Providers
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Polysubstance Use

The exception or the rule?
A question of vulnerability.

Stephen A. Wyatt, D.O.

Addiction Psychiatrist

Presenter(s)

Stephen A. Wyatt, D.O, is a Board-Certified Psychiatrist with added subspecialty certification in Addiction Psychiatry. He practiced emergency medicine for 12 years prior to entering a psychiatry residency at University Hospitals of Cleveland. He then was accepted into the NIDA clinical research fellowship in addiction psychiatry at the Yale School of Medicine. He is a former Adjunct Professor of Psychiatry at UNC. He started the addiction psychiatry fellowship at the Mountain Area Health Education Center in Asheville, NC. He is the Immediate Past Chairman of the Coalition on Physician Education in Substance Use Disorders a national organization focused on addiction medicine medical school education. He was a Co-Chair for the 2020 focused update of the ASAM Clinical Guidelines for Office Based Opioid Treatment. He is a clinical expert for the SAMHSA funded Provider Clinical Support System, PCSS; Medication Assisted Treatment and Implementation Projects. He is an Opioid Response Network Champion.

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PCSS

Medications for Opioid Use Disorders

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- PCSS-MOUD aims to increase the knowledge and skills of healthcare and counseling professionals about available evidence-based treatment approaches for substance use disorder (SUD) with a particular focus on opioid use disorder (OUD). PCSS-MOUD provides free training and mentoring to practitioners on the use of medications for OUD (MOUD) and the integration of these services into mainstream health care.

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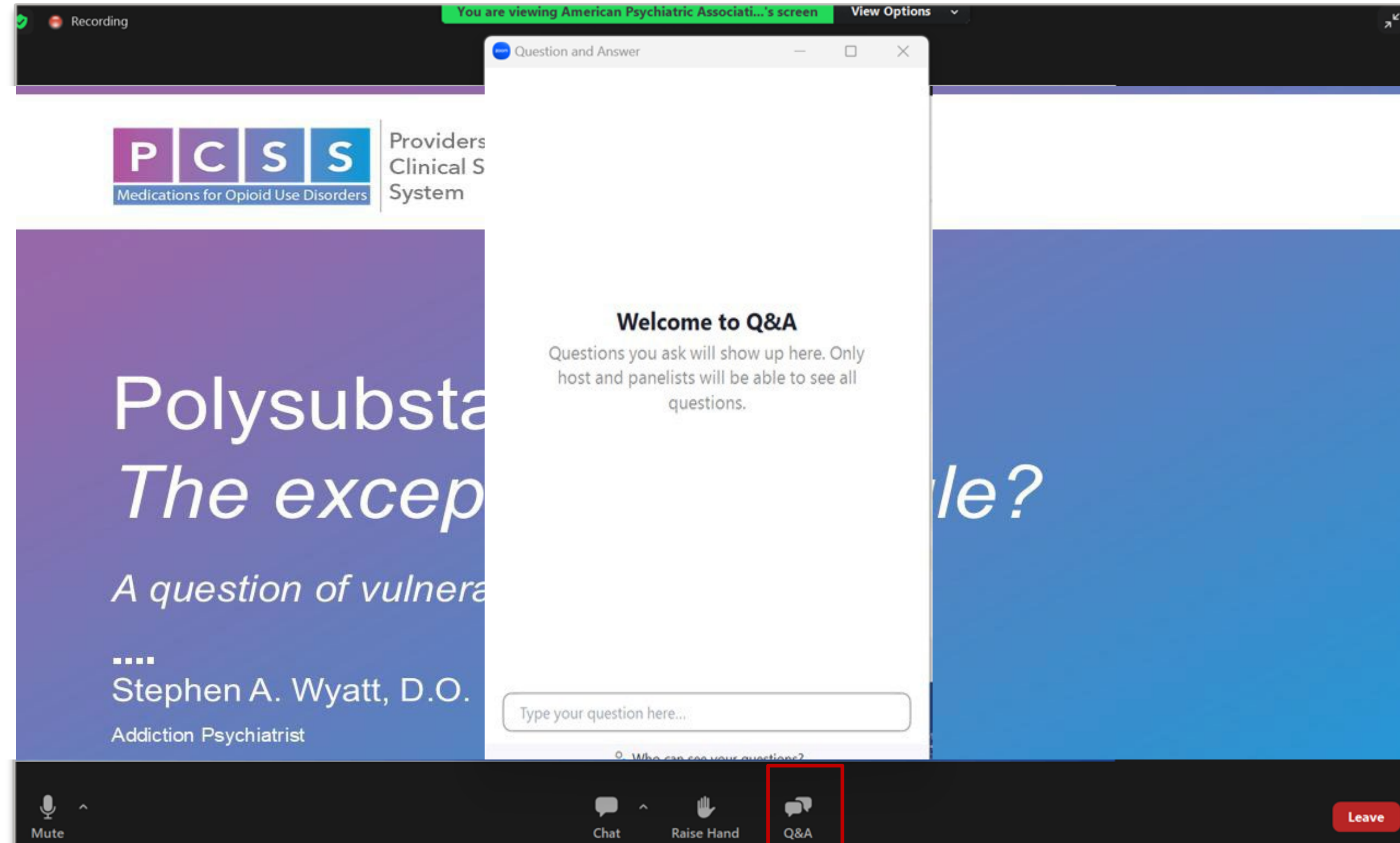
We'll reserve 10 to 15 minutes at the end of the presentation for Q&A.



