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Who Is Becoming Hallucinogen Dependent Soon After Hallucinogen Use Starts?1

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Abstract

This study, based upon epidemiological survey data from the United States (U.S.) National Household Surveys on Drug Abuse (NHSDA) from 2000–2001, presents new estimates for the risk of developing a hallucinogen dependence syndrome within 24 months after first use of any hallucinogen (median elapsed time ~ 12 months). Subgroup variations in risk of becoming hallucinogen dependent also are explored. Estimates are derived from the NHSDA representative samples of non-institutionalized U.S. residents ages 12 and older ($n = 114,241$). A total of 2,035 respondents had used hallucinogens for the first time within 24 months prior to assessment. An estimated 2%–3% of these recent-onset hallucinogen users had become dependent on hallucinogens, according to the NHSDA DSM-IV computerized diagnostic algorithm. Controlling for sociodemographic and other drug use covariates, very early first use of hallucinogens (age 10–11 years) is associated with increased risk of hallucinogen dependence ($p < 0.01$). Excess risk of developing hallucinogen dependence was found in association with recent-onset use of mescaline; excess risk also was found for recent onset users of ecstasy and of PCP. This study's evidence is consistent with prior evidence on a tangible but quite infrequent dependence syndrome soon after the start of hallucinogen use; it offers leads that can be confirmed or disconfirmed in future investigations.

Keywords

hallucinogen; dependence; logistic regression; epidemiology; recent-onset

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Introduction

In this study of United States (U.S.) community residents, the primary aims are to draw upon the diagnostic criteria presented in the American Psychiatric Association's Fourth Edition of its Diagnostic and Statistical Manual (DSM-IV) in order to estimate the risk of developing a hallucinogen dependence syndrome within 24 months after first use of any hallucinogen, and to explore subgroup variations in the risk of becoming hallucinogen dependent soon after the onset of hallucinogen use (American Psychiatric Association, 1994). As background to research on the incidence of hallucinogen dependence, or risk of *becoming* a case of hallucinogen dependence, it may be beneficial first to provide an orientation to recent estimates regarding the prevalence of *being* a recently active hallucinogen user in the U.S., based upon the National Household Survey on Drug Abuse (NHSDA, recently renamed the National Survey on Drug Use and Health). During the calendar year (CY) 2001, an estimated 4.3 to 4.9 million individuals age 12 or older used a hallucinogen on at least one occasion. This interval surrounds a survey point estimate of about 4.6 million, or 2.0% of the population (U.S. SAMSHA, 2002a, 2002b). During CY2001, about 1.5 million of these individuals had used a hallucinogen for the *first* time that year, and there is some evidence consistent with a downward trend in prevalence of hallucinogen use (U.S. SAMSHA, 2003).

Public health concern about hallucinogen use surfaced during the middle 20th century in the U.S., but no longer is limited to this country. Concerns have been expressed in the United Kingdom, where 13% of university or college-attending students were found to have tried the mixed stimulant-hallucinogen methylenedioxymethamphetamine (MDMA, hereinafter ecstasy); corresponding estimates from the U.S. and Spain are 12.7% and 1.6%, respectively (Webb et al., 1996; Martinez et al., 1999; Johnston et al., 2003). Soellner (2005) has presented epidemiological evidence that ecstasy is now ranks second (behind marijuana) as the most preferred illegal drug among young people in Germany. In Australia, ecstasy is the third most commonly used illegal drug (Degenhardt et al., 2005). A focus upon adolescents and college-age young people in these studies seems pertinent because the effective 'interval of risk' for starting to use hallucinogens and for becoming hallucinogen dependent seems to be quite narrow: very few people experience these onsets during childhood and very few have onsets after age 25 years (e.g., see Chilcoat & Schutz, 1996). Peak values are seen between age 16 and 24 years.

Notwithstanding prior epidemiological evidence of the type just cited, there are gaps in knowledge about hallucinogen dependence, which is of particular importance given recent dynamic changes in the popularity of hallucinogenic compounds (e.g., see U.S. SAMSHA, 2002a, 2002b). Indeed, while some recent studies have offered support for the existence of a hallucinogen dependence syndrome, open questions remain regarding (1) whether a syndrome of hallucinogen dependence actually exists (e.g., see Stone et al., in press), (2) whether the APA DSM-IV criteria represent a correct specification for the hallucinogen dependence syndrome, and (3) who is becoming dependent on hallucinogens, especially among those who have only recently started to use these drugs.

Prominent contributions to research on hallucinogen dependence include work by Cottler and colleagues (2001), who suggested that there might be a differentiable ecstasy dependence syndrome. Chung and Martin (2005) used latent class analysis to identify cases of hallucinogen problem syndromes among treatment-attending youths; Anthony and colleagues (1994) found that roughly one in 20 hallucinogen users had developed DSM-III-R hallucinogen dependence. Work by O'Brien and Anthony (2005) has aided the present study in its presentation of a DSM-IV oriented methodologic approach similar to the one used in this research; they studied who becomes dependent on cocaine shortly after the onset of cocaine use. Chen, O'Brien, and Anthony (2005) have done the same for recent-onset cannabis users. Here, we apply the same DSM-IV oriented methodological approach to the study of hallucinogen dependence among recent-onset hallucinogen users.

In this research, we start with the hope of replicating estimates from a recently completed parallel study, based upon the CY1999 NHSDA survey, in which we used a latent class approach to study hallucinogen dependence, assessed via standardized survey items designed to tap the DSM-IV criteria, but without reference to the DSM-IV criteria specifications. In that original report on latent classes of a hallucinogen dependence syndrome, we found evidence in support of two best-fitting models. One of these two models was two-class model in which nearly 10% of recent-onset users qualified for membership in a DSM-IV-like hallucinogen dependence class, and the other was a three-class model in which approximately 2% of the recent-onset users qualified for membership in a hallucinogen dependence class. The model fit indices were ambiguous without clear favor for one model over the other, although some of the fit indices leaned slightly in favor of the two-class model. Nonetheless, the idea that 10% of recent-onset hallucinogen users become dependent upon these compounds soon after onset of first use is novel and unprecedented in the literature or in theory. If this value is correct, it exceeds the estimated risk of becoming cocaine dependent soon after onset of cocaine use (e.g., see O'Brien & Anthony, 2005). In addition, there was ancillary evidence favoring the three-class model. Namely, under the three-class model, all individuals in the extreme class (2% of recent-onset users) experienced a mean of 5.2 clinical features of hallucinogen dependence, and all members of this class experienced three or more of these clinical features. In contrast, under the two-class model, some of the individuals in the 'dependence' class had experienced only two clinical features of dependence, and the mean number of clinical features for members of this class was only 3.1. For this reason, 43% of the 'cases' under the two-class model would not have met DSM-IV criteria; as such, there is reason to favor the three-class model (Stone et al., in press).

