UNIVERSITY OF CALIFORNIA, LOS ANGELES **UCLA**

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA
DEPARTMENT OF FAMILY MEDICINE
VICE CHAIR FOR RESEARCH
10880 WILSHIRE BLVD, SUITE 1800
LOS ANGELES, CA 90095-7087

To: Shari Derrow
From: Steven Shoptaw PhD
RE: Consultation Report for U.S. Sentencing Commission
Date: July 28, 2025

Attached please find my consultation for the meeting at the U.S. Sentencing Commission that will provide the basis of my testimony on August 5, 2025 on the topic:

Medical, Social, Psychological Consequences:

Methamphetamine Actual and Methamphetamine Mixed

Sincerely,

Steven Shoptaw, PhD
George Kneller Term Chair
Professor Emeritus and Vice Chair for Research, Department of Family Medicine

Medical, Social, Psychological Consequences:

Methamphetamine Actual and Methamphetamine Mixed

Report Prepared by: Steven Shoptaw PhD

for the

U.S. Sentencing Commission

August 28, 2025

Introduction

There are few published reports that link medical, social, and psychological consequences from methamphetamine use with type of methamphetamine used (actual, mixed). That means that the science base on negative health and public health effects of the more potent methamphetamine actual (i.e., ice) compared to the less potent methamphetamine mixed (i.e., powder) is largely absent. By contrast, a robust literature exists that links use of high-dose methamphetamine (whichever type of methamphetamine that can be purchased from the illicit market) with medical, social, and psychological consequences. This report outlines findings that describe links between methamphetamine use and negative health and social outcomes that are agnostic to the type of methamphetamine used (whether actual or mixed types).

Across epidemiological and clinical studies, clinically and statistically significant links between methamphetamine use and negative medical, social and psychological correlates are commonly documented. More, two factors that describe how much and how long methamphetamine is used use frequently correspond with reports on negative consequences: “Dose” (the amount and potency of the drug acutely used) and frequency of use (number of times used per day, days used per week/month).

Dose

It is difficult to gather precise estimates of dose of methamphetamine used on any occasion as the drug is illegal, which makes a barrier for persons who might provide samples to scientists for analysis. One proxy of dose is the amount of money spent on the drug, which has limits given costs for methamphetamine varies vary depending on market forces (Wilkins et al., 2020). More, when asked to estimate amount spent on methamphetamine individuals have difficulty recalling what they themselves spent per dose of drug as many report receiving drug gratis during use episodes with friends or others who use together and share their drugs.

A new, non-peer reviewed report provides estimates of average and median self-reported methamphetamine doses from 68 people who regularly use methamphetamine who were seen at a drug checking site in Los Angeles. In addition to reports of times used per day used, participants “donated” 112 samples of methamphetamine donations that were analyzed for methamphetamine potency using liquid chromatography-mass spectrometry, an test that provides precise results of drug potency (Friedman et al., 2025). Findings showed average self-reported dose of methamphetamine used was 0.96 g of methamphetamine daily (median 0.36 g). Self-report and drug purity data were entered into an equation to calculate a methamphetamine oral amphetamine equivalent (MOAE), with estimations of daily mean and median MOAE exposure being 1,549.0 mg and 516.6 mg, respectively (Figure 1).

These are exceptionally high estimates of amphetamine equivalents daily, independent of type of methamphetamine ingested (actual – ice, or mixture - powder). For contrast, maximum daily dose of amphetamine listed on the package insert of amphetamine (Desoxyn) marketed as a second line treatment for obesity is 25 mg. The maximum amphetamine dose for childhood attention deficit hyperactivity disorder treated using mixed amphetamine salts (Adderall) on the package insert is 30 mg daily; 20 mg daily for adults. Maximum dose of lis-dexamphetamine, prodrug for

amphetamine, is 70 mg per day. Clearly, at low doses, amphetamine has therapeutic value. The much higher doses of MOAE by participants in the Friedman et al (2025) study have no therapeutic value and instead have been shown to produce neurotoxicity in preclinical models (Alburges et al., 2015). An in-depth discussion of scientific evidence on methamphetamine effects on brain and behavior is found at: Ashok et al., 2017.