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All speakers have been advised that any recommendations involving clinical medicine must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in patient care. All scientific research referred to, reported, or used in the presentation must conform to the generally accepted standards of experimental design, data collection, and analysis.

Educational Objectives

At the conclusion of this activity participants should be able to:

1. Explain the incidence and impact of polysubstance use.
2. Compare the morbidity and mortality of various combinations of drugs, including alcohol and tobacco.
3. Apply the information from this presentation in assisting in the establishment of a treatment plan for polysubstance using patients.

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What is Polysubstance Use?

What is the prevalence?

Importantly, Who are the vulnerable?

Definition of Polysubstance Use

- The use of more than one drug at a time is polysubstance use. This includes when two or more are taken together or within a short time, either intentionally or unintentionally. It is common in some demographics.
- Intentional polysubstance use occurs when a person takes a drug to increase or decrease the effects of a different drug or wants to experience the effects of the combination.
- Unintentional polysubstance use occurs when a person takes drugs that have been mixed or cut with other substances, like fentanyl, without their knowledge.
- Whether intentional or not, mixing drugs is never safe because the effects from combining drugs may be stronger and more unpredictable than one drug alone, and even deadly.

CDC cdc.gov/stop-overdose/caring/polysubstance-use.html

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Figure 4: Heatmap Highlighting Polysubstance Co-Occurrence Percentage by Drug Group, United States, 2024

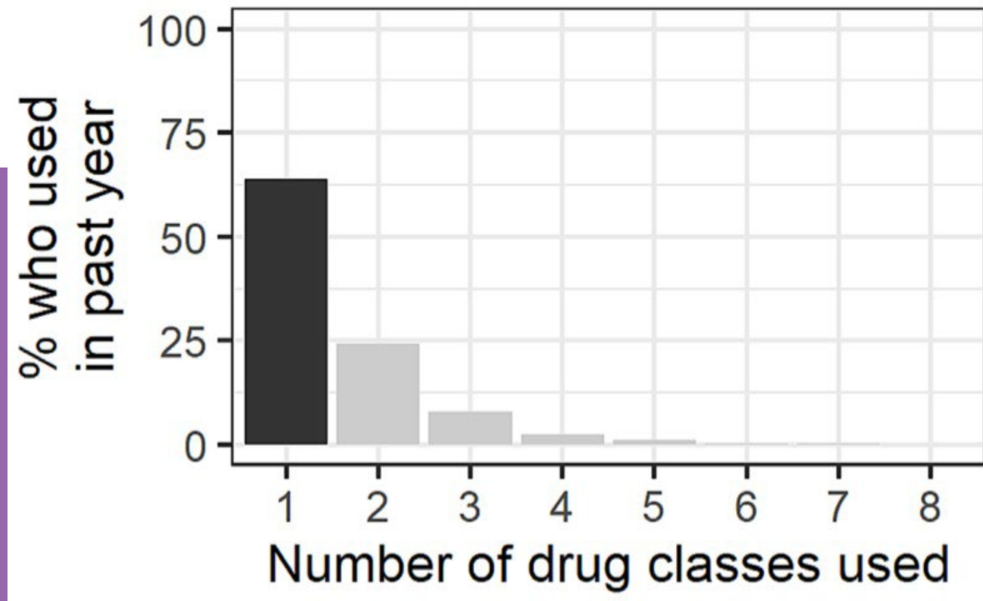
	Stimulant	Psychedelic	Opioid	Empathogen	Dissociative	Depressant	Cannabis	Alcohol
Alcohol	34%	1%	16%	2%	3%	10%	36%	0%
Cannabis	36%	3%	15%	3%	3%	6%	1%	49%
Depressant	19%	0%	38%	0%	1%	8%	14%	33%
Dissociative	47%	3%	21%	6%	1%	5%	36%	41%
Empathogen	47%	7%	27%	0%	9%	3%	52%	41%
Opioid	41%	0%	14%	2%	2%	16%	15%	22%
Psychedelic	24%	6%	7%	9%	5%	1%	60%	38%
Stimulant	14%	1%	34%	2%	3%	7%	30%	38%

