

A Scoping Review of Gender, Sex and Sexuality Differences in Polysubstance Use in Adolescents and Adults

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Abstract

Background: Polysubstance use is a common, problematic behavior that increases risk of harm to self and others. Research suggests that rates may vary based on gender, sex and sexuality. Understanding the current state of this literature may inform prevention and treatment of polysubstance use, leading to reduced public health burden.

Objectives: This review aimed to synthesize research on gender, sex and sexuality differences in polysubstance use in adults and adolescents.

Methods: A scoping review was conducted using all EBSCO databases, PubMed and Google Scholar to identify articles examining the effects of gender, sex and sexuality on polysubstance use. Polysubstance use was defined broadly as the use of any combination of substances over any time period and included licit (alcohol, tobacco) and illicit substances, concurrent and simultaneous use, from lifetime to daily use and use at any frequency. Studies were considered if they were published in peer-reviewed journals between January 1990 and October 2020 and were written in English. Publicly available data sources were also utilized to fully capture prevalence data that has not been published elsewhere.

Results: Findings were mostly inconsistent and often conflicting. Only two findings were generally consistent: adult men were overall more likely to report polysubstance use than adult women, and sexual and gender minorities report more frequent polysubstance use than non-minorities.

Conclusions: Research has been unable to clearly elucidate differences in polysubstance use prevalence and patterns according to gender, sex and sexuality. Several recommendations are offered to advance future research and address limitations of current research.

INTRODUCTION

Substance use and substance use disorder (SUD) are pervasive problems. More than 5% of individuals aged 15 or older worldwide (~283 million people) meet criteria for alcohol use disorder (AUD), and rates are similar for those 12 or older in the U.S. (~14.8 million people or 5.4% of the total U.S. population; World Health Organization, 2018; Substance Abuse and Mental Health Services Administration, 2019). The prevalence of SUD (disorders with illicit drugs, including cannabis and not including alcohol and tobacco) is less common but still present in 0.7% of individuals aged 15–64 worldwide and in ~8.1 million Americans 12 and older (~3.0% of the total U.S. population; Substance Abuse and Mental Health Services Administration, 2019; World Drug Report, 2020). Almost 17.5% of individuals 15 or older worldwide use tobacco, and a higher prevalence rate has been observed in Americans 12 or older (58.8 million or 21.5% of the total U.S. population; Substance Abuse and Mental Health Services Administration, 2019; United Nations Office on Drugs and Crime, 2020).

People experience a myriad of harmful effects from substance use, including impaired relationships, vehicle accidents and incarceration (Columbia University National Center on Addiction and Substance Abuse, 2010; Karjalainen *et al.*, 2012; American Psychiatric Association, 2013). Substance

use is also associated with a variety of mental and physical illnesses (Walker and Druss, 2017; Degenhardt *et al.*, 2018; Singh *et al.*, 2018). Moreover, there are indirect economic effects, including healthcare costs and lost productivity that collectively total \$730 billion annually in the U.S. (U.S. Department of Justice and National Drug Intelligence Center, 2011; U.S. Department of Health and Human Services, 2014; Centers for Disease Control and Prevention, 2019). Although single substance use is common, many people report using multiple substances throughout their lives (Substance Abuse and Mental Health Services Administration, 2019). Data from the NSDUH indicate that, within the same 1-year period, Americans aged 12 or older who reported consuming alcohol also used other substances at least once: 32.7% used any tobacco product, 22.2% used cannabis and 11.2% used other illicit drugs (Substance Abuse and Mental Health Services Administration, 2019).

Polysubstance use broadly refers to the use of more than one substance over a specified time period (Connor *et al.*, 2014). Use is generally categorized as either *concurrent* (i.e. two or more substances within a specified, but not necessarily overlapping, timeframe) or *simultaneous* (i.e. two or more substances within a pharmacologically overlapping timeframe; Olthuis *et al.*, 2013; Connor *et al.*, 2014). Accordingly, in this review, the term ‘polysubstance use’ refers to any

combination of substances over any time period, specifying the substance combinations and timeframe whenever possible. Polysubstance use is related to considerable problems beyond the relative associations of single substance use. For instance, adolescents who have used multiple substances in the past year (i.e. combinations of alcohol, cannabis and tobacco) are more than twice as likely to engage in problematic behaviors (e.g. starting fights, lying) than adolescents who have used only alcohol in the past year (Silveira *et al.*, 2019). Furthermore, polysubstance use translates into direct risk for SUD diagnoses. The risk of meeting *DSM-IV* illicit substance dependence (American Psychiatric Association, 2000) by young adulthood was higher in adolescents who concurrently use alcohol, cannabis and cigarettes (3.2 times more likely than nonusers) than adolescents who use alcohol only (1.3 times more likely than nonusers; Moss *et al.*, 2014). Similarly, adults who met criteria for AUD and SUD (vs. AUD only) were more likely to meet criteria for other conditions such as mood disorder (Saha *et al.*, 2018).

Gender, sex and sexuality differences in polysubstance use

Gender, sex and sexuality are likely critical factors to understanding polysubstance use rates and patterns. Sex refers to biological differences between men and women. Gender refers to socially determined roles along dimensions of masculinity and femininity as well as personal identity within the context of these norms (National Institutes of Health, no date; Hyde *et al.*, 2019). Sexuality encompasses identity, attraction and behavior toward others (Bailey *et al.*, 2016).

There are gender and sex differences in substance use rates and patterns (for review, see McHugh *et al.*, 2018b). In addition, research suggests substance use behavior may also vary as a function of sexuality (McCabe *et al.*, 2003; Marshal *et al.*, 2008). Until recently (e.g. Demant *et al.*, 2017; McHugh *et al.*, 2018a), substance use literature has generally failed to differentiate between sex, gender and sexuality, focusing primarily on heterosexual men, which limits understanding of substance use relationships with these constructs (Zimmerman, 1980; Kinney *et al.*, 1981; Johnson and Fee, 1994; Baird, 1999; Mazure and Jones, 2015). In fact, there have been no attempts to synthesize the literature examining the roles of gender, sex and sexuality as they relate to polysubstance use. As such, the current review aims to fill this gap, focusing in particular on gender and sexual minority subgroups (National Institutes of Health, Office of Womens Health, no date; Auerbach, 1992; Schroeder and Snowe, 1994; Feldman *et al.*, 2019).

Current review aims

In summary, although polysubstance use is a common and concerning phenomenon in adolescents and adults, a clear understanding of potential differences based on gender, sex and sexuality has been slow to emerge. A synthesis of the current state of the literature on the relationship between these factors and polysubstance use may facilitate the identification of critical next steps in prevention and treatment development. The current scoping review aims to advance the literature by (a) providing a critical overview and synthesis of potential sex, gender and sexuality differences in polysubstance use in adolescents and adults, with a focus on how these relationships may differ according to varying operationalizations of

polysubstance use and (b) providing concrete suggestions for improving research in this area.

METHODS

The current review was conducted using published guidelines for scoping studies (Arksey and O'Malley, 2005). Studies were first electronically searched between September 2019 and October 2019 using all EBSCO databases, PubMed and Google Scholar. Backward reference searching of relevant articles (e.g. reviews) was also conducted, and a repeated search was conducted in October 2020 to find additional studies. Studies were considered eligible if they were published in peer-reviewed journals between January 1990 and October 2020 and were written in English. Publicly available data sources were also referenced to capture additional prevalence information that has not been published elsewhere. Specifically, NSDUH offers datafiles for individual years and data concatenated from 2002 to 2018. For the purposes of the current review, the Public Use Data Analysis System was consulted with crosstab analyses run on the National Survey on Drug Use and Health: Concatenated Public Use File (2002 to 2018). For each analysis, 'Rc-Age Category Record (3 Levels)' [CATAG2] was set as the column variable, 'Imputation Revised Gender' [IRSEX] was set as the control and the row variable was first set as 'Rc-Illicit Drug and Alcohol Use - Pst Yr' [ILLANDALC] then 'Rc-Illicit Drug and Alcohol Dep or Abuse - Past Year' [UDPYLAAL]. Column percentages were first gathered for male and female respondents aged 12-17 then aged 26 and older who engaged in past year illicit drug and alcohol use, then for respondents who met for past year illicit drug and alcohol dependence/abuse (Substance Abuse and Mental Health Data Archive, no date).

Three searches were conducted. First, articles on polysubstance use and gender in the general population were reviewed. Search terms included 'polysubstance use,' 'multiple substance use,' 'dual substance use,' 'concurrent use' and 'simultaneous use' to encapsulate polysubstance use, and 'sex' and 'gender' as possible search terms for gender. This search yielded 2470 results from EBSCO, 21,719 from PubMed and 2490 from Google Scholar. Results were sorted by relevance and were reviewed using titles, abstracts, and indexing fields until results became generally repetitive or no longer relevant. Studies involving exclusively one gender, examining psychiatric or physical comorbidity or exclusively examining multiple drugs separately (versus concurrent or simultaneous use) were excluded. Studies were included if they examined concurrent or simultaneous polysubstance use and reported the main effects of its relation to gender or sex. In any instances where the interpretation of the main effects was not clear, attempts were made to clarify with the contact authors. Any questions about eligibility criteria were discussed and resolved within the research team.

To locate studies that did not use gender as an indexing field, a second search was conducted using only the aforementioned polysubstance use search terms. This search yielded 24,365 results from EBSCO, 537,873 from PubMed and 3690 from Google Scholar. The review process mirrored that of search one, except studies examining concurrent or simultaneous use were examined with greater detail, particularly in the results section, to identify any gender-related analyses. Any study that included the main effects of sex or gender in

primary or secondary analyses was included. Eligible articles from searches one and two were then arranged by the primary age group featured: adult population (age 18 or over) or adolescent population.

A third search was conducted to locate polysubstance use studies featuring gender and sexual minorities. The search consisted of polysubstance use terms and terms encapsulating gender and sexual minorities ('gender minorities,' 'sexual minorities,' 'LGBT,' 'LGBTQ' and 'transgender'). This search yielded 149 results from EBSCO, 368 from PubMed and 42 from Google Scholar. Again, the review process mirrored that of search one, except that articles were not divided by age group due to the small number of results. Across all three searches, a total of 63 articles were eligible: 18 adolescent studies, 37 adult studies and 8 sexual and gender minority studies.