Figure 1. Grams per day, percent concentration, mg of oral amphetamine equivalent of 112 samples of methamphetamine donations in Los Angeles

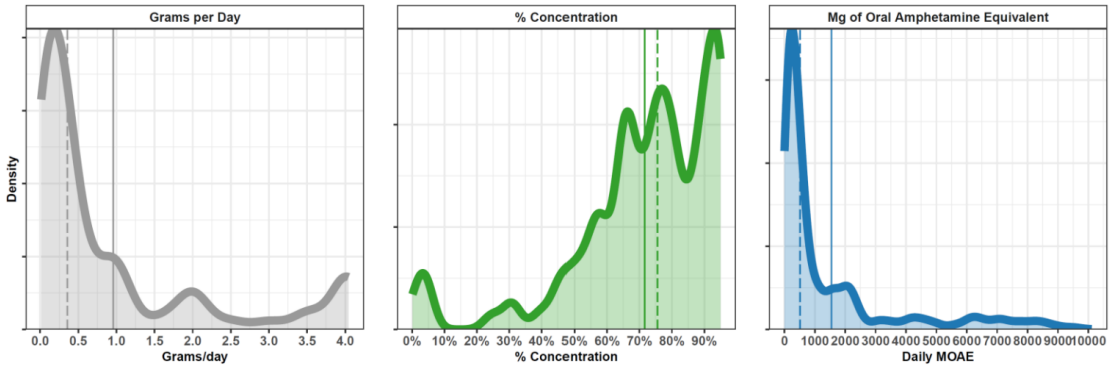


Figure. Distributions, Median, and Mean Grams per Day Consumed, Percent Concentration (Purity), and Estimated mg of Oral Amphetamine Equivalent Self-Administered Among Regular Consumers in LA
For each panel, a dashed vertical line shows the distribution mean, and a dashed solid line shows the distribution mean. Left: The distribution of self-reported grams of methamphetamine ingested per day among regular consumers participating in drug checking services in Los Angeles. Center: Percent concentration (purity) of expected methamphetamine samples provided by clients at drug checking services in Los Angeles. Right: the estimated distribution of milligrams of oral amphetamine equivalent (MOAE) consumed among drug checking clients in Los Angeles.

Acute Impacts of Methamphetamine on Inflammation. One method that can document acute physical effects of methamphetamine on body compartments that does not involve providing the drug to people involves collecting clinical observations of individuals who attend clinic and provide urine drug screens documenting recent methamphetamine use (past 72 hours). Findings can then be compared with measures collected from individuals who do not use methamphetamine (urine drug screen verified). Biological markers that show differences between samples collected from individuals with acute use of methamphetamine and those from individuals who do not use methamphetamine can provide evidence of putative drug effects.

Using this model early observations showed significantly higher levels of pro-inflammatory cytokines measured in gut for participants with acute use of methamphetamine compared to those who did not use the drug, independent of HIV serostatus in gay and bisexual men (Fulcher et al., 2018). Recent methamphetamine use among gay and bisexual men corresponded with diagnosis of rectal gonorrhea and chlamydia compared to men without acute methamphetamine

use. This evidence provides an acute synergistic biobehavioral mechanism linked to methamphetamine use for promoting HIV and sexual transmitted infection transmission among gay/bisexual men. Among gay/bisexual men living with HIV, methamphetamine use increases circulating pro-inflammatory cytokines even when treated with antiretroviral therapy for HIV (Carrico et al., 2018), a finding consistent with clinically relevant impairments in maintaining viral suppression observed for gay/bisexual men living with HIV who are on antiretroviral therapy (Fulcher et al., 2021).

Together these findings show methamphetamine use on a specific day (acute) dysregulates immune function in gut and in circulating blood. These acute biological effects in immune dysregulation from methamphetamine use provides some data to explain increased likelihood of HIV and STI transmission, especially in the setting of unprotected sex. These also partially explain likelihood observations of poor sustained viral suppression among people living with HIV who use methamphetamine that are additional to simply attributing this to non-adherence with antiretroviral medication.

