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Drug use disorders in the polydrug context: new epidemiological evidence from a foodborne outbreak approach

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Abstract

As epidemiologists studying foodborne illness outbreaks, we do not ask luncheon attendees to say which food caused their illnesses. Instead, we use measurement and analysis methods to estimate food-specific risk variations. Here, we adapt the foodborne outbreak approach to develop new estimates of drug use disorder risk for single-drug and polydrug users, without attributing the syndrome to a specific drug when multiple drugs have been used. We estimate drug use disorder risk for cannabis-only users as a reference value. We then derive comparative relative risk estimates for users of other drug subtypes, including polydrug combinations. Data are from the 2002 to 2003 U.S. National Comorbidity Survey Replication, a nationally representative sample of household residents (18+ years), with standardized drug use and drug dependence assessments. Multiple logistic regression provides odds ratio estimates of relative risk. With this approach, for every 1000 cannabis-only users, an estimated 17 had become cases (1.7%). By comparison, polydrug users and cocaine-only users had much greater cumulative incidence (>10%), even with adjustment for covariates and local area matching ($P < 0.001$). Using this approach, we find exceptionally low risk for cannabis-only users and greater risk for polydrug and cocaine-only users.

Keywords

epidemiology; drug use disorders; drug dependence; drug addiction; polydrug; multiple drug use; tobacco; alcohol; conduct problems

Introduction

Public health research challenges of polydrug use and use of multiple drugs have surfaced in periodic calls and program announcements for new research issued from the directors of the United States' National Institute on Drug Abuse (NIDA) starting in the mid-1970s.[1] One rarely addressed challenge of this type involves epidemiological estimation of the risk of becoming a case of a drug use disorder when users have tried multiple subtypes of

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internationally regulated drugs, sometimes with co-occurring alcohol use or tobacco use as well.[2,3]

Making estimates of this type, epidemiologists generally have worked in a tradition that is consistent with pharmacological laboratory approaches and not always within the framework of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) from the American Psychiatric Association (APA).[4] Namely, an attempt is made to investigate experience with each drug subtype, and to assign drug-specific diagnoses (e.g., cannabis use disorder), most typically via a checklist of clinical features (CFs) and standardized questions about which drug has caused each CF. In time, this epidemiological approach might be expected to change in the direction of the DSM-5 Substance Use Disorder (SUD) terminology and SUD subtypes. Meanwhile, the terms drug use disorder and drug dependence have been retained in epidemiological field studies.

In this context, when use of multiple drugs is observed, the number of drugs used as well as antecedent polydrug combinations can be studied as predictors of occurrence of each drug-specific syndrome.[5–8] Before DSM-5, diagnoses for unspecified drug dependence and polysubstance dependence were allowable. Sometimes clinicians have used the 304.7[0–3]–304.8[0–3] diagnostic codes for complex polydrug-using patients using at least three different drugs indiscriminately (excluding caffeine or nicotine), showing no preference for any specific one, and showing a minimum of three drug-attributable CFs within a 12 months period. Nonetheless, epidemiological estimates for these diagnostic codes are rare.

Great humility is required about epidemiological evidence that requires the polydrug users themselves or clinician examiners to say which drug has caused each and every CF of the drug use syndromes whose epidemiology we seek to understand. We always have had to acknowledge that these causal attributions at the level of the individual case necessarily constrain validity owing to wide variations in understanding of clinical pharmacology and drug interactions, uncertain knowledge, or incorrect beliefs about the effects of various drug subtypes and their combinations. Validity constraints are especially narrow in large sample epidemiological field studies when drug users are asked to say which drug caused each symptom and CF, irrespective of whether the study design is retrospective, cross-sectional, or prospective.[6,9,10] Heterogeneity across or within study samples adds more uncertainty about validity, especially in the context of multicountry surveys.[11]

Attempting to confront these challenges directly, we have been trying to work out a research approach for large sample epidemiological studies on these topics, with a reach toward investigations used to identify causes of food-borne illness outbreaks, that is, when the measurements ask about symptoms or other CFs of drug use disorders as might have been experienced in a syndrome cluster, and with separate questions on which drugs have been used. This measurement approach departs from the widely used drug-specific approach for research on drug use disorders, and presumes that users of multiple drugs might be uncertain about which drug has caused each symptom or clinical feature.

