Evidence for a hallucinogen dependence syndrome developing soon after onset of hallucinogen use during adolescence

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Abstract

This study uses latent class methods and multiple regression to shed light on hypothesized hallucinogen dependence syndromes experienced by young people who have recently initiated hallucinogen use. It explores possible variation in risk. The study sample, identified within public-use data files of the 1999 National Household Survey on Drug Abuse (NHSDA), consists of 1186 recent-onset hallucinogen users, defined as having initiated hallucinogen use within 24 months of assessment (median elapsed time since onset of use ~12 to 13 months). The recent-onset users in this sample were age 12 to 21 at the time of assessment and were between the ages of 10 and 21 at the time of their first hallucinogen use. The NHSDA included items to assess seven clinical features often associated with hallucinogen dependence, which were used in latent class modelling. Latent class analysis, in conjunction with prior theory, supports a three-class solution, with 2% of recent-onset users in a class that resembles a hallucinogen dependence syndrome, whereas 88% expressed few or no clinical features of dependence. The remaining 10% may reflect users who are at risk for dependence or in an early stage of dependence. Results from latent class regressions indicate that susceptibility to rapid transition from first hallucinogen use to onset of this hallucinogen dependence syndrome might be influenced by hallucinogenic compounds taken (for example, estimated relative risk, RR = 2.4, 95% CI = 1.6, 7.6 for users of MDMA versus users of LSD). Excess risk of rapid transition did not appear to depend upon age, sex, or race/ethnicity. Copyright © 2006 John Wiley & Sons, Ltd.

Key words: hallucinogen, dependence, epidemiology, survey

Introduction

The main aims of this research are to study the possible emergence of a hallucinogen dependence syndrome among young people who recently initiated hallucinogen use and to offer an initial characterization of population subgroups where there might be excess risk of this syndrome (excess relative to the reference subgroup for an odds ratio estimate). Hallucinogens are a category of drugs that includes a heterogeneous array of compounds, such as lysergic acid diethylamide

(LSD), mescaline, and mixed stimulant-hallucinogen drugs such as 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), as well as diverse compounds such as phencyclidine (PCP), peyote, and psilocybin (see US Substance Abuse and Mental Health Services Administration, 1999). Hereinafter, MDMA and ecstasy are used as interchangeable terms, referring to the mixed stimulant-hallucinogen that the SAMHSA research team has grouped with other 'hallucinogens' in keeping with conventions that date back at least 30 years.

Research on hallucinogen dependence has been hampered not only because of the diverse nature of the chemical compounds within the general class of 'hallucinogen' drugs but because of other salient issues, which include a scepticism about whether there is such a thing as 'hallucinogen dependence', how to assess it and possible variation in susceptibility to becoming dependent on hallucinogen drugs.

Dependence on hallucinogen drugs has been reported (for example, Jansen, 1999) but its character does not conform to the profile of clinical features that appear in the context of dependence upon opium derivatives. In hallucinogen dependence there seem to be no withdrawal features of the type seen after cessation of long-sustained heroin use, such as nausea, vomiting, and low-grade fever, as described by Kleber (1999). Noting the absence of physical withdrawal features, the American Psychiatric Association task panels for the third edition of the APA Diagnostic and Statistical Manual acknowledged hallucinogen abuse but not dependence (DSM-III). Subsequent revisions of the DSM assume existence of a hallucinogen dependence syndrome. Nevertheless, there has been little epidemiological, preclinical, or clinical research on this syndrome – notwithstanding rare exceptions such as the work of Cottler et al. (2001), who found evidence for a dependence syndrome secondary to MDMA use.

Evidence assembled from the limited number of published epidemiological estimates suggests that the vast majority of users of hallucinogens do not appear to transition to hallucinogen dependence. Early reports based on the criteria established in the 1987 revision of the DSM-III estimated that, among the 10% to 11% of the US population age 15 to 54 years old who had tried hallucinogen drugs at least once, only one in 20 (5%) had transitioned to DSM-III-R hallucinogen dependence (Anthony et al., 1994). According to some studies using DSM-IV criteria, an even lower proportion of users develop hallucinogen dependence. For example, Kendler et al. (1999) gave a 0.2% estimate of hallucinogen dependence syndrome among hallucinogen-using female twins. The recent US National Survey on Drug Use and Health (NSDUH) has produced the following pertinent estimates:

- 14%–15% of the U.S. population age 12 years and older have tried a hallucinogen drug at least once;
- 1.7% to 2% of the population have used in the year prior to assessment; and

- 0.1% of the population has a recently active syndrome of hallucinogen dependence, experiencing multiple clinical features in the year prior to assessment (US National Survey on Drug Use and Health, 2003).

These NSDUH analyses pertain to recently active cases of hallucinogen dependence ('prevalence') but not to the topic of the present investigation, which includes estimation of the rate at which new users might be developing dependence ('incidence'). As explained in our research group's prior articles on this topic, an especially valuable set of estimates about the rates at which drug users develop clinical features of drug dependence and other drug-related hazards can be derived by focusing the epidemiological analysis on the individuals who have just started to use a drug, as identified within large community samples (for example, see Chen and Anthony, 2003, 2004; Storr et al., 2004; Anthony et al., 2005; Chen et al., 2005; O'Brien and Anthony, 2005).