RESULTS

Table 1 provides a summary of the findings from the literature review ($N = 63$). Results are displayed in three categories of polysubstance use consistent with the search strategy: adolescent, adult and gender and sexual minorities (adolescent and adult inclusive). In general, across adolescent, adult and gender and sexual minority studies of polysubstance use, operationalizations of polysubstance use varied widely, in terms of the frequency measured, the type of polysubstance use (concurrent or simultaneous), substance specificity and measures of frequency. Of the 63 studies, 38% studied sex ($n = 24$) and 63% studied gender ($n = 40$); only one study measured both sex and gender (Day *et al.*, 2017).

Adolescent polysubstance use

Adolescent concurrent polysubstance use

Findings on gender differences in adolescent concurrent polysubstance use are contradictory. According to 2002–2018 concatenated data from NSDUH (Substance Abuse and Mental Health Data Archive, no date) of almost 255 million respondents aged 12 or older, 10.3% of boys and 11.9% of girls aged 12–17 used both alcohol and at least one non-alcohol, non-tobacco recreational substance concurrently in the previous year, reflecting a nominally higher prevalence of polysubstance use for girls than for boys. Similarly, 0.8% of boys and 0.9% of girls met criteria for both past year AUD and a past year illicit SUD (SAMHSA, 2019). These polysubstance use rates are consistent with the national Monitoring the Future findings of single substance use trends which note that the gender gap (boys having historically higher rates) has narrowed, and even reversed with some grades and specific substances (e.g. past year cannabis use in 8th graders) as more girls are endorsing substance use behaviors (Miech *et al.*, 2020).

Conversely, several polysubstance use studies report that adolescent boys have greater odds than adolescent girls of concurrently using multiple substances (Epstein *et al.*, 1999; Göbel *et al.*, 2016; Petrou and Kupek, 2018; Rose *et al.*, 2018; Zuckermann *et al.*, 2019). These differing findings may be due to the year(s) of data collection because of the aforementioned changing trends in adolescent substance use (Miech *et al.*, 2020). Indeed, one study of Canadian 9th through 12th graders found that although girls were less likely to use two substances between 2013 and 2016, they were

more likely to do so between 2017 and 2018 (Zuckermann *et al.*, 2019). Yet, after accounting for year and race, boys were more likely to report polysubstance use at all levels (i.e. use of 2, 3 and 4 substances), demonstrating how many additional factors may influence the relationship between gender and polysubstance use. A study of Swedish 15- and 16-years-olds found that boys were more likely than girls to engage in concurrent polysubstance use between 1988 and 2005, but for the cohort assessed between 2008 and 2011, no gender differences emerged (Evans *et al.*, 2020). Furthermore, one study of 662 Canadian adolescents ($M_{age} = 15$) found no difference between boys and girls regarding their allocation into a class of high probability past year concurrent polysubstance use (Merrin and Leadbeater, 2018). It is critical to note that the studies cited in this paragraph report the relationship between gender and polysubstance use substances without distinguishing between substance types being co-administered. Given these inconsistent findings, we speculate that studying polysubstance as a dichotomous construct that encompasses any combination of substances may be inadequate to accurately capture gender differences in adolescent polysubstance use.

Additional information emerges when specifying concurrent polysubstance use drug combinations. Multiple studies found boys more likely than girls to concurrently use combinations of alcohol, tobacco, cannabis and cocaine (Smit *et al.*, 2002; Font-Mayolas *et al.*, 2013; Banks *et al.*, 2017), but one study of midwestern American juvenile detainees found no gender differences for combinations of cannabis with alcohol and/or other substances (Banks *et al.*, 2019). Another American multi-site study of 4129 adolescents found boys more likely than girls to endorse past month concurrent alcohol, tobacco and cannabis use, but results were no longer significant after adjusting for age, household income, parent education and parent marital status (Purcell *et al.*, 2020). Analyses conducted in over 100,000 16-year-old across 35 European countries found that concurrent use of most combinations of alcohol, tobacco, cannabis and other illicit drug use was greater in boys, but girls outnumbered boys for concurrent use that included tranquilizers or sedatives (Kokkevi *et al.*, 2014). Analyses examining the concurrent use of alcohol and tobacco were mixed. One national study of 14,667 Americans aged 12–18 found boys more likely than girls (Banks *et al.*, 2017), another study of 1501 Spanish high school students found girls more likely than boys (Font-Mayolas *et al.*, 2013) and a Dutch national study of 6236 students aged 12–16 found no gender differences in their concurrent use (Smit *et al.*, 2002). Taken together, gender differences in polysubstance use may vary according to specific substance combinations; however, definitive findings and directionality of such differences are inconclusive given the limited research.

Adolescent simultaneous polysubstance use

Although most adolescent studies investigate concurrent substance use, some do examine simultaneous use. Concatenated NSDUH data of American adolescents aged 12–17 between 2002 and 2018 show no gender differences in prevalence of using an illicit drug during their most recent alcohol consumption (1.7% for both boys and girls; SAMHSA, 2019). Simultaneous polysubstance use research in adolescents typically concerns simultaneous alcohol and cannabis use (SAC). Overall, boys exhibit higher odds and have a higher frequency of SAC use than girls (Collins *et al.*, 1999; Hoffman *et al.*, 2000;

Table 1. Characteristics and gender/sex difference and sexuality difference results of included studies (N = 63)

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Adolescents (n = 18) Banks <i>et al.</i> , 2017	Cross-sectional	<ul style="list-style-type: none"> National Survey on Drug Use and Health (NSDUH), 2011–2014 14,667 American students 47.4% girls 61.9% White M_{age} = 16.6 	<p>Concurrent:</p> <ul style="list-style-type: none"> past 30-day A + Ca, Ca + T, A + T, A + Ca + T, coded as yes/no for each combination 	Sex	Age, income	<ul style="list-style-type: none"> Compared with girls, boys were more likely to belong to the typologies A + Ca, Ca + T, A + T, A + Ca + T (vs. A only)
Banks <i>et al.</i> , 2019	Cross-sectional	<ul style="list-style-type: none"> 238 detained youth 19.6% girls 77.3% non-White M_{age} = 15.5 	<p>Concurrent:</p> <ul style="list-style-type: none"> past-year Ca + A, Ca + Oth, Ca + A + Oth, coded as yes/no for each combination Oth included e.g. spice, NPM, E, Meth 	Gender	None	<ul style="list-style-type: none"> No gender differences between Ca-use typology: Ca + A, Ca + Oth, Ca + A + Oth (vs. Ca only)
Collins <i>et al.</i> , 1998	Longitudinal	<ul style="list-style-type: none"> RAND Adolescent Panel Study 4070 12th graders 54% girls 75% White M_{age} = 15.4 	<p>Simultaneous:</p> <ul style="list-style-type: none"> past year A + D, A + U, A + Ca, Co + Oth on the same occasion, coded as yes/no for each combination 	Gender	<p>Model 1: none Model 2: age; race/ethnicity; income; parent education/occupation; social influences; family, school and church factors; problem behavior/lifestyle factors</p>	<p>Model 1:</p> <ul style="list-style-type: none"> Compared with girls, boys were more likely to use A + Ca No gender differences in illicit drug use (excluding Ca) + A/Ca <p>Model 2:</p> <ul style="list-style-type: none"> Compared with girls, boys were more likely to use A + Ca (vs. no PSU) No gender differences in illicit drug use (excluding Ca) + Oth (compared with A + Ca)

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Epstein <i>et al.</i> , 1999	Longitudinal	<ul style="list-style-type: none"> • 2,354 6th and 7th graders • 52% girls • 84% White • $M_{age} = 12.6$ 	Concurrent: - lifetime and past month A, T, Ca, each coded as 0–3 total substances <ul style="list-style-type: none"> • composite PSU frequency index 	<i>Gender</i>	Ethnicity	<ul style="list-style-type: none"> • Compared with girls, boys engaged in more PSU according to the composite frequency and past month variables
Evans <i>et al.</i> , 2020 ^a	Repeated cross-sectional	<ul style="list-style-type: none"> • Young in Värmland (YiV) study, 1988–2011 • 20,057 Swedish adolescents • 49% girls • Race NR • Age = 15 to 16 	Concurrent: <ul style="list-style-type: none"> • lifetime A + T, and past school year drunkenness+I, each coded as yes/no; subjected to LCA 	<i>Sex</i>	None	<ul style="list-style-type: none"> - Compared with girls, boys were more likely to be in the PSU class (lifetime A + Ci, drunkenness+I) versus no/low use class (no substance use or lifetime A only) for first 3 cohorts (1988–1991, 1995–1998, 2002–2005) - No significant sex differences in the 2008–2011 cohort
Font-Mayolas <i>et al.</i> , 2013	Cross-sectional	<ul style="list-style-type: none"> • 1,501 Spanish high school students • 50.6% girls • Race NR • $M_{age} = 14.0$ 	Concurrent: <ul style="list-style-type: none"> • past 6-month T, A, Ca, Co, ≥ 2 substances used coded as yes/no 	<i>Gender</i>	None	<ul style="list-style-type: none"> • No gender differences in PSU when whole sample included • When only drug users included, girls were more likely to report PSU
Göbel <i>et al.</i> , 2016 ^a	Cross-sectional	<ul style="list-style-type: none"> • Second International Self-Report Delinquency Study (ISRD-2), 2006 • 33,566 European adolescents • 50.6% girls • Race NR • $M_{age} = 13.9$ 	Concurrent: <ul style="list-style-type: none"> • lifetime and past-month A, Ca, and E/speed/ LSD/H/Co coded as yes/no and frequency of past-month use coded as never, 1–2 times, or ≥ 3 times; subjected to LCA 	<i>Gender</i>	None	<ul style="list-style-type: none"> • Compared with girls, boys were more likely to be classified as PSU (recent use of A, Ca and Oth) compared with non-users