In a direct adaptation of the epidemiologic research approach used in foodborne illness outbreak investigations for rapid evaluation of multiple foods that might be causal vehicles

for the outbreak, this study's approach is focused on evaluation of multiple drugs as might contribute to occurrence of drug use syndromes. In brief, investigating postluncheon or banquet outbreaks, epidemiologists assemble a list of meal attendees, formulate a syndromic illness case definition, a case ascertainment plan for coverage of pertinent CFs of the syndrome, and a list of food subtypes (including beverages). Then, all attendees are contacted for interview or questionnaire assessments, without asking which food caused which CF. Estimates of food-specific syndrome attack rates are derived from the observed retrospective data; estimates of risk differences or ratios are derived from contingency table analyses (e.g., cross-product ratios from 2 × 2 tables). If required, stratified analyses or a generalized linear model is used to estimate subgroup variation in risk (e.g., food–food combinations), and to hold constant extraneous influences on illness reporting or illness experience (e.g., male–female differences). Appendix I describes an epidemiology laboratory exercise used to teach students about foodborne outbreaks, and offers online materials with additional detail.[12]

In this contribution, we seek to demonstrate this research approach as applied to drug use disorders in a widely known nationally representative sample of 18+ year olds that included quite a few polydrug users, namely, the National Comorbidity Survey-Replication (NCS-R) sample. In the process, we estimate suspected effects of drug subtypes used singly and in combination on risk of developing a drug dependence syndrome as a form of drug use disorder, and we study subgroup variations in risk, while holding constant potential determinants. In an extension of the typical foodborne outbreak analysis, we use life table analyses to address possible length biases due to varying retrospection intervals since onset of drug use.

In this study, the drug use disorder assessments used in the NCS-R required the presence of maladaptive drug use via a gating procedure described in three prior papers, as well as syndromic clustering of at least three symptoms or CFs associated with drug dependence. In anticipation of DSM-5, the standardized assessment items included coverage of craving, but it was not possible to anticipate that DSM-5 would shift its polythetic threshold to require just two criteria to be met, as opposed to the three required under DSM-IIIR and DSM-IV. For these reasons, we argue that the resulting diagnostic assessment resembles but is not the same as any DSM-IV or DSM-5 diagnostic assessment, as might be made when an expert clinician examines an individual patient. Instead, the construct under study is a syndromic form of a drug use disorder that we term *drug dependence with maladaptive drug use* (DDwMDU). This case terminology refers back to a World Health Organization Expert Committee's advocacy for use of the term drug dependence, but adds an element of maladaptive drug use that the APA's experts have integrated with the original drug dependence construct. When multiple drugs have been used and a dependence syndrome cannot be attributed to a particular drug, the construct under study most closely resembles the international and APA categories known as unspecified drug dependence or polysubstance dependence.[13]

A final clarification involves our use of life table conventions as illustrated in our “cannabis-only” estimates, which pertain to individuals whose cannabis use started at an onset age before or at the drug use disorder onset age. Those using both cannabis and cocaine in the

same year as DDwMDU syndrome onset are counted as polydrug users with the cannabis plus cocaine combination. As in the life table approach, the experience of our cases is right-censored at the DDwMDU syndrome onset age. In this fashion, we ensured that later postdisorder drug use did not qualify as a cause of onset of the drug use syndrome under study here.

Materials and methods

Data to demonstrate our novel epidemiological approach are in public use datasets from the NCS-R,[14] with English-speaking community participants, age 18 years and older, all from the 48 coterminous U.S. states, drawn via multistage area probability sampling, recruited, and assessed using an ethics committee approved protocol in 2000–2002. A participation level of 71% yielded 9282 respondents. A public use dataset version of the NCS-R data is available online,[15] including the local area cluster and stratum required to perform this project's analyses.

The key response variable in this study, DDwMDU, is defined as the occurrence of a syndromic clustering of at least three CFs of drug dependence over a 12-month period, with at least one manifestation of maladaptive drug use, resembling but not identical with DSM-5's “Substance Use Disorder” with respect to internationally regulated drugs. Here, MDU refers to drug use that threatens life or limb (e.g., recurrent driving under the influence) or that is socially maladaptive with failure to live up to social role expectations and obligations. The *social maladaptation* concept is one introduced by research groups led by Kellam,[16] Rutter,[17] and Rolf.[18] Syndrome specifications and measurement of the DDwMDU syndrome via a “gated” Part 1 module of the UM-CIDI (Composite International Diagnostic Interview) are described in Figure 1 and Appendix II, and in other papers that provide supportive validity evidence. [19–22]

The UM-CIDI assesses DDwMDU only when there is extramedical use of one or more subtypes of the inhalants or internationally regulated drugs (hereinafter, IRD), by which is meant using the drug to get high or otherwise beyond the boundaries of approved indications, with measurement as explained in a prior article[23] and Appendix II. In the sample, among 2918 extramedical users of internationally regulated drugs (EMIRD) with complete age of onset data, 1509 had consumed just one IRD subtype before or at DDwMDU onset (e.g., 1409 “cannabis-only” users); 1409 had antecedent use of at least two IRD subtypes (Table 1). As noted in the introduction, drug-specific onset ages were used to ensure that all drug use started before or at syndrome onset age (hereinafter, IRD used extramedically before DDwMDU onset).