The aim of this research project is to draw upon the strengths of modern epidemiology and biostatistics, coupled with a sociological tradition of latent class analysis, in order to shed light on hallucinogen-related disturbances of mental life and behaviour. The latent class approach requires no assumption about the existence of a hallucinogen dependence syndrome as formulated by the APA task panel (although the task panel's expert judgement has been used in the specification of survey items about clinical features of the dependence syndrome). Latent class models may eventually help us probe more completely some epidemiological and aetiological hypotheses about rapid transitions from first drug use to first onset of drug dependence, akin to work on earlier stages of drug involvement (for example, Reboussin and Anthony, 2001). Aside from a prior investigation by Chung and Martin (2005) that studied latent classes of DSM-IV hallucinogen abuse and dependence criteria in a sample of youth who were engaged in drug treatment programmes, little research has used latent class methods to study hallucinogen use disorders. In this study, our focus was upon people who had only recently started to use a hallucinogen (within 24 months prior to the date of assessment; median elapsed time since onset of use ~12 to 13 months) and we excluded all who had started to use in prior years.

The present study draws its evidence from the National Household Survey on Drug Abuse conducted

in the calendar year (CY) 1999, which had a national sample survey large enough to yield a sizeable number of hallucinogen users and which asked about drug dependence-associated clinical features that might have emerged in early stages of use. This paper

- examines evidence for or against the existence of a discrete class of hallucinogen dependent users among young recent-onset hallucinogen users; and
- explores the associations between the onset of the hallucinogen dependence syndrome and selected characteristics of the recent-onset hallucinogen users, with specific focus upon age, sex, race-ethnicity, and history of drug use.

We focus on characteristics that remain unchanged in response to the onset or level of hallucinogen use or the start of problems and clinical features of dependence (for example, race, ethnicity and other 'exogenous' covariates). In addition, to tease apart some of the heterogeneity within the 'hallucinogen' drug class, we use a multiple-regression approach to check whether excess risk of hallucinogen dependence is associated with use of one specific hallucinogen compound versus another. In a companion paper (Stone et al., under review), we are taking the NHSDA DSM-IV diagnostic algorithms at face value, whereas here we are applying the more innovative latent class methods. We compare the two approaches in the discussion section of this article.

Methods

Study participants

Data for this research are from the public use data file from the CY1999 National Household Survey on Drug Abuse (NHSDA, now known as the National Survey on Drug Use and Health, NSDUH). Detailed information on the NHSDA multistage sampling and methodology is available (US SAMHSA 1999, 2000). CY1999 was the first year the survey sample size was large enough to permit the latent class approach and multiple regression methods applied in this new research. It was not possible to borrow information from more recent NHSDA/NSDUH surveys due to major changes in the field survey methodology, including changes in the assessment of the clinical features of hallucinogen dependence.

In brief, each year the survey team draws a nationally representative survey sample of non-

institutionalized civilians in the US, age 12 years and over. In 1999, the survey initiated a state-based sampling plan, which became logistically demanding as the number of interviews over a geographically dispersed area dramatically increased; the survey response rate was just over 60%. From among the 66 706 respondents who completed the survey, the NHSDA survey team designated a randomly selected subsample of 53 560 individuals to appear in the public use data file. This subsampling procedure represents an effort to protect the confidentiality of study participants and has been designed so that analyses of the public use dataset will yield valid survey estimates not appreciably distant from values obtained when all survey respondents are included. All participants listened to disclosure statements read aloud by field staff and were given the option to decline participation prior to survey administration, in accordance with the protocol approved by the cognizant Institutional Review Board (IRB).

Among the 53 560 respondents in the CY1999 NHSDA public use data file there were 1186 recent-onset hallucinogen users age 21 years or younger, with recent onset made operational by taking the difference of the age of the respondent when interviewed (in years) and the age of onset of hallucinogen use (in years) to gauge the recency of onset of hallucinogen use (within the past 12 months, or within an interval of 24 months before assessment). Regrettably, the NHSDA responses provide no means to convert recency of onset of hallucinogen use into a continuous variable; the age difference used to identify recent-onset users is an integer of value 0 or value 1. By exclusion of past-onset hallucinogen users the research achieves focus on recent-onset hallucinogen users and places limits upon the influence of elapsed time since initiation of use, which otherwise may provoke a distorted view of rapid transition from first drug use to development of clinical features associated with drug dependence (for example, see Anthony and Petronis, 1995). Our research group recently applied the same array of methods to the study of rapid emergence of a tobacco dependence syndrome soon after onset of tobacco smoking (Storr et al., 2004), rapid emergence of cocaine dependence after onset of cocaine use (O'Brien and Anthony, 2005), and rapid emergence of cannabis dependence after onset of cannabis use (Chen et al., 2005); here, we apply these methods to hallucinogen dependence.

Assessment

In CY1999, NHSDA standardized assessments were collected using an audio computer-assisted self-interviewing (ACASI) process to help promote privacy and to foster more complete and accurate reporting. After building rapport, interviewers instructed the participants on how to use the computer. While listening to an audio recording of each item, consenting participants used a laptop keypad to enter responses about themselves and their involvement with drugs.

One set of questions assessed the participant's involvement with hallucinogens, such as the hallucinogen compounds ever used, and age of first use. Hallucinogens mentioned explicitly in the NHSDA survey questions were LSD, PCP, peyote, mescaline, psilocybin, and the mixed stimulant-hallucinogen MDMA, or ecstasy; respondents also were allowed to name hallucinogens not on this list, which comprise our 'not otherwise specified' or NOS category of hallucinogens. Participants who had used hallucinogens in the 12 months prior to their interviews were directed to seven items assessing clinical features associated with dependence for these six hallucinogenic compounds collectively rather than specifically. The items were selected to tap DSM-type criteria:

- *Salience* of drug involvement, for example 'Did you have a period of a month or more when you spent a great deal of time getting, using, or getting over the effects of hallucinogens?'
- Difficulty with *control* of use, for example 'Have you used hallucinogens much more often or in larger amounts than you intended to?'
- Subjectively felt *tolerance*, for example 'Have you built up tolerance for hallucinogens so that the same amount had less effect than before?'
- *Narrowing* of the non-drug behavioural repertoire, for example 'Has your use of hallucinogens often kept you from working, going to school, taking care of children or engaging in recreational activities?'
- Problems with *emotions*, for example 'Has your use of hallucinogens caused you to have any emotional or psychological problems such as feeling uninterested in things, feeling depressed, feeling suspicious of people, feeling paranoid, or having strange ideas?'
- Problems with *health*, For example, 'Has your use of hallucinogens caused you to have any health problems?'
- Desire to – or difficulty in efforts to – *cut down* on use, for example 'Did you want to or try to stop or cut down on your use of hallucinogens but found you couldn't?'