As for covariates associated with occurrence of the dependence syndrome among recent-onset users of the 'hallucinogen' compounds, under both the 2 and 3-class models, we found no excess risk of belonging to the 'hallucinogen dependence' class based on sex, race, or age at onset of hallucinogen use, but we did find sub-group variation in relation to the specific compounds that had been used. With a reference group specified to include users of LSD only or hallucinogen compounds 'not otherwise specified' (LSD/NOS; e.g., 'shrooms'), under the three class model, we found excess risk of belonging to the DSM-IV-like hallucinogen dependence class in association with recent onset use of ecstasy (Stone et al., in press).

Here, the study aims are similar, but there are several key differences between the present study and our latent class study, starting with the absence of a latent class exploration in this study. Instead, in order to avoid the ad hoc character of a latent class analysis, we have taken advantage of the diagnostic convention represented by the DSM-IV hallucinogen dependence constructs and made operational by the NHSDA research team for this important nationally representative sample of US community residents who just started to use hallucinogens. In addition, the present study makes use of more recently released data (from 2000–2001), which may be important, given the dynamic status of hallucinogen trends in the U.S.

1.1 Specific Aims

The specific aims of this study include (a) seeking support for or against the possibility that a DSM-IV-like hallucinogen dependence syndrome develops for a substantial fraction of recent-onset users of the NHSDA 'hallucinogen' compound group within 24 months of starting use of these compounds, and (b) searching for possible subgroup variations in risk of developing this syndrome soon after onset of use. With respect to the first aim, we note that a recent decline in the prevalence of hallucinogen use within the U.S. might be interpreted as an indication that a very small proportion of hallucinogen users are becoming dependent, to the extent that prevalence is determined by the combination of incidence (risk of starting use) and average duration of use, which should be extended by development of a hallucinogen dependence process. With respect to the second aim, we note that our latent structure approach carried a suggestion of excess risk of hallucinogen dependence among recent onset users of ecstasy, relative to users in our LSD/NOS reference category. Here, using more recent data, we probe for additional evidence that ecstasy users might be at excess risk of developing a dependence syndrome within 24 months after onset of use. Some observers may question the validity of the DSM-IV hallucinogen dependence construct, the NHSDA computerized diagnostic assessment, or the NHSDA inclusion of PCP and ecstasy in the hallucinogen category. We have addressed these issues via a combination of methodologic approaches and discussion.

2. Methods

2.1 Participants

Data for this study are from the public use data files of the National Household Survey on Drug Abuse (NHSDA) from two calendar years; CY2000 and CY2001 (n= 114,241). This cross-sectional survey has been designed to include a nationally representative sample of non-institutionalized U.S. citizens, aged 12 years and older. Multi-stage sampling procedures have been used to obtain a sample of dwelling units (e.g., households, homeless shelters) and individuals within each dwelling. Whereas the NHSDA oversamples youths, this over-sampling is counterbalanced in the analysis steps via inverse sampling probability weights. Study participants were given the opportunity to decline participation, and provided consent in accord with an Institutional Review Board approved protocol. Approximately 75% of eligible individuals sampled during CY2000 and CY2001 participated in the study (U.S. SAMHSA, 2002a).

2.2. Assessment

2.2.1. Key Response Variables and Covariates—The key response variable in this study is hallucinogen dependence among recent-onset hallucinogen users. As assessed for the NHSDA, the ‘hallucinogens’ category encompassed LSD, peyote, mescaline, and psilocybin as specific compounds. The NHSDA team also placed the mixed stimulant-hallucinogen ecstasy and the dissociative anesthetic phencyclidine (PCP) into this ‘hallucinogens’ category, together with ‘other hallucinogens,’ which may be regarded as a residual sub-category for more rarely encountered or non-specific compounds (e.g., baby Hawaiian woodrose seeds, ‘shrooms’). The covariates of central interest here are age, sex, race/ethnicity, level of education, family income, size of metropolitan statistical area (MSA), and number of drugs used prior to first hallucinogen use.

2.2.2. Hallucinogen dependence—Hallucinogen dependence was ascertained via 11 questions included in the NHSDA interviews; these items tap clinical criteria listed for hallucinogen dependence in the DSM-IV. The NHSDA public use data files included a recoded hallucinogen dependence variable that was derived from a SAMHSA-specified computerized diagnostic algorithm. This algorithm identified hallucinogen users who met at least three of the seven DSM-IV clinical hallucinogen dependence criteria (U.S. SAMSHA, 2002a, 2002b, 2003). In our analyses, respondents who did not meet these criteria for hallucinogen dependence were coded with a ‘0’ value; those meeting criteria were coded with a value of ‘1’. (Readers may wish to consult Stone et al., in press, and this article’s appendix materials for more details on the assessment of hallucinogen dependence. The NHSDA questions and assessment protocols are readily available within internet documents such as <http://webapp.icpsr.umich.edu/cocoon/SAMHDA-STUDY/03580.xml>, last accessed 8 March 2006.)

2.2.3. Recent-onset hallucinogen use—Recent-onset hallucinogen users can be identified via a NHSDA-derived variable that designates individuals who had started using one or more of these drugs within 24 months of the date of assessment. The label ‘recently active, past-onset’ was assigned to active users (i.e., had used in the past 12 months), who do not qualify as recent-onset users. The guiding conceptual model is one in which we might expect to see hallucinogen dependence develop among a small proportion of recent-onset users, but with subgroup variation in risk, as explained below and in our prior papers in this series (e.g., see O’Brien and Anthony, 2005; Chen et al., 2005; Stone et al., In Press).

