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HALLUCINOGEN DRUGS: EPIDEMIOLOGICAL ESTIMATES FOR THE RISK OF A DEPENDENCE SYNDROME EMERGING SOON AFTER ONSET OF USE

presented by

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has been accepted towards fulfillment
of the requirements for the

M.S. degree in Epidemiology

for Dr. James C. Anthony
Major Professor's Signature

December 7, 2007
Date

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By

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Epidemiology

2007

ABSTRACT

HALLUCINOGEN DRUGS: EPIDEMIOLOGICAL ESTIMATES FOR THE RISK OF A DEPENDENCE SYNDROME EMERGING SOON AFTER ONSET OF USE

By

Alejandro De La Torre Sanclemente, M.D

Analyzing epidemiological data from 2000-2001, Stone and colleagues estimated that roughly 2% -3% of recent-onset hallucinogen users in the United States (U.S.) develop a hallucinogen dependence syndrome rapidly (i.e., as measured within 24 months after first use of any hallucinogen) —with excess risk of hallucinogen dependence occurring among recent-onset users of ecstasy, phencyclidine (PCP), or mescaline.In this masters thesis research project, the main aim was to strengthen and confirm support for these epidemiological estimates. The new estimates are based on data from the National Surveys on Drug Use and Health (NSDUH) conducted in 2002-2003, with representative samples of community-dwelling U.S. residents age 12 years and older (n=109,309). The key response variable in this study is hallucinogen dependence among recent-onset hallucinogen users. In this new study, a total of 2026 respondents were found to be recent-onset HU, and an estimated 2% -3% had developed hallucinogen dependence within 24 months after starting HU. In the prior research, there was little male-female difference in risk of becoming dependent; the findings of this thesis research project here are consistent with this finding. In sum, the project's evidence confirms the estimated 2%-3% risk of becoming hallucinogen dependent within 24 months after onset of HU, as well as the excess risk associated with use of ecstasy or PCP (relative to LSD only).

This work is dedicated to my family, Alejandro De La Torre B. (Father), Gloria Amparo Sanclemente (Mother) and Vanessa De La Torre (Sister), for all their invaluable support.

ACKNOWLEDGEMENTS

I wish to thank my mentor and thesis advisor, Dr. James C. Anthony, for his guidance and support as I completed this work. I also want to thank my other committee members, Dr. Naomi Breslau, Dr. Carlos Rios and Dr. Hwan Chung, for their advice and patience during this process. A debt of gratitude is owed to Dr. James C. Anthony and Dr. Carlos Rios for their help and encouragement to make all this possible.

This research was supported by the NIDA awards D43TW05819, Dr, James C. Anthony, principal investigator and training director, K05DA015799, and R01DA09897, as well as a post doctoral research fund at Michigan State University, College of Human Medicine, Department of Epidemiology.

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INTRODUCTION

In this master's research project, drawing upon the most recently available epidemiological data for the United States (US), the main aim was to challenge or to confirm a previously published epidemiological estimate for the risk of developing a hallucinogenic dependence syndrome within a span of 0-24 months after first use of one or more compounds in the heterogeneous class called 'hallucinogens', with due attention to illusinogens (i.e., phencyclidine) and mixed stimulant-hallucinogens (e.g., 3,4 methylenedioxymethamphetamine, known by slang terms MDMA and ecstasy), as well as as various compounds with hallucinogen-type effects (e.g. gamma-hydroxybutyrate, GHB). Specifically, these thesis project seeks to probe results based upon a national sample survey conducted in 2000-2001 in which, an estimated 2%-3% of hallucinogen users in the US were found to have developed a hallucinogen dependence syndrome within a span of 24 months after first hallucinogen use (Stone et al.2006; 2007).

Tapping data gathered during the 2002–2003 calendar years (CY), this research project re-estimates the probability of rapid transition from hallucinogen use to dependence, and also looks into a possible male-female difference in risk of becoming hallucinogen dependent soon after onset of hallucinogen use, testing whether males and females are equally likely to experience clinical features associated with hallucinogen dependence. Finally, there also are estimates for the degree to which the dependence syndrome associated with these compounds might vary across different types of users, with a specific focus upon users of MDMA, phencyclidine (PCP), and mescaline. In the 2000-

2001 data, as compared to other compounds in the 'hallucinogen' group, these compounds were associated with an increased risk of becoming dependent soon after onset of use (Stone et al., 2007). (Note: Whereas phencyclidine no longer is generally regarded as a 'hallucinogen' drug, and whereas MDMA is a mixed stimulant-hallucinogen, the research teams for recent US national surveys have grouped all of these drugs with mescaline, psilocybin, LSD, and other 'psychedelic' drugs into a single 'hallucinogens' drug class. In this research project, this pharmacological heterogeneity is addressed through multiple regression analyses.)