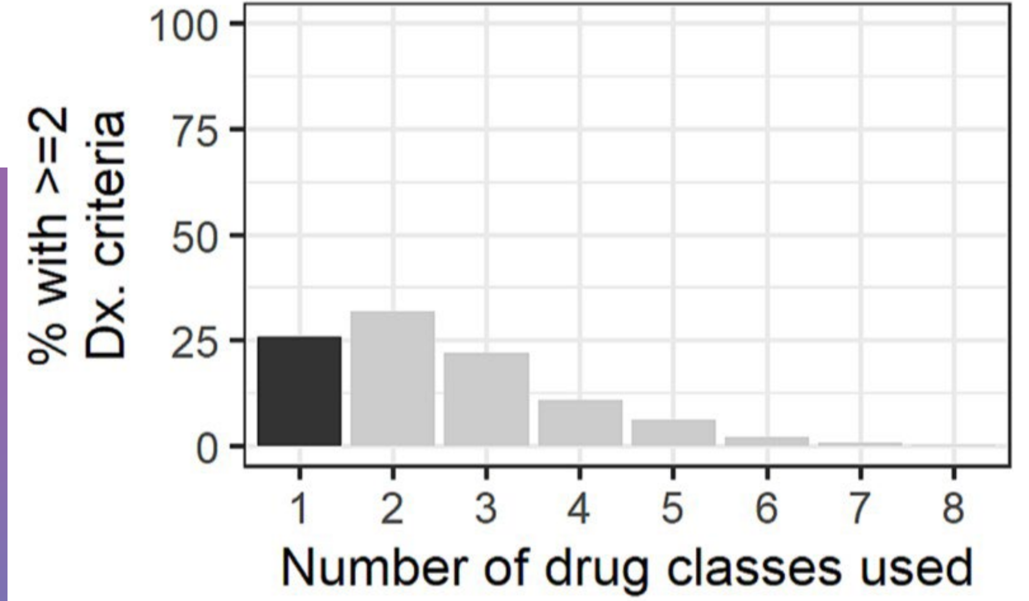
Legend scale: 0, 10, 20, 30, 40, 50

Note: Percentage calculated by row.

DAWN Report 2024

Any level of disordered use compared to those with low level use.





- 64% of people with past-year use were categorized as having a mono-use.
- Majority used alcohol alone (90%), followed by tobacco (8%), cannabis (2%),

Two or more diagnostic criteria of any SUD

Mono use is now 26%

Use of two or more substances is 74%

Bailey AJ, 2023

National Survey on Drug Use and Health (NSDUH) from years 2015- 19.

Disordered use compared to those with Low Level Use.

