POLYSUBSTANCE USE: DIAGNOSTIC CHALLENGES, PATTERNS OF USE AND HEALTH

Jason P. Connor 1,2,3*, Matthew J. Gullo 1,2, Angela White 1, Adrian B. Kelly 1

1 Centre for Youth Substance Abuse Research, Faculty of Health and Behavioural Sciences, The University of Queensland, Brisbane, QLD 4029, Australia
2 Alcohol and Drug Assessment Unit, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia
3 Discipline of Psychiatry, School of Medicine, The University of Queensland, Brisbane, QLD 4029, Australia

Length: Abstract: 194; Manuscript 2376 Words (2457 with references)

Tables: 0

Figures: 0

* Corresponding Author:

Jason P Connor, PhD, FAPS
Centre for Youth Substance Abuse Research
The University of Queensland
K-Floor, Mental Health Centre
Royal Brisbane and Women’s Hospital
Herston, Queensland
Australia, 4029

Ph: 0011 61 7 3365 5150
Fax: 0011 61 7 3365 5488
E-mail: Jason.Connor@uq.edu.au

This is the preprint version of a journal article accepted for publication. Please cite as:

**Purpose of Review:** Polysubstance use is common, particularly among some age groups and sub-cultures. It is also associated with elevated risk of psychiatric and physical health problems. We review recent research findings, comment on changes to polysubstance diagnoses, report on contemporary clinical and epidemiological polysubstance trends, and examine the efficacy of preventive and treatment approaches.

**Recent Findings:** Approaches to describing polysubstance use profiles are becoming more sophisticated. Models over the past 18 months that employ Latent Class Analysis typically report a no use or limited range cluster (alcohol/tobacco/marijuana), a moderate range cluster (limited range, plus amphetamine derivatives) and an extended range cluster (moderate range, plus nonmedical use of prescription drugs and other illicit drugs). Prevalence rates vary as a function of the population surveyed. Wider-ranging polysubstance users carry higher risk of comorbid psychopathology, health problems and deficits in cognitive functioning.

**Summary:** Wide-ranging polysubstance use is more prevalent in sub-cultures such as ‘ravers’ (dance club attendees), and those already dependent on substances. Health risks are elevated in these groups. Research into prevention and treatment of polysubstance use is underdeveloped. There may be benefit in targeting specific polysubstance use and/or risk profiles in prevention and clinical research.

**Key Words:** polysubstance; drugs; comorbidity; psychopathology; prevention
Key Points

- Polysubstance use is common, as evidenced by recent epidemiological and clinical studies.
- Wider-ranging polysubstance use is associated with poorer health outcomes.
- Research into polysubstance prevention requires stronger methodological designs.
- Targeting specific polysubstance use and/or risk profiles may be effective in future clinical and prevention research.
INTRODUCTION AND DEFINITIONS

The term polysubstance use broadly describes the consumption of more than one drug over a defined period, simultaneously or at different times for either therapeutic and/or recreational purposes. In substance use prevention and treatment, it usually refers to multiple illicit drug use, but it can also include licit and prescription medication used for non-medical purposes.

Diagnostically, there have been some changes since the introduction of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) [1*] that relate to the substance use disorder spectrum, and polysubstance dependence specifically. Polysubstance Dependence has been removed from DSM-5. It was historically diagnosed by use of three or more substances (excluding caffeine and nicotine) with no single substance dominating. Key to diagnosis was the lack of a specific drug preference, with the primary motivation for use being uninterrupted intoxication. Dependence criteria also needed to be met for substances as a group, but not for any individual substance. The diagnostic terms of Abuse and Dependence for all substances have also been removed from DSM-5 based on evidence for unidimensionality of diagnostic criteria [2*]. The non-dichotomised diagnosis term Substance Use Disorders is now represented on a continuum of severity ranging from 2 ‘mild’ to 11 ‘severe’. Patients who use multiple substances will be diagnosed by substance type, and graded on this scale. This subtle change means that the relatively small but clinically unique group of patients who previous DSM Polysubstance Dependence criteria, will now be subsumed into a broader diagnostic umbrella. This may have implications from a comparative, epidemiological standpoint- although most population level research has not included diagnostic criteria or severity, only frequency of substance use. The prospective
clinical implications are not yet known. Nor is the reliability of clinical assessments of the DSM-5 severity index.

