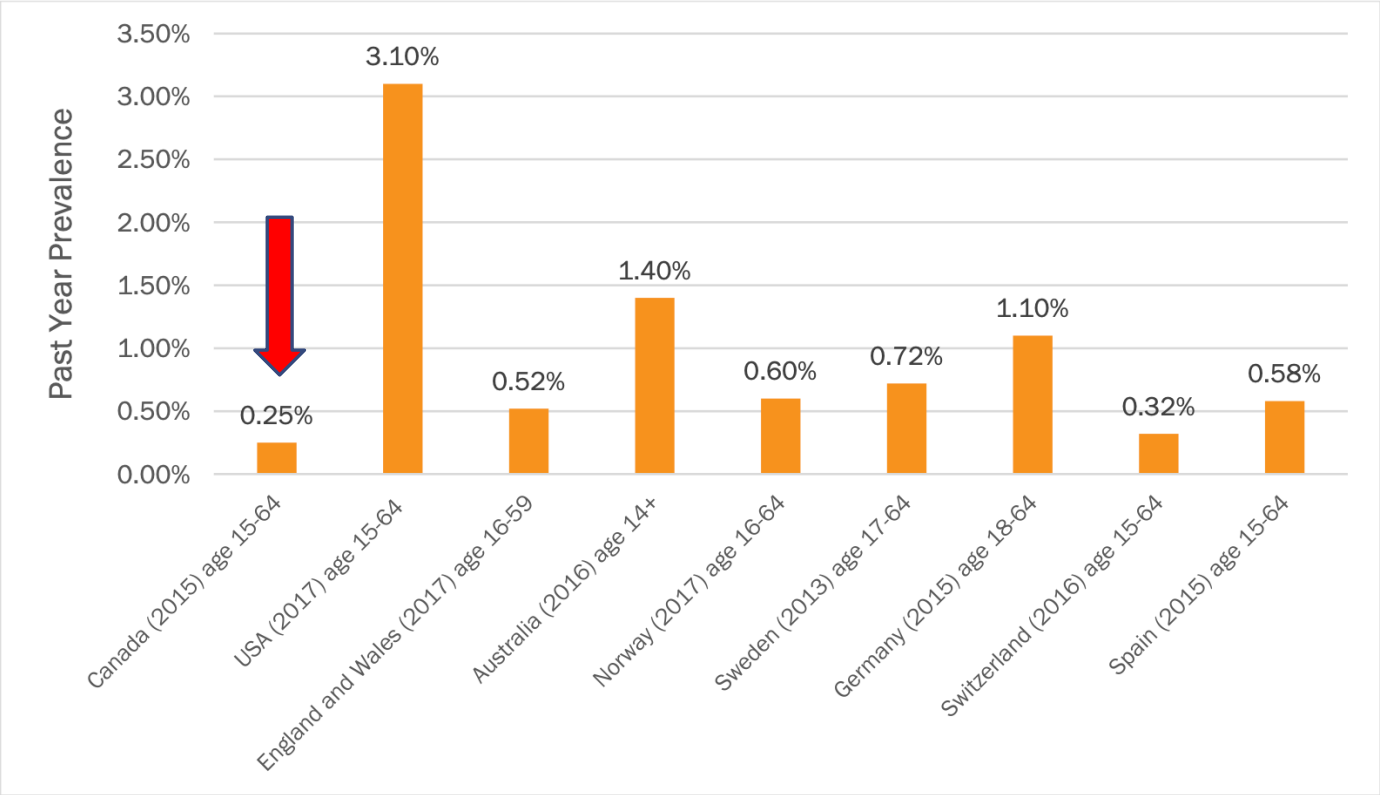
To mitigate bias, I will only use generic names of medications for this presentation, identify off-label use, and present both positive and negative studies

OBJECTIVES

1. Describe the prevalence of methamphetamine-induced psychosis
2. Describe the relationship between methamphetamine-induced psychosis and primary psychotic disorders
3. Provide an overview of the management of methamphetamine-induced psychosis

HOW COMMON IS METHAMPHETAMINE USE

Figure 4. Prevalence of self-reported past-year amphetamine and methamphetamine use among the general population by country



Source: United Nations Office on Drugs and Crime 2019[19]

Note: Prevalence estimates are for both amphetamine and methamphetamine.

While 0.25% may seem low, specific populations are disproportionately affected

1. Street involved youth
2. Urban men who have sex with men
3. Those at risk for illicit opioid toxicity

More details in “extra slides”

Canadian Drug Summary: Methamphetamine. CCSA. March 2020

Canadian Psychiatric Association
Association des psychiatres du Canada

Original Research

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
1-12

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DOI: 10.1177/07067437231158933
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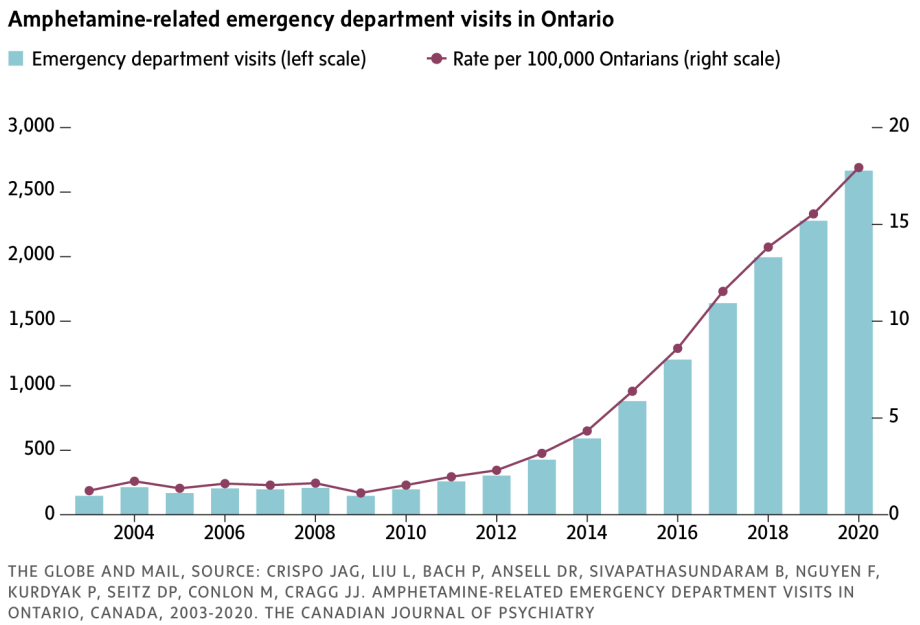
SAGE

Amphetamine-Related Emergency Department Visits in Ontario, Canada, 2003-2020

Visites au service d'urgence liées aux amphétamines en Ontario, Canada, 2003-2020