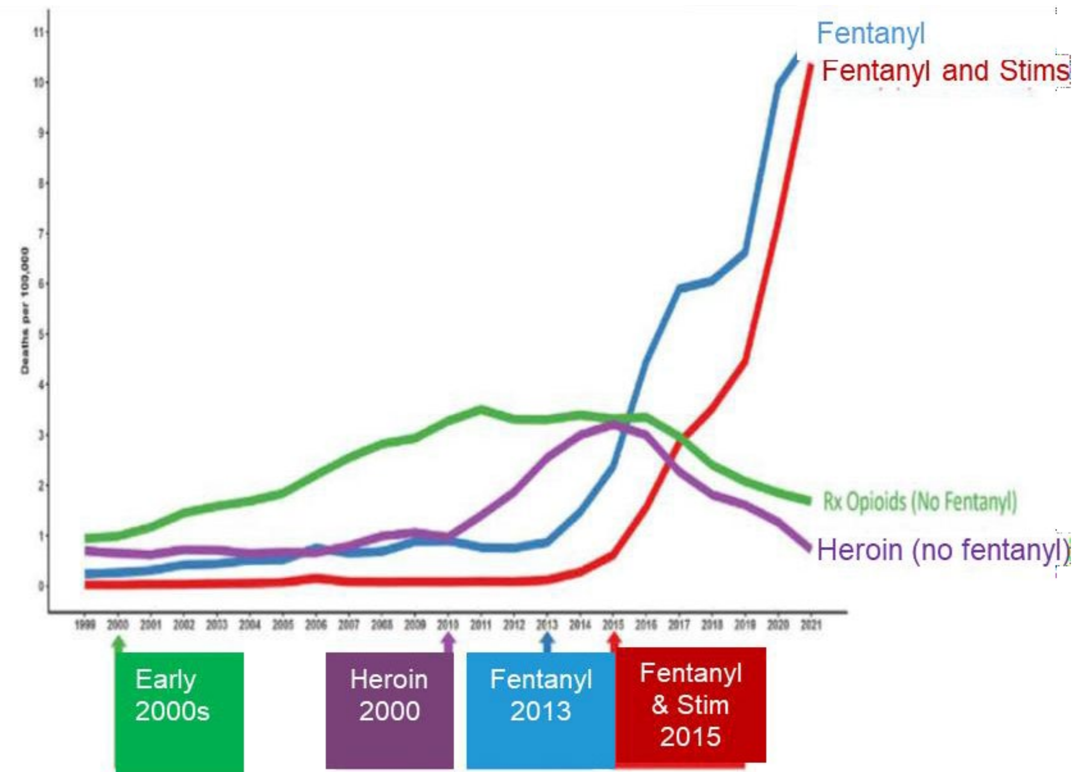
- An estimated 29% of the general population did not report any substance use in the past year and were excluded from this analysis.
- The individuals who reported receiving alcohol/drug treatment, only 22% of individuals had a mono-use pattern
- Importantly, this data suggest, mono-use is the most common pattern of substance use at the population level, almost two-thirds of people who use substances. However, once problems with substance use emerge, mono-use becomes the exception

Bailey AJ, 2023

National Survey on Drug Use and Health (NSDUH) from years 2015- 19.

Implications of various combinations of drugs.
Opioids (1/3)

- Understanding polysubstance use that involves opioids applies not only in the context of within class opioid misuse but also co-occurring use of opioids with a wide array of other substances importantly depressants and stimulants.
    - Due to an increased potential for overdose, relapse, and various adverse comorbid problems.
- As the death toll from overdoses rose from 38,329 to 106,699 between 2010 to 2021 in the United States the percent involving both fentanyl and stimulants rose from 0.6% to 32.3%. This number climbed to 41.3% in 2024.



Cicero TJ, 2020, Freidman F 2022,

Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research, 2025;334;(15):1321,

Implications of various combinations of drugs.
Opioids (2/3)

- Factors behind the increased combination of opioid and stimulant use is multifactorial;
  - The increase in availability of methamphetamine.
  - The reduction in certain Rx opioids making stimulants more attractive as pills.
  - The combination can result in a synergistic high.
  - The stimulant can balance out the effects of opioids, attaining some “normalcy” by relieving some of the fatigue and lethargy.
- These drugs can be and sometimes are, combined in pill form without the user's knowledge contributing to the overdose potential.
- The pharmacodynamic overdose potential of stimulants in combination with opioids is the stimulants potential for causing severe vasoconstriction increasing oxygen demand while the opioid depressant effects a slowing of the respiratory rate along with the adverse effect on the normal medullary respiratory center response.

Ciccarone D, 2021

Implications of various combinations of drugs. Opioids (3/3)

Implications of various combinations of drugs.
Opioids (3/3)

- **Depressants and Opioids**
- Alcohol/Benzodiazepines combined with opioids, as both are central nervous system depressants they increase the risk of fatal overdose, severe respiratory depression, and coma.
  - Alcohol can cause “dose dumping” or the rapid release from the time release property of a pharmaceutical opioid resulting in a rapid as compared to a slow release of the full dose.
- As pregabalin and gabapentin misuse has increased in recent years in individuals with an SUD and in particular opioids exposure has been associated with a 49% increased risk of an opioid overdose.
  - Misuse of Gabapentin is an overdose risk for an individual using opioids overdose and has played a role in the statistics.