The four specific aims of the study are:

AIM 1 To seek support for or against the possibility that a hallucinogen dependence syndrome emerges rapidly for more than a small minority of recent-onset hallucinogen users.

AIM 2 To provide evidence for or against the presence of subgroup variations in risk of developing hallucinogen dependence syndrome soon after onset of use.

AIM 3 To explore a possible male-female variation in the estimated risk of becoming hallucinogen dependent soon after onset of use.

AIM 4 To assess the possibility that these risks may vary among of rapid transition individuals of different racial/ethnic backgrounds.

CHAPTER 1

1. BACKGROUND AND SIGNIFICANCE

1.1 Overview

This master's thesis research project is concerned with the occurrence of a syndrome of drug dependence that sometimes occurs in the context of repeated use of one or more of the chemicals grouped under the name of 'hallucinogens'. The name 'hallucinogen' might seem to imply that these drug compounds uniformly cause the experience of hallucinations, which are defined by the American Psychiatric Association's Diagnostic and Statistical Manual, Fourth Revision (DSM-IV) as "sensations that have no corresponding objective reality". Hallucinations can occur in various forms that parallel the human senses. Visual hallucinations involve the sense of sight, or "seeing things." Auditory hallucinations generally involve hearing voices, and are the most common of the hallucinations. Sometimes, a hallucination can include both voices and some visual experience; mental health professionals describe this as an "auditory-visual hallucination." Smelling non-existent smells or feeling things on or under one's skin that do not actually exist are forms of somatic hallucinations. Somatic comes from soma, the Greek word for body; thus, somatic hallucinations are bodily hallucinations. However, this claim now is known to be controversial, and some of the drug compounds grouped under the heading of 'hallucinogens' do not seem to cause true hallucinations. A most interesting recent double-blind study on this topic sought to contrast the psychotropic ('mind-changing') effects of glutamate antagonist drug compounds such as phencyclidine (PCP) and S-ketamine with the effects of serotonergic drug compounds such as lysergic acid diethylamide (LSD), psilocybin, and N,N-dimethyltryptamine (DMT). What the

experimenters found was consistent with the idea that 'hallucinogen' compounds that activate serotonergic neurotransmission systems in brain will induce changes in the mental life and behavior resembling the so-called 'positive' symptoms of schizophrenia (e.g., hallucinations or other forms of formal thought disorder; inappropriate affect), whereas those activating or antagonizing the glutamate neurotransmission systems will induce changes in the mental life and behavior that resemble the so-called 'negative' symptoms of schizophrenia such as body perception disturbances, attention deficits, and catatonia-like motor phenomena (Gouzoulis-Mayfrank et al., 2005).

There also is controversy about whether methylenedioxymethamphetamine (MDMA) truly is a hallucinogen drug. With compounds of related chemical structure (e.g., d-amphetamine), MDMA has central nervous system (CNS) stimulant effects, and there is human laboratory evidence of psychotropic activity in the mental life domains described above in terms of the positive and possibly negative symptoms of schizophrenia. This combination of effects originally led MDMA to be classified as a 'mixed stimulant-hallucinogen' drug, but some observers now claim that it does not cause true hallucinations as defined above. Instead, the distortions of mental life might be characterized as 'illusions' with the drug user experiencing a sensory-perceptual distortion while retaining insight into the experience as one that is illusory rather than one that is a true hallucination without such insight. Some observers prefer not to classify MDMA as a hallucinogen at all, preferring to place it in another category of compounds called empathogens or entactogens, with an emphasis upon drug effects in the domains of empathy, sociability, and feelings of closeness with others located within the setting of the drug experience. Nonetheless, the federal government continues to sort MDMA with

the other hallucinogens mentioned above in its epidemiological surveillance systems, and for this reason, this thesis research project acknowledges that classification.