This review examines key polysubstance use research, published predominately over the past 18 months. Studies thematically cluster around using innovative statistical methods to describe polysubstance trends, recent evidence of psychiatric and physical health risks for multiple substance users, and advances in imaging and neuropsychological research on polysubstance users. We also review evidence for prevention and treatment, and recommend how recent research could be integrated to maximise efficacy of prevention and treatment approaches to polysubstance use.

**REASONS FOR USE**

There are many reasons why some people choose to use multiple rather than single substances. It can be to *enhance effects*, by combining drugs with similar Central Nervous System (CNS) mechanisms such as alcohol and benzodiazapines [3] or two or more anxiolytic-hypnotics [4]. Drugs with different CNS actions may also be combined to accentuate the perceived benefits of each substance, for example opioids/benzodiazepines [5,6,7], stimulants/opioids [8] and stimulants/hallucinogens [9].

Substances are used simultaneously or sequentially to *ameliorate the adverse effects* of drug craving or withdrawal. For example, stimulants are used to overcome dysphoria, and CNS depressants such as benzodiazepines, to manage withdrawal symptoms of anxiety and agitation. *Opportunistic* access, experimentation and conformity to subculture substance use norms are also motivators for multiple drug use. Substance users can be proficient at
assessing the cost/benefit ratios of drug effects, and their use is frequently driven by market forces. The well documented reduction in the availability of heroin in Australia (circa 2000) saw heroin use increasingly supplemented with amphetamines [10]. As with other drug use, polysubstance use is more common among socioeconomic disadvantage [11]. It is especially common in some sub-cultures such as ‘ravers’ (dance club attendees), with recent reports of up to 75% using multiple substances, with on average five drugs used at the last rave attended [12]. Opportunistic and experimental drug use can establish powerful positive drug outcome expectancies that reinforce ongoing use and elevate risk of dependence [13].

There has been increased media interest [14] in the combined use of caffeine (in the form of ‘energy’ drinks) and alcohol, reportedly to extend and enhance intoxication. Short-term behavioural effects and perceived levels of elevated synergistic intoxication have not been found in experimental studies using low doses of caffeine and alcohol [15*,16*]. Further research independent of industry funding is recommended to validate the short and longer term risks of the higher doses of alcohol and energy drinks typically consumed in real world settings [17**].

**PREVALENCE AND CURRENT PATTERNS OF MULTIPLE SUBSTANCE USE**

In 2013, large scale survey research on polysubstance use was conducted in the US [18**,19*,20**], UK [21**], Australia [22**,23**], Denmark [24**], and Latin American countries [25**,26**,27**]. Operationalizations of polysubstance use have typically been based on lifetime prevalence [23**,24**,26**,18**], 1-12 month prevalence [21**,19*,27**,20**,25**,26**,22**], and simultaneous polysubstance use (multiple substances used on the same occasion) [26**,22**]. There have been challenges in
capturing simultaneous polysubstance use, because respondents could not be specifically asked about all of the often-large number of combinations of drug-pairs. Simultaneous polysubstance use has been most frequently assessed in smaller studies of high-risk populations, including club/bar patrons [28*] and clinical/subclinical populations [29*, 30*].

Latent Class Analysis (LCA) analyses of a comprehensive range of drugs reveal that uses fall into a small number of clusters of increasing drug involvement. These included: a limited range cluster (who use alcohol/tobacco/marijuana); a moderate range cluster (in which amphetamine derivatives are added) and an extended range cluster (in which the nonmedical use of prescription drugs, and other illicit drugs is added) [22**,24**,31,23**].