THE GLOBE AND MAIL, SOURCE: CRISPO JAG, LIU L, BACH P, ANSELL DR, SIVAPATHASUNDARAM B, NGUYEN F, KURDYAK P, SEITZ DP, CONLON M, CRAGG JJ. AMPHETAMINE-RELATED EMERGENCY DEPARTMENT VISITS IN ONTARIO, CANADA, 2003-2020. THE CANADIAN JOURNAL OF PSYCHIATRY

The rate of amphetamine-related emergency department visits in Ontario increased nearly 15-fold between 2003 and 2020

ED visits between January 1, 2019, and June 30, 2020

5,006 patients after study exclusions:

- 74.0% <40 years of age
- 46.9% residential instability
- 41.3% material deprivation
- 47.4% mood disorder
- **44.7% psychotic disorder**
- 70.2% experienced anxiety
- 31.4% prior opioid use
- 53.4% prior other substance use

James AG et al. CJP. 2023

Original Research

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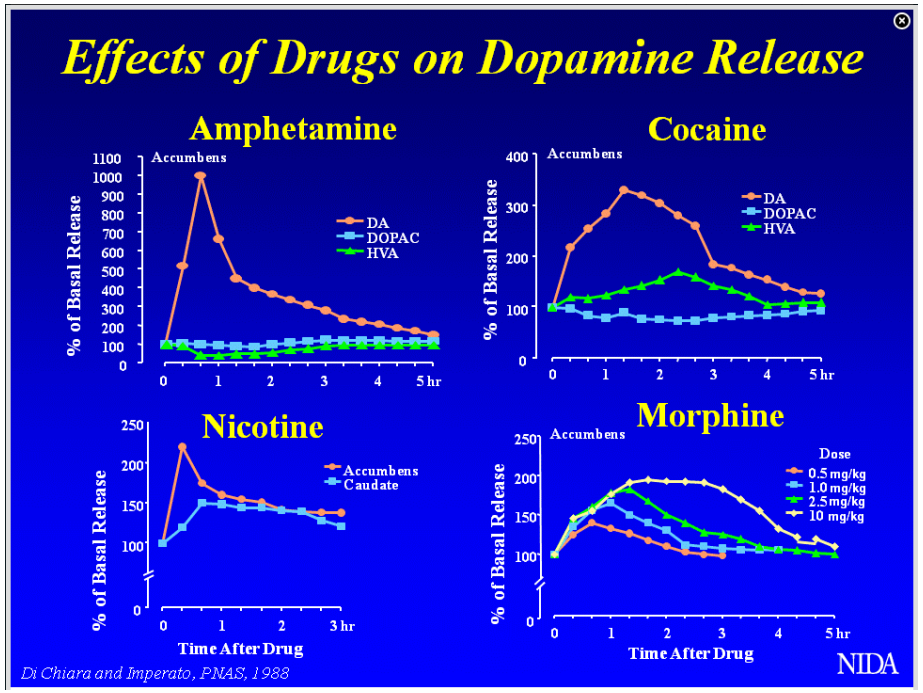
The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
1-12

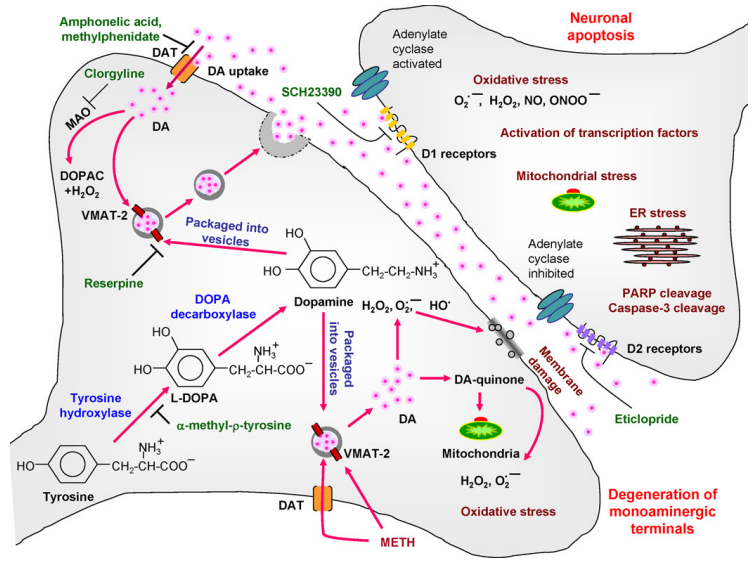
DOI: 10.1177/07067437231158933
TheCJP.ca | LaRCP.ca
SAGE

- Recent increases in the rate of amphetamine-related ED visits were least pronounced among younger (18–24 years) and older (50+ years) adult
- Seventy-five percent of individuals returned to the ED for any reason within six months
- **Psychosis and use of other substances were both independently associated with ED revisit for any reason within six months** (psychosis: AOR = 1.54, 95% CI = 1.30–1.83; other substances: AOR = 1.84, 95% CI = 1.57–2.15)
- Having a primary care physician was negatively associated with ED revisit (AOR = 0.77, 95% CI = 0.60–0.98)

James AG et al. CJP. 2023

METHAMPHETAMINE IS NEUROTOXIC





Krasnova I et al. *Brain Res Rev*. 2009

Massive dopamine release

Cytotoxic damage

METHAMPHETAMINE IS NEUROTOXIC

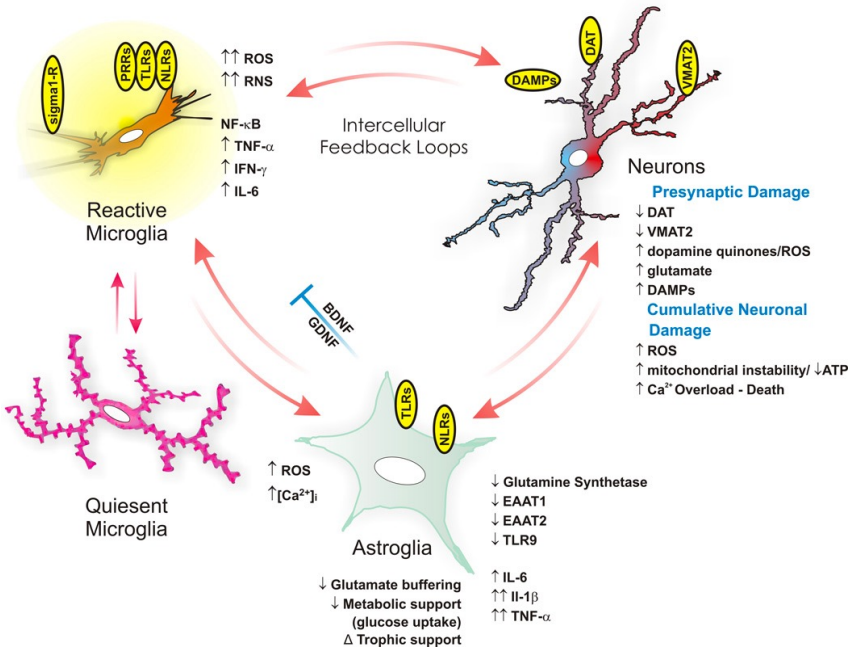
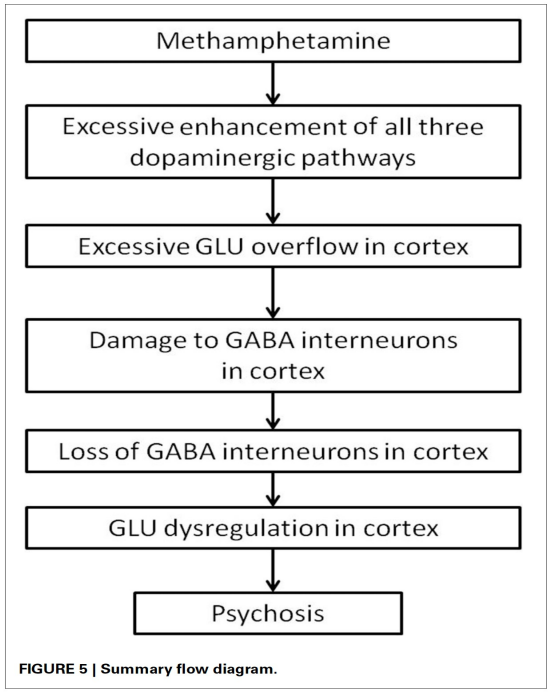