The rest of this chapter is organized in relation to sub-sections on the historical background of the present research project, which is based upon a reading of the references cited; an overview of epidemiological surveillance data on hallucinogen use in the population from the mid-20th century to the present time, based primarily upon epidemiological data systems created by the National Institute on Drug Abuse (NIDA) and now maintained by the Substance Abuse and Mental Health Services Administration (SAMHSA); a brief review of the mechanisms of action and pharmacological effects of the main drug compounds within the 'hallucinogens' category (based mainly upon the work of Jacobs, 1987; Abraham et al., 1996; Julien, 1995; Schuster et al., 1998; von Sydow, 2002) and finally an introduction to the topic of the hallucinogen dependence syndrome and the potential public health significance of this syndrome, which is the primary focus of this research project.

What follows next in this chapter is a review of issues pertinent to the background and public health significance of the master's thesis research project on one of the suspected adverse consequences of hallucinogen use -- namely, a syndrome of drug dependence that can follow repeated use of hallucinogen drugs. The next sub-section provides some historical background and sets the stage for epidemiological research on the extra-medical use of hallucinogen drug compounds (i.e., use outside the boundaries of medical supervision or prescription). It should be noted that within the United States most hallucinogen use is extra-medical because a drug compound found to have effects like

those of the 'hallucinogens' named above typically is assigned to the highest level of drug control ('Schedule I' of the federal controlled substances legislation) and cannot be used legally outside the context of tightly regulated research projects with medical supervision. Underground chemists continue to synthesize new compounds with hallucinogen, empathogen, or entactogen effects, but the prevailing federal legislation gives the government broad powers to assign these compounds to Schedule I on the basis of the superficial resemblance of their effects to the effects of other Schedule I drugs, even before there is experimentation to examine risk/benefit ratios. Notwithstanding the objections of some psychiatrists and noteworthy evidence of potential benefits in the psychotherapeutics context, a general assumption within the U.S. Department of Justice and the Drug Enforcement Administration is that the risks associated with new compounds that have hallucinogen effects always will outweigh any potential benefits (e.g., see Griffiths et al., 2006). Sociologist Philip Jenkins has characterized the present situation and future forecast for the United States in the 21st century, as follows:

> "As neurochemistry and chemical technologies advance, the stage is set for persistent confrontations between an entrenched anti-drug bureaucracy and the demonized phantom chemists, the evil scientific masterminds. The outcome, in short, will be recurrent synthetic panics" (Jenkins, 1999, p.197).

But the story of hallucinogens did not begin with pharmaceutical chemistry experiments. Instead, the start of the story was many 1000s of years ago.

1.2 Historical Background

Over a span of thousands of years, humans discovered many plants capable of changing the human mental life and experience, even sometime transporting the individual to what he felt as a new reality (Ray, 1972). Not only in the tropics, but also in arctic regions, human culture has evolved to encompas "visions" associated with mystical insight. For example in the Americas alone, 80 to 100 plants have been consumed at different times, and by different groups, because of the plants' psychotropic properties. Elsewhere in the rest of the world, the most commonly used psychotropic plans are from just seven species, and some feel that this is more a reflection of cultural differences than of botanical differences (Ray, 1972). These plants and the psychoactive chemicals they contain are classed as hallucinogens because their distinguishing characteristic, to our society, is a specific distortion of perception and states of consciousness, known as a hallucination. The word hallucinogen derives from the late Latin, alucinari, meaning to wander in mind, talk idly, or prate (Abraham, et al., 1996). The history of hallucinogens is one of the most compelling in pharmacology. In many cultures hallucinogens have been used for religious or mystical experiences. For example, the Hindu holy book, Rig Veda, mentions soma, a sacred substance used to induce higher levels of consciousness. Soma is thought to have been derived from the the hallucinogenic mushroom Amanita muscaria. The Aztecs in pre-Columbian Mexico described the ceremonial use of teotlaqualli, a paste made from the hallucinogenic flowering plant, ololiuqui, sometimes called 'morning glory' Rubbed on the skin of Aztec priests and soldiers, it was thought to eliminate fear and place the user in a proper mental state to serve the Aztec gods.

Hallucinogens have also been proposed as a cause of the "immoral and illicit" behavior of alleged witches in the Salem, Massachusetts witch trials (Abraham, et al., 1996).