Primary study estimates are from weighted contingency table analyses and multiple unmatched unconditional logistic regressions, as well as conditional logistic regressions with area matching. The approach is one that holds constant other UM-CIDI covariates (e.g. conduct disorders), with measurements described in Appendix II. Unmeasured macroinfluences such as local drug availability and law enforcement variations are held constant via this area matching. Uses of analysis weights and Taylor series linearization for variance estimation are noted in the tables.

Results

Overall, the DDwMDU syndrome was observed among an estimated 69 of every 1000 IRD users (i.e., ∼7%). A similar estimate was observed for those who had used cannabis, irrespective of other drugs used. A larger estimate was seen for those who had used drugs other than cannabis (128–173 for every 1000 extramedical users, or ∼12–17%). It follows that this study's DDwMDU syndrome might well be rare when use is restricted to cannabis. As shown in Table 1, for every 1000 users of “cannabis only,” an estimated 17 had developed DDwMDU by the assessment date (1.7%). By comparison, antecedent use of all other drug subtypes was followed by excess risk of developing the drug dependence syndrome under study ($P < 0.05$), especially for users of cocaine only and for polydrug users with extramedical use of at least 2 or 3 drug subtypes (which primarily refers to cannabis in combination with other drugs).

The subgroup of cannabis-only users can be studied as a reference category, as shown in Table 2. Table 2 estimates (with $P < 0.05$) disclose excess DDwMDU risk for three EMIRD subgroups, (1) cocaine-only users; (2) users of 2 subtypes; (3) users of 3+ subtypes, across a series of conditional and unconditional regression models. In the NCS-R sample, there were too few cases for statistically precise estimation of DDwMDU risk associated with the prescription IRD only and other (NOS) IRD only subgroups. Appendix III provides more detailed versions of Table 2, including relative risk (RR) estimates from conditional models that constrain alternative suspected influential antecedents (e.g., early conduct problems).

Another set of conditional logistic regression models was used to evaluate the association between DDwMDU onset and drugs used before DDwMDU with a sequenced exclusion of each of the 10 possible IRD combinations found among individuals who had used more than two IRD. In this fashion, via exclusion, we aimed to identify IRD combinations that might be shaping likelihood of developing DDwMDU. The analyses of age- and sex-adjusted models did not show important change in the estimates for the subgroups of individuals who used IRD in two or more groups and individuals who used three or more IRD (Appendix IV). To rule out alcohol use disorders (AUDs) as a potential confounding variable, we conducted a postestimation analysis with exclusion of all for whom AUDs preceded DDwMDU. The resulting postexclusion estimates did not differ appreciably from the estimates before exclusion (Appendix V).

Discussion

In a departure from prior epidemiologic research, we did not ask users or clinician examiners which drug caused each of the reported symptoms or other CFs of their drug use syndromes. Using the alternative approach demonstrated here, which substitutes data analysis in place of respondents' causal judgments, we controlled potential confounding explicitly via regression analyses, and discovered exceptionally low DDwMDU syndrome risk for cannabis-only users, with a much greater risk for polydrug users, especially when more than two drug subtypes were used (generally, cannabis in combination with other IRD). The cocaine-only subgroup also had excess risk of the DDwMDU syndrome. RR

estimates for other syndrome predictors and correlates have been produced and are reported in our tables, but should be regarded as exploratory until replication firms up the evidence.

Studying DDwMDU occurrence using this alternative approach offers some methodological and practical advantages worth mentioning. First, drug use syndromes of this type can be assessed using questionnaire or interview items that focus on the syndrome and its CFs, in place of items that ask users to make causal judgments about specific effects of each of the drugs under study. The result includes reduced respondent burden and time, and there might be an improvement in the validity of the resulting estimates. Second, effect estimates can be derived in a fashion that constrains error (e.g., error when a user of cannabis and cocaine incorrectly attributes harmful effects to cocaine rather than to cannabis). Third, the resulting evidence might help guide future research for harm reduction, as when riskier combinations can be identified via data analyses of the type used to elicit more toxic food–food combinations in the illness outbreak context.