Image from Wikipedia Commons

Immune activation

Damage to cortical GABAergic function



Hsieh JH et al. *Front Hum Neurosci*. 2014

OTHER POSSIBLE REASONS FOR NEUROTOXICITY

Route of administration?

Contamination?

- Other amphetamine-type substances
- Other substances

Dose?

Peak plasma d-amphetamine levels (Kish SJ. *CMAJ*. 2008):

- 110 ng/mL in regular ADHD treatment
- 1600 ng/mL in a “real-life” study of unsupervised recreational methamphetamine users
- ~14.5x higher

PREVALENCE OF METHAMPHETAMINE-INDUCED PSYCHOSIS

- Estimates of the epidemiology of transient methamphetamine-induced psychosis vary widely (23–76%)

  Salo R et al. *Psychiatry Res*. 2011

  Salo R et al. *Psychiatry Res*. 2013

- A 2018 systematic review and meta-analysis of 17 observational studies (n=4,095) estimated the prevalence of psychotic disorders attributed to methamphetamine use to be 42.7%

  Lecomte T et al. *Psychiatry Res*. 2018

WHAT ABOUT PRESCRIBED PSYCHOSTIMULANTS?

Moran and colleagues (*NEJM*, 2019) assessed 337,919 adolescents and young adults who received a prescription for a stimulant for ADHD

110,923 patients taking methylphenidate were matched with 110,923 patients taking amphetamines

- 1 in 660 patients on psychostimulants developed psychosis, and the risk was higher for amphetamines versus methylphenidates
- Increased risk of psychosis with use of amphetamines (0·21%) and methylphenidate (0·10%) treatment

PRESCRIPTION PSYCHOSTIMULANTS AND READMISSION TO ER

Canadian Drug Safety and Effectiveness Research Network

- Cressman et al. studied 183 young people who received a stimulant prescription at specified time intervals and were subsequently hospitalized for psychosis or mania
- One-third of subjects received another stimulant prescription within 100 days after hospital discharge
- Of these, 45% were readmitted for psychosis or mania at a median of 18 days after the subsequent stimulant prescription

“We conclude that initiation of prescription stimulants is associated with an increased risk of hospitalization for psychosis or mania”

Cressman AM et al. *J Clin Psychopharmacol.* 2015

POPULATION AND ACUITY ARE KEY

My takeaways:

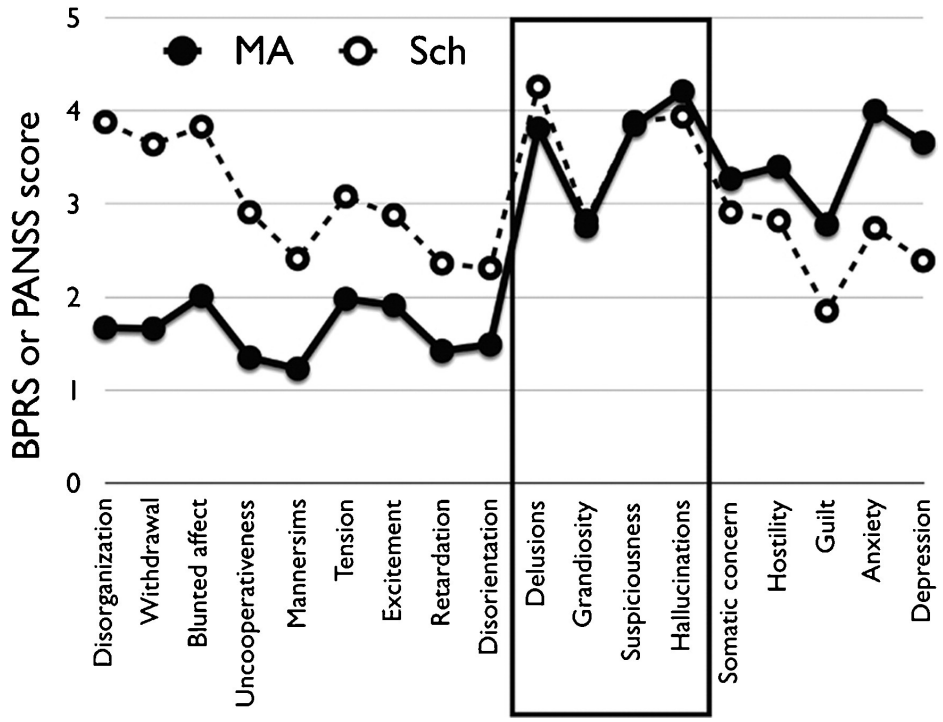
- The risk of inducing a psychotic event or disorder with prescription psychostimulants is low in the general population (1 in 660 in a large study)
- However, the risk is markedly higher for those who have already had a psychotic episode requiring hospitalization following the initiation of psychostimulants
- This risk of readmission to hospital in the latter group is high if psychostimulants are restarted

DSM-5: SUBSTANCE USE AND PSYCHOSIS

Three groups to consider

1. Transient perceptual disturbances in intoxication
2. Substance-induced psychotic disorder
3. Primary psychotic disorder in the context of substance use

SYMPTOMS ALONE DO NOT DISTINGUISH PRIMARY FROM STIMULANT-INDUCED PSYCHOSIS



- Scores were most similar for the positive symptoms of psychosis: delusions, grandiosity, suspiciousness, and hallucinations
- MA users had lower scores on the “negative” symptoms
  - Blunted affect
  - Disorganization
  - Social withdrawal
- MA users had higher scores on affective symptoms, such as hostility, anxiety and depression

Panenka WJ et al. *Drug Alcohol Depend*. 2013

SUBSTANCE USE & MISUSE
2019, VOL. 54, NO. 4, 549–559
https://doi.org/10.1080/10826084.2018.1521430

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

A Systematic Review of the Symptom Profile and Course of Methamphetamine-Associated Psychosis

Alexandra Voce[a], Bianca Calabria[b,c], Richard Burns[a], David Castle[d,e], and Rebecca McKetin[c,f]

WHAT SYMPTOMS ARE COMMON IN SUBSTANCE-INDUCED PSYCHOSIS?