According to Abraham et al. (1996) the oldest hallucinogen is thought to be the fly-agaric mushroom, Amanita muscaria, discovered in Siberia, perhaps when humans saw it being consumed by reindeers and the resulting disordered behavior. In 1845 Jacques Moreau published the first text on hallucinogens, in which he observed that such drugs enabled imagined thoughts to become sensory expressions. Later, in 1860 the mycologist, M.C. Cooke did notable work differentiating opiates from the other "sisters of sleep" among the hallucinogens. De Vezc in 1907 a half century later first classified specific chemicals compounds in hallucinogenic plants, a process that was refined definitively in subsequent research by the toxicologist Louis Lewin. Lewin emphasized the perceptual effects of these plants, as well as their use and potential for misuse. Seeking to explore their spiritual effects, the psychologist William James received a supply of mescal buttons from Weir Mitchell, ingested them, became ill for 24 hours, but failed to hallucinate. His experiments with nitrous oxide and ether were more successful (James, 1902). By the 1920s and the 1930s ethnobotanical and psychopharmacological work blossomed in field studies completed by Safford, Reko, and later, Schultes (Schultes and Hofman, 1980). The first synthetic hallucinogen, lysergic acid diethylamide 25 LSD, was discovered in 1938 by a Swiss chemist called Albert Hoffman while was working in a Sandoz Corporation pharmaceutical laboratory. He was conducting research on possible medical applications of various lysergic acid compounds derived from ergot, a fungus that develops on rye grass. Searching for compounds with therapeutic value, Hofmann created

more than two dozen ergot-derived synthetic molecules. The 25th was called LSD. With the discovery of the hallucinogenic properties of LSD in 1938, the aboriginal patterns of hallucinogen use historically restricted by religious ritual, and the botanical origins of the plants consumed were changed, doors were opened to the possibility of recreational drug use. With the introduction of LSD to Europe and to the United States in 1949, an era was begun in which extremely potent agents became available to millions of persons for uses that ranged from the religious to the recreational. These developments set the stage for epidemiological processes and the diffusion of hallucinogen use on a scale not previous imagined.

1.3 Hallucinogen Epidemics in the United States

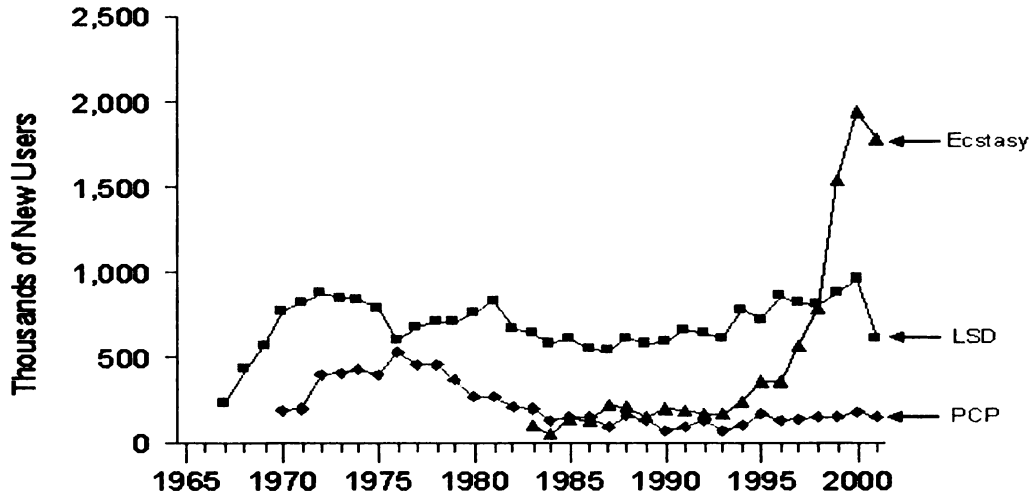
Without the baby boom of the immediate post-wars years of 1946-1956, there may well have been no epidemia of hallucinogen drug use in the United States. The market and demand for LSD and other hallucinogenic compounds remained at quiet low levels through the 1950's, as chronicled in R.H. Blum's account of these years in Utopiates (Blum et al., 1964). All this changed before 1965 when the United States government raised its Food and Drugs Safety laws via legislation entitled the Drug Abuse Control Amendments (DACA). The DACA were enacted in response to growing public concern about anecdotal evidence of increasing extra-medical use of LSD, cannabis and other drugs sold on the street (i.e., without medical supervision) There also was media publicity about LSD casualties (e.g., The LSD associated death of a daughter of actor- comedia Arthur Linklotter), Apparently the publicity about casualties may have contributed to curiosity and risk taking propensities of adolescents and young adults of the post war II

baby boom era with a associated increases in the demand for and consumption of LSD and related hallucinogen compounds. These demographic and sociological phenomena have been covered in the popular press and also in the academic literature (Cohen, 1965; Maclean, JR et al., 1967)

