

Polysubstance Use: Emerging Patterns, Health Consequences and Priorities for Integrated Public Health Action

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Abstract: Polysubstance use refers to the intentional or unintentional exposure to more than one psychoactive substance within a defined period. It includes simultaneous use, sequential use and the consumption of products adulterated with an unexpected substance. This pattern is clinically important because the effects of different substances may be additive, synergistic or difficult to predict. Combinations involving opioids, alcohol, benzodiazepines, stimulants, cannabis, tobacco, pharmaceutical drugs and new psychoactive substances are associated with overdose, respiratory depression, cardiovascular events, injuries, psychiatric symptoms, treatment discontinuation and premature mortality. Contemporary overdose epidemics increasingly involve multiple substances rather than a single drug, especially combinations of synthetic opioids with stimulants or sedatives. However, surveillance and treatment systems remain largely substance-specific. Evidence supports comprehensive assessment, medication treatment for individual substance-use disorders, management of withdrawal and psychiatric comorbidity, contingency management for stimulant and polysubstance use, overdose education and naloxone distribution where opioid exposure is possible. No single pharmacological treatment is approved for “polysubstance use disorder” as a unified condition; treatment must address each substance, the reasons for combined use and the patient’s social context. India’s 2019 national survey documented substantial use of alcohol, cannabis, opioids, sedatives and inhalants but did not provide a sufficiently detailed national estimate of overlapping use. Emerging detection of new psychoactive substances among Indian treatment seekers adds complexity. Public health systems require integrated surveillance, non-stigmatizing services, toxicology capacity, harm reduction, prescription monitoring and long-term recovery support.

Keywords: polysubstance use; substance-use disorder; overdose; opioids; stimulants; harm reduction.

INTRODUCTION

The term “polysubstance abuse” has historically been used to describe problematic use of more than one psychoactive substance. Contemporary clinical and public health practice increasingly prefers **polysubstance use** or **multiple substance-use disorders**, because the word “abuse” can be stigmatizing and does not distinguish occasional exposure from a diagnosable disorder. Polysubstance use generally refers to the use of two or more substances either simultaneously, within a short interval, sequentially or during the same broader period. Exposure may be intentional—for example, using a stimulant to counter sedation—or unintentional, as when a counterfeit tablet or illicit drug contains fentanyl, xylazine or another undeclared compound.

This distinction matters because polysubstance use is not one homogeneous behaviour. A person who smokes tobacco and drinks alcohol occasionally has a different risk profile from someone combining opioids and benzodiazepines, or a patient with opioid dependence who intermittently uses

methamphetamine. Some individuals meet criteria for more than one substance-use disorder, whereas others have one primary disorder accompanied by episodic use of additional substances.

Global drug markets and patterns of consumption are becoming increasingly complex. The United Nations Office on Drugs and Crime estimated that 316 million people aged 15–64 years used a controlled drug in 2023; cannabis remained the most frequently used, followed by opioids, amphetamines, cocaine and ecstasy.[1] These categories overlap because individuals may use more than one drug. The public health challenge is therefore not adequately represented by substance-specific prevalence alone.

Why People Combine Substances

Polysubstance use occurs for diverse reasons. Some individuals seek to intensify desired effects. Alcohol may be combined with stimulants to prolong social activity, while opioids and sedatives may be used together to enhance relaxation or euphoria. Others use one substance to moderate the unwanted effects of another—for example, benzodiazepines to reduce stimulant-related anxiety or stimulants to remain awake after opioid use.

Combined use may also reflect availability rather than deliberate pharmacological planning. People may purchase whatever substance is accessible, inexpensive or locally popular. Social networks, nightlife settings, occupational stress, homelessness, incarceration and unstable drug supplies influence patterns of use.

Prescription and non-prescription medicines contribute to polysubstance exposure. Sedatives, opioid analgesics, antihistamines, cough preparations and gabapentinoids may be combined with alcohol or illicit drugs, sometimes without recognition of the interaction. Counterfeit tablets create additional risk because their appearance may suggest a familiar medicine while their composition is unpredictable.