Limitations of note include our reliance on cross-sectional and retrospective self-report survey data, one of the more ubiquitous deficiencies in this type of epidemiological research, including almost all food-borne illness investigations conducted by public health departments. With respect to our RR estimates, common unmeasured genetic or other individual-level susceptibility traits might be affecting propensities to explore a variety of drug subtypes as well as the propensity to develop drug dependence (e.g., openness to experience as a trait). Furthermore, the NCS-R sample was not large enough to yield statistically precise RR estimates for some specific drug–drug combinations (e.g., cocaine + prescription pain relievers). Finally, the UM-CIDI “other drug” subtype is too heterogeneous to be recommended for use in new investigations.

Potential directions for future studies include application of this approach in prospective and longitudinal studies, including randomized prevention trials with samples large enough and measurements sufficiently refined to be informative about risk of specific forms of drug use disorders. The approach also might prove to be helpful in some clinical research contexts, as in evaluation of risks when cannabis and opioids are being used within medically prescribed boundaries, or in the clinical trials context when abbreviated drug use disorder assessments are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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J.C. Anthony was responsible for study conceptualization and design; C. Lopez-Quintero managed the literature searches, conducted the statistical analyses, and created the tables. Both authors contributed to writing up the evidence, and have approved the final manuscript.

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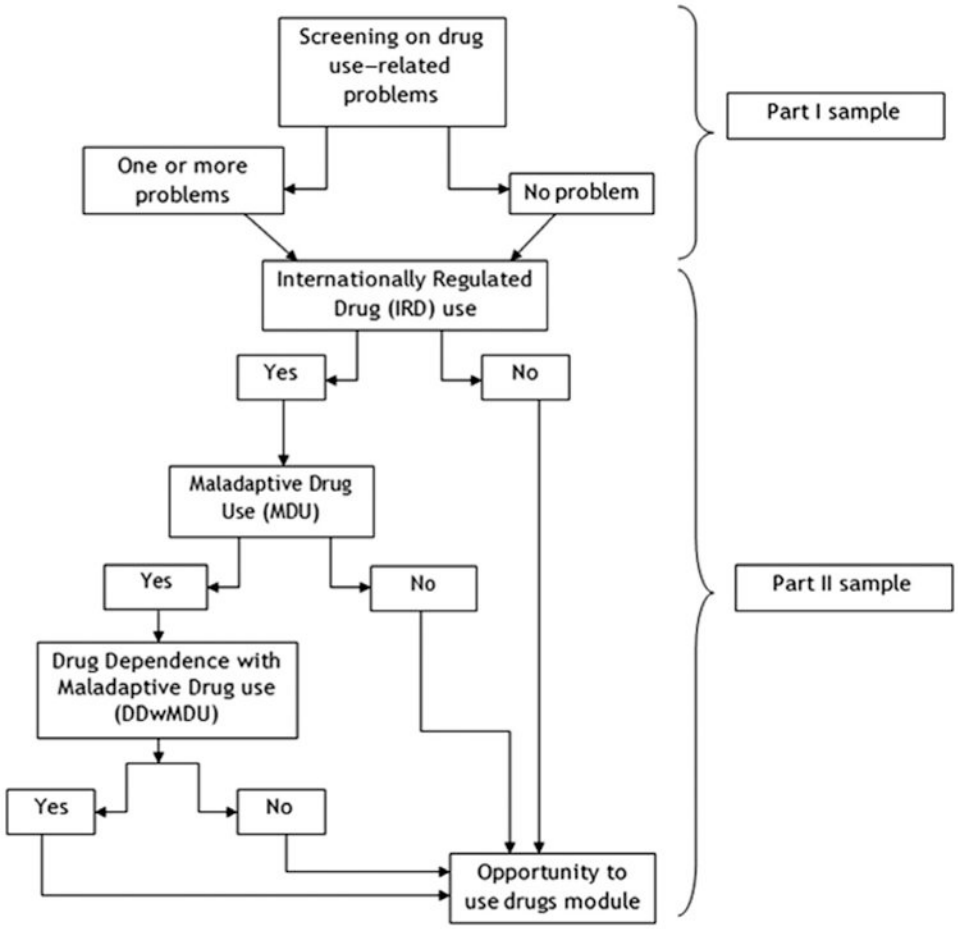

Figure 1.

Assessment of drug dependence with maladaptive drug use (DDwMDU) in the Composite International Diagnostic Interview (CIDI).