An epidemiological picture of the incidence of hallucinogen use has been re-constructed via retrospective surveys first conducted in the mid-1970s. According to this research these data exhibited two notable periods of increase, between 1966 and 1970, the annual number of hallucinogens initiates rose almost sixfold, from an estimated 168,000 to an estimated 956,000. This increase was driven primarily by use of LSD. The second period of increase in first-time hallucinogen use began in 1992 when there were an estimated 706,000 new users. By 2000, the number of initiates rose to 1.7 million, not appreciably different from the estimates for 2001 (1.6 million). The hallucinogen increase in the 1990s appears to have been driven by increases in use of Ecstasy. The estimated numbers of Ecstasy users has been rising since the late 1980, as shown in table 1. There were 1.9 million initiates in 2000 and 1.8 million in 2001 (not a statistically significant decline). Estimated LSD incidence dropped from 958,000 new users in 2000 to 606,000 in 2001, as shown in table 1. Combined data from SAMHSA's 2004 and 2005 NSDUH indicate that an annual average of 943,000 persons aged 12 or older were recent initiates of hallucinogens (i.e., they had used hallucinogens for the first time in the 12 months before the survey). Of these recent hallucinogen initiates, 52.3% had used psilocybin mushrooms and 42.9% used Ecstasy in the past year. Recent female hallucinogen initiates were more likely than recent male hallucinogen initiates to have used Ecstasy (49.5% vs. 37.7%). In contrast, recent male hallucinogen initiates were more likely than

recent female hallucinogen initiates to have used psilocybin mushrooms (61.1% vs. 41.1%) (SAMHSA, 2005).

Table 1: Estimated Annual Numbers of New Users of Ecstasy, LSD, and PCP: 1965-2001



Source: National Survey on Drug Use and Health (NSDUH)

In the graph we can see how from the mid 1960s until the early 1970s the estimated number of new initiates of LSD and PCP increased. However, from 1975 until 1985 the estimated number of new initiates of PCP decreased and has remained steady since. The estimated number of new users of LSD has remained relatively steady since the mid 1970s until 2001, when it dropped.

Based on SAMHSA's National Household Survey on Drug Abuse, in 2001 almost 1.4 million youth aged 12 to 17 had used hallucinogens at least once in their lifetime. The prevalence of lifetime hallucinogen use among youths aged 12 to 17 was at its highest level in 2001 (6.1%) but declined somewhat to 5.7 % in 2002. Among young adults aged

18 to 25, use increased from 14.3 percent in 1992 to 24.2 percent in 2002. There is, however, some encouraging news from NIDA's Monitoring the Future (MTF) survey, an annual survey used to track drug abuse trends among adolescents in middle and high schools across the country. Between 2001 and 2005, annual ecstasy use decreased by 52 percent in 8th-graders, 58 percent in 10th-graders, and 67 percent in 12th-graders. Prevalence of lifetime MDMA use decreased significantly from 2004 to 2005 among 12th graders.

More than 11 million persons aged 12 or older reported using ecstasy at least once in their lifetimes, according to the 2004 NSDUH. The number of current users (use in past month) in 2004 was estimated to be 450,000 (SAMHSA, 2005).

In 2001 an estimated 8.1 million (3.6%) of Americans aged 12 or older had tried Ecstasy at least once in their lifetime. This is more than the estimated 6.5 million (2.9%) lifetime users in 2000. Among youth, Blacks were less likely than whites, Asians, or Hispanics to have used any hallucinogen in their lifetimes. Blacks and Hispanics were more likely than whites and Asians to perceive great risk in trying LSD once or twice (SAMHSA, 2004).