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Hoffman <i>et al.</i> , 2000	Repeated cross-sectional	<ul style="list-style-type: none"> 70,516 7th and 12th graders in New York State Gender NR Race NR M_{age} NR 	Simultaneous: <ul style="list-style-type: none"> past 6-month A + Ca, A + Co coded as yes/no 	Gender	Model 1: none Model 2: demographics and survey year Model 3: individual substance use rates: average daily A, past 30-day use frequency of Ca/Co respectively and product of A and drug use frequency	<ul style="list-style-type: none"> Model 1: Probabilities of simultaneous use greater for boys versus girls Model 2: A + Co was higher for boys Model 3: Controlling for the individual substance rates of use, girls were more likely to use A + Ca and A + Co in combination than boys
Kokkevi <i>et al.</i> , 2014	Cross-sectional	<ul style="list-style-type: none"> European School Survey Project on Alcohol and Other Drugs (ESPAD) survey, 2011 wave 101,401 16-year-old students in 36 European countries 41.9% girls Race NR M_{age} = 16 	Concurrent: <ul style="list-style-type: none"> past 30-day use of 'risky' substance combinations: ≥ 6 T/day, A use ≥ 10 times, any Ca, and any lifetime use of S and Oth, coded as yes/no, and past 30-day 'risky' use defined total number of substances used at a 'risky' level 	Gender	None	<ul style="list-style-type: none"> More boys (vs. girls) used 2 and 3+ substances Compared with girls, more boys endorsed substance combinations: T + A, Ca + Oth, A + Ca, T + A + Ca, T + A + Ca + Oth, A + O, A + Ca + Oth, A + Ca + S + Oth Compared with boys, more girls endorsed the substance combinations: S + Oth, T + S, T + S + Oth, T + Ca + S + Oth, Ca + S, T + Ca + S, T + A + Ca + S, A + Ca + S
Merrin and Leadbeater, 2018 ^a	Longitudinal	<ul style="list-style-type: none"> Victoria Healthy Youth Survey (V-HYS), 2003–2013 662 Canadian youth 41.9% girls Race NR M_{age} = 15 	Concurrent: <ul style="list-style-type: none"> past year use of T, HED, Ca, Oth, coded as yes/no; subjected to LCA 	Sex	None	<ul style="list-style-type: none"> Similar proportions of boys and girls in poly-use class (highest probabilities of T, HED, Ca, Oth) and co-use class (high probabilities of HED and Ca, low probabilities of T and Oth) Low-use class (low probabilities of T, HED, Ca, Oth) had more girls than boys

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Patrick <i>et al.</i> , 2018 ^a	Cross-sectional	<ul style="list-style-type: none"> Monitoring the Future (MTF), 1976–2016 84,805 US 12th graders 48.4% girls 70.9% White M_{age} NR 	Concurrent and Simultaneous: <ul style="list-style-type: none"> A use coded as: no A past year, past-year A but no BA past 2 weeks, or A past year and BA past 2 weeks; Ca coded as: no Ca past year, Ca past year but not past 30 days, or Ca past year and past 30 days; past-year A + Ca (overlapping drug effects) coded as yes/no, subjected to LCA 	Gender	Race/ethnicity, parent education, high school grades, whether the student had definite plans to graduate from a 4-year college, frequency of evenings out with friends, truancy, past year use of any illicit drugs other than Ca	<ul style="list-style-type: none"> Compared with girls, boys were more likely to be in simultaneous A + Ca-heavier use group (high probabilities for: simultaneous A + Ca, A, BA and past 30-day Ca) versus simultaneous A + Ca-lighter use (high probabilities of A + Ca, past-month Ca, A without BA), concurrent use (high probabilities of Ca and A without B), or A-only (high probabilities of A without BA, Ca, A + Ca) No gender differences in risk of being in A-only class versus either simultaneous A + Ca-lighter use or concurrent classes
Patrick <i>et al.</i> , 2019	Cross-sectional	<ul style="list-style-type: none"> Monitoring the Future, 2005–2015 1719 nationally representative 12-graders 53.2% girls 61.8% White M_{age} NR 	Simultaneous: <ul style="list-style-type: none"> past-year A + Ca, coded as yes/no 	Gender	Model 1: none Model 2: race/ethnicity, college plans, grades, parents in the home, religiosity, parental education, geographic region, cohort and A, T, Ca use	<ul style="list-style-type: none"> In Models 1 and 2, the odds of A + Ca were higher for boys (vs. girls)
Petrou and Kupek, 2018	Cross-sectional	<ul style="list-style-type: none"> Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS), 2002–2013 134,387 Scottish students Gender NR Race NR 2 classes, $M_{age} = 13$ and 15, respectively 	Concurrent: <ul style="list-style-type: none"> regular PSU, coded as yes/no; defined as having: Avg of ≥ 1 T/week, $A \geq 1$ times/week, and past-month illicit drug use heavy PSU coded as yes/no defined as engaging in ≥ 2 out of 3: ≥ 60 T past week, ≥ 21 units of A past week, illicit drugs most days 	Gender	School year, ethnicity and socioeconomic quintile	<ul style="list-style-type: none"> Compared with girls, boys had higher odds of use of regular and heavy PSU

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Purcell <i>et al.</i> , 2020	Cross-sectional	<ul style="list-style-type: none"> Healthy Passages, Wave 3, 2009–2011 4129 US adolescents 51% girls 25% White M_{age} = 16.10 	Concurrent: <ul style="list-style-type: none"> past 30-day A + Ca, A + T, and T + Ca, A + Ca + T, coded as yes/no 	Sex	Model 1: none Model 2: age, parental education, parental marital status, household income	<ul style="list-style-type: none"> Model 1: no sex differences in A + Ca, A + T, T + Ca; boys more likely to use A + T + Ca Model 2: no sex differences
Rose <i>et al.</i> , 2018 ^a	Cross-sectional	<ul style="list-style-type: none"> Rural Adaptation Projects, fourth year 7074 low-income rural adolescents 51.8% girls 29% White M_{age} = 14.8 	Concurrent: <ul style="list-style-type: none"> lifetime A, T, Ca, prescription drugs NP, I, coded on 7-point frequency scale, subjected to LCA 	Gender	Race/ethnicity, free/reduced lunch, number of parents living at home	<ul style="list-style-type: none"> Compared with girls, boys had higher odds of being at risk for more types of substances used
Smit <i>et al.</i> , 2002 ^b	Cross-sectional	<ul style="list-style-type: none"> Dutch National School Survey on Substance Use, 1999 6236 nationally surveyed Dutch students Gender NR 76.2% Dutch origin M_{age} = 14 	Concurrent: <ul style="list-style-type: none"> past month use of ≥ 2 substances: A, T, Ca, E, Am, Op, H, and Co, coded as yes/no, entered into HOMALS 	Gender	None	<ul style="list-style-type: none"> No gender difference in risk of becoming ordinary PSU (user of A + T) Compared with girls, boys had greater risk of becoming user of Ca + A/T or a user of E/Co/Am or H + A/T/Ca
Terry-McElrath <i>et al.</i> , 2013	Cross-sectional	<ul style="list-style-type: none"> Monitoring the Future, 1976–2011 34,850 nationally represented American students Gender NR Race NR 12th grade students 	Simultaneous: <ul style="list-style-type: none"> past-year A + Ca; 2 variables created: any simultaneous use coded as yes/no, and simultaneous use most or every time, coded as yes/no 	Gender	Model 1: none Model 2: year, psychosocial and demographic variables Model 3: year, all psychosocial, demographic and substance use measures	<ul style="list-style-type: none"> Model 1: Compared with girls, boys had higher odds of reporting any simultaneous A + Ca Model 2: Boys had higher odds of any simultaneous A + Ca use Model 3: Controlling for substance use frequency, girls showed higher odds of simultaneous A + Ca use than boys

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Zuckermann <i>et al.</i> , 2019	Cross-sectional	<ul style="list-style-type: none"> • COMPASS (2013–2018) • 79,879 Canadian 9–12th graders (43,312 included in PSU analyses) • 46.1% girls • 80.2% White • M_{age} NR 	Concurrent: <ul style="list-style-type: none"> • past year use of ≥ 2 substances: A, T, Ca, e-cig, coded as number of substances used 	Gender	Model 1: none Model 2: study year/sample and race	<ul style="list-style-type: none"> • Model 1: Compared with girls, boys were more likely to report PSU at all levels (i.e. 2, 3 and 4 substances), AY 2013/2014–2016/2017 until 2017/2018 when more girls reported PSU • Model 2: Compared with girls, boys were more likely to report PSU; difference increased with each substance used
Adults ($n = 37$) Bäck <i>et al.</i> , 2010 ^c	Cross-sectional	<ul style="list-style-type: none"> • NSDUH, 2006 • 55,279 non-institutionalized civilians • 51.6% women • 64,1% White • M_{age} NR (majority >35yo) 	Concurrent: <ul style="list-style-type: none"> • current use or abuse/dep of prescription Op and past-year A or T, each coded as yes/no 	Gender	None	<ul style="list-style-type: none"> • No gender differences in the number of current prescription Op users who endorsed past-year A or T
Bassiony and Saleem, 2020	Cross-sectional	<ul style="list-style-type: none"> • 100 treatment seeking adults diagnosed with SUDs • 7% women • Race NR • $M_{age} = 30.7$ 	Concurrent: <ul style="list-style-type: none"> • positive urine screen of ≥ 2: Ca, codeine, hypnotics, A, opium, tramadol, Hal, H, coded as yes/no 	Sex	None	<ul style="list-style-type: none"> • Compared with women, men were more likely to report PSU
Beswick <i>et al.</i> , 2001	Cross-sectional	<ul style="list-style-type: none"> • 116 treatment seeking Op users • 29% women • Race NR • $M_{age} = 35.5$ 	Simultaneous: <ul style="list-style-type: none"> • Benz+H, Cr + H (timeframe NR) each coded as yes/no 	Gender	None	<ul style="list-style-type: none"> • Compared with women, men were more likely to use Benz+H • Women were more likely to use Cr + H

(Continued)

Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Bunting <i>et al.</i> , 2020 ^a	Cross-sectional	<ul style="list-style-type: none"> • Criminal Justice Kentucky Treatment Outcome Study (CJTOS), 2015–2017 • 6569 justice-involved individuals • 18.1% women • 60.7% White • $M_{age} = 32.7$ 	<p>Concurrent:</p> <ul style="list-style-type: none"> • use days 30 days prior to incarceration of: A, Co, Ca, H, prescription Op, Am, T, subjected to LPA 	<i>Gender</i>	Age, years of education, race, unemployment, homelessness, county lived in, financial strain, injection drug use, physical health, anxiety symptoms, depression symptoms, stress-related health consequences	<ul style="list-style-type: none"> • Compared with women, men were more likely to be in primary A group (~daily A + Ca, prescription Op ~50% of month) and primary Bup group (daily Bup + Ca, prescription Op, Am and S-Op), compared with those in group with no drug use >15 days/month • No gender differences in odds of being in primarily H class (~daily use of H, co-use of Ca + prescription Op) or T PSU group (frequent prescription Op and ~ daily T; co-use of Ca + Am) compared with those in group with no drug use >15 days/month
Byqvist, 2006	Cross-sectional	<ul style="list-style-type: none"> • MAX-98 Project, 1998 • 5539 Swedish heavy drug users (past-year narcotic injection or drug use daily/nearly daily for the past month) • 23% women • Race NR • M_{age} NR 	<p>Concurrent:</p> <ul style="list-style-type: none"> • past 12-month CNS + Op, CNS + Ca, Op+Ca, CNS + Op+Ca, CNS + Op+ ≥ 1 narcotics, Op+other narcotics; predominant substance was used as a basal point of reference 	<i>Gender</i>	None	<ul style="list-style-type: none"> • Compared with women, men had greater prevalence of PSU, with Ca appearing more often in drug combinations; for women Op was more common • Combinations of narcotics were somewhat more prevalent among men • No gender differences in use of another substance for those with A as primary • For those with CNS as primary: more women used Op+S; more men used Ca + A • For those with Op as primary: more men used Ca • For those with Ca as primary: more women misused CNS + E

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Chan <i>et al.</i> , 2019 ^a	Cross-sectional	<ul style="list-style-type: none"> National Drug Strategy Household Surveys (NDSHS), 2004, 2007, 2010, 2013, 2016 20,350 nationally representative sample of Australians 58% women Race NR $M_{age} = 24.5$ 	<p>Concurrent:</p> <ul style="list-style-type: none"> past-year use of T (ordinal variable based on frequency), A (ordinal variable based on AUDIT-C), and yes/no variables of Tr/sleeping pills, meth/Am, Ca, H, Co, E, Hal, and ketamine, subjected to LCA 	<i>Gender</i>	Age, sexuality, psychological distress, language, income, socio-economic index for area	<ul style="list-style-type: none"> Compared with women, men were more likely to be categorized as Class 2 (high probability of A risk and I, and moderate probability of Ca, minimal Oth) and as Class 3 (high probability of A risk and Ca and higher probability of Oth)
Earleywine and Newcomb, 1997	Longitudinal	<ul style="list-style-type: none"> 470 community sample 73.2% women 67% White $M_{age} = 29.9$ 	<p>Concurrent:</p> <ul style="list-style-type: none"> frequency of past 6-month use of T, A, Ca, and Oth <p>Simultaneous:</p> <ul style="list-style-type: none"> frequency of past 6-month: T + A, Ci + Ca, A + Oth, Ca + Oth 	<i>Sex</i>	None	<ul style="list-style-type: none"> Compared with women, men had more simultaneous use of A + T No sex differences on any other measure of drug use
Egan <i>et al.</i> , 2013	Cross-sectional	<ul style="list-style-type: none"> Study to Prevent Alcohol Related Consequences, College Drinking Survey, 2009 4090 undergraduate students 63.5% women 81.4% White $M_{age} = 20$ 	<p>Simultaneous:</p> <ul style="list-style-type: none"> past-year NMPS+A at same time, coded as yes/no <p>Concurrent:</p> <ul style="list-style-type: none"> past-year NMPS+A coded as yes/no 	<i>Gender</i>	<p>Model 1: none</p> <p>Model 2: academic classification, race, parents' education level, GPA, sensation seeking, past 30-day A, past 30-day HED, past 30-day I, past 30-day, Ca, past 30-day illicit drug use, past-year prescription drug use (excluding Stim)</p>	<ul style="list-style-type: none"> Model 1: men had greater odds of reporting simultaneous NMPS+A past-year; no gender differences in simultaneous versus concurrent A + NMPS Model 2: no gender difference in simultaneous A + NMPS versus past-year A or in simultaneous versus concurrent A + NMPS

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Evans <i>et al.</i> , 2017 ^d	Cross-sectional	<ul style="list-style-type: none"> National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Wave 2, 2004–2005 33,107 adults 58% women 75.7% White M_{age} NR 	Concurrent: <ul style="list-style-type: none"> lifetime presence of drug+A abuse and/or dep, coded as yes/no 	Gender	None	<ul style="list-style-type: none"> Compared with women, men were more likely to have ever had a PSU-related disorder
Evans <i>et al.</i> , 2017 ^e	Cross-sectional	<ul style="list-style-type: none"> NESARC Waves 1 and 2, 2001–2002 and 2004–2005 2860 non-institutionalized US adults 35.7% women 66.6% White M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past 12-month PSU SUD, coded yes/no 	Gender	None	<ul style="list-style-type: none"> Compared with women, men had a higher probability of poly-SUD persistence
Falk <i>et al.</i> , 2008	Cross-sectional	<ul style="list-style-type: none"> NESARC, Wave 1, 2001–2002 43,093 adults Gender NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-year A + drugs (Ca, Co, Op, Hal, Am, S, H, I, O), each coded as yes/no Past year AUD and DUD, coded as yes/no 	Gender	None	<ul style="list-style-type: none"> Compared with women, men more likely to use A + O Men more likely to have past-year AUD + DUD Men more likely to have past-year AUD + CUD
Fernández-Calderón <i>et al.</i> , 2015 ^a	Cross-sectional	<ul style="list-style-type: none"> 4102 patients in public therapeutic communities in Spain 13.2% women Race NR M_{age} = 36.6 	Concurrent: <ul style="list-style-type: none"> diagnoses of abuse/dep of: A, Ca, Co, Op, Am and derivatives, S, Benz, each coded as Abuse vs. Dep vs. Absence of SUD, subjected to LCA 	Gender	None	<ul style="list-style-type: none"> No gender differences between membership in Class 1 versus 2, Class 1 versus 4 or Class 2 versus 4 Gender differences between membership in Class 1 versus 3, Class 2 versus 3 and Class 3, versus 4 identified in table but directionality not discernible and not discussed

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Fernández-Calderón <i>et al.</i> , 2020 ^a	Cross-sectional	<ul style="list-style-type: none"> 1345 partygoers who reported past-year use of ≥ 1 substance 32.5% women 54.1% Spain country of residence $M_{age} = 26.9$ 	Simultaneous: <ul style="list-style-type: none"> substance use at last party attended: A, Ca, Co, E, Am, Meth, ketamine, GHB, magic mushrooms, LSD, Benz, H, poppers, each coded as yes/no; subjected to LCA 	Sex	Model 1: none Model 2: age, sexual orientation, education, employment, socioeconomic status, country of residence, last recreational setting attended	<ul style="list-style-type: none"> Model 1: Sex differences between class membership identified in table but directionality not discernible and not discussed Model 2: Compared with participants in the low PSU class (high use of A + Ca, mean of 2.3 substances used), those in the extensive PSU/Stim class (E + A + Am + Ca, mean of 4.7 substances used) were at lower odds of being men
Grant & Harford, 1990 ^f	Cross-sectional	<ul style="list-style-type: none"> National Household Survey on Drug Abuse, 1985 9630 respondents of national US survey 46.9% women Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-month or past year A + Co Simultaneous: <ul style="list-style-type: none"> past-year or past-month A + Co at same time 	Sex	None	<ul style="list-style-type: none"> Compared with women, men had higher prevalence of both concurrent and simultaneous past-year and past-month A + Co use
Grant & Harford, 1990 ^g	Cross-sectional	<ul style="list-style-type: none"> National Household Survey on Drug Abuse, 1985 9630 respondents of national US survey 46.9% women Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-year A, S, and Tr Simultaneous: <ul style="list-style-type: none"> past-year A + S and A + Tr at the same time (or within a couple of hours) 	Sex	None	<ul style="list-style-type: none"> No sex differences in percentage of S users who used A + S concurrently Concurrent users of A + S who reported simultaneous use were more likely to be men versus women A greater percentage of men versus women reported both concurrent and simultaneous use of A + Tr

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Griesler <i>et al.</i> , 2019	Cross-sectional	<ul style="list-style-type: none"> NSDUH, 2016–2017 29,241 past-year prescription Op users in the US Gender NR Race NR M_{age} NR 	<p>Concurrent:</p> <ul style="list-style-type: none"> past-year prescription Op (misused without prescription, misused own prescription, misused both without a prescription and with one's own prescription) + past-month nicotine use and dep, past-year A, Ca, Co, H, Benz, Stim, coded as no use, use only, or dep/ disorder for each substance 	Gender	None	<ul style="list-style-type: none"> Across all prescription Op user and misuser groups, men had higher rates of Co than women Women were more likely to use prescription Op+Benz Men who were Op users or who misused without a prescription only were more likely to report nicotine dep Men who were Op users, who misused without a prescription only or who misused with and without a prescription were more likely to report AUD Men who were Op users and who misused without a prescription only were more likely to report CUD Men who were Op users or who misused without and with a prescription were more likely to report H Men who were Op users, who misused without a prescription only, or who misused with and without a prescription were more likely to report Stim misuse
Grigsby and Howard, 2019 ^c	Cross-sectional	<ul style="list-style-type: none"> NSDUH, 2016 26,033 civilian non-institutionalized US, 12+ yo, reporting past month substance use 51.5% women 63.4% White M_{age} NR 	<p>Concurrent:</p> <ul style="list-style-type: none"> past month use of Op, Op+illicit drugs (T/A), Op+illicit drugs (Ca, Co, H, LSD, PCP, E, ketamine, DMT/AMT/ FOXY, salvia, Meth, l), Op+ > 1 recreational drug, drug use only 	Gender	None	<ul style="list-style-type: none"> Men had a higher risk of past-month prescription Op misuse with illicit drug or PSU