Trauma, depression, anxiety, attention-deficit symptoms, chronic pain and sleep disturbance frequently coexist with substance use. Self-medication may provide temporary relief but can reinforce dependence and obscure the underlying disorder. Treatment should therefore explore what each substance does for the person rather than simply record a list of drugs.

Pharmacological Interactions and Acute Toxicity

The consequences of polysubstance use depend on the substances, doses, timing, route, tolerance and underlying health conditions.

Multiple central nervous system depressants

Opioids, alcohol, benzodiazepines, barbiturates and certain sedating medicines suppress central nervous system activity. When combined, their respiratory-depressant effects may be greater than expected from either substance alone. A person who tolerates a usual opioid dose may develop fatal respiratory depression after adding alcohol or a benzodiazepine.

Sedation also increases the risk of aspiration, falls, burns, road crashes and sexual assault. Because different substances have different half-lives, clinical deterioration can recur after apparent improvement.

Opioids and stimulants

Opioid–stimulant combinations are increasingly prominent in overdose mortality. Stimulants do not reliably “protect” against opioid-induced respiratory depression. Instead, they may mask sedation temporarily, encourage repeated dosing and produce simultaneous cardiovascular stress and respiratory toxicity.

Fentanyl contamination of stimulant supplies creates risk among people who do not intentionally use opioids and have little opioid tolerance. In recent United States data, polysubstance overdose increasingly involved synthetic opioids combined with methamphetamine or cocaine.[4] Although this pattern cannot be directly generalized to every country, it illustrates how rapidly changing drug supplies can transform risk.

Alcohol and cocaine

Concurrent alcohol and cocaine use produces cocaethylene in the liver. This active metabolite persists longer than cocaine and is associated with additional cardiovascular and hepatic toxicity. The combination can increase impulsivity and the likelihood of consuming larger quantities of both substances.

Cannabis and other drugs

Cannabis is commonly used with alcohol, tobacco or stimulants. Combined cannabis and alcohol use can produce greater psychomotor impairment than either substance alone. High-potency cannabis may also worsen anxiety, paranoia or psychosis, particularly when used with stimulants.

New psychoactive substances

Synthetic cannabinoids, designer benzodiazepines, synthetic opioids and other new psychoactive substances may be sold alone or mixed with established drugs. Their potency, metabolism and interactions are often poorly characterized. Routine toxicology screens may not detect them, complicating diagnosis and surveillance.

Chronic Health Consequences

Repeated polysubstance use affects nearly every organ system. Alcohol and hepatotoxic medicines can accelerate liver injury. Stimulants and tobacco increase cardiovascular risk, while opioids and sedatives impair respiratory function. Injecting several drugs may increase injection frequency, vein damage and exposure to HIV, hepatitis B, hepatitis C and bacterial infections.

Cognitive effects include impaired attention, memory and executive function. Sleep disruption, malnutrition and repeated intoxication or withdrawal further reduce cognitive capacity. These effects can undermine treatment participation and employment.

Psychiatric consequences are common. Anxiety, depression, psychosis, impulsivity and suicidal behaviour may precede or follow substance use. Distinguishing a primary psychiatric disorder from a substance-induced syndrome requires careful longitudinal assessment. Treatment should not be withheld while clinicians wait for complete diagnostic certainty.

Polysubstance use is also associated with housing instability, family conflict, violence, incarceration and financial hardship. These social consequences can become causes of continued use, creating a self-reinforcing cycle.

Overdose and Mortality

Overdose risk is the most immediate public health concern. Multiple substances can obscure the clinical picture and complicate emergency management. Naloxone reverses opioid toxicity but does not reverse poisoning from alcohol, benzodiazepines, stimulants or xylazine. Nevertheless, naloxone should be administered whenever opioid exposure is possible because it can restore breathing related to the opioid component.