2.2.4. Drugs used prior to use of the NHSDA ‘hallucinogen’ compounds—We assessed the number of drugs used before initiation of these ‘hallucinogen’ compounds in order to control for a possible susceptibility to become hallucinogen dependent that may occur as a result of prior exposures to drugs other than hallucinogens. To create this crude index, for each of 10 other drug categories assessed in the NHSDA (i.e., tobacco, alcohol, cocaine/crack, heroin, cannabis, inhalants, pain relievers, anxiolytics, psychostimulants other than cocaine, and sedative-hypnotics), a value of ‘1’ is given when a hallucinogen user reported having ever used that drug and the age of first use was prior to the age of onset of hallucinogen use. Based upon the value obtained from these 10 drug categories, “number of

drugs used prior to using hallucinogens” was then derived by adding the values, with a range from zero to 10.

2.3 Data Analyses

In the present study, both unweighted and weighted estimates are presented when providing information for the study sample as a whole. For the estimates referring specifically to recent-onset users, or recently-active past-onset users, only weighted information is provided. Appendix tables that include the unweighted estimates can be found by accessing the online version of this paper at <http://dx.doi.org> by entering doi:xxxxxxx. Weighted estimates take probability of selection into account, and also have been adjusted to incorporate post-stratification for non-response under assumptions that the non-respondents are similar to respondents.

In the initial analysis steps, the task was to characterize the distribution of hallucinogen experience within the total population, with a contrast of recently active past-onset users versus recent-onset hallucinogen users. In subsequent analyses, the task was to estimate the risk of developing hallucinogen dependence among recent-onset hallucinogen users. STATA 7.0 survey commands were used in combination with logistic regression to regress the logit-transformed odds of becoming hallucinogen dependent on the covariates of interest. Our final exploratory analyses involved repeating the above analyses but adding covariate terms for the specific hallucinogens being used, leaving out “users of LSD and/or the other hallucinogen compounds not specified by the above-listed names.” This omitted subgroup serves as a reference against which to gauge the hallucinogen dependence risk experience for users of the other named compounds. The logic of this approach is one that we previously used to estimate risk of becoming cocaine dependent soon after onset of cocaine use, with due attention to the possibility that crack-smoking might enhance risk of dependence. As such, we elaborated that regression analysis with one dummy-coded (0/1) term for individuals who had used crack-cocaine as well as cocaine hydrochloride powder, as well as a separate term for users whose experience included only crack-cocaine use. The subgroup of powder-only users (i.e., no crack-smoking) was left as a reference (e.g., see Chen and Anthony, 2004; O’Brien & Anthony, 2005). In the present context, there were six named hallucinogen drug compounds under study, plus a residual category for other miscellaneous hallucinogens. We specified users of LSD and/or these residual compounds (‘NOS,’ not otherwise specified) as the (omitted covariate) reference subgroup, and we simultaneously introduced dummy-coded (0/1) covariate terms for each of the other specifically named hallucinogen compounds. The resulting regression slopes for these dummy-coded covariates allow us to estimate risk of becoming hallucinogen dependent for users of each specifically named hallucinogen versus the reference group who tried LSD/NOS hallucinogens only, holding constant the use of all other named hallucinogenic drugs, and also adjusting for all other sociodemographic characteristics. In this manner, we have used multiple regression methods to estimate the relative risk of becoming hallucinogen dependent for users of each of the named compounds under study, with the experience of the LSD/NOS hallucinogen users taken as a reference comparison.

Given the study design and focus on occurrence of a hallucinogen dependence syndrome among recent-onset hallucinogen users (a relatively rare outcome), the resulting odds ratios (OR) may be interpreted as relative risk (RR) estimates when the covariates of interest are exogenous with respect to the development of hallucinogen use or dependence (i.e., not likely to be influenced by use or dependence). Even when the covariates are endogenous with respect to hallucinogen use or dependence, these odds ratios can be interpreted as a simple gauge of the strength of association between the covariates and the odds of observing hallucinogen dependence soon after onset of hallucinogen use. We present and interpret the width of the 95% confidence intervals and p-values to convey statistical uncertainty of the study evidence, with a Taylor linearization approach to derive variances for complex sample survey data. Readers with a frequentist orientation may wish to pay more attention when p-values are below 0.05 and less attention when p-values are 0.05 or greater.

An important technical note is that all of the designated ‘recent-onset’ hallucinogen users are individuals who have started to use this type of compound within 24 months of the date of assessment, as determined by a comparison of the timing of hallucinogen onset to the timing of the assessment. However, the theoretical range for values of elapsed time between onset of use and the date of assessment can be as long as 24 months or as short as one month (or less). Hence, all of the ‘recent-onset’ users have started ‘within 24 months’ of the date of assessment of hallucinogen dependence, but the median elapsed time since onset of use will be less than 24 months. Values for the exact date of the assessment are not included in the public use datasets in order to help protect the confidentiality of the NHSDA participants. Nonetheless, based upon the available data, we can gauge that the median elapsed time is roughly 12–13 months. A more detailed overview of this technical detail has been provided by O’Brien & Anthony (2005), Chen, O’Brien, & Anthony (2005), and Stone et al. (In Press).

3. Results

Tables 1 and 2 offer a description of the study sample, with special attention paid to active hallucinogen users who have started hallucinogen use within the 24 months prior to assessment, and separately, active users whose first use of hallucinogens occurred 24 months or more prior to assessment (“recently active, past-onset users”). Table 1 highlights sociodemographic characteristics; Table 2 focuses on drug use characteristics of the users. In these tables, unweighted proportions (UP) and weighted proportions (WP) are provided for the ‘all persons’ column, and weighted proportions (WP) only are provided for the ‘recently active, past-onset users’ and the ‘recent-onset users of hallucinogens’.

A total of 2,035 respondents, 1.8% of the total sample of 114,241 individuals, were found to have tried hallucinogens for the first time within 24 months of interview assessment (median elapsed time ~ 12–13 months). In the sample, 2.4% (n = 2,716) were currently active users who had started hallucinogen use 24 months or more prior to survey assessment.

