Are you thinking what I'm thinking? Defining what we mean by "polysubstance use"

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Abstract

The rise in drug overdoses and harms associated with the use of more than one substance has led to increased use of the term 'polysubstance use' among researchers, clinicians, and public health officials. However, the term retains no consistent definition across contexts. The current authors convened from disciplines including sociology, epidemiology, neuroscience, and addiction psychiatry to propose a recommended definition of polysubstance use. An iterative process considered authors' formal and informal conversations, insights from relevant symposia, talks, and conferences, as well as their own research and clinical experiences to propose the current definition. Three key concepts were identified as necessary to define polysubstance use: (1) substances involved, (2) timing, and (3) intent. Substances involved include clarifying either

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(1) the number and type of substances used, (2) presence of more than one substance use disorder, or (3) primary and secondary substance use. The concept of timing is recommended to use clear terms such as simultaneous, sequential, and same-day polysubstance use to describe short-term behaviors (e.g., 30-day windows). Finally, the concept of intent refers to clarifying unintentional use or exposure when possible, and greater attention to motivations of polysubstance use. These three components should be clearly defined in research on polysubstance use to improve consistency across disciplines. Consistent definitions of polysubstance use can aid in the synthesis of evidence to better address an overdose crisis that increasingly involves multiple substances.

Keywords

polysubstance use; concept; measurement; substance use disorder

Introduction

In the U.S., the fourth wave of the overdose crisis is fueled by use of multiple substances, surpassing opioid use alone. Nearly two-thirds of opioid-related fatalities involved co-use of another substance, most commonly psychostimulants such as cocaine and/or methamphetamine (1). Since at least 2016, the number of non-fatal opioid overdoses treated in emergency departments that also involved amphetamines, cocaine, and benzodiazepines has also increased (2,3). Individuals who engage in substance co-use may represent higher-risk populations, as they are more likely to be impacted by the criminal justice system and to have physical and mental health comorbidities, which contribute to increased overdose risk (4–8). Other co-use patterns have increased in recent years as well. For example, rates of co-use of alcohol and cannabis are on the rise among young adults (9,10). When used simultaneously with overlapping effects, alcohol and cannabis co-use is associated with heavier use and greater harm, such as acute physical effects, unsafe driving behavior, and use disorders among adolescents and young adults (11–13). The increased harms from substance co-use have led to an expanded focus on "polysubstance use" by researchers, clinicians, policy makers, and public health practitioners. Within the past several years, federal agencies have begun to recognize the importance of addressing co-use and have responded by issuing polysubstance use-specific requests for proposals and allocating opioid response grants to studies that address multiple substance use disorders at the community level (14,15). However, despite increased attention, the term "polysubstance use" has never been clearly defined. In response to the expanded cross-disciplinary focus on polysubstance use, the authors, spanning disciplines from sociology, epidemiology, neuroscience, psychology, and addiction psychiatry, and representing clinical and research scientist perspectives, have proposed a definition of polysubstance use to be recommended for the field. All authors had formal and informal conversations, gathered insights from relevant symposia, talks, and conferences, as well as reflected on their own research and clinical experiences. Then, an iterative process with authors AB, JL, RS, ANLC occurred whereby they proposed and fine-tuned components of a definition. Once all components were agreed upon, the definition via draft of this commentary was sent to ARW, SDC, and MC to ensure it reflected their earlier insights. The goal of the current synthesis is to

provide the field of addiction research with a shared concept of polysubstance use through a discussion of the key components of the phenomenon and recommendations for how to use the term "polysubstance use."

Key Components of Polysubstance Use

We first considered the core components of the behavior of polysubstance use. To fully define the behavior of polysubstance use, we propose consideration of (1) substances involved, (2) timing, and (3) intent of use. Each core concept is elaborated upon below.

Substances Involved

Polysubstance use inherently includes the use of more than one substance. The use of multiple substances can be delineated by: (1) the number and type of substances used, (2) presence of more than one substance use disorders, and (3) primary and/or secondary substance use or other trajectories of use.

The number and type of substances involved can range substantially, based on subpopulation setting, and timeframe. While no systematic data are available, the majority of persons who use drugs use more than one drug and the number and types of substances consumed vary across settings. Operationally, data on the number and type of substances involved can be collected via self-report or toxicology (including post-mortem toxicology). However, the number of substances actually measured in polysubstance use research tends to vary considerably. For example, there is substantial literature devoted to the study of alcohol and cannabis as a discrete combination (e.g., 16–19), as well as polysubstance use involving opioids and stimulants (e.g., 4,6,20,21). These studies may not include data on all substance types. Based on the authors' experiences, they find that frequently, the co-use of alcohol, cannabis, and tobacco with other substances are overlooked in studies of illicit drug use (22). Nicotine may be particularly taken for granted as a presumed substance for individuals engaging in polysubstance use involving illicit substances (23,24). Many researchers may not collect or report data on nicotine use, however it can be a critical component of polysubstance use (e.g., co-administration such as cannabis and tobacco in a cigarette) (25). Additionally, polysubstance use behaviors may increase smoking in ways not yet fully explored (e.g., cue reactivity). Comprehensive assessment of a full range of substances is recommended.