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Husky <i>et al.</i> , 2007	Cross-sectional	<ul style="list-style-type: none"> NESARC, Wave 1, 2001–2002 42,565 nationally represented American adults 57.1% women Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> current T status (daily, occasional, previous), current A and drug abuse and dep (past year); drug diagnoses included abuse and dep for Op, Stim, Ca, Hal, S, Tr, I, and solvents, coded as A Abuse/Dep vs No Current A Abuse/Dep and Current Drug Abuse/Dep vs No Current Drug Abuse/Dep 	Gender	Race, education, marital status and age	<ul style="list-style-type: none"> Women with a current AUD had greater odds of being a daily or occasional T user compared with men Women with DUD had greater odds of being daily T user versus men and similar odds of being an occasional T user
Jackson <i>et al.</i> , 2020	Cross-sectional	<ul style="list-style-type: none"> 1360 past-year A and Ca using college students 62% women 69% White M_{age} = 19.8 	Concurrent: <ul style="list-style-type: none"> past 3-month A + Ca, but not simultaneously, coded 0 = no use past 3 months, to 7 = \geq daily 	Gender	None	<ul style="list-style-type: none"> Simultaneous A + Ca users were more likely to be men (compared with A-only users) No gender differences in concurrent A + Ca users and A-only users
			Simultaneous: <ul style="list-style-type: none"> past 3-month frequency of A + Ca at same time so effects overlapped, recoded ordinal frequencies to days 			
John <i>et al.</i> , 2018 ^a	Cross-sectional	<ul style="list-style-type: none"> National Drug Abuse Treatment Clinical Trials Network, TAPS Tool Study (CTN-0059) 2000 adult primary care patients 56.2% women 28.9% White M_{age} = 46 	Concurrent: <ul style="list-style-type: none"> past-year SUD variables: T, A, Ca, Co, prescription Op/HI, and Oth (i.e. S, Meth, prescription Stim/Am, Hal, I, other nonspecific drugs), coded as yes/no, subjected to LCA 	Sex	Model 1: none Model 2: age, race/ethnicity, education, employment, marital status, study site	<ul style="list-style-type: none"> Model 1: Men had increased odds of having multiple SUDs (≥ 2) Model 2: Men had increased odds of having multiple SUDs (≥ 2) compared with having a single SUD Model 2: Men were at increased odds of being in the Medium SUD Class (high prevalence of TUD), moderate prevalence of AUD, CaUD and CoUD, and low prevalence of Op and Oth DUD) and high SUD class (high prevalence of SUD for Op, T and Co and moderate prevalence of Oth SUDs) compared with low SUD class (low prevalence of all SUD)

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Linden-Carmichael <i>et al.</i> , 2019	Cross-sectional	<ul style="list-style-type: none"> 1017 young adults with past-month A use 32.2% women 71.5% White $M_{age} = 21.66$ 	Simultaneous: <ul style="list-style-type: none"> past-year A + Ca (occurring within a few hours of each other), coded as yes/no 	Sex	None	<ul style="list-style-type: none"> Compared with women, men were more likely to be A + Ca users (versus A-only users)
Maffli and Astrudillo, 2018	Cross-sectional	<ul style="list-style-type: none"> Swiss national monitoring system (act-info), 2013–2015 10,009 patients in substance-related treatment in Switzerland Sex NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> all combinations of A, Ca, T, Co, Op, hypnotics-S, and Oth, each combination coded as yes/no 	Sex	None	<ul style="list-style-type: none"> All subgroups showed majority of men except the combination A/hypnotics-S, which showed majority women
McCabe and West, 2017	Longitudinal	<ul style="list-style-type: none"> NESARC, Wave 1 and Wave 2, 2001–2002 and 2004–2005 34,653 non-institutionalized US adults Sex NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> ≥ 2 past year SUDs, coded as yes/no for each substance: A, Ca, Co, H, Hal, I, prescription Op, S, Stim, and Tr 	Sex	Model 1: none Model 2: race, age, marital status, income, geographical region, sexual identity, past-year nicotine dep, past-year anxiety disorders, past-year mood disorders, lifetime personality disorders	Model 1 and Model 2: In all models, men were at increased odds of developing multiple SUDs and having 3-year persistence of multiple SUDs
McCabe <i>et al.</i> , 2017	Cross-sectional	<ul style="list-style-type: none"> NESARC-III, 2012–2013 36,309 nationally representative American adults Sex NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-year, prior to past year, and lifetime use of each substance: A, Ca, Co, H, Hal, I, prescription Op, S or Tr; Stim, and Oth (e.g. E and ketamine) 	Sex	Model 1: none Model 2: age, race, anxiety disorder, mood disorder, personality disorder, eating disorder, posttraumatic stress disorder	Model 1 and Model 2: <ul style="list-style-type: none"> Compared with women, men had a higher prevalence of multiple SUD in lifetime, before past year and past year

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Meshesha <i>et al.</i> , 2018	Cross-sectional	<ul style="list-style-type: none"> 358 college students who reported ≥ 2 past-month HD episodes 60% women 79% White $M_{\text{age}} = 18.76$ 	Concurrent: <ul style="list-style-type: none"> past-month HD, Ca, and PSU, coded as HD + Ca, or HD + PSU (≥ 2 illicit drugs) 	Gender	None	<ul style="list-style-type: none"> Women were less likely to be in the drug-using groups compared with men
Midanik <i>et al.</i> , 2007	Cross-sectional	<ul style="list-style-type: none"> National Alcohol Survey (NAS), 2000 7612 US adults 50% women Race NR $M_{\text{age}} = 18.76$ 	Concurrent: <ul style="list-style-type: none"> past-year A, Ca, and Co/Hal/H/NM use of U/D/painkillers; users categorized as either A-only, A + Ca, or A + Oth Simultaneous: <ul style="list-style-type: none"> past-year frequency of A+('a specific') DRUG at the same time, categorized as: A + Ca or A + Oth (Co, Hal, H, or NM use of U, D, or painkillers) 	Gender	Model 1: none Model 2: age, ethnicity, education, income, relationship status, days drinking 5+ drinks	<ul style="list-style-type: none"> Model 1: Being a man was associated with simultaneous Ca + A, and simultaneous use of Oth + A Model 2: No gender difference in concurrent use of Ca + A or Oth + A
Morley <i>et al.</i> , 2015 ^a	Cross-sectional	<ul style="list-style-type: none"> Global Drug Survey, 2012 14,869 adults living in UK, Australia, and US 31.5% women Race NR Median age = 27 	Concurrent: <ul style="list-style-type: none"> past-year drug use, coded as yes/no for each substance: Ca, E, Co, Stim, Nitrous oxide, Ketamine, Benz, Op painkillers, subjected to LCA 	Sex	Age, country of residence, sexual orientation, qualifications, occupational status, living status, past-year T, past-year A, AUDIT score, desire to use drugs less, treatment for anxiety and/or depression, personality disorder, involvement in violent incident, sexual risk-taking, emergency treatment	<ul style="list-style-type: none"> Compared with the PSU classes, participants in the Non-PSU Class (no PSU; moderate probability of Ca-only) were more likely to be women (vs. men)
Orsini <i>et al.</i> , 2018	Cross-sectional	<ul style="list-style-type: none"> 5131 NCAA college athletes 50.8% women 79.7% White $M_{\text{age}} = 18.84$ 	Concurrent: <ul style="list-style-type: none"> 2+ substances (A/T/ Ca/prescription drugs) in the last month, coded as yes/no 	Gender	None	<ul style="list-style-type: none"> Compared with women, men were more likely to report PSU

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Pakula <i>et al.</i> , 2009	Cross-sectional	<ul style="list-style-type: none"> 874 clients in treatment in Ontario, Canada reporting past-year Ca or Co use Gender NR Race NR $M_{age} = 33.5$ 	Simultaneous: <ul style="list-style-type: none"> past-year combined use of Ca + A and Co + A, each coded as yes/no 	Gender	None	<ul style="list-style-type: none"> Compared with women, men were more likely to be simultaneous users of A + Ca There were no gender differences likelihood of reporting A + Co
Roche <i>et al.</i> , 2019	Event-level	<ul style="list-style-type: none"> 179 non-treatment seeking regular drinkers from the Los Angeles area 27.53% women 31.07% White $M_{age} = 29.02$ 	Simultaneous: <ul style="list-style-type: none"> Past-month use of A, T, Ca; use of each drug each day coded as yes/no; same-day effects examined 	Sex	Age, ethnicity, source study, and person-means for each predictor variable	<ul style="list-style-type: none"> Compared with women, men were more likely to report same-day A + Ca There was a synergistic effect of A + T for women, but not men Effects of singular A and T had effect on Ca for men but not women The synergistic effect of combining T + Ca was greater among women compared with men No other sex differences observed
Ruglass <i>et al.</i> , 2020	Cross-sectional	<ul style="list-style-type: none"> 3-Campus Alcohol and Marijuana Study (3CAM) 1390 Past-year Ca using US college students 62.4% women 63.8% White $M_{age} = 19.8$ 	Concurrent and Simultaneous: <ul style="list-style-type: none"> past 3-month use of Ca and T, categorized as either concurrent Ca + T, (same time period, not simultaneously), and simultaneous Ca + T (at same time so effects overlapped) 	Sex	Model 1: none Model 2: Ca, race, SES, age, health rating, anxiety, stress level, simultaneous A and cig use, days A consumed, other substance use	<ul style="list-style-type: none"> Model 1: Simultaneous Ca + T group had a larger proportion of men relative to all other groups Model 2: Relative to Ca-only group, men (compared with women) were more likely to belong to concurrent or simultaneous Ca + T groups When compared with simultaneous users, concurrent users were more likely to be women versus men

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Sadeh <i>et al.</i> , 2020 ^a	Cross-sectional	<ul style="list-style-type: none"> 1106 adults recruited from forensic and community samples who endorsed illicit drug use and/or misuse of prescription drugs 43.4% women 72.9% White $M_{\text{age}} = 32.99$ 	Concurrent and Simultaneous: <ul style="list-style-type: none"> lifetime use of: Op Co, Ca, psychedelics, BA, prescription drug misuse and use of multiple drugs at once, subjected to LCA 	Gender	None	<ul style="list-style-type: none"> Women were more likely than men to be in recreational Ca group (occasional Ca and BA) Men had greater representation in the heavy substance use profiles (heavy Ca Group: high Ca with low levels Oth; heavy multidrug intoxication group: highest levels of simultaneous PSU, and heavy BA, moderate Ca, Co, prescription drug misuse and low levels of H; Heavy Op+PSU, high H, prescription drug misuse and Co)
Saha <i>et al.</i> , 2018	Cross-sectional	<ul style="list-style-type: none"> NESARC-III 36,309 US non-institutionalized civilian population Sex NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-year: A + T only, A + Ca only; A + T + Ca only; and A + other drug use (T/Ca/Sed/Op/Co/Am/club drugs/Hal/H/Oth Past-year AUD only; AUD + TUD only; AUD + CaUD only; AUD + TUD + CaUD only; and AUD + other DUDs (that might include TUD or CaUD in addition to other DUDs) 	Sex	Race/ethnicity, age, marital status, education, income, Urbanicity, region	<ul style="list-style-type: none"> Men more likely to report concurrent A + drugs and AUD-DUD Compared with respondents in A-only group, those using A + T more likely to be men Men more likely to be in A + Ca Group versus A-only Compared with those in AUD-only group, respondents in A + T + Ca Group more likely to be men Odds of using A + other drugs greater among men Compared with those in AUD-only Group, those in AUD + TUD Group more likely to be men Compared with those in AUD-only group, those in AUD + CaUD group more likely to be men Odds of being in AUD + TUD + CaUD group greater among men