3.1 Recent-onset and persistent hallucinogen use descriptive statistics

The distinction between the risk of becoming a hallucinogen user versus the prevalence of being a persistent hallucinogen user can be seen in a comparison of the “All Persons”

column proportions to the corresponding proportions in the “Recently Active Past-Onset Users” columns and with the “Recent-Onset Users” columns of Tables 1 and 2. The “All Persons” proportions are, in a sense, the “expected” values for the population against which we can compare the “observed” values for hallucinogen users. For example, in the contrast of weighted proportions we see that the male-female ratio in the total survey population is 48.1% to 51.9%. In the “Recently Active Past-Onset Users” column, we see the male-female ratio is 65.5% to 34.5%, an observed excess of males relative to the expected population estimate of the male-female ratio. However, in the “Recent-Onset Users” column, we see no more than a slight male excess: 53.2% vs. 46.8%, not appreciably different from the expected values. Here, being male is not associated with becoming a recent-onset hallucinogen user, but is associated with being a recently-active past-onset user.

As compared to the past-onset hallucinogen users, the recent-onset users were slightly younger, as can be seen by comparing the weighted population estimates, row by row. For example, looking at weighted values (WP), an estimated 23% of the recent-onset hallucinogen users were 16–17 years old at the time of survey assessment, as compared to roughly 10% of the recently active, past-onset users.

Similar row by row comparisons reveal that members of the study population who designate themselves as non-Hispanic Whites were somewhat over-represented among the recent-onset hallucinogen users, and even more over-represented among recently-active past-onset users, as compared to the ‘All Persons’ proportion. Despite public health concern about hallucinogen use among college-attending young people, college seniors and graduates were under-represented among recent-onset hallucinogen users as compared to the total population, and those without a high school diploma were over-represented. No remarkable differences were evident for social status differences as gauged via a measure of annual family income. Similarly, with respect to size of the metropolitan statistical area (MSA) of residence, there were no remarkable differences in the contrast of recent-onset hallucinogen users against the total study population, or against recently active, past-onset users.

Based on weighted estimates in Table 2, approximately 2.0% of the recent-onset hallucinogen users in the study population were found to have become hallucinogen dependent since onset of hallucinogen use within 24 months prior to the survey assessment (median elapsed time ~ 12–13 months). An estimated 5% of the recently active, past-onset users qualified as active cases of hallucinogen dependence; the corresponding value is 0.1% for the total population, which includes ‘never-users’ in the denominator. Most of the recently-active past-onset cases of hallucinogen dependence in this country had started their hallucinogen use at some time in the 20th century and do not qualify as recent-onset hallucinogen users in the 21st century. As discussed elsewhere (e.g., see O’Brien and Anthony, 2005), the underlying general epidemiological process is one that leads to an accumulation of drug dependent cases among the recently active past-onset users in the study population, consistent with the idea that dependence helps sustain persistence of drug use. For readers interested in the specific clinical features of dependence endorsed by recent-onset users of hallucinogens, an appendix table can be found by accessing the online version of this paper at <http://dx.doi.org> by entering doi:xxxxxxx.

Examination of Table 2, row-by-row, reveals the greater accumulated hallucinogen experience of the past-onset users. For example, an estimated 1%–2% of the recent-onset hallucinogen users had used hallucinogens (any form) on at least 101 days during the 12 months prior to assessment, as compared to almost 6% of the recently active past-onset hallucinogen users. However, 40% of the recent-onset hallucinogen users had consumed hallucinogens on only 1–2 days in the past 12 months, as compared to 29% of the recently active, past-onset users.

Looking across the array of hallucinogenic compounds, it is possible to see that with increased duration of hallucinogen use there developed more variety in the compounds used. For example, roughly 3% of recent-onset users had tried mescaline. By comparison, an estimated 21% of recently active, past-onset users had tried this specific type of hallucinogen drug. Similarly, recent-onset users were more likely to have used only one type of compound listed in the NHSDA hallucinogen group, as compared to the recently active, past onset users (65% vs. 20%).

3.2 Risk and relative risk estimates

The main relative risk estimates from this study are presented in Tables 3 through 5; unweighted risk and relative risk estimates are available in the appendixes. Crude estimates (without covariate adjustment) are provided in Table 3, while Table 4 provides estimates that are statistically adjusted for all other listed covariates. Table 5 provides both crude and covariate-adjusted estimates for the compound-specific variables (unweighted and weighted).

As shown in Table 3 (statistically unadjusted), among recent-onset users, there was no more than very modest subgroup variation in hallucinogen dependence risk among recent-onset users in relation to sex (male vs. female), educational level, family income, or population density. However, the age at which first hallucinogen use occurred and self-designated race/ethnicity were associated with becoming dependent on hallucinogens within the first 24 months after the onset of use.

According to the weighted but covariate-unadjusted estimates, recent-onset users who began to use hallucinogens at ages 10 or 11 years were an estimated 24 times more likely to have become dependent on hallucinogens soon after onset, as compared to recent-onset users who began to use when they were 18 to 20 years old (estimated weighted and unadjusted relative risk, $wuRR=24.1$; 95% confidence interval, $CI=3.5, 168.0$; $p=0.001$; table 3). Whereas the cell counts for this analysis are small, Fisher's exact methods show evidence of departure from the null ($p=0.013$). The corresponding unweighted estimate was not appreciably different ($uuRR=16.4$; 95% $CI=2.8, 95.3$; $p=0.002$; data shown in appendix table 3). As shown in Table 4, this association remained very strong even when all other listed covariates were held constant via regression modeling (i.e., sex, race/ethnicity, family income, and number of drugs used prior to first hallucinogen use), as reflected in the very large weighted and covariate-adjusted relative risk estimate ($waRR=33.3$; 95% $CI=1.9, 471.0$; $p=0.015$).

A total of 46 recent-onset hallucinogen users never had engaged in extra-medical drug use in years prior to their age of onset of hallucinogen use; none had developed DSM-IV

hallucinogen dependence. Otherwise, number of prior drugs was not associated with dependence risk (Table 3, bottom rows).