Centers for Disease Control and Prevention [CDC], 2020b; Gomes T, et.al., 2017; CDC Drug Overdose Deaths in the United States, 2023–2024

Implications of various combinations of drugs.

Alcohol

- Roughly half of all drug poisonings involve alcohol.
- Alcohol co-involvement for all opioid overdose deaths increased nonlinearly from 12.4% in 1999 to an estimated 16% in 2022
- Alcohol and other drugs contribute to a 10 times increase in the rate of successful suicides.
- Co-occurring Methamphetamine use can mask the effects of alcohol resulting in impaired persons not recognizing their impairment and more likely to engage in further alcohol/drug use and dangerous behaviors, e.g., driving.
- The specific combination of cocaine and alcohol produces cocaethylene, a metabolite that increases the duration of cocaine and is more toxic than either cocaine or alcohol alone, in the liver.

Becker T. et.al., 2021, Tori ME, et.al.,2020, NIAAA 2026, Timko C, et.al., 2018

Polysubstance Use and CoMorbid Problems
Developmental Problems in Children

- Prenatal polysubstance use is highly prevalent among individuals born with fetal alcohol spectrum disorders, with nearly 40% of infants having been exposed to at least one other substance.
  - Animal studies have established prenatal combinations of cocaine/alcohol can result in coordination problems and neuropsychological differences including heightened hyperactivity compared to either substance alone.
  - There have been similar animal studies identifying coordination problems with cannabis/alcohol combinations.
- Polysubstance exposure has resulted in an increased risk of externalizing behaviors, ADHD, and long-term growth and behavioral problems have been found in adolescence.
- Cognitive impairments associated with prenatal polysubstance exposure can include general cognitive ability, e.g. memory, language, and self-regulation compared with single and non exposures.
- NOTE: There is also an environmental factor with a noted increase in four or more ACEs

Jarlenski MP, et.al. 2020, Popova et al., 2024;; Rouzer et al., 2025; Breit et al., 2019; Rouzer et al., 2023; Conradt et al., 2019; Garrison-Desany et al., 2022; Ryan etal., 2024; Beauchamp et al., 2020;Fisher et al., 2011; Lowe et al., 2024; Lowe et al., 2021;Nygaard et al., 2017, Burns et al., 2021; Rockhold et al., 2025

Polysubstance Use and CoMorbid Problems
Young People

- Studies consistently find that adolescents who used alcohol at or before age 14 are considered early-onset users and are:
  - Associated with alcohol-induced developmental delays in core executive functioning skills (e.g., self-regulation),
  - Long-term psychobiological problems and alcohol-related harms.
  - More likely to engage in other risky behaviors, **including progressing to using multiple other substances** (cannabis, other illicit drugs, etc.), both independently and concurrently.
- From 2020 to 2023, there were 22,966 opioid overdose deaths among youth aged 15 to 24 years.i . Fentanyl and other synthetic opioids were most commonly involved.
  - Overall, approximately half of all opioid overdose deaths in this age group (n = 11 657; 50.8%) involved polysubstance use.
  - Collectively, stimulants (e.g., methamphetamine, cocaine, and/or other psychostimulants) were involved in 65.3% (n = 7609) of all polysubstance-involved overdose deaths and 33.1% of all opioid overdose deaths.

Montemayor BN, et.al. 2024; Buchholz C, et.al., 2023

Polysubstance Use and CoMorbid Problems Mental Health Problems (1/4)

Polysubstance Use and CoMorbid Problems
Mental Health Problems (1/4)

- Use of other substances in addition to methamphetamine significantly increased the odds of a history of physical and/or sexual abuse, suicidal ideation and attempt(s) along with other mental health symptoms..
- Opioid overdoses,often involved suicidal intent (44 % passive and 7 % active).
  - Active suicidal intent was positively associated with hospitalization.
  - Use of ≥5 substances vs.1 substance, associated with an opioid overdose is associated with having thoughts of self-harm or suicide in the 2 weeks before survey completion.
  - Participants who reported active/passive intent more commonly used cocaine or crack (27 %) with opioids during their last overdose relative to unintentional overdoses (16 %).
- Over half of opioid overdoses among individuals in addiction treatment involved some degree of suicidal thinking.
  - 274 participants who had experienced a non-fatal opioid overdose, 78% used heroin and 43% used prescription opioids
- In addition to opioids, 40 % of most recent non-fatal overdoses involved sedatives/sleeping pills, 25 % alcohol, 25 % marijuana, 22 % cocaine or crack, and<10 % other substances.