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Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Schauer <i>et al.</i> , 2015	Cross-sectional	<ul style="list-style-type: none"> • NSDUH, 2003–2012 • 378,459 nationally representative adults • Sex NR • Race NR • M_{age} NR 	Concurrent: <ul style="list-style-type: none"> • Past-month T, Ca, coded as yes/no for each combination of use 	Sex	Year, age and race/ethnicity	<ul style="list-style-type: none"> • Compared with Ca-only and T-only users, a higher percentage of co-users of Ca + T were men
Subbaraman and Kerr, 2015	Cross-sectional	<ul style="list-style-type: none"> • National Alcohol Survey (NAS), 2005 and 2010 • 8626 nationally represented American adults • 52.4% women • Race NR • M_{age} NR 	Concurrent and Simultaneous: <ul style="list-style-type: none"> • past-year Ca + A (separately always) and simultaneous Ca + A, categorized as mutually exclusive groups 	Gender	Age, race/ethnicity, education, employment, relationship status, 5+ in a day, avg daily number drinks	<ul style="list-style-type: none"> • Risk of simultaneous and concurrent use (relative to only use) did not differ by gender
Tucker <i>et al.</i> , 2020 ^a	Cross-sectional	<ul style="list-style-type: none"> • RAND American Life Panel (ALP) • 1877 national sample of US adults ages 30–80 • 48% women • 69% White • M_{age} = 56 	Concurrent: <ul style="list-style-type: none"> • past-month use of A, heavy A, T, e-cig with nicotine, Ca, e-cig with hash oil, prescription M without prescription, coded as no days, non-daily use, and daily/near daily use, subjected to LCA 	Gender	Race, ethnicity, marital status, education, age, income, social functioning, mental functioning, physical functioning	<ul style="list-style-type: none"> • The HD with T/Ca Class (high likelihood of HD, moderate likelihood of daily/almost daily T, and non-daily Ca use) versus to Abstinent Class (slightly elevated daily/near daily T use) was associated with being a man • No gender differences in likelihood of being in T with Prescription Drugs/Ca Class (moderate likelihood of non-daily and daily/near daily T, and non-daily prescription drug misuse and Ca use, but low likelihood of A) versus Abstinent Class

(Continued)

Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Votaw <i>et al.</i> , 2020 ^a	Cross-sectional	<ul style="list-style-type: none"> NSDUH, 2015–2017 1253 national survey of adults with past-month Tr misuse Gender NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-month BA, prescription Op, Stim, and S (e.g. zolpidem, eszopiclone, zaleplon, temazepam, triazolam, barbiturates) misuse, subjected to LCA 	Gender	Age, race/ethnicity, total number of motives for misuse of Tr, misuse behaviors and past month psychological distress score	<ul style="list-style-type: none"> Men had greater odds of expected membership in BA and Ca Use Class (high probabilities of BA and Ca, moderate probabilities of Co, Hal, prescription Op and prescription Stim misuse) and the Op Use Class (high probability of prescription Op use; moderate probabilities of BA, Ca, Co, H, prescription Stim, and Meth use), as compared with the limited PSU Class (moderate BA, Ca and prescription Op misuse; near-zero probabilities of other substance use)
Sexual and gender minorities (<i>n</i> = 8)				Sex	None	
Coulter <i>et al.</i> , 2019 ^a	Cross-sectional	<ul style="list-style-type: none"> Youth Risk Behavior Survey (YRBS), 2015 119,437 adolescents in the US 50.1% girls 49.7% White 85.7% heterosexual M_{age} NR 	Concurrent: <ul style="list-style-type: none"> lifetime and past-month A and HED (coded as never A, A in lifetime but not past month, past-month A, but no past-month HED, 1 to 5 HED days past month, ≥6 HED), lifetime and past-month T (cigarette and cigars measured separately), coded as never T, T but not in past month, T 1–5 days past month, ≥6 past-month T, and lifetime and past-month Ca (coded as never, 1–2 times past month, 3–9 times past month, 10–19 times past month, ≥20 past month); subjected to LCA 	Sex	None	<ul style="list-style-type: none"> Women were more likely than men to be in the Experimental Users Class (lifetime A, Ca and T but no current use) and Ca-A Users Class (past-month Ca/A, and majority engaged in past month HED) compared with the nonusers class (mostly abstinent from A, T, Ca in lifetime) Men were more likely than women to be T-A users, medium-frequency 3-substance users and high frequency 3-substance users compared with Nonusers Youth who identified as heterosexual were less likely than those who identified as gay/lesbian or bisexual to be classified as any use class compared with the Nonusers Class Sexual minority girls had greatest propensity to be classified in PSU Classes relative to Nonusers Class

(Continued)

Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Day <i>et al.</i> , 2017	Cross-sectional	<ul style="list-style-type: none"> • Biennial Statewide California Student survey, 2013–2015 • 32,072 California middle and high school students • 51.2% girls • 1% transgender • 33.5% White • $M_{age} = 14.74$ 	<p>Simultaneous:</p> <ul style="list-style-type: none"> • past-month use of ≥ 2 drugs at same time: A, T, Ca, I/NP pain medication, any other drug, pill, or medicine to get 'high' or NP, coded as yes/no 	<i>Gender and sex</i>	<p>Model 1: none</p> <p>Model 2: sexual identity, race and ethnicity, and age</p> <p>Model 3: victimization, depressive symptoms, perceived risk of substance use</p>	<p>Models 1, 2 and 3: transgender youth are at heightened risk for PSU compared with nontransgender peers</p> <p>Model 3: men reported higher odds of PSU</p>
Dermody, 2018 ^a	Cross-sectional	<ul style="list-style-type: none"> • Youth Risk Behavior Surveillance System (YRBS), 2015 • 15,624 nationally representative American students in grades 9–12 • 49.7% girls • 83% heterosexual • 43.9% White • M_{age} NR 	<p>Concurrent:</p> <ul style="list-style-type: none"> • past-month A, BA, e-cig, Ca, T (cigarettes measured separately from chewing tobacco/snus/snuff, cigars/cigarillos/little cigars), coded as 0 = none, 1 = at least once; subjected to latent mixture modeling 	<i>Sex</i>	<p>race/ethnicity, sex and age</p>	<ul style="list-style-type: none"> • Relative to heterosexual youth, gay/lesbian-identified youth were at risk of being T + Ca Co-Users (elevated T + Ca), bisexual youth at risk of being in all 4 substance-using classes, and 'not sure' sexuality youth at risk of being PSU/T Users (elevated on all substances except T) • Among boys, no association between sexual minority status and likelihood of being classified in Ca/T Co-Users Group relative to the Non-Users Group (low probabilities of all substances) • Girls who identified as sexual minorities had greater likelihood of being classified in Ca/T Co-Users Group and PSU/T Group than Non-Users Group relative to heterosexual girls • No additional sex differences in sexual minority-related disparities were supported

(Continued)

Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Jun <i>et al.</i> , 2019	Longitudinal	<ul style="list-style-type: none"> Growing Up Today Study (GUTS), Cohorts 1 and 2 12,428 participants assessed 20–35 yo 55.2% women Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past-year probable T dependence, A abuse and Dep, and drug abuse and Dep; co-occurring multiple SUDs (≥ 2) coded as yes/no 	Gender	Model 1: sexual orientation, gender identity, age, race/ethnicity, region of residence	<ul style="list-style-type: none"> Compared with completely heterosexuals, sexual minority (i.e. mostly heterosexual, bisexual, lesbian/gay) participants were generally more likely to 2+ SUDs Differences in likelihood of ≥ 2 SUDs between completely heterosexual individuals and those who are mostly heterosexual and lesbian/gay were greater among women than men; no significant gender differences in likelihood of ≥ 2 SUDs between bisexual and completely heterosexual individuals No differences in likelihood of having ≥ 2 SUDs between cisgender and gender minority individuals
Kecejevic <i>et al.</i> , 2017	Longitudinal	<ul style="list-style-type: none"> GUTS, Cohort 1 13,519 sexual minority and heterosexual participants followed 12–29 yo 58% girls/women 93% White baseline $M_{age} = 14.6$ 	Concurrent: <ul style="list-style-type: none"> past-year use of ≥ 3 substances: T, HED, Ca, E, Co, H, LSD, Meth/Am, misuse of prescription Tr, prescription Op, prescription sleeping pills, prescription Stim 	Gender	race/ethnicity, region of residence, report of an adult or sibling living in the household who drinks A	<ul style="list-style-type: none"> Compared with their same-gender completely heterosexual peers, sexual minorities evidenced higher risk for concurrent PSU over all repeated measures Differences between sexual minorities and completely heterosexuals were larger among women than men
Nguyen <i>et al.</i> , 2021	Event-level	<ul style="list-style-type: none"> 147 young adult smokers 51.7% women 41.5% sexual minority 40.8% White $M_{age} = 22.7$ 	Simultaneous: <ul style="list-style-type: none"> 30-day record of same-day use of each of the following: T + Ca, T + A, Ca + A, T + Ca + A 	sex	age, sex, education, race, psychological distress	<ul style="list-style-type: none"> No sex differences in same-day PSU compared with no use or single substance use between women and men Compared with heterosexual peers, sexual minorities had higher odds of same-day T + Ca and T + Ca + A compared with no PSU No significant associations for same-day T + A and A + Ca No interaction between sexual identity and sex

(Continued)