3.2.1. Race-Ethnicity—Self-designated Hispanic recent-onset hallucinogen users were somewhat less likely to become dependent as compared to non-Hispanic White recent-onset hallucinogen users (wuRR= 0.2; 95% CI= 0.04, 0.9; $p= 0.037$); please note that out of 200 Hispanic users, only two of them were found to be incident cases of hallucinogen dependence (i.e., 1%), when the expectation based upon all users is 2.8%. Covariate adjustment widened the confidence interval and produced a p -value of 0.055, but none of the covariates qualified as confounding variables with respect to this association, in that the point estimate was identical before and after covariate adjustment (wuRR=0.2=waRR). Under these circumstances, adjustment for these covariates is unnecessary, and the unadjusted estimate is to be preferred on the basis of its greater statistical precision. Readers interested in the ‘Other’ race-ethnicity category may appreciate the apparent excess risk of hallucinogen dependence for this subgroup of the U.S. population relative to non-Hispanic Whites, but we note that these RR estimates are not statistically robust as gauged in relation to conventional p -value standards. Future research with larger samples can clarify this situation, with more detailed and refined race-ethnicity categories within the ‘Other’ subgroup. (Ordinarily, when a subgroup shows excess risk with $RR>2.0$, the association is regarded as being modest-moderate in size and as having public health significance.)

3.2.2. Social status—To examine the association between social status and hallucinogen dependence we analyzed data from the survey measure of family income. Both crude and adjusted analyses revealed minimal income-related variation in risk of becoming hallucinogen dependent soon after onset of use. An alternate proxy for social status is level of education. In a subsidiary analysis, we restricted the sample to individuals who were 18 years and older (old enough to have completed high school), and added education level to the adjusted model. After controlling for sex, age, race/ethnicity, family income, and the number of drugs used prior to the first use of hallucinogens, little variation in the risk of dependence was seen in relation to the level of education achieved.

3.2.3. Specific compounds—In Table 5, we present crude and covariate-adjusted estimates for the use of each specific compound listed separately, in reference to individuals who have used LSD and/or one of the not otherwise specified (NOS) hallucinogens but have not used any of the other compounds under study. An estimate of excess risk of rapid transition to dependence associated with using multiple compounds also is provided. According to the estimates, both crude and covariate-adjusted, and with the LSD/NOS subgroup of users as a reference category, mescaline use is associated with moderately strong excess risk of becoming hallucinogen dependent soon after onset of hallucinogen use (waRR=6.8; 95% CI= 2.4, 19.7; $p<0.001$), as is the use of psilocybin. Psilocybin use presents an interesting case in that the crude RR estimate and the covariate-adjusted RR estimate both have the same value of 2.1. That is, covariate adjustment made no difference in that estimate, and accordingly the crude RR estimate is superior by virtue of its greater statistical precision. As such, the study supports excess risk of hallucinogen dependence in association with recent-onset use of psilocybin (wuRR=waRR=2.1; $p=0.04$). Excess risk

(relative to the experience of the recent-onset LSD/NOS users) also was seen for the mixed stimulant-hallucinogen ecstasy (waRR=6.2; 95% CI=2.1, 18.2; p=0.001) and for the dissociative anesthetic PCP (waRR=4.4; 95% CI=1.8, 10.5; p=0.001).

In a separate regression analysis, we studied the extent to which risk of becoming hallucinogen dependent might depend upon the number of compounds used. The resulting estimates indicate that recent onset users who try a greater number of NHSDA defined 'hallucinogens' are more likely to have developed hallucinogen dependence as compared to recent-onset users who have used only one such compound. Of course, the number of compounds used might be endogenous with respect to dependence. That is, as the dependence process unfolds, the user might seek out and sample from a more extended array of hallucinogen drugs.

Because the NHSDA "hallucinogen" drug category is very heterogeneous, we conducted a post-hoc analysis from which we excluded all users of PCP only, all users of ecstasy only, and all users who had used just PCP and ecstasy only. According to this analysis, the study estimates continue to indicate excess risk for users of mescaline (waRR= 22.4; 95% CI= 16.0, 31.5; p=0.001) and for users of psilocybin (waRR= 1.6; 95% CI= 1.04, 2.5; p=0.03), relative to those using LSD/NOS hallucinogens (data not shown in a table).

4. Discussion

The main findings of this study may be summarized succinctly. First, it appears that approximately 2% to 3% of recent-onset hallucinogen users develop a hallucinogen dependence syndrome within 24 months after onset of use (median elapsed time since onset of hallucinogen use ~ 12–13 months), not appreciably different from the risk estimates previously obtained when a latent class approach was used in place of the NHSDA research team's DSM-IV-based approach (Stone et al., in press). As such, from a population perspective, whether the DSM-IV approach is taken or an alternative latent class approach is taken, the occurrence of hallucinogen dependence among recent-onset hallucinogen users is tangible but infrequent. Second, there is no evidence of a gender gap regarding the risk of hallucinogen dependence among the recent-onset users. Among the recently-active past onset users, there was a noticeably larger proportion of men, but this was not true among the recent-onset users. Third, Hispanics may be less likely to develop hallucinogen dependence soon after the start of hallucinogen use, when compared to non-Hispanic Whites. Hallucinogen use among Hispanics and among members of the 'Other' race-ethnicity subgroup deserves more detailed scrutiny in future studies with greater statistical precision and power to detect relatively modest relative risk estimates. Fourth, the study does not lend support to the idea of subgroup variation in the risk of rapid transition from first hallucinogen use to dependence in relation to family income, the population density of the area in which the hallucinogen user lives, or history of other extra-medical drug use. However, risk of hallucinogen dependence seems to be very low if the hallucinogen is the first drug used. Fifth, individuals who begin using hallucinogens in early adolescence (i.e., prior to age 12–13) may be at a substantially greater risk of transitioning rapidly to dependence than those who commence hallucinogen use at a later age. (Even with Fisher's exact methods used to address the small numbers of early-onset users in this sample, this

association achieves a robust p-value of 0.0132). Based upon the small number of users in the very young age group (10–11 years old at onset of use), until replicated in larger samples, this age-related variation in risk of becoming hallucinogen dependent must be regarded as a matter of speculation. Elsewhere (i.e., in other age groups), the risk of becoming hallucinogen dependent is quite modest during the first 1–2 years after onset of use. Finally, risk of hallucinogen dependence varied across type of compound under study, with moderate-strong RR estimates of considerable statistical robustness for recent onset users of mescaline ($p < 0.001$), recent-onset users of ecstasy ($p = 0.001$), and users of PCP ($p = 0.001$), and with a weaker but still noteworthy RR estimate in association with recent-onset use of psilocybin ($RR = 2.1$; $p = 0.04$).