Gicquelaisa RE, Drug and Alcohol Dependence 212 (2020)

Polysubstance Use and CoMorbid Problems Mental Health Problems (2/4)

Polysubstance Use and CoMorbid Problems
Mental Health Problems (2/4)

- Veterans with MDD, GAD, and a sexual assault history reported significantly greater SUD symptoms and poly-SUD than those without such comorbidities.
  - 12.6% did not meet criteria for SUD
  - 49.6 % met criteria for one SUD,
  - 37.8% for poly-SUD (37.8 %), with 25.6% for two, 7.9% for three, and 3.9% for more than four SUDs. (3.9 %).
    - 52.4% percent met criteria for alcohol use disorder and 53.1% stimulant use disorder, (53.1 %). Among participants meeting criteria for alcohol use disorder or stimulant use disorder, over 78 % of participants met criteria for severe misuse (>six or more symptoms).
- These results were from a residential treatment-seeking, veteran population however consistent with independent associations of these mental health conditions and substance use severity and underscore the unique association of these conditions on polysubstance use..
- Notably, these differences were found within a treatment-seeking sample pointing to the importance of these comorbidities (depression, anxiety, and trauma-related symptoms) to be addressed as part of their treatment for SUDs.

Flynn AJ, et al, 2026

Polysubstance Use and CoMorbid Problems
Mental Health Problems (3/4)

- Comparing Bipolar patients with and without either AUD or PSU. The three groups differed for predominant polarity. Note: It has been identified that the predominant and first-episode polarity most often remains the dominant polarity.
  - The most common predominant polarity in BD without SUD was mania,
  - In BD with AUD and in BD with PSU it was depression.
  - Uncertain predominant polarity was the least common in BD without SUD and BD with PSU, whereas in BD with AUD, manic predominant polarity was least common.
  - Predominant polarity matched onset polarity in all groups.
- Across clinical studies, 42% to 71% of patients showed consistency in their predominant polarity, meaning that at least two-thirds of lifetime episodes in a single person are restricted to one pole of the illness.
  - There has been evidence of a longitudinal decrease of alcohol/other drug abuse during the course of the illness in the manic predominant polarity group.
- Several studies tried to identify the most common predominant polarity in BD patients. Their results were that depressive polarity prevailed..

Janiri D, 2017

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Polysubstance Use and CoMorbid Problems
Mental Health Problems (4/4)

- Methamphetamine use increases the likelihood of psychotic symptoms. Additional frequent cannabis use increases the likelihood.
- A Swedish registry study identified, relapse was most common for those whose first substance induced psychosis was induced by cannabis (25.7%), followed by multi-substance use (23.8%) and (meth)amphetamine (19.7%).

NIH Publication No. 23-MH-8110 Revised 2023

Wide-ranging substance users had more severe substance use and mental health symptoms and need more intensive service resources.