Since 2013, there has been more research on polysubstance use in teen populations [20**,27**,25**,23**,18**] and young adults [26**,19*,24**,21**,22**]. Amongst teenagers, polysubstance use was most commonly limited in range [23**,18**] but the prevalence of use was high. Between 18% (lifetime prevalence in 12-17 year olds; [23**]) and 34% (prior to age 16; [18**]) of teenagers report limited range polysubstance use. These findings suggest that use of certain drugs may occur in the context of other drug use (e.g., alcohol use increases the risk of experimentation with smoking; [32]). Research on simultaneous polysubstance use in this age group is needed to clarify the extent to which this occurs. In older groups, those who report polysubstance use in the last 12 months are also very likely to report simultaneous use [22**].

Non-medical prescription drug use (NMPDU) has gained recent attention. In the US National Survey on Drug Use and Health [33], 6.3% (> 12 years) reported NMPDU in the past year,
and 2.7% reported NMPDU use in the past month. Prevalence rates were 4.8% for pain relievers, 2.1% for tranquilizers, 1.2% for stimulants, and 0.3% for sedatives. Rates were higher in those aged 18-25 years (14.4-15.5% for past year) than in 12-17 year olds (7.8-8.7%) and those aged 26 years and older (3.8-4.8%). In a Nationally representative sample of US high school seniors (modal age 18 years), life time prevalence of non-medical benzodiazepines use was 7.5% [34]. Nonmedical users of prescription opioids have higher rates of alcohol and illegal drug use than medical prescription drug users and nonusers [35*,36*,37]. There is some evidence that polysubstance use involving NMPDU is higher in young adult women than men [26**,19*]. In Australia, a nationally representative survey data revealed a small but distinct cluster of young adults who engaged in sedative and alcohol use (past year prevalence, 1.3%) [22**].

Limited range polysubstance use in adolescence may increase the risk of expanded polysubstance use in young adulthood. Panel survey designs show that in the teen years (12-17 years), extended range polysubstance use is comparatively rare (2%), but is much higher (13.5%) in the 18-29 age group [22**,23**]. In research that retrospectively assesses early polysubstance use, limited range polysubstance use is associated with later drug use, including NMPDU [18**]. Young adult males (around 18-35 years) are at elevated risk of extended polysubstance use [26**,22**,27**,38]. Other correlates include being single, low education, and being employed [21**,22**]. Expansion of polysubstance use to include amphetamine derivatives and cocaine is often associated with reaching the legal age for club/dance attendance. In club/dance venues, polysubstance use is widespread [25**] and prevalence rates are far higher than in other venue types [28*].
COMORBID PSYCHOPATHOLOGY AND HEALTH

Latent Class Analyses (LCA) show that those reporting use of wide ranging multiple substances have poorer mental health than those that use no or few substances. For example, they report higher levels of general psychological distress [23**,22**] and more symptoms of anxiety and depression [31]. Alcohol users that are classified by LCA as having concurrent illicit drug use are more likely to have generalized anxiety and major depressive disorders [39]. In a treatment seeking, cannabis using population, wide-ranging substance users identified by LCA had higher levels of depression, anxiety, manic-excitement and more positive psychotic symptoms than patients who used no other illicit substances [40]. LCA studies have also identified elevated sexual risk behaviours, and infectious disease prevalence among polysubstance users [41,42]. Polysubstance use is especially prevalent in treatment seeking substance abusers [43], sexual health high risk populations including men who have sex with men (MSM) [44], HIV infected MSM [45] and transgender women [46].