Several of the more important study limitations merit attention before detailed discussion of these findings. As is always the case, results of this type deserve replication, confirmation or disconfirmation, and fortunately it is possible to seek replication in future national surveys now being conducted. With respect to the study design, the NHSDA is a cross-sectional survey, and is not prospective. However, with a focus upon recent-onset hallucinogen users, we have attempted to simulate relative risk estimates that might be obtained through a prospective design. To the extent that an insidious hallucinogen dependence process might yield selective attrition from a prospective study sample, then the cross-sectionally-derived estimates may actually be superior to prospectively-derived estimates, as explained by Chen and Anthony (2004).

With respect to the sampling approach, roughly 25% of individuals eligible to participate in the NHSDA declined to take part in the study. The 75% interview completion value denotes respectable general population sample survey participation in recent years, but it is possible that study participants differed from the individuals who declined to participate.

With respect to assessment of the key response variables, the study gained strength because the NHSDA team applied the same set of hallucinogen dependence diagnostic criteria (DSM-IV) to all compounds in the NHSDA ‘hallucinogen’ category and because the assessment protocol was the same for all these compounds. This approach is essential if we are to make interpretable comparisons about the risk of hallucinogen dependence, as it might vary across different types of compounds (e.g., see Anthony et al., 2005). Nonetheless, some readers might be concerned that the NHSDA measure of hallucinogen dependence was not compound-specific. As such, except for users who have tried one and only one of the hallucinogen compounds, it is not possible to assert which hallucinogen has caused the dependence. It was for this reason that we turned to a multiple regression approach in our investigation of compound-specific risk of hallucinogen dependence. While the lack of compound-specificity might be regarded as a limitation in this study, it is not clear that users of multiple hallucinogens can accurately state which hallucinogen has caused which clinical feature of hallucinogen dependence. For someone concurrently using ecstasy and LSD, it might be the LSD that gives rise to the report of tolerance, but ecstasy that gives rise to the report of spending more time seeking and using the drug, and the user might not be able to differentiate these two causal processes. Future research may benefit from an analysis of the clinical features associated with each compound separately, with a check on the hypothesis advanced by Cottler and colleagues (2001) — namely, that dependence upon ecstasy is a

distinctive syndrome that requires its own set of criteria and measurement. In addition, some observers might argue with the National Household Survey's inclusion of phencyclidine (PCP) within the 'hallucinogen' category, as well as the inclusion of ecstasy. This concern motivated our post hoc analysis, which produced essentially congruent findings with respect to the hallucinogens mescaline and psilocybin, relative to LSD/NOS compounds.

Notwithstanding limitations such as the ones just mentioned, the present study provides new estimates on the risk of becoming dependent on hallucinogens shortly after the onset of hallucinogen use. Due to the relatively small pool of prior empirical studies regarding the epidemiology of hallucinogen dependence, evidence from the present study may be useful — at least as a lead to future research on this under-studied topic.

The results from this study suggest that individuals who begin to use hallucinogens early in adolescence may require extra attention because of an especially rapid transition to dependence. Future research is warranted to see if this intriguing association holds elsewhere — that is, with larger samples, in other times and places. Finally, the evidence from this study may provide a new starting point for understanding the epidemiology of hallucinogen use and dependence in the 21st century, with a focus on recent-onset users and the problem of making a rapid transition from first use to a clinically recognizable syndrome of hallucinogen dependence. In future research that builds from findings such as these, it may be possible to learn more about the process through which some specific hallucinogenic compounds are more or less likely to elicit clinical features of dependence, and to explore the possible interactions between specific compounds and sociodemographic characteristics that may impinge upon the risk of becoming hallucinogen dependent soon after onset of hallucinogen use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected sociodemographic characteristics of all persons, recently active past-onset hallucinogen users, and the subset of recent-onset hallucinogen users. Data from U.S. 2000–2001 National Household Survey on Drug Abuse.

	All Persons		Recently Active Past-Onset Users of Hallucinogens*		Recent-Onset Users of Hallucinogens**		
	n	%uwt***	%wt	n	%wt	n	%wt
All Persons	114241	100.0	100.0	2716	100.0	2035	100.0
Sex							
Male	54753	47.9	48.1	1684	65.5	1004	53.2
Female	59488	52.1	51.9	1032	34.5	1031	46.8
Age at interview (in years)							
12 to 13	12417	10.9	3.4	40	0.9	78	2.7
14 to 15	12655	11.1	3.6	196	4.6	325	13.2
16 to 17	11787	10.3	3.4	424	9.8	585	23.0
18 to 20	13964	12.2	5.4	899	29.9	662	36.2
21 to 25	21560	18.9	7.7	946	30.8	338	18.5
26 to 34	14835	13.0	14.6	164	15.7	42	5.3
35 and older	27023	23.7	61.9	47	8.3	5	1.0
Race / Ethnicity							
Nonhispanic White	79927	70.0	72.8	2218	83.5	1597	77.6
Nonhispanic Black/African American	13449	11.8	11.3	105	4.0	100	5.8
Hispanic	14168	12.4	10.8	215	7.8	200	10.2
Other	6697	5.9	5.1	178	4.7	138	6.4
Education							
College Senior or Graduate	16073	14.1	22.4	255	15.7	104	7.6
Some College	21432	18.8	22.0	678	26.9	375	22.1
High School Graduate	27211	23.8	29.6	729	27.6	395	21.6
Less than High School Graduate	49525	43.4	25.9	1054	29.8	1161	48.6
Family Income							
0 to \$19,999	25799	22.6	20.0	796	26.4	531	27.2
\$20,000 to \$49,000	45873	40.2	39.1	1061	40.1	772	37.0

	All Persons		Recently Active Past-Onset Users of Hallucinogens *		Recent-Onset Users of Hallucinogens **	
	n	%uwt ***	%wt	n	%wt	%wt
\$50,000 to \$74,999	20546	18.0	18.7	393	14.9	15.7
\$75,000 +	22023	19.3	22.2	466	18.6	20.1
Population density						
MSA of 1 million +	41880	36.7	43.9	990	46.4	43.9
MSA < 1 million	41684	36.5	33.5	1137	36.3	36.7
Segment not in MSA	30677	26.9	22.6	589	17.3	19.4

* Recently active use in the past 12 months but with onset 2+ years before survey assessment date.