Table 1. Continued

Author (Year)	Design	Sample	Polysubstance use measurement	Sex/ gender	Covariates in sex/gender model	Gender/sex differences results
Schauer <i>et al.</i> , 2013	Cross-sectional	<ul style="list-style-type: none"> 4840 American students from 6 southeastern colleges 71.2% women 93.7% heterosexual 46.7% White $M_{age} = 23.5$ 	Concurrent: <ul style="list-style-type: none"> past 30-day T, Ca, A, coded as 0–3 according to the number of substances used 	Sex	Depressive symptoms, perceived stress, satisfaction with life, sensation seeking, Big 5 personality traits	<ul style="list-style-type: none"> Among men, no association between sexual orientation and number of substances used Homosexually and bisexually identified women were more likely to report using greater number of substances than heterosexually identified women
Silveira <i>et al.</i> , 2019 ^a	Cross-sectional	<ul style="list-style-type: none"> Population Assessment of Tobacco and Health (PATH) Study, Wave 1, 2013–2014 6127 nationally represented American youth 15–17 yo Gender NR Race NR M_{age} NR 	Concurrent: <ul style="list-style-type: none"> past year T, A, Ca, NP Stim, Sed, and Tr, Co, Meth, speed, H, I, solvents, Hal, coded as yes/no; subjected to LCA 	Gender	Class proportions, sensation seeking, age, race/ethnicity, urban, grade, parent education, past year internalizing problems, past year externalizing problems, sexual orientation	<ul style="list-style-type: none"> Compared with women, men had lower likelihood of membership in A + Ca + T Predominant AM Class (higher probabilities of A + Ca than T), but a higher likelihood of membership in A + Ca + T Predominant T Class (higher probabilities of T than A + Ca) relative to Abstainer Class (low probabilities of T, A and drugs) Compared with those of straight sexual orientation, those identifying as lesbian, gay, bisexual or something else had higher likelihood of membership in A + Ca + T Predominant T Class and A + Ma + T + Oth (high probabilities of A, Ca, T, non-prescribed painkillers/Sed and Oth) relative to Abstainer Class

Note. A = alcohol, Am = amphetamines, AUD = alcohol use disorder, AUDIT-C = Alcohol Use Disorder Identification Test-Consumption, AY = academic year, BA = binge alcohol/drinking, Benz = benzodiazepines, Bup = buprenorphine, Ca = cannabis, Co = cocaine/crack, CNS = central nervous system drugs, primarily amphetamines, D = downers, Dep = dependence, DUD = drug use disorder, E = ecstasy, e-cig = electronic cigarette, H = heroin, Hal = hallucinogens, HD = heavy drinking, HED = heavy episodic drinking, I = inhalant, LCA = latent class analysis, LPA = latent profile analysis, LSD = lysergic acid diethylamide, M = medication, Meth = methamphetamine, NM = non-medical, NR = not reported, NP = not as prescribed/not prescribed, Oth = other drug/other illicit drug, Op = Opioids/opiates, PS = prescription stimulants, PSP = Phencyclidine, PSU = polysubstance use/user, S = sedatives, Stim = stimulants, SUB = substance use disorder, T = tobacco/cigarette, Tr = tranquilizers, U = uppers, UD = use disorder, yo = years old, Sex/Gender column refers to whether sex and/or gender were included in the analysis examining its association with polysubstance use. The term(s) is written in boldface italicized text if it was a primary aim of the study analyses (vs. secondary aim). Study type is specific to how the gender/sex differences were analyzed. ^aStudy used LCA/LPA or latent mixture modeling to identify classes of substance use/PSU; for details regarding classes, see original article. ^bStudy used homogeneity analysis through alternating least squares (HOMALS) to identify Clusters of substance users who resemble each other. ^cStudy includes participants under the age of 18, but $M_{age} > 18$; therefore, article included in adult section of table. ^dArticle title is: Gender differences in the effects of childhood adversity on alcohol, drug and polysubstance-related disorders. ^eArticle title is: Gender and race/ethnic differences in the persistence of alcohol, drug and poly-substance use disorders. ^fArticle title is: Concurrent and simultaneous use of alcohol with cocaine: results of national survey. ^gArticle title is: Concurrent and simultaneous use of alcohol with sedatives and with tranquilizers: results of a national survey.

Terry-McElrath *et al.*, 2013; Patrick *et al.*, 2018, 2019). However, two of these studies conducted additional analyses controlling for overall substance use frequency and showed that girls were then more likely to engage in any SAC use (Hoffman *et al.*, 2000; Terry-McElrath *et al.*, 2013). This discrepancy suggests that although boys may engage in SAC use more frequently than girls, this difference may be more reflective of boys' higher base usage rate of each substance, which, in turn, increases the probability that both substances will be used on the same day. Therefore, although girls engage in SAC use less frequently than boys, girls may still be more likely to simultaneously use alcohol and cannabis during any single episode of substance use.

Adult polysubstance use

Adult concurrent polysubstance use

Compared with results from adolescent studies, adult studies of gender differences in polysubstance use, examined as a single category of any combination of substances, have produced more consistent findings. According to the concatenated data from NSDUH between 2002 and 2018, 16.3% of men and 11.2% of women aged 26 and older reported using both alcohol and at least one illicit drug in the previous year (SAMHSA, 2019). Men are more likely than women to engage in concurrent polysubstance use (e.g. compared with use of a single substance or no substance use) across several populations: the general population, incarcerated individuals, those who engage in heavy drinking episodes and individuals seeking substance use treatment (Falk *et al.*, 2008; Morley *et al.*, 2015; Schauer *et al.*, 2015; Meshesha *et al.*, 2018; Chan *et al.*, 2019; Grigsby and Howard, 2019; Bassiony and Seleem, 2020). Rates of polysubstance use have grown faster for men than for women over the 21st century (Schauer *et al.*, 2015). Rates of multiple SUDs are higher for men than for women as indicated by 2002–2018 concatenated NSDUH data, with 0.9% of men and 0.4% of women meeting criteria for both past year AUD and a past year illicit SUD (SAMHSA, 2019). Men are also more likely than women to have multiple SUDs compared with a single SUD or no SUDs in general populations (Falk *et al.*, 2008; Evans *et al.*, 2017a; McCabe and West, 2017; McCabe *et al.*, 2017; John *et al.*, 2018) and in individuals in SUD treatment (Fernández-Calderón *et al.*, 2015). Furthermore, men have higher rates of maintaining these multiple SUDs over 3 years (Evans *et al.*, 2017b). When categorizing people who engage in multiple substance use as a single group, epidemiological data consistently find men engaging in polysubstance use more than women.

When polysubstance use is examined more precisely with different combinations of substances, adult gender differences are less consistent. A Swedish national survey found that men were more likely to include cannabis in their concurrent polysubstance use, whereas women were more likely to include opiates (Byqvist, 2006). In a Swiss sample of people receiving treatment for SUDs, some substance combinations were more common in men, such as combining alcohol with cannabis, cocaine, opioids or tobacco and combining cocaine with opioids; combinations like alcohol and hypnotics-sedatives were more common in women (Maffli and Astudillo, 2018). Some studies also found men more likely than women to concurrently use combinations of alcohol, tobacco and cannabis as well as meet diagnostic criteria for combinations of alcohol, nicotine and cannabis use disorders (Saha *et al.*, 2018; Tucker *et al.*, 2020), whereas another study found women with AUD

were more likely to use tobacco than men (Husky *et al.*, 2007). However, a number of studies found men more likely than women to use certain specific combinations: concurrent cocaine use in those who use prescription opioids (Griesler *et al.*, 2019), combinations of binge drinking, cannabis use and prescription opioid use in adults who misuse tranquilizer medications (Votaw *et al.*, 2020), combinations of heavy opioid, prescription drug and cocaine use along with the use of other substances (Sadeh *et al.*, 2020) and combinations of alcohol, tobacco, cannabis and prescription drugs in college student athletes (Orsini *et al.*, 2018). Similarly, in incarcerated Americans who endorsed pre-incarceration opioid use and same-day polysubstance use (one year prior), men were more likely to be classified in polysubstance groups characterized by greater past month, near daily alcohol use, buprenorphine use and co-use of stimulants and opioids, compared with individuals classified as having no >15 days of drug use over the past month (Bunting *et al.*, 2020).

Other studies have found substance combinations equally likely across genders. For instance, no gender differences were found in the likelihood of concurrent alcohol and cannabis use (Subbaraman and Kerr, 2015; Jackson *et al.*, 2020), or the likelihood of alcohol use in those who endorsed past year prescription opioid use (Back *et al.*, 2010). In addition, two previously mentioned studies had gender difference findings that varied according to specific combinations analyzed. Although Byqvist (2006) observed gender differences in concurrent polysubstance combinations that included cannabis and opiates separately, they did not observe any gender differences in other substance use in those who endorsed alcohol as their primary substance. Similarly, although Falk *et al.* (2008) found that in those who met criteria for AUD, men were more likely to have a comorbid cannabis use disorder, there were no gender differences in the odds of having any other comorbid use disorder. Despite population-level gender differences in polysubstance use, these differences vary according to substance combinations, making it difficult to synthesize findings.

Adult simultaneous polysubstance use

Similar to concurrent polysubstance use, gender differences in simultaneous use vary depending on the substance combinations considered. Recounting their last drinking session, 4.2% of men and 2.0% of women aged 26 or older endorse using an illicit drug while consuming alcohol, according to concatenated NSDUH data between 2002 and 2018 (SAMHSA, 2019). Similarly, higher simultaneous polysubstance use rates are found in men than women for combinations of alcohol with cigarettes (Earleywine and Newcomb, 1997), cannabis (Midanik *et al.*, 2007, for general population; Pakula *et al.*, 2009; Linden-Carmichael *et al.*, 2019; Jackson *et al.*, 2020, for treatment-seeking population), cocaine (Grant and Harford, 1990a), sedatives (Grant and Harford, 1990b), tranquilizers (Grant and Harford, 1990b in the general population; Beswick *et al.*, 2001 in patients receiving opiate use treatment), nonmedical prescription stimulants (significant in a bivariate model; Egan *et al.*, 2013) and any illicit drugs in a general adult population (Midanik *et al.*, 2007). Higher simultaneous cannabis and tobacco use rates in men have also been reported (Ruglass *et al.*, 2020). In contrast, a Canadian study found no gender differences in the odds of reported simultaneous alcohol and cocaine use in the previous year (Pakula *et al.*, 2009), and another study found no gender differences in past year SAC use (Subbaraman and Kerr, 2015).