- Persecutory delusions, auditory and visual auditory hallucinations were by far the most reported symptoms (reported in 65–84% of studies)
- Hostility, conceptual disorganization, and depression were reported in a large proportion of studies (31–53%)
- Negative symptoms were found in <20%

Voce A et al. *Subst Use Misuse*. 2019

SUBSTANCE USE & MISUSE
2019, VOL. 54, NO. 4, 549–559
https://doi.org/10.1080/10826084.2018.1521430

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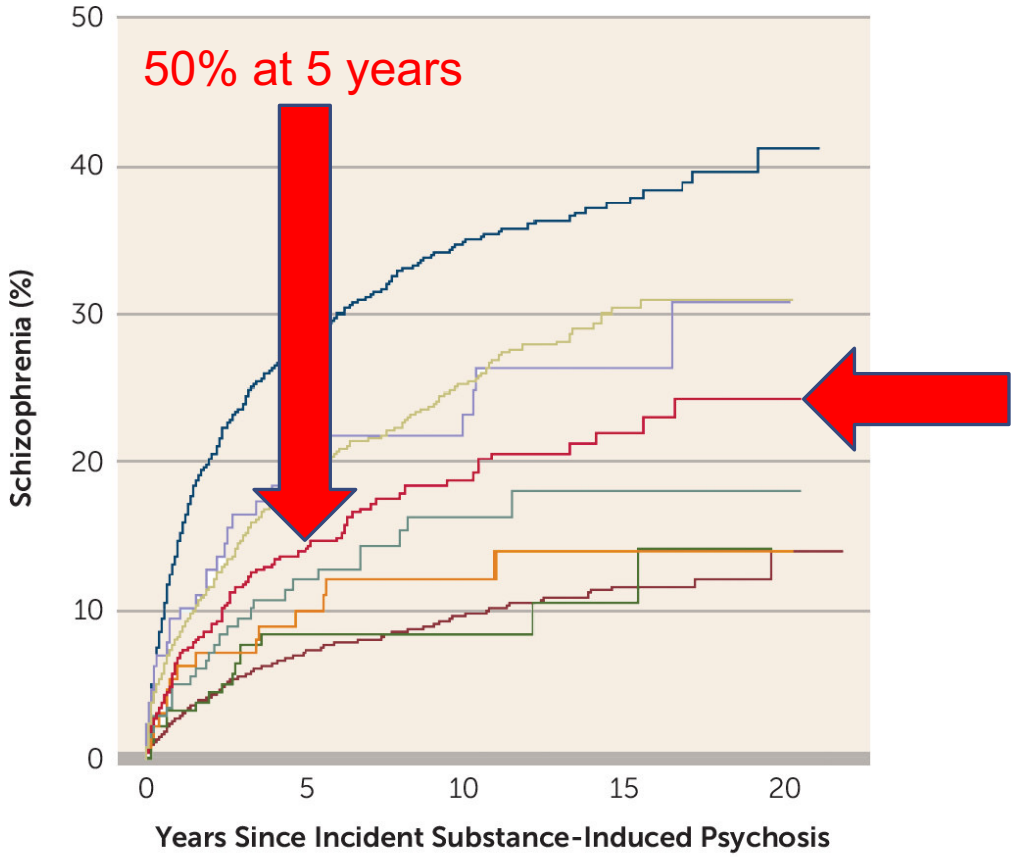
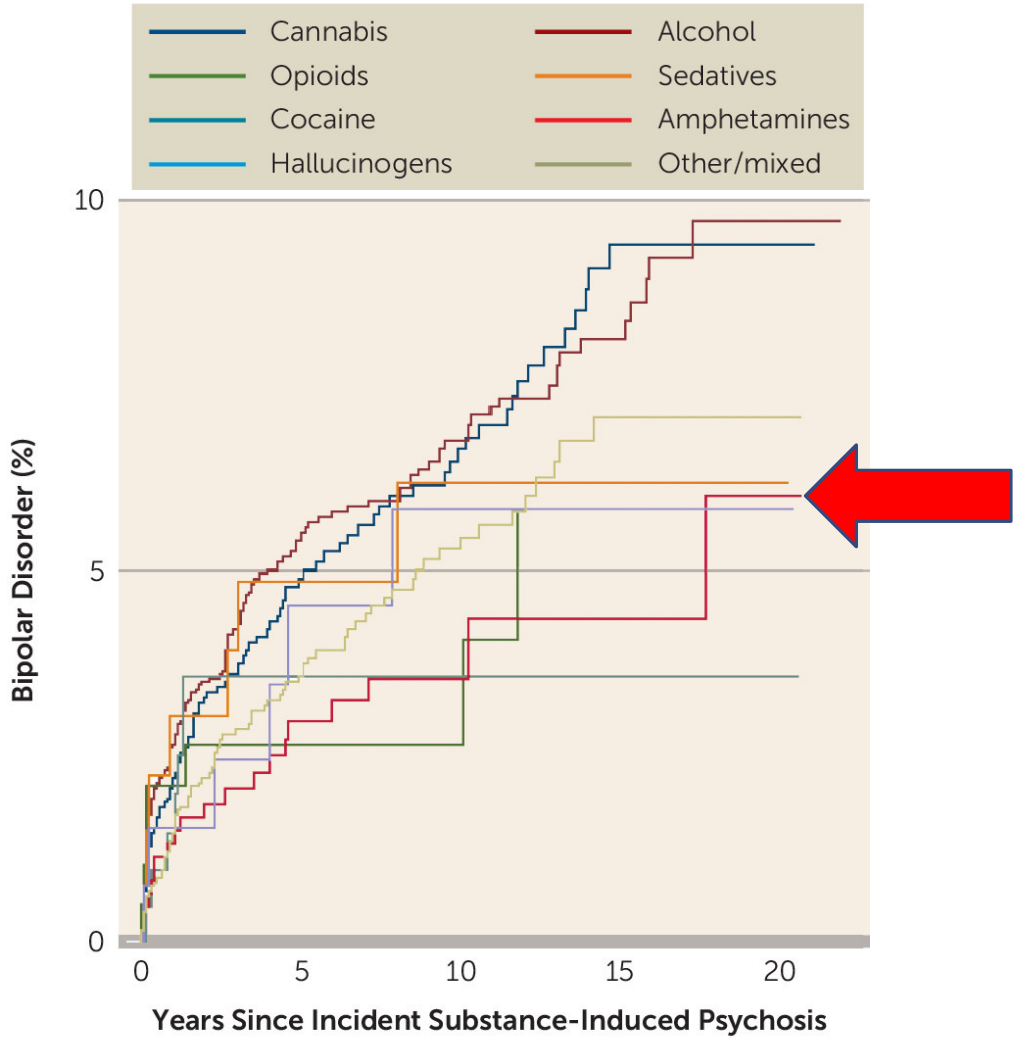
HOW LONG DOES SUBSTANCE-INDUCED PSYCHOSIS LAST?