Venla E,2025

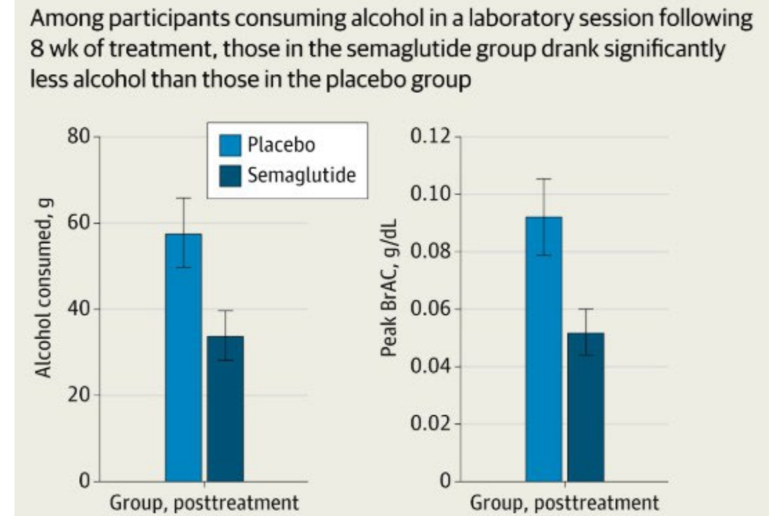
Assessment

- Screening Test (ASSIST) psychometric tool using the specific substance involvement score (SSIS) measures among U.S. college students to evaluate the **relationships** among 11 substance screens (prescription opioids, heroin, tobacco, alcohol, cannabis, cocaine, methamphetamine, prescription stimulants, inhalants, sedatives, and hallucinogens).
  - Data from the American College Health Association’s National College Health Assessment (fall 2019–spring 2021).
- The review showed significant positive correlations for all substance screens, with the strongest correlations seen between screens for heroin and prescription opioids. Cannabis ranked highest in screening for alcohol risk, alcohol highest in screening for tobacco and cannabis risk, prescription opioids highest in screening for heroin and cocaine, and inhalants highest in screening for other illicit drugs.

Qeadan F, 2025

Treatment
GLP 1 Medications

- Low-dose semaglutide was shown to reduce the amount of alcohol and tobacco use during a posttreatment laboratory self evaluation.
  - 9 weeks of semaglutide led to reductions in weekly alcohol craving relative to placebo,
  - Greater relative reductions in cigarettes per day in a subgroup of participants with current cigarette use.
- GLP-1s target the brain's reward pathway and system: the ventral tegmental area, nucleus accumbens, and prefrontal cortex.
  - Influencing the release of dopamine in the brain results in blunting motivation, pleasure and reward.
  - This reduction of reward signaling thus reduces craving for food, alcohol and other drugs.
  - They can also reduce stress-induced alcohol seeking.
- Patients with OUD, a GLP-1 medication reduced their cravings for opioids by 40% over three weeks.
- People with OUD and AUD who took GLP-1s had a 40% lower rate of opioid overdose and a 50% lower rate of alcohol intoxication.



GLP 1s may assist patient in reducing their use and potential for changes in behavior.

Hendershot CS, et.al,, 2025

Treatment

- There is evidence that the use of disulfiram can not only alter the response to alcohol but also cocaine making an adverse experience for both.
  - Cochran Review 2024 - Disulfiram may decrease the frequency of cocaine use but may have little or no effect on the amount of cocaine use or on the number of people who prematurely interrupt treatment.
- Secondary substance use can consistently moderated associations between treatment and primary drug use. Months without any secondary substance use, showed treatment was strongly associated with decreased odds of primary drug use compared to months of secondary use and a weaker association.
- There is evidence that patients treated for polysubstance use showed improved life satisfaction, executive functioning, and psychological distress following 1 year of abstinence.

Traccis F, 2024; Wang et al,2017, Hagan et al., 2017).

Treatment Continued

- Community actions
  - Distribution of naloxone through cost-effective, pharmacy- and community-based programs; expanding the locations of naloxone distribution centers, particularly in underserved populations including rural communities, and the unhoused.
- Treatment providers need to assess for concurrent substance use disorders and offer evidence-based treatments.
  - Reduce the stigma associated with both inpatient and outpatient treatment of the PSU patient.
  - Bear in mind the strong potential for polysubstance and the need to address substance use beyond the "primary drug use disorder."
  - Assess for SUDs in prenatal care and support efforts at early childhood development.
  - Assess for and provided integrative treatment for underlying mental health disorders.
  - Provide care in a trauma informed setting.

Summary

- First is the importance of a motivational engagement then thorough assessment of substance use patterns. Failure to integrate the co-occurring use of other substance classes probably leads to inaccurate assessment of risk for acute outcomes, such as overdose, and of overall severity.
- With the evidence of the importance of polydrug mechanisms it is important that there is consideration beyond the differences in pharmacology of various drugs and look further to the large differences on presentation at the clinical level.
- Stimulants are becoming far more common and are often used with other substances.
- Particularly poor health is associated with polysubstance use over time. This is despite the greater frequency of medical and substance use treatment by polysubstance users. Thus the need for more effective interventions for people using particular combinations of substances.
- This includes increasing the general medical system and public's awareness of the dangers of polysubstance use through effective educational efforts that provide clear communication about harms of mixing substances.

CDC 2024, Stop Overdose, Polysubstance Use Facts

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- Designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder (MOUD).
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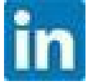 PCSS-MOUD: Educate, Train, Mentor

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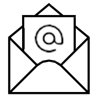 pcss@aaap.org

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