Frequency

Frequency of use of high-dose methamphetamine is used consistently corresponds with negative medical, social and psychological consequences. Using the power of an observational cohort funded by the National Institute on Drug Abuse (Pamina Gorbach and Steve Shoptaw MPI), data were collected from 515 gay and bisexual men who live in in Los Angeles and followed for over 11 years. By purpose, half of mSTUDY cohort members were men who use drugs, half do not; half of mSTUDY cohort members are living with HIV, half are not.

Self-reported frequency of use, collected in six-month panels produced reliable and meaningful behavioral phenotypes, i.e., patterns of methamphetamine exposure among gay and bisexual men. These patterns were: (1) people who do not use methamphetamine over the six months, (2) people who use methamphetamine monthly or less over the six months, and (3) people who use methamphetamine or more frequently over the six months. A hallmark of these behavioral phenotypes is their stability over the 11 years. This parallels stable behavioral phenotypes common for people who use legal stimulants (caffeine, nicotine), i.e., the consistent patterns of use of caffeine and/or nicotine each day and over time. The stability of these behavioral phenotypes (patterns) among people who use nicotine facilitates measurement of negative health impacts of cigarette smoking over the lifetime using “pack/years”: the number of packs smoked per day (on average) multiplied by the number of years of regular smoking.

Among mSTUDY participants the majority reported no use of methamphetamine over any six-month period (63%). Of the 37% of participants who did report methamphetamine use over the six months, 19% reported monthly or less methamphetamine use; 18% reported weekly or more use (Shoptaw et al., 2022). Phenotypes were stable, but could shift slowly (average one year) to transition up or down in frequency of methamphetamine use. “Transitions” involved moving from no use to monthly or less or from monthly or less to weekly or more – or in reverse order from most frequent to less frequent to no use. Very few “transitions” moved from none to weekly or more, or the reverse, even with engagement in some form of treatment (Rosen et al., 2023).

These stable phenotypic patterns, when correlated with a range of medical, social, and psychological variables showed that as reported frequency of methamphetamine use increased,

the likelihood of experiencing social adversity, sexual risk behaviors, sexually transmitted infections, and chronic clinical conditions also increased. This is important as mSTUDY participants were in young and middle adulthood age ranges (18 to 45), a time of life that in general has low prevalence of chronic disease (Figure 2).

Specific outcomes using multivariable models showed escalating odds of adverse medical conditions (p's < .001) for participants who reported weekly or more frequent methamphetamine use compared to peers used methamphetamine less than monthly along:

- A positive bacterial test for sexually transmitted infections ($p < .001$)
- Detectable viral load (in HIV-positive participants; <20 c/ML blood) ($p < .001$)
- Renal conditions ($p = .047$)
- Neurological conditions ($p = .008$)
- Psychological conditions ($p = .001$)

Differences were measured between participants who reported weekly or more frequent use compared to those who used less than monthly along increased prevalence of social adversity:

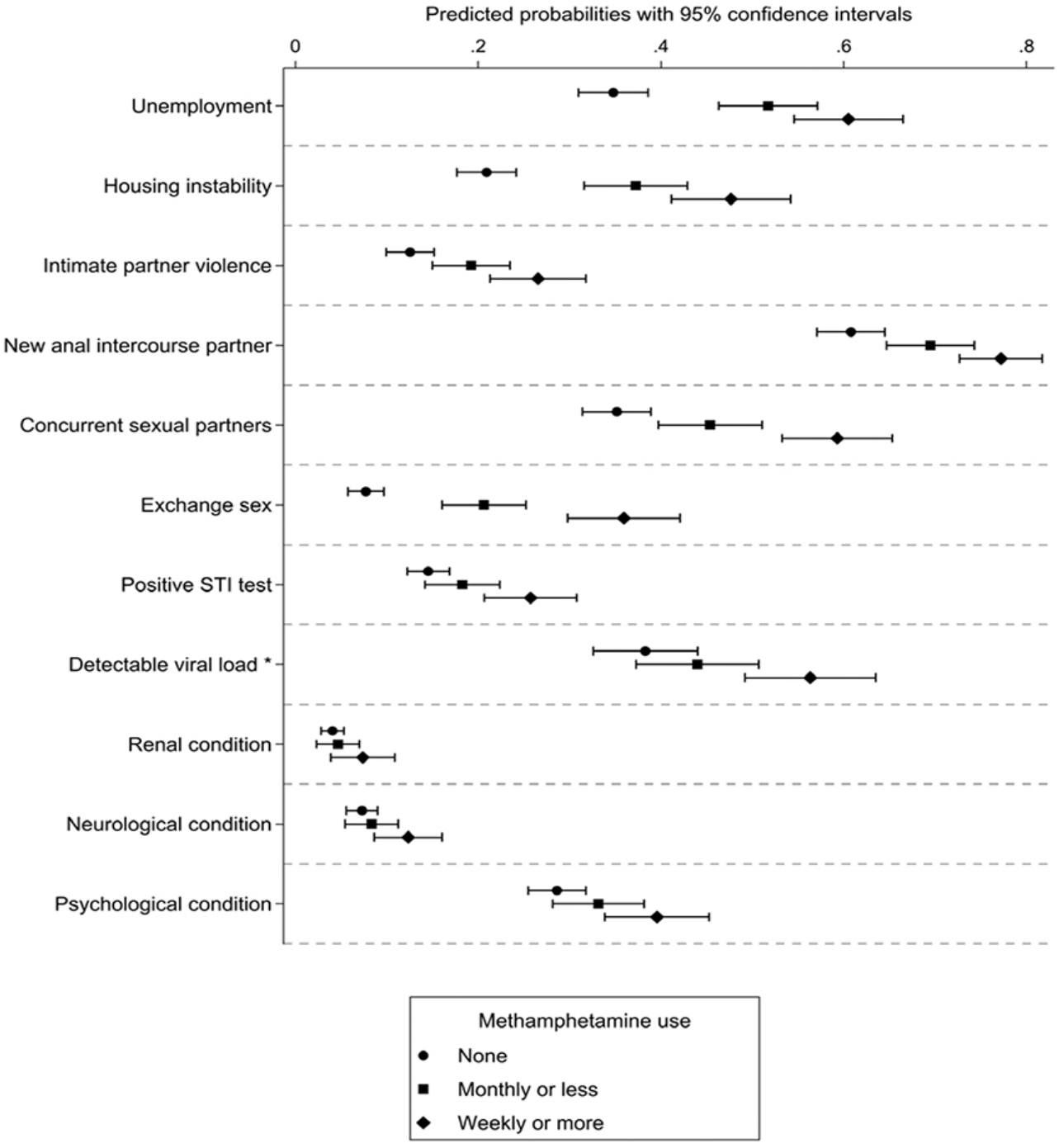
- Unemployment ($p < .001$)
- Housing instability (past 6 months)
- Having ever been incarcerated ($p < .001$)
- Experienced intimate partner violence (past year; $p < .001$).

Importantly, *any* report of methamphetamine use at any frequency corresponded significantly with indicators of underlying cardiovascular conditions and with being HIV prevalent ($p<0.001$).

A limitation to these findings is that while self-reported frequency of methamphetamine (and urine drug screens) were collected every six months, no data captured dose, nor type of methamphetamine used over the period. Still, findings from the cohort were consistent with reports using cross-sectional data (National Survey on Drug Use and Health from 2015 to 2018) where findings showed adults who reported methamphetamine use in the past year had a higher prevalence of co-occurring mental illness, other substance use disorders, and medical multimorbidity compared to adults who did not report not methamphetamine use (Han and Palamar, 2022).

The consistency in findings from different types of data (cohort, cross sectional national survey data) underscore frequency of use as a factor that predicts likelihood of most negative medical, social, and psychological consequences due to methamphetamine use over significant periods.