In 2005, 8th-graders reported a significant decrease in perceived harmfulness in using MDMA occasionally. The MTF data also show that MDMA use extends across many demographic subgroups. Among 12th-graders in 2005, for example, 3.9 percent of Whites, 3.0 percent of Hispanic students, and 1.4 percent of African-Americans reported using MDMA in the year prior to the survey (Johnston et al., 2006)

With respect to the risks of hallucinogen use, there is the 'bad trip' phenomenon , as well as other complications (e.g., dehydration) that can send users to hospital emergency rooms. SAMHSA's Drug Abuse Warming Network (DAWN) found that four hallucinogen drugs (GHB, ketamine, LSD, and MDMA) collectively account for just over 8,000 emergency department visits in 2002. Most of the patients in hallucinogen related emergency department visits were under age 26: 56% of the GHB, 68% of the ketamine, 75% of the MDMA, and 76% of the LSD related emergency department visits. Although relatively rare, hallucinogen related emergency department visits increased from 1994 to 1999, and generally decreased from 2000 to 2002 (SAMHSA, 2004).

DAWN reported that mentions of MDMA in drug abuse-related cases in hospital emergency departments numbered 2,221 for the third and fourth quarters of 2003. The majority of patients who came to emergency departments with MDMA as a factor in their admissions during that time were aged 18–20 (SAMHSA, 2005).

1.4 Mechanism of action and basic pharmacology of hallucinogens

Table 2 Complete list of the hallucinogens covered in NSDUH questions

HALLUCINOGENS
LSD, also called 'acid'
PCP, also called 'angel dust' or phencyclidine
Peyote
Mescaline
Psilocybin
Ecstasy, also called MDMA

As noted in the introduction to this report, the drugs compounds known as "hallucinogens" represent a diverse group of chemicals that can cause hallucinations or related states such us illusions (i.e., not true hallucinations in that the user appreciates that the perceptual distortion is truly not real, rather it is just an illusion, e.g., PCP).This is a heterogeneous group, with different chemical structures, different mechanisms of action, and different adverse effects. A brief description of the pharmacology and mechanism of action of the main hallucinogen compounds that are within the scope of this dissertation will be presented. As noted before, many users of hallucinogen drugs do not seek out hallucinations per se. Instead, the drugs often are consumed to promote social bonding or other unusual experiences, such us a blending of senses ('seeing sounds' or 'hearing colors').

1.4.1 Overview of this section

This thesis research project is based upon analyses of recent data from one of the national epidemiological surveillance systems already described in this chapter, namely, the National Survey on Drug Use and Health (NSDUH). Details on the mechanisms of action and pharmacological effects for each of the chemical compounds listed below can be found in Goodman and Gilman's classic textbook, The Pharmacological Basis of Therapeutics (Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition, 2005). In this section of the chapter, there is an overview of mechanisms and effects for a selection of the compounds, reported with the greatest frequency by hallucinogen users. Whereas the history of human experience with hallucinogens appears to have started with consumption of fly agaric amanita muscaria mushrooms, this specific

form of hallucinogen appears so infrequently in the field surveys that it has not been included in the following list of compounds.

1.4.2 Peyote and Mescaline

The peyote plant is a cactus (Lophophora williamsii), whose principal active ingredient is mescaline (C11H17NO3) (3,4,5-trimethoxy-ß-phenethylamine). Mescaline belongs to a family of psychoactive compounds known as phenethylamines, with a distinct chemical structure, somewhat similar to that of the neurotransmitters dopamine and norepinephrine, upon which this drug has activity. Some of the other synthetic "designer" psychedelics are phenethylamines as well (Turner et al., 2004).

The peyote cactus contains 'buttons' that can be cut from the plant and dried. The buttons can either be chewed, or may besoaked in water to produce an ingestible liquid. Peyote buttons may also be ground into a powder (SAMHSA, 2005).

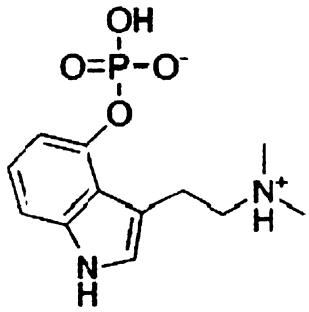
If extracted form the buttons, mescaline is administered orally in the form of powder, a tablet, a capsule, or liquid, or smoke within a vehicle such us tobacco or cannabis. In its pure liquid form, mescaline can be injected, but this method is rare. Users typically consume between 300-500 milligrams (an amount contained in 3-6 peyote buttons) (Turner et al., 2004). Possible effects can be true hallucinations, or illusions, altered perception of time and distance, synesthesia, impaired hand-eye coordination, chills and sweating, sleeplessness, increased heart rates and elevated blood pressure. These effects generally appear within 1-2 hours, and gradually disappear 10-12 hours after administration.