- In case reports, after ceasing methamphetamines symptoms lasted:
  - 36% one week or less
  - 58% one to four weeks
  - 8% persistent
- Excluding case reports, the median percentage of participants with persistent psychotic symptoms (> 1-month duration) across studies was 25%

Voce A et al. *Subst Use Misuse*. 2019

MANY WILL DEVELOP SCHIZOPHRENIA OR BIPOLAR DISORDER





Prediction of Onset of Substance-Induced Psychotic Disorder and Its Progression to Schizophrenia in a Swedish National Sample

Kenneth S. Kendler, M.D., Henrik Ohlsson, Ph.D., Jan Sundquist, M.D., Ph.D., Kristina Sundquist, M.D., Ph.D.

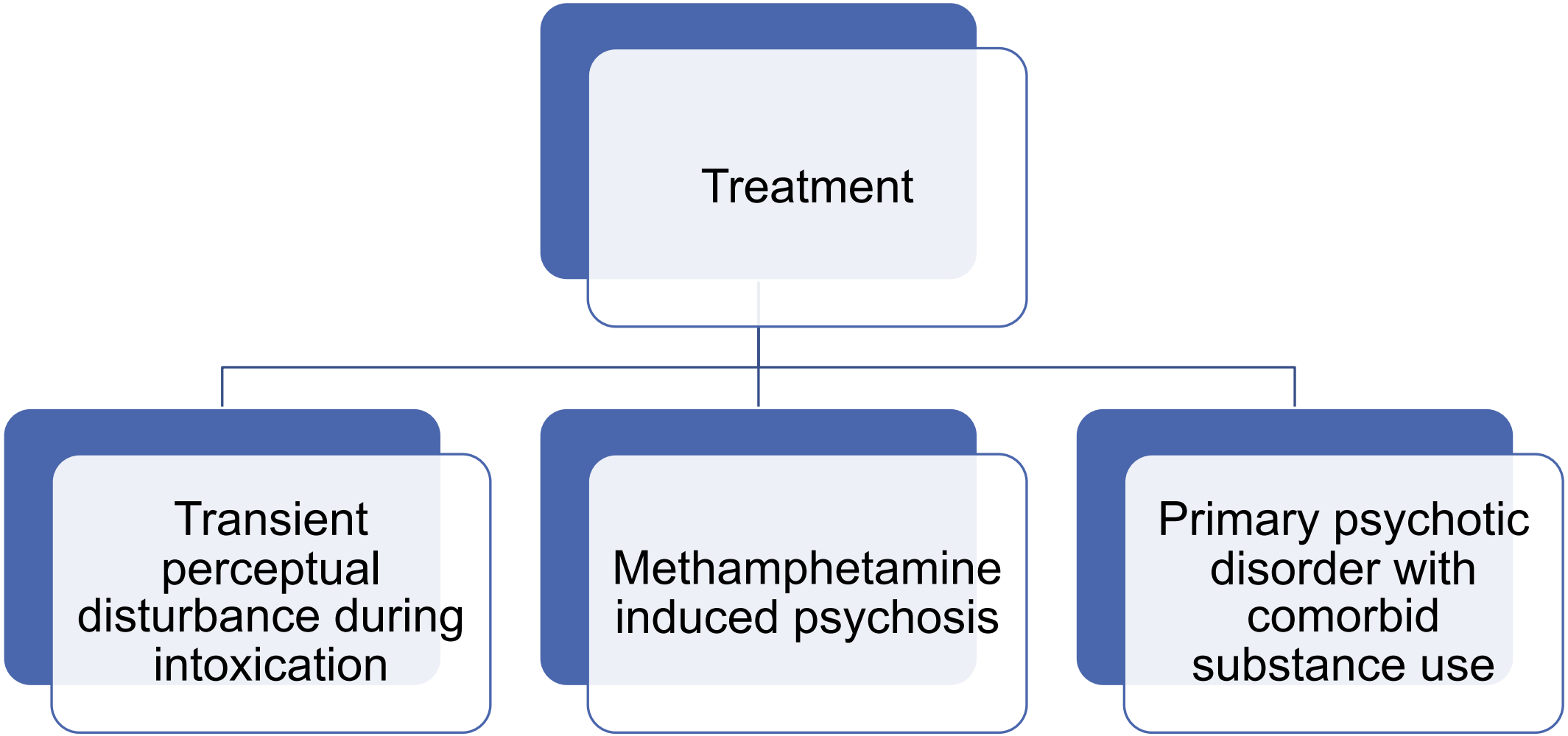
FACTORS THAT MAY PREDICT PROGRESSION TO SCHIZOPHRENIA

- Familial risk score for non-affective psychosis
- Early age at diagnosis of substance-induced psychotic disorder

  For stimulants, a cumulative hazard of ~23% at age 15, ~19% at age 20, ~12% at age 30, ~8% at age 40, ~5% at age 50
- Male sex
- Further episodes of drug abuse, alcohol use disorder, and substance-induced psychotic disorder
- Among hospitalized individuals (N=4,553), hospitalization for >8 days has a hazard ratio of 2.21 (95% CI=1.70, 2.87) compared with those hospitalized for one day

The mean time to schizophrenia conversion was 39 months

Kendler KS et al. *Am J Psychiatry*. 2019


Treatment
Transient perceptual disturbance during intoxication
Methamphetamine induced psychosis
Primary psychotic disorder with comorbid substance use

TREATMENT: SHORT TERM

- Short-term targets: agitation, psychosis
- Consider the risk/benefit ratio when deciding between conservative/supportive versus medications
- Acute risks with antipsychotic risks: seizures, falls, stroke, venothromboembolism, dystonia
- Calming environment and interactions for those who have mild agitation, mild perceptual disturbance
- High levels of distress and risk of harm to self or others → pharmacological management benefit outweighs the risk
- Benzodiazepines are most supported for agitation treatment in stimulant-induced psychosis

TREATMENT: SHORT TERM

- **Olanzapine** and **haloperidol** were efficacious in resolving psychotic symptoms, with the olanzapine condition showing significantly greater safety and tolerability than the haloperidol control