Figure 2. Odds of social, infectious diseases and medical conditions by level of self-reported use of methamphetamine over six-month periods



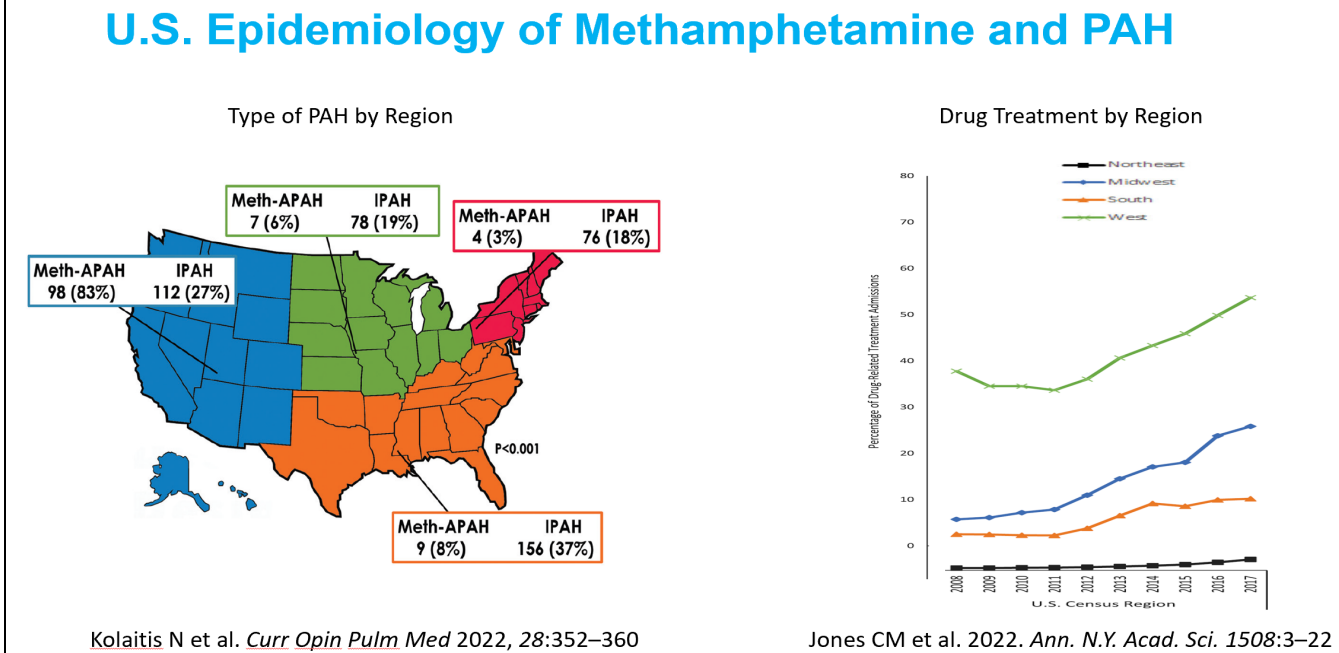
Cumulative Effects of Methamphetamine Use on Health

At the national level, epidemiological studies exist that identify links between frequent use of high-dose methamphetamine with major health conditions, especially cardiovascular, pulmonary and neuropsychiatric diseases. Evaluating prevalence and epidemiology of these diseases for persons who also methamphetamine provide rough estimates of ways methamphetamine causes or contributes to major cardiovascular, pulmonary, and neuropsychiatric diseases.

Cardiovascular disease. A strong case for contribution of methamphetamine (and other stimulants) for increasing prevalence of heart failure is provided by the National Inpatient Hospital Survey. Admissions for acute heart failure from stimulant use increased in this survey (Shetty et al., 2021), perhaps underscoring the accumulated cardiovascular damage from chronic high-dose use of methamphetamine. Over the period, epidemiological estimates of methamphetamine use nationally showed consistent and low percentages of Americans reporting methamphetamine use in the past year (Palamar et al., 2019). At the same time, estimates of methamphetamine use disorder significantly (Han et al., 2020). The increasing percentage of Americans with significant exposure to methamphetamine dependence corresponded with increases in inpatient admissions for acute heart failure.