1.4.3 Psilocybin

Extracted from mushrooms psilocybin is the phosphate ester of psilocin, or 4-hydroxydimethyltryptamine (C12H17N2O4P) (Miller, 1991). The most common psilocybin mushroom in the United States is Psilocybe cubenis. Individual mushrooms contain approximately up to two percent of the psychoactive ingredient psilocybin, while psilocin itself is only found in trace amounts (Pedersen-Bjergaard, 1998). Between 4 to 10 mgs of psilocybin is considered to be an average content for psilocybin per grams of mushroom, and that is also the usual dose ingested. Psilocybin and psilocin especially are indoles structurally related to the neurotransmitter serotonin 5-hydroxytryptamine or 5-HT (Vollenweider, 1998). The structural resemblance to serotonin also parallels with psilocybin's activity, which involves disruption of serotonergic transmission; the indole binds to and act as an agonist to the 5-HT receptors (Reid, 1980). In addition, animal studies have demonstrated that the action of this hallucinogenic drug can be blocked by 5-HT2 receptor antagonists (Vollenweider, 1998).

The mushrooms can be eaten raw, cooked, steeped into tea, dried, powdered, and taken in capsules, or smoked with a vehicle such as marijuana. Tolerance develops rapidly, and there is cross-tolerance with LSD and mescaline. Effects are usually apparent within half an hour and may last from 4-8 hours. The physiological effects of psilocybin have been described poetically as a voyage to the spirit world. These hallucinogenic effects are similar to those of LSD; however, psilocybin is two hundred times less potent and also has a shorter duration time, as compared to LSD.

Figure 1 Psilocybin chemical structure



Source: Samorini G, 1992

1.4.4 Lysergic acid diethylamide (LSD)

LSD is an exceptional hallucinogen due to its potency at microgram levels, as described by Abraham et al. 1996. It is a clear or white, odorless, water-soluble material synthesized from lysergic acid, a compound derived from a rye fungus. The precise mechanisms by which LSD alters perceptions is remain unclear. Evidence from laboratory studies suggests that LSD, as with certain hallucinogenic plants, acts on groups of serotonin receptors designated the 5-HT_2 receptors, and that its effects are most prominent in two brain regions: (1) the cerebral cortex, an area involved in mood, cognition, and perception; (2) the locus coeruleus, which receives sensory signals from all areas of the body and has been described as the brain's "novelty detector" for important external stimuli (Abraham et al., 1996)

The pure crystal of LSD can be crushed to powder and mixed with binding agents to produce tablets known as "microdots" or thin squares of gelatin called "window panes"; It also can be dissolved, diluted, and applied to paper or other materials. A common form of LSD is distributed a "blotter acid" sheets of paper soaked in LSD and perforated into 1/4-inch square, individual dosage units. Due its composition, water-soluble LSD is rapidly

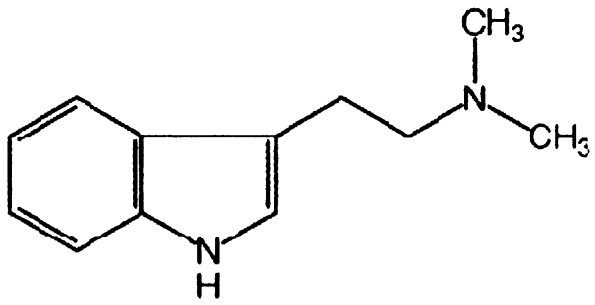
absorbed from within the gastrointestinal tract, and quickly is distributed throughout body tissues including brain. Intravenous use is rare. Physical effects of LSD (e.g., increased heart rate) are seen within 20 minutes; consciousness- modifying effects within 2 to 4 hours. Tobacco has been saturated with LSD and smoked, but the result is described as unsatisfactory to many users.

Users of LSD experience some physiological effects, such as increased blood pressure and heart rate. Sometimes there are complaints of dizziness, loss of appetite, dry mouth, sweating, nausea, numbness, and tremors, but the drug's major reinforcing effect seems to be in the sensory and emotional realms. The user's emotions may shift rapidly through a range from fear to euphoria, with transitions so rapid that the user may seem to experience several emotions simultaneously. There is no evidence that LSD produces physical withdrawal symptoms when chronic use is stopped, but a dependence syndrome has been noted, as described below.