Cochrane, 2009

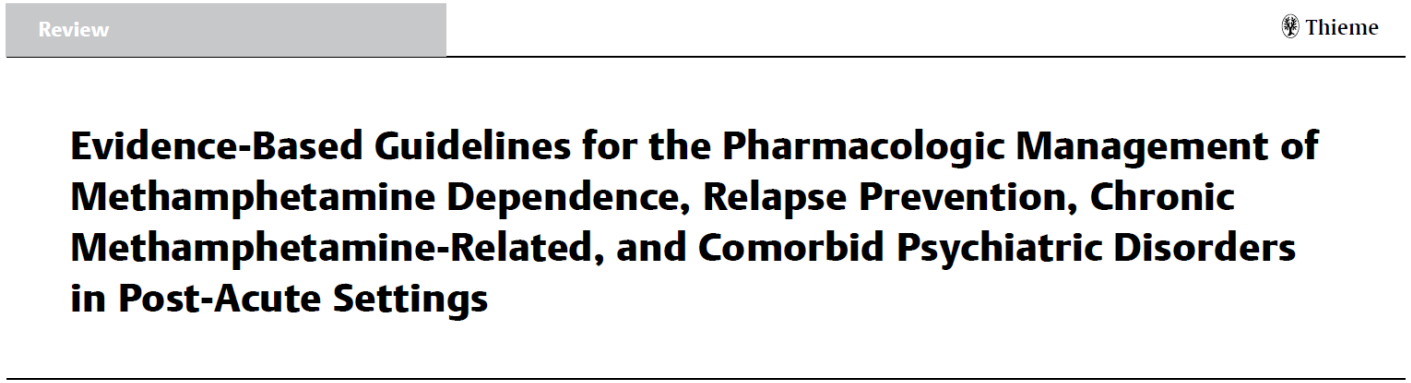
- **Aripiprazole** and **risperidone** were effective for patients with amphetamine-induced psychotic disorder. Risperidone had the greater effect on positive psychotic symptoms

Farnia et al., *Am J Drug Alcohol Abuse,* 2014

- RCT of **haloperidol** vs. **quetiapine** showed quetiapine may be used with comparable therapeutic effects and adverse events to treatment with haloperidol

Verachai V et al., *Psychopharmacology* (Berl), 2014

LONG-TERM ANTIPSYCHOTICS AND METHAMPHETAMINE INDUCED PSYCHOSIS


Review

Thieme

Evidence-Based Guidelines for the Pharmacologic Management of Methamphetamine Dependence, Relapse Prevention, Chronic Methamphetamine-Related, and Comorbid Psychiatric Disorders in Post-Acute Settings

- Neuroleptics can promote craving and relapses in methamphetamine users because of their antidopaminergic effect
- The indication for the continuation of neuroleptic therapy ought to be reviewed at the latest after 6 months of treatment in individuals presenting with a methamphetamine-associated psychosis

Härtel-Petri R et al. *Pharmacopsychiatry* 2017

https://doi.org/10.1055/s-0043-105500

FIRST EPISODE PRIMARY PSYCHOSIS AND CONCURRENT AND LONG ACTING INJECTABLE?

Abdel-Baki et al. studied patients with **first-episode schizophrenia spectrum and affective psychosis and comorbid substance use disorder** (n=237) and compared oral antipsychotic versus long-acting injectable antipsychotics

- 75% had a relapse of psychosis in three years
- The LAI group had a lower psychosis relapse rate (67.7% vs 76.7%) and higher psychosis relapse-free survival time (694 vs 447 days, P = 0.008)
- The differences in first rehospitalization rates (48.4% and 57.3%, respectively) and time to first rehospitalization (813 and 619 days, respectively; P = 0.065) between the LAI-AP first and OAP first groups were not statistically significant

Abdel-Baki A et al. *Early Interv Psychiatry*. 2020

TREATMENT: CHRONIC SCHIZOPHRENIA AND SUD

- **Dual-diagnosis patients** might do better on **clozapine**, with less relapse into abuse of drugs or alcohol
- **Comprehensive services** and **case management** are important

Buckley et al., Schizophr Bull, 2008

- **Among those with schizophrenia**, **clozapine** may reduce substance use relapse and suicidal behaviour in those refractory to other antipsychotic medications

Schell T et al., Am J Addict, 2014

FOR METH USE DISORDER ITSELF – MANY NEGATIVE TRIALS

Table 3 Brief summary of findings.

	Abstinence	Use	Retention	Harms
All Antidepressants	★★	Ø	★★	★
Aminoketone: Bupropion	★	★	★★	Ø
Atypical Antidepressant: Mirtazapine	NA	Ø	Ø	Ø
SSRI: Sertraline	Ø	NA	Ø	NA
Atypical Antipsychotics: Aripiprazole	Ø	★	Ø	Ø
Psychostimulants and Other Medications for ADHD				
All Psychostimulants: Modafinil, Dexamphetamine, Methylphenidate	★	Ø	★	NA
Methylphenidate	NA	★	★	NA
Atomoxetine	NA	Ø	Ø	Ø
All Anticonvulsant and Muscle Relaxants: Baclofen, Gabapentin, Topiramate	Ø	Ø	Ø	Ø
Topiramate	NA	★	★	★
Medications used for other substance use disorders				
Naltrexone	Ø	★	★	★★
Varenicline	NA	Ø	Ø	Ø

Shading represents the direction of effect:

(No color)	Unclear
Grey	No difference
Green	Evidence of benefit
Red	Favors placebo

Symbols represent the strength of the evidence:

NA	No evidence or not applicable
Ø	Insufficient
★	Low
★★	Moderate
★★★	High

Chan B et al., *Addiction* 2019

Psychopharmacology (2020) 237:2233–2255
https://doi.org/10.1007/s00213-020-05563-3

REVIEW

Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis

Vitor S. Tardelli[1] · Adam Bisaga[2] · Felipe B. Arcadepani[1] · Gilberto Gerra[3] · Frances R. Levin[2] · Thiago M. Fidalgo[1]

"Conclusion: Prescription psychostimulants, particularly prescription amphetamines given in robust doses, have a **clinically significant beneficial effect to promote abstinence** in the treatment of individuals with PSUD [psychostimulant use disorder], specifically the population with cocaine use disorder."