Substances involved can also be considered as the presence of more than one substance use disorders (SUDs). The diagnosis of multiple SUDs may be made by a clinician, trained researcher, or via standardized assessment tools based on an individual's self-report of their behavior. Inherent to multiple SUDs is the use of multiple substances, however the two behaviors should not be conflated as not all co-use may rise to the level of a SUD. According to the National Survey on Drug Use and Health (NSDUH) released by SAMHSA, which is known to undercount vulnerable populations, 16% of all persons with SUD have both an alcohol and other drug use disorder (26) and in 2019 substance use treatment admissions data, 50% of episodes indicated use of multiple substances (27). Increasingly in the literature, the use of "polysubstance use disorder (PSUD)" is being utilized to describe individuals with multiple SUDs (28). However, there is no DSM-5

diagnosis of "polysubstance use disorder" and we caution researchers, clinicians, and other public health persons from using this term as a diagnosis. Such a term risks homogenizing individual patterns of substance use and the public health and clinical implications. Understanding how substances interact with each other and appreciating their heterogeneity can be a key component of managing effective treatment pathways.

Another approach to considering the substances involved in polysubstance use can be to consider a primary substance of use (29). This approach is often employed in clinical trials or in clinical settings and can be a helpful approach to treatment. However, the use of additional substances is critical to consider and has only received limited attention thus far in research, especially in clinical trials which tend to have restrictive exclusion criteria. For example, in a study using secondary data of individuals identified as having opioid use as their primary SUD, researchers identified unique polysubstance use patterns and trajectories that differentially impacted relapse risks (30). More research is needed that considers how changes in primary or secondary substance use affect other substance use. Further, the conceptualization of polysubstance use built around a primary substance may not be appropriate for all populations. For some individuals, the preferred effects of a combination cannot be considered as primary or secondary. The co-use of heroin and cocaine as a "speedball" is an example of a potential misapplication of the forced selection of a primary, singular, SUD. Additionally, preferences may be overridden due to drug market and economic availability. To date, the concept of primary and secondary substance use is underdeveloped and therefore, may not provide a robust conceptualization of polysubstance use.

Timing

Research currently measures polysubstance use in timeframes ranging from 30 days (31,32) to six months (33,34) to as long as one year (35). Timeframes are often driven by the measures available in large representative datasets (e.g., NSDUH has 30-day and 12-month items). Ideally, however, timeframes should be determined by their relevance to the public health issue being explored. For example, data on single-episode and same-day polysubstance use is important for understanding overdose risk, whereas data over a six-month period or longer only characterizes a population's high-level patterns (e.g., use of X, Y, Z substance without details on how, or if, they are combined). A related issue is whether the single term "polysubstance use" is appropriate for these disparate timeframes with disparate implications. One suggestion is to describe use over longer (multi-month) periods of time as "use of multiple substances" rather than "polysubstance use." This would preserve polysubstance use as a phenomenon distinct from the use of more than one substance over extended periods of time, a behavior which is normative among people who use drugs.

At a more granular level, there are inconsistencies in the literature when it comes to describing the use of more than one drug at the same time, or together. Terms such as "simultaneous," "concurrent" and "together" are used to indicate widely divergent behaviors. For example, depending on the study, the definition of "concurrent" ranges from same day to 12 months, (36,37) and "simultaneous" ranges from immediate co-ingestion to within 3 hours of another substance (38,39). There is a need to establish

conventions in language describing near-term polysubstance use. We suggestion the following terminology: Simultaneous- multiple substances mixed together and used with one mode of administration (e.g., injecting a speedball, or smoking fentanyl sprinkled with methamphetamine); Sequential- use of multiple substances in a single episode (e.g., smoking marijuana and drinking alcohol); and Same day (self-explanatory). Even within these specified definitions, there is overlap and room for ambiguity, highlighting the importance of defining terms clearly and rigorously when describing behaviors related to polysubstance use. Reporting of polysubstance use behaviors should attend to these nuances in data collection and reporting. If data collection does not explicitly gather information on how individuals sequenced their use, then reporting of results should be conservative.

Polysubstance use, then, is inherently concerned with short-term behaviors (i.e., daily, weekly, past month). A long-term assessment of polysubstance use would rely on longitudinal collection of short-term outcomes to collect data on the nuances of simultaneous, sequential, and same day use. Further, there is a need for additional research to understand the appropriate maximum recall period that can be used in assessments of polysubstance use. When requesting individuals to report very nuanced behaviors, it is likely that small windows will be most appropriate.

Intent

One key point of consensus among authors is that the term "polysubstance use" has little salience to people who use drugs and alcohol. It is simply the way people use substances. Motivation for polysubstance use- conceptualized here as intent- may be a critical concept to explore to facilitate interventions and treatment (40). Generally, studies have found motivations for co-use include enhancement of drug effects, using one drug to reduce the aversive effects of another, coping with emotional or physical pain, and relieving withdrawal symptoms (40,41). The substances individuals select to achieve preferred effects are of importance to risk and treatment. Additionally, polysubstance use (and substance use in general) can often be defined by social context and access constraints- in terms of economic affordability and current drug supply.