A number of recent studies and reviews have reminded the health community of the often under recognised dangers of combining benzodiazepines and opiates for recreational use, or to manage chronic pain [47*,6,7]. In a large national Danish sample [6], long term opiate users with chronic pain carried a 27 times higher odds ratio (95% CI 14.85–49.15) of long-term use of benzodiazepines abuse than individuals without chronic pain. It is not entirely clear why patients with chronic pain are more likely to abuse opiates with benzodiazepines. A recent review [7] suggests that recreational consumption of benzodiazepines is the primary motivation, rather than previously documented self-medication hypotheses. Regardless of the motivations for use, patients who use both benzodiazepines and opioids
are at higher risk of non-fatal and fatal overdoses [47*], comorbid mental and physical conditions, and forensic problems [7].

**IMAGING AND NEUROPSYCHOLOGY STUDIES**

Imaging studies suggest that the abuse of multiple substances may have a cumulative or synergistic adverse effect on brain function and neurocognition [48]. Abstinent polysubstance abusers have reduced gray matter in the right temporal pole and medial frontal lobe, including the superior, cingulate and para-cingulate gyri [49*]. Abé and colleagues [50**] employed high field brain magnetic resonance spectroscopy to study differences in brain metabolite concentrations in polysubstance abuse. Polysubstance abusers were defined as meeting DSM-IV criteria for dependence on alcohol in addition to one or more psychostimulants (mostly cocaine). At 1-month abstinence, polysubstance abusers had significantly lower concentrations of N-acetylaspartate, creatine, myo-Inositol, and choline-containing metabolites in the dorsolateral prefrontal cortex than alcohol-dependent individuals, who did not differ from healthy controls. Among polysubstance abusers, levels of N-acetylaspartate metabolites in this region were strongly correlated with deficits in visuospatial and working memory performance. This suggests that long-lasting memory deficits in polysubstance abusers may be the result of persistent abnormalities in neuronal integrity. Myo-Inositol abnormalities have been detected in the temporal cortex, cerebellar vermis, and lenticular nucleus, but these were not associated with cognitive performance [51] In neither of the studies were these abnormalities related to severity of consumption.
The relationships between brain function and drug doses may differ according to age, the substances abused, or how ‘dose’ is measured. Dose-related abnormalities in frontal N-acetylaspartate have been reported in adolescent polysubstance abusers compared to cannabis-dependent individuals and controls, suggesting a greater vulnerability to neurotoxicity in younger polysubstance users [52]. Dose-related alterations in cortical serotonin signalling have also been observed in long-term abstinent polysubstance users, but these were specific to MDMA, suggesting a unique role in serotonin neurotoxicity [53]. Other studies have shown dose-dependent associations between MDMA and brain activity in the parahippocampal gyrus and superior parietal lobule during memory encoding but not retrieval [54,55]. However, these studies, and other recent investigations of inhibitory control [56] and decision-making [57], find no difference in behavioural performance between polysubstance abusers and controls. This contrasts with the body of neuropsychological evidence of impairments resulting from substance abuse [58,59].

Some have interpreted the discrepancy between neural and behavioural outcomes as reflecting the engagement of compensatory processes to achieve equivalent performance [56,55]. It is also possible that neuropsychological tasks adapted and simplified for the scanner lack sensitivity or that neuroimaging studies lack sufficient sample sizes for adequate statistical power [60]. Large differences have been reported in behavioural performance between polysubstance abusers and controls on standardized neuropsychological tests of working memory, inhibition, cognitive flexibility, self-regulation and decision-making (administered outside the scanner [61]). Test performance correlated with resting brain metabolism in the right middle temporal pole (working memory), right calcarine and bilateral posterior cingulate (self-regulation), and right middle and superior
frontal cortices (decision-making). However, only severity of cocaine use was related to brain metabolism (right middle temporal pole). Therefore, while polysubstance abuse is clearly associated with deficits in brain function and cognition, elucidating more specific relationships is made difficult by methodological differences between studies, differences in the wide range of substances abused and possibly reduced statistical power in neuroimaging studies [62*,60].