Thus, recent-onset users are asked about the same seven clinical features in regard to hallucinogens as a group. The NHSDA approach does not ask questions about clinical features of dependence upon MDMA specifically, about LSD specifically, or about any other hallucinogen specifically. (This seven-item approach to assessment of the hallucinogen dependence syndrome was changed in subsequent survey years after 1999, and this change has precluded borrowing of information across multiple survey years to increase the statistical precision of our study estimates.)

Additional details and specific items for the assessment of clinical features associated with hallucinogen dependence are provided in the appendix. Readers will note that the form of these items resembles items that have been evaluated in reliability and validity studies of the NIMH Diagnostic Interview Schedule, the Composite International Diagnostic Interview (for example, see Wittchen 1994; Ustun, et al., 1997) and other related standardized field survey instruments. Here, the latent class analysis method does not rest upon reliability of scales formed by combining these items algorithmically or in terms of summed or composite indices or scales. Rather, each item's value is treated as a mixture of signal (from the underlying substantive source(s) of variation), plus noise – and the task of LCA is to extract the signal via analysis of interdependencies among items, with the noise as residual.

History of prehallucinogen extramedical drug use was assessed via a count of the number of drugs used prior to the age when the first hallucinogen was used. The drugs counted in this tally included legal drugs such as tobacco and alcoholic beverages as well as controlled drugs such as cannabis and cocaine. This term is included as a covariate because it might be pertinent to susceptibility to become drug dependent or to a predisposition to engage in illegal drug use; alternatively, past use of other drugs might influence risk of becoming dependent upon hallucinogens (for instance, via pharmacological and neurobiological mechanisms secondary to other drug exposures).

Turning to a final methodological note, we draw attention to the fact that some of the recent-onset hallucinogen users might have tried a hallucinogen once

or twice or a few times during the interval 13–24 months prior to assessment of hallucinogen dependence but not within the 12 month interval prior to assessment. If so, they were not asked the NHSDA questions about hallucinogen dependence (these were asked only when there had been hallucinogen use within the most recent 12-month interval). Nonetheless, we included these recent-onset users in all of our analyses, under the dual assumptions that if they had developed a hallucinogen dependence syndrome their hallucinogen use would have persisted into the most recent 12 months interval, and if they had not used within the most recent 12 months interval then they had not developed a hallucinogen dependence syndrome. These dual assumptions are based upon a premise that drug dependence is a condition with rather insidious onset and a generally chronic course and is not a ‘rapid-onset, rapid-offset’ phenomenon – a topic discussed by Chen and Anthony (2004), among others (see, for example, Kleber, 1999; Storr et al., 2004; O’Brien and Anthony, 2005). We will return to this issue in our discussion of the study results.

Statistical analyses

Our approach to analysis started with necessary exploratory analyses and inspection of response distributions (see the appendix). Thereafter, latent class analyses were completed. Latent class analysis (LCA) is a statistical method that can be used to explore whether discrete classes of hallucinogen dependence syndrome are tenable and to test alternative models for commonly observed patterns of responses, in an attempt to identify underlying mixtures of subgroup distributions. Individuals are assigned to underlying subgroups or classes probabilistically, based upon profiles of congruent response patterns. In the case of an LCA of recent onset hallucinogen users, a one-class model would imply that there is no discrete hallucinogen dependence class emerging within 24 months after onset of use. An important assumption of latent class analysis is that of local independence. The assumption of local independence implies that there remains no residual interdependency among indicators to be explained, once the influence of the latent class structure has been taken into account.

The *Latent Gold* software permits use of posterior mode methods to prevent boundary solutions that thwart maximum likelihood estimation in LCA models (Vermunt and Magidson, 2000). Posterior class

probabilities are empirically derived directly from the model parameters. In this research, cases have been assigned to the class in which the cases have the highest posterior probabilities. Several sets of random starting values were used to ensure that a global rather than a local posterior mode solution had been reached. Multiple fit indices were used to guide model selection, with theory and prior evidence coming into play, as described in the paper’s results and discussion section (Magidson and Vermunt, 2004).

We also checked whether the local independence assumption was violated by estimating bivariate residuals, which represent the association between individual clinical features after class membership has been taken into account. Specifically, while fitting these models, bivariate residuals were analysed, and the residual structure was incorporated into the modelling process as needed.

After class memberships were assigned, we explored associations with other covariates to assess male-female differences in susceptibility, as well as age and race-ethnicity differences. We studied age as a covariate with multiple age categories (12–14, 15–16, and so forth), and also with age expressed in ordinal or continuous form, using higher order polynomials to probe for nonlinearity in the associations of age and occurrence of hallucinogen dependence.