Pulmonary disease. In a seminal case report of methamphetamine mixed type, repeated use of inhaled methamphetamine (“crank”) corresponded with development of pulmonary arterial

Figure 3. Cases of PAH and Methamphetamine Treatment in U.S.



hypertension (PAH; Schaiberger et al., 1993). PAH is a rare disease that requires an individual predisposition plus a second, external factor to cause the disease (2-hit hypothesis). A significant number of cases of idiopathic PAH involve methamphetamine as the identified “second hit”, and

in 2024, methamphetamine was listed as a definite drug/toxin associated with development of PAH (Kovacs et al., 2024). Showing parallel correspondence between markers of extensive methamphetamine use and disease prevalence, the map of prevalence of methamphetamine-associated PAH cases (Figure 3) corresponds with the graph of publicly available Drug Treatment within broad U.S. geographic regions. Geographic prevalence of cases of methamphetamine-associated PAH (Kolaitis et al., 2021) and episodes of publicly funded treatments for methamphetamine (Jones et al., 2022) show parallels, with highest PAH and methamphetamine treatment prevalence observed in the Western U.S., followed by the South, the Midwest, and finally the Northeast for both conditions. The correspondence of these broad national markers of prevalence for PAH and demand for methamphetamine use disorder treatment is striking in supporting cumulative frequency of methamphetamine use as a significant predictor of both cardiovascular and pulmonary diseases.

Neuropsychiatric diseases. The major, life-threatening neuropsychiatric harm from repeated high-dose methamphetamine use is stroke (Lappin and Sara, 2019), a cardiovascular disease in brain. Chronic, high-dose methamphetamine use is shown to initiate toxic neural processes in brain, which in turn correspond with development of a range of psychiatric and cognitive dysfunctions (see Jayanthi et al., 2021 for review). Using a cognitive task developed to measure frank brain injury (the Iowa Gambling Task), significant deficits in performance in making decisions of risk in settings of recent loss were identified among individuals seeking methamphetamine treatment (Lake et al., 2020). Parallel deficits were observed on this task measured in non-treatment-seeking participants who used methamphetamine in the mSTUDY cohort (Li et al., 2024).

A less prevalent, but consistent cross-cultural consequence to continued use of high-dose methamphetamine is methamphetamine induced psychosis, a condition that is difficult to distinguish clinically from paranoid schizophrenia and that may (or may not) remit with abstinence. Factors that sensitize individuals to methamphetamine induced psychosis include having have first degree relatives with schizophrenia (Chen et al. 2005). While abstinence from methamphetamine is a requirement for resolution of the negative social, psychological and legal consequences of chronic methamphetamine use, some neuropsychiatric symptoms do not fully remit and present long-term challenges to individuals and their families.

Summary

There are few to no data showing negative correlations between any negative medical, social, or psychological consequences and type of methamphetamine used (i.e., actual (ice) or mixed (powder)). Instead, evidence is strongly consistent to show links between chronic use of high-dose methamphetamine (by dose and by frequency of use) with negative medical, social, and psychological consequences. Acute impacts of methamphetamine dysregulate immune function, contributing to increased prevalence of HIV and sexually transmitted infections, as well as to impaired control of HIV. Importantly, prevalence of cardiovascular (heart attacks, strokes), pulmonary (methamphetamine associated PAH), and neuropsychiatric conditions (impaired neurocognitive performance, psychosis) correspond with measures of concentrated and sustained use of methamphetamine, which in turn contributes significantly to the burden of disease in U.S. and globally (Farrell et al., 2019).

REFERENCES

Alburges ME, Hoonakker AJ, Cordova NM, Robson CM, McFadden LM, Martin AL, Hanson GR. Effect of low doses of methamphetamine on rat limbic-related neurotensin systems. Synapse. 2015 Aug;69(8):396-404. doi: 10.1002/syn.21829. Epub 2015 Jun 11. PMID: 25963809; PMCID: PMC4481183.