**PREVENTION, TREATMENT AND FURTHER RESEARCH**

Prevention programs delivered in schools and community to reduce youth substance use generally demonstrate modest efficacy, with some studies showing small short-term effects, but poor longer term outcomes [63,64,65]. When prevention programs that specifically target adult polysubstance users are reviewed, pervasive methodological weaknesses prevent strong conclusions being drawn about efficacy [66]. Psychological treatments for alcohol, cannabis, tobacco and amphetamine are effective in reducing severity of disorders, as are pharmacological approaches to opiate, nicotine and alcohol dependence [67]. There is currently limited evidence to assess whether treating multiple substance problems concurrently is more effective than treating them individually and sequentially.

There is an intuitive appeal for targeting prevention and treatment approaches based on individual risk profiles [68,69,70]. Some promising prevention results targeting personality risk have recently been reported at 24 months follow-up [71*]. Future research may consider if specific types of polysubstance clusters, as identified in the current review, respond better to targeted prevention and treatment approaches.
Future epidemiological research needs to move beyond binary measures of drug use to polysubstance use profiles that incorporate measures of frequency/severity [40,19*,38,18**]. The could also explore longitudinal transitions in patterns of polysubstance use, particularly between ages 14 and 35, where polysubstance use frequently develops, peaks and subsides [27**,26**,25**]. The increased use of Latent Class Analysis and Latent Transition Analysis [20**] will help identify patterns of both ‘forward’ and ‘backward’ transitioning (widening/narrowing of drug types). These statistical technologies may be helpful in determining timings for prevention targets for specific drug types and combinations of drugs.

It is clear that individuals who use multiple substances are at elevated risk of developing comirbid psychiatric and other health conditions. They also have more pervasive deficits in cognitive functioning that place them at elevated risk of poorer treatment outcomes. Prevention and treatment approaches for polysubstance use are underdeveloped by comparison with treatments for abuse of single substances. Future research will tell what effects removing Polysubstance Dependence from DSM-5 will have on the identification and treatment of this group of substance users.

ACKNOWLEDGEMENTS

Jason Connor is supported by a National Health and Medical Research Council (NH&MRC) of Australia Career Development Fellowship (1031909). Matthew Gullo is supported by a NH&MRC Early Career Fellowship (1036365). Preparation of this manuscript was also supported by ARC DP130102015 to Adrian Kelly. We would like to thank Professor Wayne
Hall for his reviews and feedback on previous versions of this manuscript. We would also like to acknowledge Maddison Campbell for her editorial assistance.

CONFLICTS OF INTEREST

There are no conflicts of interest.
REFERENCES

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest


Significant reconceptualisation of substance use disorders and associated diagnostic criteria is reflected in the 2013 version of the DSM. Suggest interested readers review in conjunction with Hassin, et al., 2013 (DSM-5 Substance-related Disorders Work Group) for empirical rationale supporting modifications.


This paper published by members of the DSM-5 Substance-related Disorders Work Group provides empirical and conceptual reasons applied by this group to recommend dissembling substance abuse and dependence diagnoses, to a single severity continuum. It also provides reasons for dropping criterion legal problems and adding criterion craving.


This study examined 52 volunteers in a controlled, double-blinded, four arm cross-over trial [1) placebo, 2) alcohol, 3) alcohol in with caffeine (equivalent to one energy drink) and 4) alcohol in combination with energy drink] and found negligible evidence that energy drinks increase the short behavioral effects or perceived level of intoxication of alcohol. Conflict of Interest with Red Bull® by authors acknowledged


Review of studies examining the effects of mixing energy drinks with alcohol following consulting with Medline/Pubmed, PsycINFO, and Embase. The review found little support for energy drinks combined with alcohol impacting on the short behavioral effects or perceived level of intoxication of alcohol. Conflict of Interest with Red Bull® by authors acknowledged.

17. ** Miller P. Energy drinks and alcohol: research supported by industry may be downplaying harms. BMJ 2013; 347:f5345.