Regression models were estimated using STATA 7.0 (StataCorp, 2001). The models specified to include covariate terms to represent individual sub-classes of hallucinogen compounds. There were 63 recent-onset users who only reported using ‘not otherwise specified’ hallucinogens (NOS hallucinogens are those other than LSD and the five listed hallucinogens). These individuals were excluded from the regression analysis due to the broad heterogeneity of the NOS subgroup. In the regression analyses, we introduced covariate terms for five hallucinogen compounds, leaving out a term for LSD. Participants who had only used LSD were therefore the reference group, and this subgroup was large enough to serve as a useful reference category in the regression analyses (as described by Stone et al., under review). Applied to the two-class latent structure model, the (log-transformed) odds of belonging to the ‘hallucinogen dependent’ class versus the non-dependent class have been regressed upon all five hallucinogen covariate terms introduced simultaneously. The intercept estimate from the resulting model may be interpreted as the log odds (or log risk) of developing

hallucinogen dependence soon after onset of hallucinogen use, among users who just started to use LSD. In these analyses the odds ratio (OR) may be viewed as an approximated risk ratio (RR). The study of recent-onset users allows us to estimate the incidence of clinical features of dependence during the 24 months prior to assessment. With this set of five hallucinogen covariate terms in the model, the slope estimate for the MDMA covariate term may be interpreted as the difference in log odds of developing hallucinogen dependence for recent-onset MDMA users versus the log odds of developing hallucinogen dependence for those in the LSD hallucinogen subgroup, with the remaining covariate values held constant. Under standard assumptions, after exponentiation, this slope estimate conveys the excess (or reduced) risk that hallucinogen dependence has developed within 24 months after onset of MDMA use, with the LSD subgroup as the reference category. Slope estimates for the other hallucinogen covariate terms may be interpreted in an analogous fashion. A covariate term for a history of extra-medical use of non-hallucinogen drugs (tobacco, alcohol, cocaine, cannabis, etc.) was added to the model as a check on the possibility that prior drug use might signal excess risk

of becoming hallucinogen dependent soon after onset of hallucinogen use.

Results

Characteristics of recent onset hallucinogen users

Demographic characteristics of the 1186 youthful hallucinogen users in the sample are presented in Table 1. The sample of young recent-onset hallucinogen users included a very slight excess of males (52%), and was predominantly non-Hispanic white (79%). For 35% of the recent-onset users, the age of onset for the first use of hallucinogens was the same as the age at the time of assessment; 65% started hallucinogen use during the interval between the most recent birthday and the prior birthday.

Within 24 months of starting to use hallucinogens (median value for elapsed time since onset of use ~12–13 months) a small proportion of users were already experiencing several clinical features that tend to be associated with drug dependence. The most commonly endorsed clinical features in this sample of recent-onset hallucinogen users were

- emotional problems attributed to hallucinogen use (11%);

Table 1. Selected characteristics of recent-onset hallucinogen users in the study sample. Unweighted sample data from the US National Household Survey on Drug Abuse (1999)

Characteristics under study	n	Recency of onset*	
		<12 months (%)	12–23 months (%)
All persons	1186 (100%)	35%	65%
Age at assessment			
12–14	152 (13)	46	54
15–16	364 (31)	41	59
17–18	368 (31)	32	68
19–21	302 (25)	28	72
Sex			
Male	615 (52)	35	65
Female	571 (48)	36	64
Race/ethnicity			
Non-Hispanic White	937 (79)	35	65
Non-Hispanic Black	42 (4)	43	57
Hispanic	143 (12)	33	67
Other	64 (5)	34	66

*Recency of onset: '<12 months' designates the recent-onset users for whom the age of the respondent at the time of the interview was equal to the age of onset of hallucinogen use, whereas '12–23 months' designates those for whom the age of the respondent at the time of the interview was 1 year older than the age of onset of hallucinogen use.

- difficulty controlling use (7%);
- salience of use (7%); and
- subjectively felt tolerance (6%).

Less frequently experienced clinical features were

- narrowing of non-hallucinogen related activities (4%);
- attempts or desires to cut down on hallucinogen use (3%); and
- health problems attributed to hallucinogen use (2%).

These results are shown in the appendix.

Classes of hallucinogen 'dependence'

Alternative latent class models were fitted to the data, with a summary of the fit statistics shown in Table 2. The profile of fit statistics, with special attention given to the BIC, indicated that the two-class model might be modestly superior. However, prior theory and evidence regarding the occurrence of hallucinogen dependence suggested that a three-class model also might deserve attention. The analysis of bivariate residuals disclosed the assumption of local independence might be questionable with respect to (a) reduced activities due to hallucinogen use and (b) health problems associated with hallucinogen use. For this reason, we modified the models to allow for this bivariate residual association.

As shown in Figure 1, the more parsimonious two-class model yields one class consisting of 10% of recent-onset users, and the other class consisting of 90% of recent-onset users. Within the less prevalent class,

recent-onset users have a 50% to 70% probability of experiencing salience of hallucinogen use, difficulty cutting down on hallucinogen use, subjectively felt tolerance, and emotional problems due to hallucinogen use. The mean number of clinical features experienced by the less prevalent class was 3.1; three or more clinical features generally is taken to indicate dependence in the recent DSM-based diagnostic approach. However, just under half of the individuals in this class (46% of individuals in the less prevalent class) had experienced fewer than three clinical features (data not provided in table). Within the more prevalent class (90% of users), the estimated probability of experiencing clinical features of hallucinogen dependence is close to zero, and the mean number of clinical features was 0.1. All of the 59 recent-onset hallucinogen users who met DSM-IV criteria for hallucinogen dependence were sorted into the lower prevalence latent class; among the 1127 who did not meet the DSM-IV criteria, 96% were sorted into the higher prevalence latent class.