Blair CS, Fulcher JA, Cho GD, Gorbach PM, Shoptaw S, Clark JL. Brief Report: Impact of Methamphetamine Use and Rectal STIs on Systemic and Rectal Mucosal Inflammation. J Acquir Immune Defic Syndr. 2023 Apr 1;92(4):281-285. doi: 10.1097/QAI.0000000000003143. PMID: 36515912; PMCID: PMC9974870.

Carrico AW, Flentje A, Kober K, Lee S, Hunt P, Riley ED, Shoptaw S, Flowers E, Dilworth SE, Pahwa S, Aouizerat BE. Recent stimulant use and leukocyte gene expression in methamphetamine users with treated HIV infection. Brain Behav Immun. 2018 Jul;71:108-115. doi: 10.1016/j.bbi.2018.04.004. Epub 2018 Apr 18. PMID: 29679637; PMCID: PMC6003871.

Chen CK, Lin SK, Sham PC, Ball D, Loh el-W, Murray RM. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. Am J Med Genet B Neuropsychiatr Genet. 2005 Jul 5;136B(1):87-91. doi: 10.1002/ajmg.b.30187. PMID: 15892150.

Farrell M, Martin NK, Stockings E, Bórquez A, Cepeda JA, Degenhardt L, Ali R, Tran LT, Rehm J, Torrens M, Shoptaw S, McKetin R. Responding to global stimulant use: challenges and opportunities. Lancet. 2019 Nov 2;394(10209):1652-1667. doi: 10.1016/S0140-6736(19)32230-5. Epub 2019 Oct 23. Erratum in: Lancet. 2019 Nov 16;394(10211):1806. doi: 10.1016/S0140-6736(19)32723-0. PMID: 31668409; PMCID: PMC6924572.

Friedman JR, Koncsol AJ, Molina CA, Romero R, Feng J, Poimboeuf M, Godvin ME, Puri S, Marienfeld C, Shover CL. What Dose of Methamphetamine Do Regular Consumers Use Daily? Estimating Milligrams of Oral Amphetamine Equivalent. medRxiv [Preprint]. 2025 Jun 9:2025.05.09.25327334. doi: 10.1101/2025.05.09.25327334. PMID: 40385390; PMCID: PMC12083619.

Fulcher JA, Javanbakht M, Shover CL, Ragsdale A, Brookmeyer R, Shoptaw S, Gorbach PM. Comparative impact of methamphetamine and other drug use on viral suppression among sexual minority men on antiretroviral therapy. Drug Alcohol Depend. 2021 Apr 1;221:108622. doi: 10.1016/j.drugalcdep.2021.108622. Epub 2021 Feb 16. PMID: 33631545; PMCID: PMC8321435.

Fulcher JA, Shoptaw S, Makgoeng SB, Elliott J, Ibarrondo FJ, Ragsdale A, Brookmeyer R, Anton PA, Gorbach PM. Brief Report: Recent Methamphetamine Use Is Associated With

Increased Rectal Mucosal Inflammatory Cytokines, Regardless of HIV-1 Serostatus. J Acquir Immune Defic Syndr. 2018 May 1;78(1):119-123. doi: 10.1097/QAI.0000000000001643. PMID: 29419567; PMCID: PMC5810127.

Han BH, Palamar JJ. Multimorbidity Among US Adults Who Use Methamphetamine, 2015-2019. J Gen Intern Med. 2022 May;37(7):1805-1807. doi: 10.1007/s11606-021-06910-6. Epub 2021 Jun 2. PMID: 34080107; PMCID: PMC9130438.

Jayanthi S, Daiwile AP, Cadet JL. Neurotoxicity of methamphetamine: Main effects and mechanisms. Exp Neurol. 2021 Oct;344:113795. doi: 10.1016/j.expneurol.2021.113795. Epub 2021 Jun 26. PMID: 34186102; PMCID: PMC8338805.