** Within 24 months of the survey assessment date.

*** "uwt" indicates unweighted estimates; "wt" indicates weighted data with Taylor series linearization for variance estimation.

Note: values may not sum to 100% due to rounding error.

Table 2

Selected drug use characteristics of all persons, recently active past-onset hallucinogen users, and the subset of recent-onset hallucinogen users. Data from U.S. 2000–2001 National Household Survey on Drug Abuse.

	All Persons			Recently Active Past-Onset Users of Hallucinogens *			Recent Onset Users of Hallucinogens **		
	n	%uwt	***	%wt	n	%wt	%wt	n	%wt
All Persons	114241	100.0		100.0	2716	100.0		2035	100.0
Occurrence of DSM-IV Hallucinogen Dependence Syndrome									
Yes, 3+ Clinical Features	216	0.2		0.1	160	5.1		56	2.0
No	114025	99.8		99.9	2556	94.9		1979	98.0
Occasions of hallucinogen use (all forms) in past 12 months.									
1 to 2 days	1575	1.4		0.6	725	29.3		850	40.6
3 to 11 days	1354	1.2		0.6	877	31.8		477	24.0
12 to 100 days	1228	1.1		0.5	931	33.2		297	15.8
101 or more days	225	0.2		0.1	183	5.7		42	1.9
Never/not in past year/dk/ref	109859	96.2		98.2	0	0.0		369	17.8
LSD use in lifetime									
Yes	10432	9.1		8.9	2090	76.0		869	41.6
No	4576	4.1		3.4	620	23.8		1166	58.4
Never/dk/ref	99233	86.9		87.7	5	0.2		0	—
PCP use in lifetime									
Yes	2403	2.1		2.6	527	18.2		148	6.2
No	12610	11.0		9.6	2180	81.5		1884	93.7
Never/dk/ref	99228	86.9		87.7	9	0.3		3	0.1
Ecstasy use in lifetime									
Yes	5721	5.0		3.2	1962	75.1		1198	63.1
No	9266	8.1		9.1	749	24.7		837	36.9
Never/dk/ref	99254	86.9		87.7	5	0.2		0	—
Mescaline use in lifetime									
Yes	2679	2.4		3.5	529	20.9		65	2.9
No	12283	10.8		8.7	2178	78.8		1967	97.0

	All Persons			Recently Active Past-Onset Users of Hallucinogens *			Recent Onset Users of Hallucinogens **		
	n	%uwt ***	%wt	n	%wt		n	%wt	
Never/dk/ref	99297	86.9	87.7	9	0.3		3	0.1	
Peyote use in lifetime									
Yes	1774	1.6	2.3	349	13.1		62	2.9	
No	13195	11.6	10.0	2361	86.7		1969	97.0	
Never/dk/ref	99272	86.9	87.7	6	0.2		4	0.2	
Psilocybin use in lifetime									
Yes	7956	7.0	6.6	1847	70.5		718	33.1	
No	6963	6.1	5.7	860	29.3		1314	66.8	
Never/dk/ref	99322	86.9	87.7	9	0.2		3	0.1	
Number of hallucinogenic compounds used									
0	99461	87.1	87.8	—	—		—	—	
1	6198	5.4	4.8	556	20.1		1307	65.0	
2	3880	3.4	3.0	742	25.4		455	21.6	
3	2557	2.2	2.1	738	28.7		199	10.1	
4	1305	1.1	1.3	399	15.3		53	2.5	
5	632	0.6	0.8	185	6.4		12	0.5	
6 or more	208	0.2	0.2	96	4.1		9	0.3	
Number of drugs used prior to starting hallucinogens ****									
0	100193	87.7	88.4	147	4.5		46	1.9	
1	1284	1.1	1.0	220	7.2		130	6.3	
2	2574	2.3	2.2	438	16.8		284	13.5	
3	10190	8.9	8.4	1911	51.6		1575	78.2	

* Recently active use in the past 12 months but with onset 2+ years before survey assessment date.

** Within 24 months of the survey assessment date.

*** "uwt" = unweighted estimates; "wt" = weighted data with Taylor series linearization for variance estimation.

**** Included alcohol, tobacco, cocaine/crack, hallucinogen, inhalants, heroin, pain relievers, anxiolytic tranquilizers, stimulants other than cocaine, and sedative-hypnotics.

Table 3

Relative risk estimates for becoming hallucinogen dependent among recent-onset hallucinogen users, without statistical adjustments. Data from U.S. 2000–2001 National Household Survey on Drug Abuse.