Polysubstance overdose should not be understood only as deliberate simultaneous use. A person may unknowingly consume fentanyl in heroin, cocaine, methamphetamine or a counterfeit pill. Surveillance systems therefore need toxicological data rather than relying solely on self-reported intent.

A randomized community intervention in 67 US communities did not produce a statistically significant reduction in total overdose mortality, but it was associated with a 37% reduction in deaths involving an opioid and a non-cocaine psychostimulant. The intervention combined community coalitions, data-driven selection of evidence-based practices, treatment expansion and communication campaigns.[5] This finding suggests that population-level responses can influence certain polysubstance overdose patterns, although effects may vary by drug supply and local implementation.

Assessment and Diagnosis

Assessment should be non-judgmental, confidential and specific. Asking only for the “main drug” misses important risks. Clinicians should record every psychoactive substance, including alcohol, tobacco, prescribed medicines, over-the-counter preparations and traditional or locally available products.

For each substance, the history should include route, quantity, frequency, timing of last use, periods of abstinence, withdrawal symptoms, overdose history and reason for use. Clinicians should ask whether substances are used together and whether the person knows the composition of illicit products.

Urine or blood toxicology may support diagnosis but has limitations. Detection windows differ, common screening panels omit several substances, and a positive result does not prove intoxication or a substance-use disorder. False-positive and false-negative results occur. Toxicology should complement, not replace, clinical assessment.

Every patient should be assessed for suicide risk, pregnancy, violence, trauma, infectious disease, chronic pain, psychiatric illness and unstable housing. Family or peer involvement can be helpful when desired by the patient.

Table 1. Major polysubstance combinations, risks and management priorities

Combination or pattern	Principal reason for use	Major health risk	Immediate clinical priority	Longer-term response
Opioid plus benzodiazepine or alcohol	Enhanced sedation, relief of anxiety or sleep problems	Profound respiratory depression, aspiration and fatal overdose	Airway support, naloxone when opioid exposure is possible and prolonged observation	Medication treatment for opioid-use disorder, gradual sedative management and alcohol treatment
Opioid plus stimulant	Balancing effects, prolonged use or contaminated supply	Overdose, arrhythmia, myocardial infarction, stroke and agitation	Naloxone, airway and cardiovascular monitoring, management of hyperthermia or agitation	Opioid agonist treatment, contingency management and harm-reduction support
Cocaine plus alcohol	Social use and intensified or prolonged effects	Cocaethylene-related cardiac and hepatic toxicity, injury and impulsivity	Cardiovascular assessment and management of acute intoxication	Integrated alcohol and stimulant intervention
Cannabis plus alcohol	Social or recreational co-use	Greater impairment, road injury, panic and vomiting	Supportive care and safety assessment	Brief intervention and assessment for both disorders
Tobacco plus alcohol or illicit drugs	Habitual paired use and cue reinforcement	Cancer, cardiopulmonary disease and poorer recovery outcomes	Identify nicotine dependence during all assessments	Offer cessation treatment rather than postponing it indefinitely
Prescription sedatives plus alcohol	Sleep, anxiety or unrecognized interaction	Falls, confusion, respiratory depression and dependence	Review all prescribed and over-the-counter medicines	Coordinated prescribing, tapering where appropriate and non-drug treatment for insomnia or anxiety
Multiple injected substances	Stronger effect or changing drug availability	Overdose, HIV, viral hepatitis, endocarditis and abscesses	Overdose response and treatment of infection	Sterile equipment, opioid agonist treatment, HIV/hepatitis testing and vaccination
New psychoactive substances mixed with established drugs	Novel effects, low cost or unintended adulteration	Unpredictable toxicity and failure of routine toxicology detection	Syndrome-based supportive management and specialist toxicology advice	Early-warning surveillance, laboratory capacity and public alerts
Sequential use across days or weeks	Coping, availability or changing desired effects	Multiple substance-use disorders and fragmented treatment	Comprehensive history rather than focus on the presenting drug	One integrated care plan addressing all substances

Treatment Principles

There is no single medicine that treats polysubstance use as one disorder. Care should address each substance while maintaining one coordinated treatment plan.