Jones CM, Houry D, Han B, Baldwin G, Vivolo-Kantor A, Compton WM. Methamphetamine use in the United States: epidemiological update and implications for prevention, treatment, and harm reduction. Ann N Y Acad Sci. 2022 Feb;1508(1):3-22. doi: 10.1111/nyas.14688. Epub 2021 Sep 24. PMID: 34561865; PMCID: PMC9097961.

Kolaitis, Nicholas A.a; Saggar, Rajanb; De Marco, Teresaa. Methamphetamine-associated pulmonary arterial hypertension. Current Opinion in Pulmonary Medicine 28(5):p 352-360, September 2022. | DOI: 10.1097/MCP.0000000000000888

Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, Badesch D, Montani D. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024 Oct 31;64(4):2401324. doi: 10.1183/13993003.01324-2024. PMID: 39209475; PMCID: PMC11533989.

Lake MT, Shoptaw S, Ipser JC, Takada S, van Nunen LJ, Lipinska G, Stein DJ, London ED. Decision-Making by Patients With Methamphetamine Use Disorder Receiving Contingency Management Treatment: Magnitude and Frequency Effects. Front Psychiatry. 2020 Feb 18;11:22. doi: 10.3389/fpsyt.2020.00022. PMID: 32180733; PMCID: PMC7058183.

Lappin JM, Sara GE. Psychostimulant use and the brain. Addiction. 2019 Nov;114(11):2065-2077. doi: 10.1111/add.14708. Epub 2019 Jul 19. PMID: 31321819.

Li MJ, Hassan A, Javanbakht M, Gorbach PM, Shoptaw SJ. Decision-making task performance and patterns of methamphetamine use in people assigned male at birth who have sex with men. Exp Clin Psychopharmacol. 2024 Jun;32(3):350-357. doi: 10.1037/pha0000689. Epub 2023 Nov 2. PMID: 37917508; PMCID: PMC11063125.

Palamar JJ, Han BH, Keyes KM. Trends in characteristics of individuals who use methamphetamine in the United States, 2015-2018. Drug Alcohol Depend. 2020 Aug 1;213:108089. doi: 10.1016/j.drugalcdep.2020.108089. Epub 2020 Jun 3. PMID: 32531703; PMCID: PMC7371537.

Rosen AD, Javanbakht M, Shoptaw SJ, Seamans MJ, Lloyd-Smith JO, Gorbach PM. Association of current substance use treatment with future reduced methamphetamine use in an observational cohort of men who have sex with men in Los Angeles. J Subst Use Addict Treat. 2024 Feb;157:209228. doi: 10.1016/j.josat.2023.209228. Epub 2023 Nov 21. PMID: 37981239; PMCID: PMC10984139.

Schaiberger PH, Kennedy TC, Miller FC, Gal J, Petty TL. Pulmonary hypertension associated with long-term inhalation of "crank" methamphetamine. Chest. 1993 Aug;104(2):614-6. doi: 10.1378/chest.104.2.614. PMID: 8101799.

Shetty S, Malik AH, Ali A, Yang YC, Briasoulis A, Alvarez P. Characteristics, trends, outcomes, and costs of stimulant-related acute heart failure hospitalizations in the United States. Int J Cardiol. 2021 May 15;331:158-163. doi: 10.1016/j.ijcard.2021.01.060. Epub 2021 Jan 31. PMID: 33535075.

Shoptaw S, Li MJ, Javanbakht M, Ragsdale A, Goodman-Meza D, Gorbach PM. Frequency of reported methamphetamine use linked to prevalence of clinical conditions, sexual risk behaviors, and social adversity in diverse men who have sex with men in Los Angeles. Drug Alcohol Depend. 2022 Mar 1;232:109320. doi: 10.1016/j.drugalcdep.2022.109320. Epub 2022 Jan 19. PMID: 35093681; PMCID: PMC8885921.

Wilkins C, Romeo JS, Rychert M, Prasad J, Graydon-Guy T. Determinants of the retail price of illegal drugs in New Zealand. Int J Drug Policy. 2020 Apr 10;79:102728. doi: 10.1016/j.drugpo.2020.102728. Epub ahead of print. PMID: 32283351.