Figure 2 displays the prevalence of clinical features experienced by each class of recent-onset users under the three-class model. Of special note is the smallest of the three classes, which included 2% of the recent-onset users. Members of this class experienced a mean of 5.2 clinical features associated with hallucinogen dependence (data not shown in a table). For five of the seven clinical features, the estimated probability of the experience was greater than 80%, given membership in this class.

Within the intermediate class, which included 10% of the recent onset users, there was a mean of 2.5 clinical features, with median and mode values of two

Table 2. Model fit indices for latent classes of hallucinogen dependence: data from the US National Household Survey on Drug Abuse (1999)

		L ²	BIC	df	p-value	Classification error	AWE
Model 1	One class	731.5	-117.9	120	<0.001	0.00	3637.8
Model 2	Two class	124.1	-668.6	112	0.2	0.02	3314.8
Model 3	Three class	83.6	-652.6	104	0.93	0.04	3530.5
Model 4	Two class allowing for a local dependency*	111.9	-673.8	111	0.46	0.02	3328.0
Model 5	Three class allowing for a local dependency	70.9	-658.2	103	0.99	0.04	3535.5

*Note: There was a bivariate residual association, as described in the text. Model respecification to accommodate this bivariate residual yielded an improved model fit.

Figure 1. Two-class model. Estimated occurrence of each clinical feature of hallucinogen dependence, responses by latent class of hallucinogen dependence syndrome. Data from the US National Household Survey on Drug Abuse (1999).

Figure 2. Three-class model. Estimated occurrence of each clinical feature of hallucinogen dependence, responses by latent class of hallucinogen dependence syndrome. Data from the US National Household Survey on Drug Abuse (1999).

clinical features. In this group, however, 44% of the participants experienced three or more clinical features. Classes in this model appear to exist along a severity dimension, with one important qualitative difference: virtually all members of the third class had experienced difficulty cutting down on hallucinogen use, which is one of the cardinal features of the generic drug dependence syndrome.

Class membership and individual characteristics

Multiple logistic regression analyses were used to derive odds ratio estimates of the relative risk of developing clinical features of hallucinogen dependence soon after the onset of use (as inferred from class assignments). The response variable for these regression analyses is framed in relation to class membership; for the three-class model, we turned to the multinomial logit model.

Table 3 presents the estimates from these regressions, with the first set of columns pertaining to a multiple logistic regression analysis in which the log odds of being in the second class has been regressed on covariates listed in the rows and with the second set of columns pertaining to multinomial logistic regression results for the three class model. The first row of estimates shows estimated proportions of recent-onset users assigned to each class of the two-class model and to each class of the three-class model. The next set of rows pertains to recency of onset of hallucinogen use; these estimates disclose that risk of hallucinogen dependence does not vary appreciably in relation to recency of onset of hallucinogen use. That is, users who started within 0 to 12 months of the date of assessment were just as likely to be in the higher class(es), as compared to users who started hallucinogen use 12 to 23 months prior to assessment (Table 3, rows 1 to 3). In the next set of rows in Table 3, we see that the class membership assignments did not vary across the three sociodemographic characteristics under study; all observed risk ratio estimates are close to the null value of 1.0, and the 95% confidence intervals entrap the null value (Table 3).

Class membership and drug-use history

Even though there was no observable subgroup variation to this point in the analysis, there is evidence of variation in risk in relation to the type of hallucinogen drug compound used. As shown in Table 4, under the two-class model, with regression-based covariate adjustments, there is a tangible excess risk of being assigned to class two in association with recent-onset use of MDMA, all else in the model held constant. The strength of this association is conveyed via a relative risk estimate of 2.2 (95% confidence interval, CI = 1.5, 3.4; $p < 0.01$). Excess risk (relative to the LSD users) also was observed in association with recent-onset use of PCP, and of psilocybin (Table 4, first columns).

Results from the three-class model also are shown in Table 4. For example, the last set of columns in Table

Table 3. Estimated occurrence of hallucinogen dependence for the total sample of recent onset hallucinogen users (row 1) and in relation to selected sociodemographic characteristics, with odds ratio estimates and 95% confidence intervals (CI). Data from the National Household Survey on Drug Abuse, United States, 1999

	n	Two-class model relaxing condition of local independence		Three-class model relaxing condition of local independence			
		Estimated prevalence*		Estimated prevalence*		Estimated odds ratio (95% CI)	Estimated odds ratio (95% CI)
		Class 1	Class 2	Class 1	Class 2		
		Class 2 v. 1		Class 3		Class 2 v. 1	Class 2 v. 1
All Persons	1186	0.90 (0.88, 0.92)	0.10 (0.08, 0.12)	...	0.88 (0.84, 0.91)	0.10 (0.07, 0.13)	0.02 (0.01, 0.02)
Class proportion 95% CI							...
Recency of hallucinogen onset							
Within past 12 months	419	0.89	0.11	1.0	0.89	0.09	0.02
12–23 months	767	0.91	0.09	1.2 (0.8–1.8)	0.91	0.08	0.01
Age category**							
12–14 years	152	0.88	0.12	1.0	0.87	0.10	0.03
15–16 years	364	0.90	0.10	1.2 (0.7–2.2)	0.87	0.11	0.02
17–18 years	368	0.92	0.08	1.6 (0.7–3.4)	0.90	0.09	0.01
19–21 years	302	0.90	0.10	1.2 (0.7–2.3)	0.88	0.11	0.01
Sex							
Female	571	0.90	0.10	1.0	0.88	0.10	0.02
Male	615	0.90	0.10	1.0 (0.7–1.5)	0.88	0.11	0.01
Race/ethnicity							
Non-Hispanic White	937	0.90	0.10	1.0	0.88	0.10	0.02
Non-Hispanic Black	42	0.89	0.11	0.9 (0.3–2.4)	0.86	0.11	0.03
Hispanic	143	0.92	0.08	1.3 (0.7–2.4)	0.90	0.09	0.01
Other	64	0.88	0.12	0.8 (0.4–1.8)	0.87	0.10	0.03

Note: Covariates were not allowed to influence the latent class measurement structure.