However, this claim needs a closer look

Primary outcome: promoting **two to three weeks** of sustained abstinence

Tardelli VS et al. Psychopharmacology (Berl). 2020

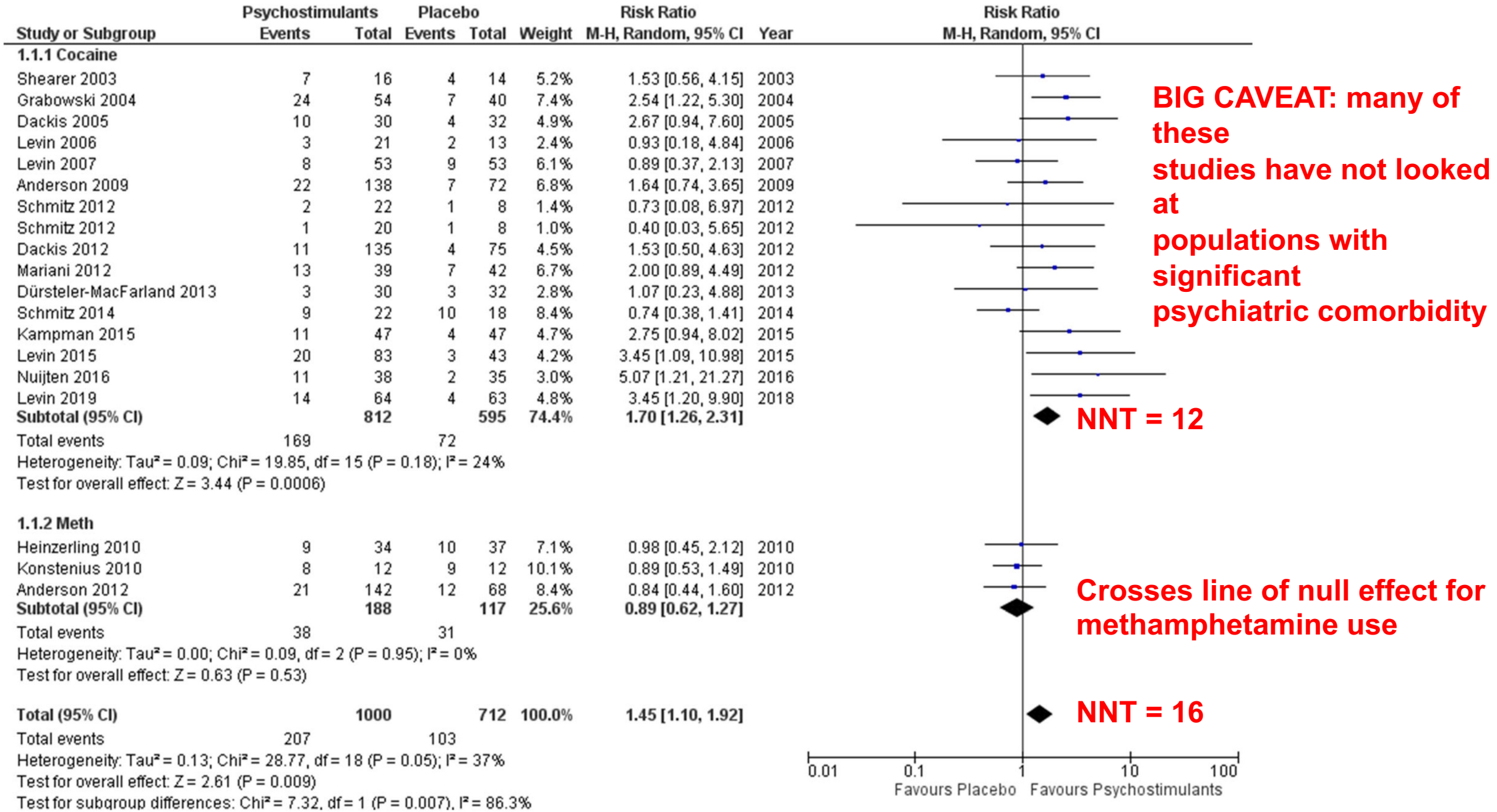


Fig. 2. Overall and by dependence drug effect of prescription psychostimulants compared to placebo for outcome sustained abstinence

Research

JAMA Psychiatry | Original Investigation

Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men

A Placebo-Controlled Randomized Clinical Trial

Phillip O. Coffin, MD, MIA; Glenn-Milo Santos, PhD, MPH; Jaclyn Hern, MPH; Eric Vittinghoff, PhD; John E. Walker, MSN; Tim Matheson, PhD, MS; Deirdre Santos, RN, MSN; Grant Colfax, MD; Steven L. Batki, MD

- By week 12, the rate of methamphetamine-positive urine test results significantly declined among participants randomized to mirtazapine vs placebo RR = 0.67
- Mirtazapine reduced positive urine test results at 24 weeks RR = 0.75 and at 36 weeks RR = 0.73 vs placebo
- Caveat: Mean (SD) medication adherence was 38.5% in the mirtazapine group vs 39.5% in the placebo group (P = .77) over 2 to 12 weeks and 28.1% vs 38.5% (P=.59) over 13 to 24 weeks

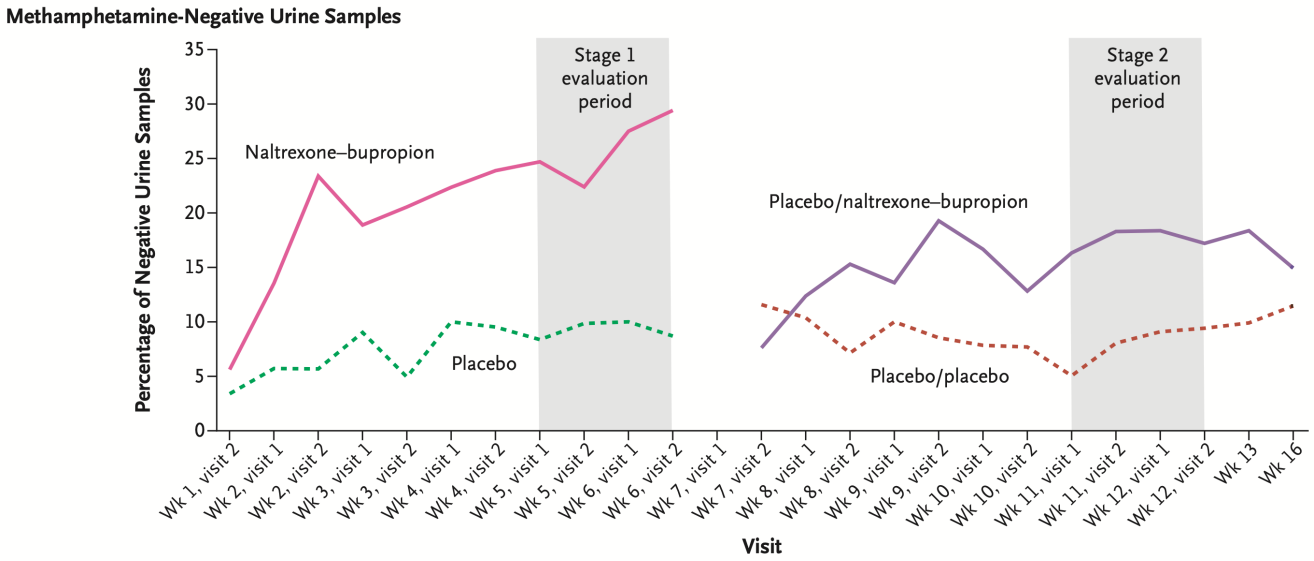
JAMA Psychiatry. doi:10.1001/jamapsychiatry.2019.3655
Published online December 11, 2019.