Intent is further relevant to clinical practice. If individuals are primarily using a second (or third, etc.) substance to enhance the effects of a primary drug of choice and intentionally pursue combined use as a preferred "high," then the co-treatment of multiple classes of substances may be warranted. These are different treatment implications than if the use of a second substance is to recover from or to minimize disruptive effects of a preferred drug such as stimulants, in which case treatment of the underlying disorder may resolve the use of compensatory substances. In this way, intent refers to the motivations of the polysubstance use patterns engaged. There is sufficient saturation in qualitative research on intent to consider use of categorical responses in quantitative research (40).

Finally, with the spread of fentanyl, there have been marked increases in unintentional polysubstance use, or use of one drug that has been contaminated or 'cut' with another. Some individuals are unknowingly exposed to fentanyl or xylazine, as these drugs are increasingly contaminating heroin and other drug markets (e.g., cocaine, pressed pills) (42–45). Individuals subjected to an unregulated drug supply may have the intent to consume

one substance but are subjected to unknown combinations. Intent, therefore, is not always a "known" factor. Several studies describe how people who use drugs assess potential contamination and the actions they take to avoid or manage it, such as buying drugs from trusted dealers, examining their drugs before using them or using small initial amounts to assess potency (46,47). Unfortunately, drug checking services, in which samples are tested via mass spectrometry, have been severely limited in scope and availability to date (48). It is important to track this phenomenon of unintentional polysubstance use because it increases overdose risk and potentially mitigates the effectiveness of treatment.

Researchers are encouraged to include questions, or report if the data collected captured unintentional polysubstance use. Ways to capture this type of data can include asking participants if they think or know any of the substances they used had fentanyl, xylazine, or another unexpected drug mixture. Comparison of self-reported substance use and biometric data is another tool to provide this data (49,50).

Recommendations

As we build a more nuanced and precise understanding of polysubstance use we must use clear definitions. When using the term polysubstance use, we suggest researchers and clinicians clearly define the (1) substances involved, (2) timing, and (3) intent. The overlap of these concepts can be considered as well. For example, there is an increased focus on high-risk patterns of polysubstance use- a clearly articulated combination of substances and timing that carries acute risk of harm (e.g., using fentanyl and benzodiazepines in the same hour). Researchers and clinicians may be particularly focused on high-risk patterns and less concerned with lower-risk (e.g., cocaine and cannabis) combinations, but this decision should be driven by the research question and clinical goals.

Polysubstance use research remains further challenged in some ways due to a lack of comprehensive, yet brief, measurement tools. No assessment tools briefly and quantitatively capture the three core components of polysubstance use. Some measurement tools are substance pattern specific (e.g., cocaine, 25), outdated (39), or require lengthy administration with a high time burden on participants (e.g., Timeline Followback, 51). Although important as an objective measure of drug use, toxicology results also have limited interpretability as positive findings may represent a single episode of use in the prior four days (e.g., benzodiazepines or cocaine) or heavy use that ceased more than several weeks ago (e.g., fentanyl or cannabis), and on their own provide no information on intent. Other substance use measures rely on latent modeling and advanced statistical techniques without providing real-time measurement of polysubstance use. Further, no validated tools capture timing (e.g., distinguish between simultaneous and same day use). Although there is current research in polysubstance use measurement, multiple tools that measure the three key components should be validated for use. Until these tools are validated, the use of ecological momentary assessment may be a promising method to measure complex polysubstance use behaviors via combination specific questions (52,53).

Complex, heterogeneous polysubstance use patterns also have important implications for statistical analysis – especially when examining within-person differences using day- or moment-level data. A common practice in investigations exploring the relative risk of

engaging in polysubstance use relative to single-substance use is to use multilevel models and conduct within-person analyses to compare "polysubstance use days" versus "single-substance use" days and oftentimes control for other substances used (11,54). While this analysis yields important information regarding unique risk factors and outcomes for specific types of polysubstance use, investigations of multiple substance use combinations is limited. Person-centered statistical approaches such as latent class analysis (LCA) can be used in the face of limitations to examine multiple substance use patterns and their predictors or outcomes using cross-sectional or daily data (55–57). Following general procedures in cross-sectional data (55) and daily data (58), LCA may be a useful approach for comprehensively characterizing polysubstance use and can be built upon to include specifications of level of use, ordering of substances, or whether the effects of the substances overlapped.

An important limitation of this proposed definition is that it was developed without direct input from persons who use drugs. Polysubstance use as a term may not resound with persons who use drugs given it is a normative behavior. Recommendations about prevention, risk reduction, and treatment options related to polysubstance use must incorporate the expertise of persons who use drugs.

As the US overdose crisis increasingly involves the use of multiple substances, there is a need for prevention and treatment strategies specific to patterns of polysubstance use. The proposed definition suggests (1) substances involved, (2) timing, and (3) intent as key components of polysubstance use to inform work by clinicians and researchers. These components should be defined whenever polysubstance use is discussed. Clarity and consistency in our language will support the development and dissemination of interventions tailored to emerging substance use patterns.

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