*Proportion of recent-onset hallucinogen users assigned to class (rows total to 100%).

**Similar null results were obtained with age as an ordinal-continuous variable, and with polynomial terms to probe for non-linearity.

Table 4. Estimated relative risk (RR) of class membership in association with specific hallucinogen compounds used, with statistical adjustment for covariates, including history of prior non-hallucinogen drug use: Data from the National Household Survey on Drug Abuse, United States, 1999^{a,b,c}

	Estimated excess risk of assignment to class two under the 2-class model ^c			Estimated excess risk of assignment to class two under the 3-class model ^c			Estimated excess risk of assignment to class three under the 3-class model ^c		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
LSD/NOS ^d	1.0			1.0			1.0		
Ecstasy	2.2	(1.5, 3.4)	<0.01	2.0	(1.3, 3.1)	<0.01	6.3	(1.7, 23.9)	<0.01
PCP	1.8	(1.0, 3.3)	0.04	1.9	(1.0, 3.4)	0.03	2.4	(0.6, 10.3)	0.23
Peyote	0.8	(0.3, 2.0)	0.65	0.6	(0.2, 1.8)	0.40	3.8	(0.8, 17.5)	0.09
Mescaline	1.9	(0.9, 4.3)	0.01	1.5	(0.6, 3.6)	0.36	7.2	(1.8, 29.7)	<0.01
Psilocybin	1.9	(1.2, 2.9)	<0.01	2.0	(1.3, 3.2)	<0.01	1.5	(0.4, 4.9)	0.52

^aAll models estimated the odds-ratio of association (OR), which may be interpreted as an RR estimate, adjusting for covariates of age, sex, race/ethnicity, number of drugs used by age 11, and all listed hallucinogen covariates, and with LSD use as a reference subgroup.

^bCovariates were not allowed to influence the class structure.

^cOther drugs used include tobacco, alcohol, marijuana, cocaine, crack, heroin, inhalants, pain relievers, tranquilizers, stimulants, methamphetamine, and sedatives.

^dThe five covariate terms for hallucinogen compounds were binary indicators for recent-onset use of the five compounds listed below. By process of exclusion, the residual category of recent-onset hallucinogen users consists of the recent-onset users of LSD or the not otherwise specified (NOS) hallucinogen category.

4 show evidence of tangible excess risk of being assigned to class three of the three-class model in association with recent-onset use of MDMA (estimated relative risk, RR = 6.3; 95% CI = 1.7, 23.9; $p < 0.01$), and with recent-onset use of mescaline (RR = 7.2; 95% CI = 1.8, 29.7; $p = <0.01$), relative to the experience of the reference group of LSD users. By conventional standards for testing departures from the null, there was no excess risk associated with recent-onset use of PCP, peyote, or psilocybin ($p > 0.05$).

Though not reported in a table, there were some interesting variations in risk in association with prior history of using drugs other than hallucinogens. In particular, when a recent-onset hallucinogen user had a history of prior use of cocaine, there was an increased likelihood of being sorted into class two (RR = 2.0, $p = 0.03$) and also into class three (RR = 2.8, $p = 0.03$). A history of extramedical use of a non-cocaine psychostimulant drug (for example, amphetamines) was associated with excess risk of belonging to the second class (RR = 2.5, $p < 0.001$) but not the third class ($p > 0.05$). In contrast, when a recent-onset hallucinogen user had a history of drinking alcoholic beverages, there was a lower risk of assignment to class three (RR = 0.1,

$p < 0.001$), but there was no alcoholic beverage association with assignment to class two ($p > 0.05$).

Discussion

The findings of this study provide intriguing new evidence about the possible emergence of a hallucinogen dependence syndrome shortly after initiation of hallucinogen use and about population subgroups that might be at excess risk of this dependence syndrome. To the extent that our three-class latent structure model has illuminated a 'hallucinogen dependence syndrome,' it is instructive that 2% of the recent-onset users were assigned to this class. This 2% estimate for the incidence of a hallucinogen dependence syndrome identified by latent class methods for young adult and adolescent-onset hallucinogen users is not appreciably different from the estimated 2% value obtained in our parallel research, which has applied the DSM-IV diagnostic approach to all recent-onset users identified in the 2000/1 NHSDA community samples. These included all adult and adolescent hallucinogen users regardless of age at onset (Stone et al., under review). Nevertheless, despite the similarity of these risk estimates, the recent-onset users assigned by the two

diagnostic methods using the NHSDA 1999 data are not the same; the latent class analysis sorted some individuals meeting the DSM-based classification of hallucinogen dependence into an intermediate class of recent-onset users.

In addition, within the present investigation, the recency of onset of hallucinogen use did not signal excess risk of developing this syndrome, nor did age at onset of hallucinogen use, sex, or race-ethnicity of the recent-onset hallucinogen users. Some reviewers knowledgeable about hazards of early-onset alcohol and cannabis use might be surprised to find no excess risk of hallucinogen dependence among the earliest-onset hallucinogen users (those under age 17). In this instance, the absence of excess risk might be traced to greater difficulty in securing supplies of hallucinogens during the early adolescent years, whereas alcohol and cannabis are more readily available to early adolescents than are hallucinogens in most US communities. Excess risk was observed in association with recent-onset use of one hallucinogen compound (MDMA) versus the experience of the LSD-only reference subgroup.