Table 1

Estimated occurrence of syndromic clustering of drug dependence with maladaptive drug use (DDwMDU) among extramedical users of internationally regulated drugs (EMIRD) in the United States; National Comorbidity Survey Replication, 2000–2002 (*n* = 2918)

	Weighted estimates for occurrence of DDwMDU		Unweighted numbers			All EMIRD users (*n* = 2918)		
							Weighted column %	
	%	SE	DDwMDU case (*n* = 247)	Non-case controls (*n* = 2671)	*P* value from chi-square test	Unweighted numbers	Column %[a]	SE
All extramedical IRD users	6.9	0.05	247	2671		2918	100.0	
Cannabis users	6.9	0.01	239	2569	0.210	2808	96.1	0.52
Cocaine users	12.8	0.01	153	888	<0.001	1041	35.0	1.09
Users of “other” IRD (not otherwise specified)	17.3	0.01	144	597	<0.001	741	23.3	1.02
EM users of prescribed IRD	15.5	1.61	132	644	<0.001	776	23.8	1.00
IRD used extramedically before DDwMDU onset[b]								
Only cannabis	1.7	0.36	33	1376		1409	50.7	1.21
Prescription IRD only	1.4	1.36	1	50		51	1.6	0.30
Only cocaine	12.3	6.71	5	23		28	1.3	0.30
Only “other” IRD (NOS)	3.3	3.32	1	20		21	0.8	0.20
Use of IRD in 2 groups	8.6	1.43	68	605		673	22.2	1.14
Use of IRD in 3+ groups	16.8	1.45	139	597	<0.001	736	23.5	1.09

[a] These column estimates are based on a denominator with nonmissing values for each covariate.

[b] There were six DDwMDU-affected EMIRD users with missing or invalid age of onset data on multiple drugs, making it impossible to confirm the sequence from onset of EMIRD use to onset of DDwMDU. Among the 673 who used IRD in 2 groups, roughly 99% of EMIRD users had used cannabis in combination with one other IRD. Among the 736 who used “IRD in 3+ groups,” 99% used cannabis in combination with two or more other IRD (e.g., cocaine + prescribed IRD).

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Table 2

Estimates of the association between occurrence of syndromic clustering of drug dependence with maladaptive drug use (DDwMDU) and drugs used before DDwMDU onset among EMIRD users in the United States. National Comorbidity Survey Replication, 2000–2002 (n = 2918)

Relative risk (RR) of occurrence of syndromic clustering of DDwMDU (all relative to DDwMDU among n = 2808 who had EM use of cannabis, Panel A, or n = 1409 who had EM use of cannabis but no other IRD use, Panel B)											
	Estimated RR from conditional logistic regression (area-matched risk sets)				**Estimated RR from conditional conditional logistic regression for discrete time data (area-matched risk sets of survival data)**				**Estimated RR from unconditional logistic regression with weights and Taylor series variance approach**			
	RR	**95% Confidence interval (CI)**		***P*-value**	**RR**	**95% CI**		***P*-value**	**RR**	**95% CI**		***P*-value**
Panel A												
Prescription IRD use[a]	2.3	1.7	3.0	<0.001	2.2	1.7	3.0	<0.001	2.6	1.7	3.9	<0.001
Cocaine use[b]	1.9	1.4	2.6	<0.001	2.0	1.5	2.7	<0.001	2.3	1.6	3.3	<0.001
"Other" IRD use (NOS)[c]	2.9	2.2	3.9	<0.001	2.7	2.0	3.6	<0.001	3.2	2.3	4.3	<0.001
Panel B												
IRD used extramedically before DDwMDU onset												
Only cannabis (ref)	1				1				1			
Prescription IRD only	1.0	0.1	7.7	0.984	0.5	0.1	4.3	0.532	0.9	0.1	7.3	0.941
Only cocaine	9.8	3.4	28.1	<0.001	3.8	0.6	24.1	0.162	7.9	1.8	34.7	0.008
Only "other" IRD (NOS)	1.9	0.3	14.7	0.540	*d*	–	–	0.987	1.9	0.3	14.1	0.524
Use of IRD in 2 groups	4.6	3.0	7.1	<0.001	5.4	3.4	8.8	<0.001	5.1	3.0	8.6	<0.001
Use of IRD in 3+ groups	8.7	5.8	12.9	<0.001	9.9	6.3	15.5	<0.001	10.8	6.3	18.6	<0.001

NOTE: All models in Panel A and Panel B include covariate adjustment for sex, age, and age squared.

[a]This model also holds constant EM use of cocaine and of drugs in the "other" subgroup.

[b]This model also holds constant EM use of prescription IRD and of drugs in the "other" subgroup.

[c]This model also holds constant EM use of prescription IRD and cocaine.

[d]Too few cases for sufficiently precise estimation of RR or 95% CI, as indicated by *P*-value.