Conversely, women report higher rates of simultaneous use of crack and opiates in adults in treatment for opiate use (Beswick *et al.*, 2001). Women were also more likely to be categorized as an extensive polysubstance use/stimulant group (characterized by ecstasy, alcohol, amphetamines and cannabis; mean of 4.7 substances used), compared with a low polysubstance use group (characterized by alcohol and cannabis use; mean of 2.3 substances used) based on use at the last attended party in a U.S. general population (Fernández-Calderón *et al.*, 2020). An event-level study of non-treatment seeking individuals examined same-day alcohol, tobacco and cannabis combinations and found that on a given day men were more likely to progress from using a single substance (i.e. tobacco or alcohol) to simultaneously co-administering cannabis, whereas women were more likely to progress from simultaneously using two substances to simultaneously using all three substances (Roche *et al.*, 2019). These event-level results suggest that gender differences in simultaneous polysubstance use may not only depend on the specific substances being used but also may depend on the number of substances being simultaneously consumed. Taken together, these findings highlight the inconsistent gender differences that emerge when examining polysubstance use as concurrent or simultaneous, and as different combinations of substances.

Gender and sexual minorities

Adolescent and adult gender minorities

The exploration of non-binary gender and polysubstance use has focused largely on individuals who identify as transgender i.e. those whose gender identity differs from their assigned sex at birth (Baker, 2017). A representative study of 32,072 California students' grades 7–12, including 335 transgender youth, examined simultaneous polysubstance use of alcohol, cigarettes, cannabis or other drugs within the previous 30 days (Day *et al.*, 2017). Transgender adolescents were five times more likely to engage in past 30-day simultaneous polysubstance use than their cisgender peers (i.e. those whose gender identity matches their assigned sex at birth; Baker, 2017); the risk was even higher when these individuals also endorsed high levels of victimization (i.e. physical or verbal assault or harassment). Even though this study dichotomizes gender into transgender versus cisgender, findings suggest that gender minorities may be of heightened risk to engage in polysubstance use. Nevertheless, a study of 12,428 American young adults found no difference between gender minorities and cisgender individuals in likelihood of having multiple past year SUDs (Jun *et al.*, 2019). However, Jun and colleagues acknowledged these results as based on a small sample of gender minorities (< 1% of their sample), and they only examined SUDs rather than rates of substance use and polysubstance behaviors.

Sexual minorities

Compared with research on gender minorities, more research exists on polysubstance use in sexual minorities. Studies categorized sexual minorities in one of two ways: either lesbian/gay, bisexual and (in some cases) a third category of 'something else' or 'unsure,' (Schauer *et al.*, 2013; Dermody, 2018; Coulter *et al.*, 2019; Silveira *et al.*, 2019; Nguyen *et al.*, 2021) or as mostly heterosexual, bisexual or mostly/completely gay/lesbian (Keckojevic *et al.*, 2016; Jun *et al.*, 2019). Results indicate that sexual minority adolescents and

young adults are more likely than heterosexual adolescents and adults to engage in polysubstance use. Two studies of adolescent heterosexual and sexual minority individuals categorized participants according to use patterns. Adolescents who identified as sexual minorities were more likely to be categorized into any one of several polysubstance use classes that accounted for lifetime and past month use and were characterized by concurrent use of combinations of alcohol, cannabis or tobacco, compared with a non-user classification (Coulter *et al.*, 2019). Those identifying as lesbian, gay, bisexual or something else had a higher likelihood of being classified in groups characterized by higher probabilities of past year concurrent use of alcohol, cannabis, tobacco and other drugs, relative to the group characterized by low probabilities of tobacco, alcohol and drugs (Silveira *et al.*, 2019). Similarly, past year use of any three or more substances studied longitudinally across aged 12–29 were more likely in sexual minorities (Keckojevic *et al.*, 2016). Finally, same-day cigarette and cannabis use and same-day cigarette, cannabis and alcohol use, compared with no polysubstance use, were also more likely in sexual minorities (Nguyen *et al.*, 2021). The increased risk in adolescent and young adult groups is particularly concerning given that adolescent polysubstance users versus non-users are much more likely to develop SUDs in young adulthood (Moss *et al.*, 2014).

Notably, gender differences in polysubstance use have been found in some of these studies of sexual minorities and heterosexual individuals. Sexual minority women, compared with heterosexual women, have reported greater odds of polysubstance use and higher likelihood of being classified into a polysubstance use group for past month combinations of alcohol, cannabis and tobacco (Schauer *et al.*, 2013; Dermody, 2018; Coulter *et al.*, 2019), past year combinations of three or more substances (Keckojevic *et al.*, 2016), and two or more SUDs (for comparisons of completely heterosexual vs. mostly heterosexual and lesbian/gay; no significant gender effect when comparing bisexual individuals to completely heterosexuals; Jun *et al.*, 2019). No significant differences were observed between sexual minority and heterosexual men in these studies. Lastly, one study predicting same-day alcohol, tobacco and cannabis use found no interaction between sexual minority status and gender (Nguyen *et al.*, 2021). Overall, these results suggest a heightened risk of polysubstance use in sexual minorities, particularly women, early in life.

DISCUSSION

Understanding how polysubstance use trends differ based on gender, sex and sexuality is critical for prevention and treatment. However, based on the available research and the findings of the current review, it is difficult to generate a clear picture in this regard. For one, there are simply not enough studies using similar methodologies to confidently synthesize the findings. Significantly more studies examining polysubstance use trends, and how they differ by gender, sex and sexuality with comparable methods are necessary before any conclusions can be drawn.

The findings in this review were mostly inconsistent and often conflicting. In fact, only two findings seem clear. First, at the population level, adult men were overall more likely to report polysubstance use behaviors than adult women. Second, even with the paucity of available research, sexual

and gender minorities report more polysubstance use than non-minorities. Conversely, findings on gender differences in adolescent polysubstance use were mixed, and neither adolescent nor adult polysubstance use patterns were clearer when broken down into specific substance combinations. Below we highlight potential methodological and conceptual limitations that may have contributed to this lack of consistency and identify next steps for researchers to avoid or overcome such issues.

(1) *Operationalization of polysubstance use:* The varying findings were likely due to the inconsistent operationalization of polysubstance use. Polysubstance use definitions differed in degree of overlap (concurrent vs. simultaneous), time-frame considered for concurrent use (ranging from past month to lifetime), method of measurement (using multiple substances vs. having multiple SUDs), substance specificity (analyses by specific substance combinations vs. use of a dichotomous ‘any polysubstance use’ variable) and substances considered (ranging from alcohol, tobacco and cannabis, to a vast number of potentially psychoactive substances). Moreover, a large percentage of the reviewed studies did not clearly define polysubstance use at all (e.g. no specifiers of concurrent vs. simultaneous use or timeframe when poly-use could have occurred).

Researchers should be sure to operationalize ‘polysubstance use’ as clearly as possible in the future. This distinction is critical because our findings suggest that there are differential substance-related consequences based on the timeframe and specific substance combinations being used. Simultaneous polysubstance use is more strongly associated with deviant behavior, interpersonal conflicts and greater SUD severity than concurrent polysubstance use (McCabe *et al.*, 2006; Midanik *et al.*, 2007; Baggio *et al.*, 2014). Furthermore, specific substance combinations confer substantially greater immediate risk when used simultaneously vs. others. For example, the simultaneous combination of opiates and sedatives is more hazardous than tobacco and cannabis because of the increased risk for overdose and death in the former. Under most situations, the qualifiers of either ‘concurrent’ or ‘simultaneous’ use and the timeframe and number of substances considered should always be described. Timeframes considered should be standardized to past month, past year or lifetime to maximize comparability with population-based national substance use surveys. Dichotomous, ‘any substance’ operationalizations of polysubstance use are far less informative than examining common and/or specific substance combinations. Future research should strive to examine polysubstance use in a more standardized and detailed manner.

(2) *Inclusion of gender and sexual/gender minority status as a variable:* Due to recent efforts, inclusion of sex as a variable in preclinical and clinical research is increasing (Woitowich *et al.*, 2020). Yet, despite these measurable improvements, the inclusion and statistical examination of sex and gender as variables are still rare (Geller *et al.*, 2018; Sugimoto *et al.*, 2019), and inclusion and examination of gender and sexual minorities are rarer still. Men and women respond differently to drugs (Roche and King, 2015; Zucker and Prendergast, 2020), have different patterns of substance use and show different SUD prevalence. To understand the etiology and treatment of polysubstance use, it is imperative that future studies enroll similar numbers of men and women and compare gender differences in the outcome variables.

Moreover, omitting or amalgamating minority groups fails to acknowledge the meaningful differences (e.g. individualized experiences and behaviors) as they relate to outcomes such as substance use (Tate *et al.*, 2014; Bailey *et al.*, 2016; Hyde *et al.*, 2019). Therefore, future studies should also aim to be more inclusive with how they assess gender and sexuality. For those unsure of how to assess these variables, the Adolescent Brain Cognitive Development study has provided a short and simple guide to collect such data (Potter *et al.*, 2020).

(3) *Individual differences in substance use behavior:* Few studies statistically accounted for individual differences in substance use behavior when comparing genders, even though frequency of use at the within-person level may be strongly associated with polysubstance use rates. To discern differences in patterns of polysubstance use, it is necessary to disentangle within-person effects (i.e. patterns of use within a specified timeframe) from between-person effects (i.e. tendency for heavier users of one drug to be heavier users of all drugs and/or likelihood for heavier users of multiple drugs to have co-use days by chance). To account for this potential confound, we suggest that person-level means for the frequency of each studied substance be statistically controlled. If frequency of use is not controlled for, then the group (e.g. gender) who has higher basal substance use rates will almost always be biased to show higher polysubstance use rates as well. Indeed, the results of the three studies that controlled for substance use frequency at the individual level support this notion (Hoffman *et al.*, 2000; Terry-McElrath *et al.*, 2013; Roche *et al.*, 2019). In sum, future polysubstance use studies should assess and control for substance use frequency at the individual level, particularly when analyzing gender differences.

In conclusion, polysubstance use is a prevalent and problematic behavior that warrants additional study. Although it seems highly plausible that patterns of polysubstance use would vary by gender, the limited overall number of studies and disparate methodological approaches have given rise to inconsistent and often conflicting results. Surprisingly, the most consistent findings stem from the least studied group: gender and sexual minorities. Studies in this population have mostly suggested that gender and sexual minorities are more likely to report polysubstance use, suggesting that these individuals may be at heightened risk for development of SUD and in need of early intervention. Additional well-powered studies with a clear operationalization of polysubstance use and sound methodological and statistical approaches are needed to clarify the role of gender and sexuality in polysubstance use.

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CONFLICT OF INTEREST STATEMENT

None declared.

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