	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases	%	Weighted RR estimates		
				RR*	95% CI	p value
All Persons	2035	56	2.8%	–	–	–
Sex						
Male (ref)	1004	24	2.4%	1.0	–	–
Female	1031	32	3.1%	1.3	0.7–2.4	0.493
Age of hallucinogen onset						
10 to 11	6	2	33.3%	24.1	3.5–168	0.001
12 to 13	133	8	6.0%	1.5	0.5–4.8	0.484
14 to 15	442	10	2.3%	0.8	0.3–1.8	0.535
16 to 17	559	14	2.5%	0.5	0.2–1.5	0.224
18 to 20 (ref)	608	18	3.0%	1.0	–	–
21 to 25	242	3	1.2%	0.3	0.1,1.5	0.146
26 and older	45	1	2.2%	0.6	0.1–5.0	0.661
Education						
College Senior or Graduate	104	0	0.0%	–	–	–
Some College	375	12	3.2%	1.5	0.7–3.2	0.334
High School Graduate	395	11	2.8%	1.3	0.6–2.8	0.584
Less than High School Grad (ref)	1161	33	2.8%	1.0	–	–
Race / ethnicity						
Nonhispanic White (ref)	1597	42	2.6%	1.0	–	–
Nonhispanic Black	100	3	3.0%	1.5	0.4–5.7	0.58
Hispanic	200	2	1.0%	0.2	0.04–0.9	0.037
Other	138	9	6.5%	2.4	0.9–6.1	0.072
Family income						
0 to \$19,999	531	14	2.6%	1.5	0.7–3.4	0.289

	Weighted RR estimates			
	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases	Estimated Risk of Becoming Dependent	
			RR*	95% CI p value
\$20,000 to 49,000 (ref)	772	18	2.3%	1.0 – –
\$50,000 – \$74,999	329	12	3.6%	1.9 0.7–5.0 0.212
\$75,000 +	403	12	3.0%	1.7 0.7–4.1 0.271
Population density				
MSA of 1 million +	743	19	2.6%	0.7 0.3–1.4 0.296
MSA < 1 million (ref)	793	23	2.9%	1.0 – –
Segment not in MSA	499	14	2.8%	0.6 0.3–1.5 0.307
Number of drugs used prior to starting hallucinogens				
None	46	0	0.0%	– – –
1	130	5	3.8%	1.0 0.3–3.1 0.963
2	284	10	3.5%	1.0 0.4–2.4 0.946
3 or above (ref)	1575	41	2.6%	1.0 – –

* Estimated RR based on odds ratios from logistic regression with weighted data and taylor series linearization for variance estimation to estimate 95% confidence intervals (CI), and associated p-values.

Table 4

Relative risk estimates for becoming hallucinogen dependent among recent-onset hallucinogen users, with statistical adjustment for all listed covariates. Data from U.S. 2000–2001 National Household Survey on Drug Abuse.

	Weighted RR Estimates		
	RR*	95% CI	p value
Sex			
Male (ref)	1.0	–	–
Female	1.3	0.7–2.4	0.404
Age of first hallucinogens use			
10 to 11	33.3	1.9–471	0.015
12 to 13	1.9	0.6–5.9	0.292
14 to 15	0.8	0.3–1.9	0.584
16 to 17	0.5	0.2–1.5	0.227
18 to 20 (ref)	1.0	–	–
21 to 25	0.3	0.1–1.4	0.113
26 and older	0.7	0.1,5.5	0.723
Family Income			
0 to \$19,999	1.4	0.6–3.1	0.421
\$20,000 to 49,000 (ref)	–	–	–
\$50,000 – \$74,999	1.5	0.5–4.6	0.434
\$75,000 +	1.6	0.7–3.9	0.304
Race / ethnicity			
Nonhispanic White (ref)	1.0	–	–
Nonhispanic Black	1.8	0.5–6.6	0.390
Hispanic	0.2	0.04–1.0	0.055
Other	2.6	0.9–7.2	0.069
Number of drugs used prior to starting hallucinogen			
None	–	–	–
1	0.64	0.2–1.9	0.415
2	0.83	0.3–2.1	0.694
3 or more (ref)	1.0	–	–

* Estimated adjusted RR based on odds ratios from covariate-adjusted logistic regression with weighted data and Taylor series linearization to estimate 95% confidence intervals (CI), and associated p-values.

Table 5

Crude and adjusted relative risk estimates for becoming hallucinogen dependent among recent-onset hallucinogen users, in relation to hallucinogenic compound used. Data from U.S. 2000–2001 National Household Survey on Drug Abuse.

	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases	Crude Estimates*			Adjusted Estimates**		
			Unweighted		weighted	Unweighted		weighted
			Estimated Risk of Becoming Dependent uRR [~] 95% CI	p value	Estimated Risk of Becoming Dependent uRR [~] 95% CI	Estimated Risk of Becoming Dependent 95% CI	p value	Estimated Risk of Becoming Dependent aRR [~] 95% CI
All Persons	2035	56	–	–	–	–	–	–
Lifetime Hallucinogen Use								
LSD/NOS	870	36	1.0	–	1.0	–	–	–
PCP	148	15	3.8	1.9–7.6	<0.001	4.9	2.2–10.8	<0.001
Ecstasy	1199	46	3.5	1.7–7.2	<0.001	4.4	1.8–11.0	0.002
Mescaline	65	9	2.5	1.0–6.3	0.049	5.5	1.9–15.4	0.001
Peyote	62	6	1.2	0.4–3.8	0.708	0.4	0.1–1.8	0.220
Psilocybin	718	29	2.0	1.1–3.6	0.015	2.1	1.0–4.2	0.040
Number of Hallucinogenic compounds used								
1	1307	17	1.0	–	–	1.0	–	–
2	455	15	2.6	1.3–5.2	0.008	2.1	1.0–4.5	0.059
3	199	11	4.4	2.0–9.6	<0.001	5.9	2.4–14.6	<0.001
4 or more	74	13	16	7.5–34.8	<0.001	20.9	8.1–50.8	<0.001

Note: Estimates based on logistic regression, with statistical adjustment for covariates.

Note: Data based on variance estimates via Taylor Series linearization with statistical adjustment for covariates.

* In the crude model, the risk estimates for each specific hallucinogenic compound are in reference to individuals who used LSD and/or hallucinogen compounds not otherwise specified (NOS) but not the other listed drugs. The estimates are adjusting for other hallucinogens used, but not adjusting for other covariates.

** In the adjusted model, the risk estimates for each specific hallucinogenic compound are in reference to individuals who use LSD but not the other listed drugs. The drug estimates are adjusting for sex, age, race/ethnicity, family income, and number of other drugs used prior to first hallucinogen use, but not for the number of hallucinogenic compounds used. The model based estimates for the number of hallucinogenic compounds used is adjusted for all covariates listed above, except for covariate terms to indicate use of specific hallucinogens.