Before detailed discussion of these main findings, the latent class modelling results should be evaluated in relation to two alternative approaches to selection of the most appropriate model. One approach is based strictly upon consideration of model fit statistics, and the other approach incorporates prior evidence and theory.

Any observer wedded to model fit statistics by themselves might favour a two-class model with accommodations for bivariate residuals, when the perspective is narrowed to the model fit indices alone. However, many experts on the epidemiology of hallucinogen dependence might argue against the two-class model, after an examination of that model's class-specific profile of reported clinical features and after consideration of the estimated proportion of recent-onset users assigned to this class. The selection of a two-class model in this research is consistent with prior work by Chung and Martin (2005), which used latent class analysis to study hallucinogen abuse and dependence within a population of treatment going youth. While fit indices favoured a two-class model in their research, the authors believed that a three-class model more closely matched current DSM-IV diagnostic criteria. In addition, existing estimates of hallucinogen dependence among hallucinogen users are in a range substantially lower than the 10% of users who were sorted into the second class under

the two-class model (values were well under 2% to 5%) – even though prior studies have summarized a lifetime of hallucinogen experience, up to and including the date of the assessment (see Anthony et al., 1994; Kendler et al., 1999). It is important to note that the present study consists solely of young individuals, aged 21 years or younger; prior studies included older participants as well. According to a constructed variable developed by SAMHSA and the NHSDA survey team as an operational case definition for hallucinogen dependence by DSM rules, approximately 5% of these recent-onset hallucinogen users, age 21 years or younger, had developed dependence on hallucinogens. Our own secondary analysis of the entire 1999 NHSDA public use data file ($n = 53\,560$) revealed that 76% of individuals who qualified for the SAMHSA operational case definition of hallucinogen dependence were age 21 or younger. The overrepresentation of young people among these cases may help account for the fact that a slightly greater occurrence of dependence was detected in our sample, despite its focus on recent-onset users. We note that onset of illegal drug use prior to age 21 often has been associated with an excess risk of developing drug problems (see Robins and Przybeck, 1985; Anthony and Petronis, 1995).

In the light of these considerations, we believe that the three-class model deserves close attention; its model-fit indices were not as favourable but were not appreciably different from values for the two-class model. In addition, the three class model evoked a subgroup consisting of 2% of the recent-onset hallucinogen users for whom there is a rather high probability of experiencing clinical features within 24 months after onset of hallucinogen use (>80% for five of seven clinical features). Recent-onset users sorted into this class reported a substantially greater mean number of clinical features than did users sorted into the second class of the two-class model (5.2 clinical features versus 3.1 clinical features, respectively). Moreover, 100% of the participants belonging to the third class qualified as hallucinogen dependence cases according to the SAMHSA-operationalized DSM case definition (in the two-class model only 54% met the operationalized criteria; data not in table). Moreover, the 2% estimate is congruent with prior estimates from other studies. Using NHSDA data from 2000 and 2001, our own parallel investigation which used the SAMHSA-operationalized DSM case definition of hallucinogen dependence, estimated that 2% to 3% of recent-onset

users, regardless of age, met dependence criteria (Stone et al., under review). In addition, based on lifetime history reports from the US National Comorbidity Survey (NCS) sample, Anthony et al. (1994) reported that one in 20 hallucinogen users (5%) had developed DSM-III-R hallucinogen dependence. As compared to the 5% value from the NCS study of the lifetime history of hallucinogen users, the present study's estimate of 10% under the two-class model for recent-onset users is quite inconsistent with the prior evidence; the present study's estimate of 2% under the three-class model for recent-onset users is more consistent with the 5% (lifetime) summary value.

These considerations lead us to speculate that the second class of the two-class model and the second class of the three-class model might represent recent-onset hallucinogen users who are in a precursor or prodromal state prior to onset of a hallucinogen dependence syndrome – which might have considerable overlap with the DSM concepts of non-dependent hallucinogen abuse. Until a longitudinal study of the recent-onset hallucinogen users with this class assignment can be completed, it will be impossible to resolve whether this class should be interpreted as a prodromal or precursor state with respect to hallucinogen dependence, or as a distinctive class of individuals who will not develop the full syndrome of hallucinogen dependence, but who might qualify as cases of DSM-IV non-dependent hallucinogen abuse.

Several limitations should be noted. There are, of course, limitations inherent in the CY1999 NHSDA methodology, its community-residence sampling frame and levels of respondent non-participation, as well as its survey methods in general (US Substance Abuse and Mental Health Services Administration, 1999). In particular, the survey design involves looking backwards to identify recent-onset users and to characterize them in relation to just-experienced and just-reported clinical features of hallucinogen dependence. These cross-sectional snapshots of hallucinogen users, taken within the first 24 months after onset of hallucinogen use, do not have the power to resolve important open questions about the stability and generalization of the classes. Future research might yield a different set of findings with respect to a more extensive array of clinical features of hallucinogen dependence assessed in other samples and as other hallucinogenic compounds are distributed. Cottler et al. (2001) reported that an MDMA dependence syndrome could be reliably

assessed when DSM-IV criteria are evaluated via a self-report, but there has been no clinical reappraisal study to evaluate whether the CY1999 survey interview can yield the same answers as might be obtained via cross-examination, probing, and other techniques of standardized clinical assessment of drug dependence syndromes (for example, see Anthony et al., 1985).