Withdrawal and acute stabilization

Alcohol and benzodiazepine withdrawal can cause seizures or delirium and may require medically supervised treatment. Opioid withdrawal is rarely fatal but is intensely distressing and increases the likelihood of rapid return to use. Stimulant withdrawal commonly causes fatigue, depression and suicidal thinking.

Attempting abrupt withdrawal from several substances simultaneously may be unsafe. Stabilization should prioritize life-threatening withdrawal, overdose risk and severe psychiatric symptoms.

Pharmacological treatment

Methadone and buprenorphine are effective treatments for opioid-use disorder and should not be withheld because a patient also uses stimulants, cannabis or alcohol. Continued non-opioid use may require additional intervention, but stopping opioid agonist treatment can increase mortality.

Effective medicines are also available for alcohol- and tobacco-use disorders. Pharmacological treatment should be matched to diagnosis, contraindications and patient preference.

No medication has consistently demonstrated broad effectiveness for stimulant-use disorder. This gap is particularly important because stimulant–opioid use is increasing in several settings.

Psychosocial interventions

Motivational interviewing, cognitive behavioural therapy, relapse-prevention strategies, family interventions and community reinforcement can be tailored to multiple substances.

Contingency management provides tangible incentives for objectively verified behavioural goals. A systematic review and meta-analysis of 74 trials involving 10,444 adults receiving medication for opioid-use disorder found that contingency management improved abstinence from stimulants, polysubstance use, illicit opioids and cigarettes and improved attendance and medication adherence.[6] Effects after incentives stop may be less durable, and implementation requires ethical, financial and regulatory support.

Harm reduction

Treatment should not be restricted to people ready for complete abstinence. Overdose education, naloxone access, sterile injecting equipment, testing for HIV and viral hepatitis, vaccination, wound care and advice against using alone can reduce mortality while recovery goals evolve.

Patients should be warned that reduced tolerance after detoxification, imprisonment or hospitalization increases overdose risk. Mixing depressants and using an unfamiliar supply should be discussed explicitly.

Public Health Significance

Polysubstance use exposes the limitations of substance-specific programmes. A clinic may treat opioids but ignore alcohol, tobacco or stimulant use, even though these substances determine overdose, adherence and long-term health.

Surveillance systems also tend to count one “primary” drug. This underestimates overlapping exposure and may misdirect prevention. Overdose records should capture all substances identified through toxicology and investigation.

Prevention must address commercial and illicit drug environments. Alcohol and tobacco policies, safer prescribing, regulation of sedatives, prescription monitoring and control of counterfeit medicines are relevant alongside illicit-drug interventions.

Stigma remains a major barrier. Language portraying people as “abusers” or “addicts” can reduce help-seeking and influence clinical decisions. Substance-use disorders should be treated as health conditions requiring sustained, evidence-based care.

Global Trends and Recent Advances

The current drug landscape is characterized by high-potency synthetic opioids, expanding stimulant markets, counterfeit tablets and rapidly evolving psychoactive substances. UNODC’s 2025 assessment

documented continued growth and diversification of drug markets, while WHO reported major global gaps in treatment coverage for substance-use disorders.[1,7]

Drug-checking technologies, wastewater surveillance, forensic toxicology and rapid overdose reporting are increasingly used to detect changes in supply. Their public health value depends on timely communication to clinicians and communities.

Mobile health tools can support appointment reminders, recovery monitoring and peer support. However, they should not replace medication, counselling, housing and social services. Digital exclusion and privacy risks require attention.

Indian Perspective

India's National Survey on Extent and Pattern of Substance Use estimated that alcohol was the most commonly used psychoactive substance, followed by cannabis and opioids among the drug categories assessed. Approximately 2.8% of Indians aged 10–75 years were estimated to use cannabis products and 2.1% to use opioids; sedative and inhalant use were also identified.[8] These estimates describe individual substance categories and should not be added together because the same person may appear in more than one category. The survey did not provide a sufficiently detailed national estimate of simultaneous or sequential polysubstance use.