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



Evaluate the efficacy and safety of extended-release injectable naltrexone (380 mg every three weeks) plus oral extended-release bupropion (450 mg per day) in adults with moderate or severe methamphetamine use disorder

The primary outcome was a response, defined as at least three methamphetamine-negative urine samples out of four samples obtained at the end of stage 1 or stage 2, and the weighted average of the responses in the two stages is reported

The weighted average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1 percentage points

IM Naltrexone is not yet available in Canada

Trivedi M et al. *NEJM*. 2021

OBJECTIVES

1. Describe the prevalence of methamphetamine-induced psychosis
2. Describe the relationship between methamphetamine-induced psychosis and primary psychotic disorders
3. Provide an overview of the management of methamphetamine-induced psychosis

TOMORROW

- Cases
- Psychosis, ADHD
- Psychosocial treatments
- Harm reduction

THANK YOU

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Comments, questions and suggestions

EXTRA SLIDES: POPULATIONS HEAVILY AFFECTED BY METH USE

CRYSTAL METHAMPHETAMINE USE: STREET YOUTH

Vancouver At-Risk Youth Study

- 1019 street-involved youth (age 14-26) surveyed between 2005 and 2012
- 69% reported any prior crystal methamphetamine use

Uhlmann et al., *Am J Drug & Alcohol Abuse*, 2014

CRYSTAL METHAMPHETAMINE USE: URBAN MEN WHO HAVE SEX WITH MEN

Crystal Methamphetamine Initiation Among HIV-Positive and HIV-Negative Men Who Have Sex With Men in Vancouver, Canada: A Longitudinal Analysis

N.J. Lachowsky[1,2], M. Hull[2,3], S. Colyer[2], Z. Cui[2], J. Zhu[2], H.L. Armstrong[2,3], M. Taylor[4], J. Edwards[4], G. Olarewaju[2], R. Hogg[2,5], E.A. Roth[6], D.M. Moore[2,3], Momentum Health Study

1. School of Public Health & Social Policy, University of Victoria, Victoria, Canada
2. British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada
3. Faculty of Medicine, University of British Columbia, Vancouver, Canada
4. Health Initiative for Men, Vancouver, Canada
5. Faculty of Health Science, Simon Fraser University, Burnaby, Canada
6. Department of Anthropology, University of Victoria, Victoria, Canada

- Over the 4-year study period, 698 GBMSM completed 3,085 study visits (median follow-up of 2.49 years). **Crystal use in the 6 months prior to survey:**
  - 20.1% of GBMSM
  - 44.3% HIV-positive GBMSM
  - 10.3% HIV-negative GBMSM

With permission from the authors

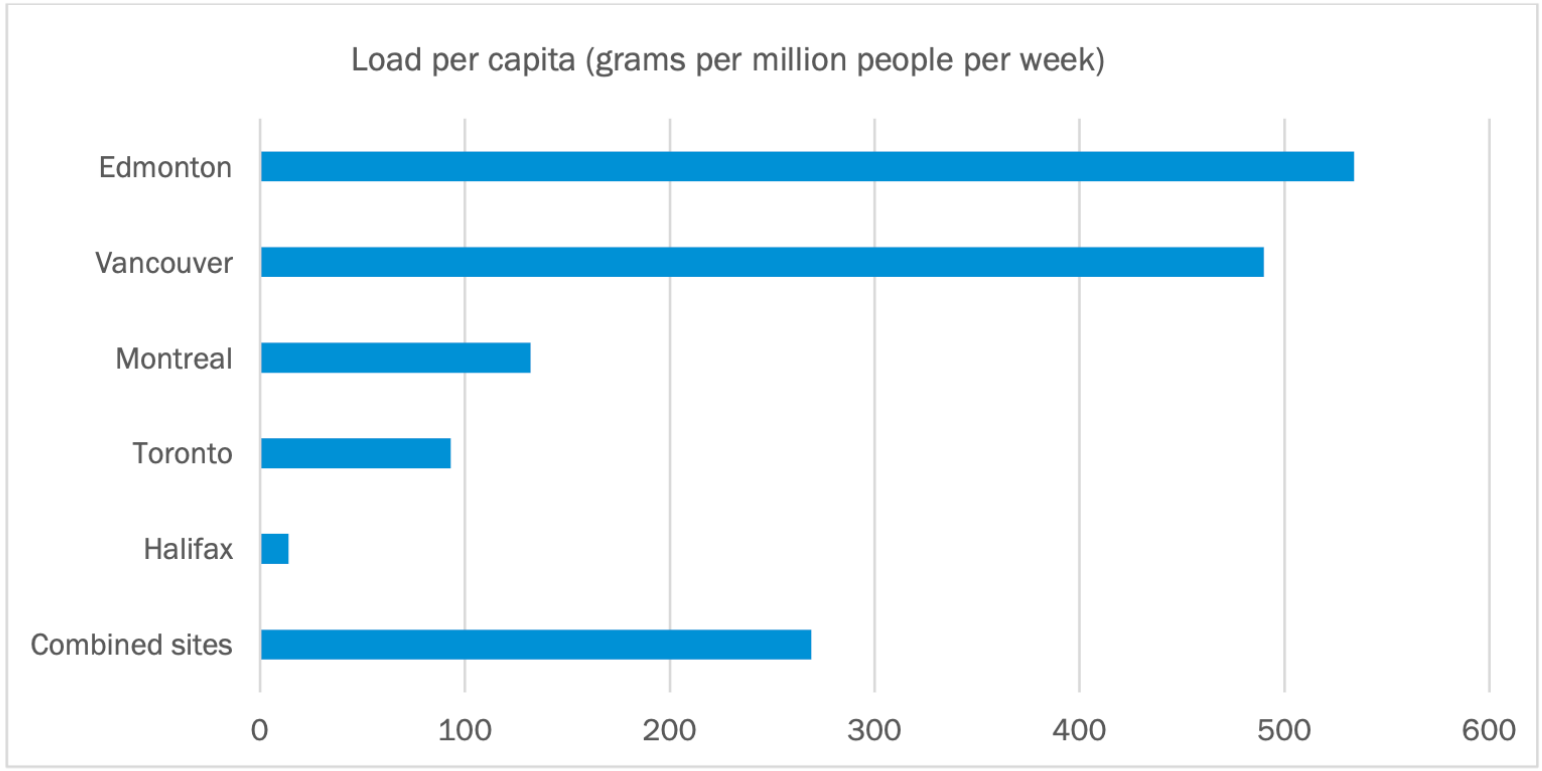
CRYSTAL AMPHETAMINE USE: OPIOID TOXICITY DEATHS

Among the **completed illicit drug toxicity deaths, methamphetamine has increased from 14% in 2012 to 44% in 2020**

British Columbia Coroners Service. 2022

VARIABILITY BY LOCATION

Figure 3 Wastewater-based estimates of methamphetamine in Canada (March 2018 to February 2019)



Source: Statistics Canada (2019)[18]

Canadian Drug Summary: Methamphetamine. CCSA. March 2020