We also should return to an issue mentioned in our methods section. Namely, the current investigation requires an assumption that hallucinogen dependence develops insidiously, over time and has a relatively chronic course with persistence over a span of weeks and months as opposed to an acute onset and short-term course of the type seen in 'rapid onset, rapid offset' conditions (for example, the 'common cold'). If there is a form of hallucinogen dependence that has the 'rapid onset, rapid offset' form, then this investigation's research approach might be underestimating the risk of hallucinogen dependence within 24 months after onset of hallucinogen use. In future research, the possibility of underestimation can be probed by asking recent-onset hallucinogen users about clinical features experienced during the 24 months after onset of use. In addition, measurement error in the assessment of elapsed time since first hallucinogen use (underestimation, or overestimation) might have affected the study's point estimates and 95% confidence intervals.

A concern might also be expressed about the many different types of pharmacological compounds combined within the single hallucinogen drug category of the NHSDA convention. When hallucinogens first became popular as street drugs, compounds that produced hallucinogenic effects were grouped together into a single group (Haddad, 1976). However, some investigators now question whether PCP and MDMA actually should be grouped with other hallucinogens (for example, Carroll, 1990); DSM-IV treats PCP as separate from hallucinogens and some investigators advocate separation of MDMA and ecstasy-type mixed stimulant-hallucinogens from the general hallucinogen category (for example, see Topp et al., 1997; Schuster et al., 1998). Moreover, it has been suggested that a new revision of the DSM should include a separate category for the dependence syndrome associated with use of MDMA (for example, see Nichols, 1986; Liester et al., 1992; Cottler et al., 2001). Based upon this study's estimates under the three-class model, as well as the two-class model, and with the defining clinical features held constant across drug types, there is some evidence that

MDMA use is associated with excess risk of experiencing clinical features associated with hallucinogen dependence, relative to the experience of LSD users.

In this context, we must again emphasize that this methodological approach is one that holds constant the standardized criteria and survey questions used to assess hallucinogen dependence and users are not asked to name a specific compound that has caused each clinical feature. Rather, when they have used one or more hallucinogen drug, they are asked whether 'any' hallucinogen use has persisted despite emotional problems due to the drug use, or whether 'any' hallucinogen use has been followed by the experience of subjectively felt tolerance. For this reason, in our two-class model estimates of excess risk associated with psilocybin or the other individual drug compounds (PCP, MDMA), we cannot assert that the psilocybin users have developed 'psilocybin dependence'. Rather, the psilocybin users have been found to be more likely to develop a hallucinogen dependence syndrome of a non-specific character (not linked to a specific compound except via the regression-based estimate of relative risk).

The study findings also include results from exploratory analyses regarding which clinical features are most frequently reported among young recent onset hallucinogen users, as well as an assessment of variation in the risk of dependence based on subgroup characteristics. The most common clinical features emerging soon after onset of use were continued use of hallucinogens despite emotional problems due to the drugs, salience of use, difficulty controlling use, and subjectively felt tolerance. (The appendix provides additional details that may be of value to interested readers.)

Within the collection of prior studies on hallucinogen dependence, most did not have the benefit of a nationally representative sample of recent-onset hallucinogen users. Nor is there prior research on how risk of becoming hallucinogen dependent might relate to the use of specific hallucinogenic compounds. The present study has attempted to shed light on these issues and may set the stage for future and more probing research on the possible hallucinogen dependence syndrome and on the topic of which young people become hallucinogen dependent soon after onset of hallucinogen use.

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Appendix

Estimated occurrence (in percentages) of clinical features of hallucinogen dependence syndromes among 1186 recent-onset hallucinogen users, by sociodemographic characteristics. Data from the National Household Survey on Drug Abuse, US, 1999.

1. **Salience** of drug involvement: 'Did you have a period of a month or more when you spent a great deal of time getting, using, or getting over the effects of hallucinogens?'
2. **Control** (intake control difficulties): 'Have you used hallucinogens much more often or in larger amounts than you intended to?'
3. **Tolerance** (subjectively felt): 'Have you built up tolerance for hallucinogens so that the same amount had less effect than before?'
4. **Narrowing** of non-drug behavioural repertoire: 'Has your use of hallucinogens often kept you from working, going to school, taking care of children or engaging in recreational activities?'
5. Problems with **emotion**: 'Has your use of hallucinogens caused you to have any emotional or psychological problems such as feeling uninterested in things, feeling depressed feeling suspicious of people, feeling paranoid, or having strange ideas?'
6. Problems with **health**: 'Has your use of hallucinogens caused you to have any health problems?'
7. **Cut down** desires or failed attempts: 'Did you want to or try to stop or cut down on your use of hallucinogens but found you couldn't?'

	Salience (%)	Control (%)	Tolerance (%)	Narrowing (%)	Emotion (%)	Health (%)	Cut down (%)
All persons (n = 1186)	7.1	7.3	5.8	3.8	11.0	2.1	3.0
Age at assessment							
12–14 (n = 152)	9.2	6.6	7.2	3.9	11.2	2.0	5.9
15–16 (n = 364)	6.9	8.0	6.6	4.4	12.6	1.9	3.0
17–18 (n = 368)	6.8	5.7	4.9	3.8	9.8	2.4	3.0
19–21 (n = 302)	6.6	8.6	5.3	3.0	10.3	2.0	1.7
Sex							
Male (n = 615)	6.8	7.6	5.5	4.1	10.4	1.8	3.3
Female (n = 571)	7.4	6.8	6.1	3.5	11.6	2.5	2.8
Race/ethnicity							
Non-Hispanic white (n = 937)	7.3	7.4	6.4	3.5	11.3	1.7	2.9
Non-Hispanic black (n = 42)	7.1	7.1	7.1	7.1	14.3	0.0	9.5
Hispanic (n = 143)	6.3	7.0	2.1	3.5	7.0	4.2	2.1
Other (n = 64)	6.3	6.3	4.7	6.3	12.5	4.7	3.1

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