This commentary highlights that for ethical reasons, laboratory studies examining the effects of combining energy drinks and alcohol have applied lower-levels of alcohol intoxication. They report these studies are largely irrelevant and do not reflect intoxication levels or night time environments on which public health concerns have been raised. The authors also express caution that a significant majority of these studies have been funded by energy drink producers, and further independent studies are warranted.


A nationally representative study of polydrug use in the early teens. The study found a very high rate of polydrug use in under 16s (34.1%).


Using LCA, this study of American college students found that NMPM (past year) was most common in girls.

* A rare study employing latent transition analysis of drug use. The study was one of the first to examine transitions in drug use and associated correlates, and one of the few to be based on teenage populations.


* Applied latent class analysis to London and UK nationally representative survey samples. The study demonstrates higher rates of polydrug use in urban versus regional areas, and demographic correlates of polydrug use.


* The only nationally representative study of polydrug use in young adult Australians. Demonstrates a high prevalence of polydrug use (13.2%) and found polydrug use associated with males, low education and high income. This is one of the few studies to examine simultaneous polydrug use.


* This nationally representative study is a rare study of polydrug use in teenagers. 18.3% were limited range polydrug users (based on lifetime prevalence), and 2% were extended range polydrug users.

In this study of a Danish nationally representative sample, 3 classes of polydrug use were established, and class membership was associated with sexual and physical abuse. Gender differences in these associations were evident.


This is one of the few studies of adolescent polydrug use. It was found that 13.9% of Spanish adolescents reported polydrug use.


Using a national sample of Brazilian college students (n = 12544), this study used multiple measures of polydrug use, including simultaneous use. 18-34 year old males were most likely to report polydrug use.


In one of the largest studies of its type, polydrug use (past month) in Latin American countries using regression modelling of household surveys. Polydrug use (21% overall) was most prevalent in the 18-34 year age group. Ecstasy users were the most likely to have engaged in wide range use of other substances.


This study examined the prevalence of illicit drug use in the UK night time economy. Results indicated that in the Electronic dance music scene, illicit drug use is prolific, compared to the bar scene.

* This study focused on a large sample of adult amphetamine users. The study found that, compared to drug abstinent people, polydrug users of meth and marijuana had higher depression, and polydrug users of heroin/cocaine had higher arrest rates, and poorer physical health.


* This study examined simultaneous polydrug use in cannabis users (n = 226). Participants reported simultaneous polydrug use during their first-ever use.


34. McCabe SE, West BT. Medical and Nonmedical Use of Prescription Benzodiazepine Anxiolytics among U.S. High School Seniors. Addict Behav 2014 (accepted for publication).

This cross-sectional study of university students compared medical and nonmedical users of prescription opioids. Consistently higher alcohol and illegal drug use was evident in nonmedical versus medical prescriptive opioid users.


Based on a large sample of American undergraduates, this study compared appropriate, medical misusers, and nonmedical misusers of stimulants. The study showed that misusers had high rates of other substance use.


A comprehensive, clinically orientated review which highlights risks of co-administration of CNS depressants and opioids. Clinical management and treatment guidance provided.


First study to investigate regional gray matter differences between polysubstance abusing alcohol-dependent individuals and individuals with alcohol dependence only.


This study describes the qualitatively and regionally different neurobiological abnormalities after one month of abstinence in polysubstance abusers with alcohol-dependence compared to individuals with only alcohol dependence. It suggests that deficits in polysubstance abusers’ visuospatial and working memory may be, in part, the result of low N-acetylaspartate in the dorsolateral prefrontal cortex.


60. Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. Arch Gen Psychiatry 2011; 68:773-780.


This article highlights the importance of how dose is operationalized and its impact of observed relationships.


This innovative substance prevention study is one of the few that 1) report longer term outcomes (24mths) and 2) have applied a selective, targeted treatment (based on personality risk). A large number of students (n=2643) were randomised by school to either brief personality-targeted interventions to risk youth, or standard drug education. Targeted students reported significantly less consumption across multiple indices.