Patterns vary greatly by state, sex, age and social context. Alcohol and tobacco commonly coexist with other drug use but may not be fully represented in treatment records focused on an illicit “primary substance.” Pharmaceutical opioids, sedatives, cough preparations and inhalants require particular attention.

A multicentre AIIMS report published in 2023 provided objective evidence of new psychoactive substances among Indian treatment seekers. Some detected substances were not under international control at the time of the study, illustrating the need for updated laboratory surveillance and clinical preparedness.[9]

India has de-addiction centres, opioid-substitution services and national programmes addressing drug demand reduction. Important gaps include uneven geographic access, inadequate integration with general hospitals and primary care, limited women- and adolescent-friendly services, weak overdose surveillance and insufficient availability of naloxone and harm-reduction interventions.

Criminalization and fear of law enforcement may discourage disclosure and emergency help-seeking. Public health and legal systems should distinguish trafficking from personal health needs and treatment engagement.

Challenges and Limitations

Polysubstance use lacks a single universally applied epidemiological definition. Studies may count use on the same occasion, use within 30 days, use within one year or the presence of two substance-use disorders. Prevalence estimates are therefore difficult to compare.

Self-report can underestimate stigmatized or illegal use. Toxicology improves detection but may identify exposure without clarifying frequency, intention or clinical importance. New substances may remain undetected. Treatment trials often exclude people with severe psychiatric illness, unstable housing or several substance-use disorders. Consequently, evidence is frequently derived from less complex patients than those seen in routine practice.

Another challenge is excessive focus on abstinence from every substance as the only successful outcome. Reduced overdose, fewer high-risk combinations, treatment retention, stable housing and improved function are also meaningful outcomes.

Future Directions and Policy Priorities

National surveys should measure overlapping use explicitly, including same-day combinations, sequential patterns and multiple diagnosed disorders. Overdose surveillance should integrate emergency departments, poison centres, forensic laboratories and mortality systems.

India should expand toxicology capacity for synthetic opioids, designer benzodiazepines, synthetic cannabinoids and other new psychoactive substances. Rapid alerts should inform clinicians, treatment services and people who use drugs.

Treatment should be organized around the person rather than the “primary substance.” Services should offer opioid agonist treatment, alcohol and tobacco treatment, mental healthcare, infectious-disease services and social support within coordinated pathways.

Naloxone should be accessible to people using opioids, their families, peers, first responders and community organisations. Its use should be promoted even when the apparent substance is a stimulant or counterfeit medicine because unrecognized opioid contamination is possible.

Research should evaluate Indian patterns of polysubstance use, gender differences, adolescent exposure, pharmaceutical misuse, treatment retention and overdose. Pragmatic trials are needed for contingency management and integrated community care.

CONCLUSION

Polysubstance use is not an uncommon complication of substance use; it is increasingly the prevailing clinical and epidemiological reality. Its risks arise from pharmacological interaction, unpredictable drug composition, psychiatric comorbidity and fragmented healthcare.

The most dangerous combinations include opioids with alcohol or sedatives and opioids with stimulants. Yet risk cannot be reduced to a list of combinations. The person's tolerance, route of administration, health status, social setting and access to emergency care are equally important.

Effective management requires comprehensive assessment, treatment of each substance-use disorder, management of psychiatric and physical comorbidity, overdose prevention and long-term recovery support. Medication for opioid-use disorder should not be withheld because other drug use continues, and harm reduction should not be delayed until abstinence is achieved.

For India, the principal priorities are nationally representative measurement of overlapping use, expanded toxicology and overdose surveillance, integrated treatment services and greater attention to pharmaceutical and new psychoactive substances. A humane public health response must replace stigmatizing labels with evidence-based care and recognize that reducing death and disability is an essential outcome even when complete abstinence is not immediately achieved.

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