1.4.5 Dimethyltryptamine (DMT)

The compound DMT N,N-diemethyltryptamine, Nigerine, desoxybufotenine, 3-(2-dimethylaminoethyl) (Figure 3) indole is a white, pungent-smelling, crystalline solid with a melting point of 49-50 degrees Celsius, hydrochloride salt hygroscopic, picrate m.p. 171-172 degrees Celsius and methiodide m.p. 215-216 degrees Celsius. It is insoluble in water, but soluble in organic solvents and aqueous acids. DMT was first synthesized in 1931, and demonstrated to be hallucinogenic in 1956. It has been shown to be present in many plant genera (Acacia, Anandenanthera, Mimosa, Virola) and is a major component of several hallucinogenic snuffs (cohoba, parica, yopo)

Figure 2 Dimethyltryptamine (DMT)



Source: Callaway JC,1998

Both the parent compound tryptamine and the N-methyltransferase system which is capable of converting it to DMT, occur in humans, but there is as yet no evidence that DMT is formed "in vivo". DMT has nonetheless been identified in trace amounts in the blood and urine of both normal controls and of schizophrenic patients, but its origins and functions are unknown. Following intramuscular administration, maximum blood levels of about 100 ng/ml are observed in 10 minutes, coincident with the maximum changes in electroencephalographic responses. The plasma clearance t-1/2 [half-life] is about 15 minutes. Elevated blood levels of indoleacetic acid (IAA) are seen during the time of peak effect. Urine levels of IAA are also elevated and account for about 30% of the administered drug. An increase in 5-hydroxy-IAA excretion suggests the involvement of serotonin in DMT action. Unchanged DMT is not excreted.

With intramuscular injection of DMT, there is an abrupt threshold of activity shown with 30mg, and a complete psychedelic experience results from the administration of 50-70 mg (75 mg subcutaneously, 30 mg by inhalation). An unusual feature of the induced intoxication is the speed of onset and short duration.

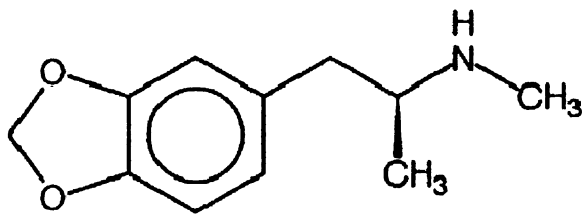
Within 5 minutes of administration there is mydriasis [dilated pupils], tachycardia [rapid heart beat], a measurable increase in blood pressure, and related vegetative disturbances which usually persist througout the drug experience. In 10-15 minutes, the full intoxication is realized, generally characterized by hallucinations with the eyes either open or closed, and extensive movement within the visual field.

1.4.6 Methylene dioxymethamphetamine (MDMA)

MDMA is also known by street slang name as Ecstasy. This compound is a synthetic, psychoactive drug chemically similar to the stimulant methamphetamine and the hallucinogen mescaline. It appears to affect serotonin neurotransmission at presynaptic and postsynaptic sites. It was synthesized by the Merck drug company in the early 20^{th} century, and did not re-surface in the illegal drug literature until about 50 years later. Studies in animals (rats and nonhuman primates) indicate that MDMA affects serotonergic transmission. A growing literature also offers some evidence of chronic serotonergic dysfunction in humans (Haddad et al., 1976). Although MDMA usually does not cause true hallucinations, it causes changes in mood and the perception of music, reputedly increases interpersonal communication, and fosters feelings of intimacy and empathy (Parrot et al., 1988; Greer et al., 1986). In high doses, MDMA can interfere with the body's ability to regulate temperature. This can lead to a sharp increase in body temperature (hyperthermia), sometimes followed by liver, kidney, or cardiovascular system failure. Users of MDMA face many of the same risks as users of other stimulants such as cocaine and amphetamines. These include increases in heart rate and blood pressure, a special risk for people with circulatory problems or heart disease, and other symptoms such as muscle tension, involuntary teeth clenching, nausea, blurred vision,

faintness, and chills or sweating. MDMA generally comes in the form of small tablets, capsules, or white powder. In street markets, those buying MDMA may actually get a combination of any of the following: MDMA, MDA, MDE, Caffeine, Dextromethorphan, Ephedrine, Glyceryl guaiacolate, and phenylpropanolamine. Trying to calculate dosages from tablets containing unknown quantities of MDMA can be difficult, but a good quality tablet of street ecstasy generally contains an average of between 75 and 100 mg MDMA (Byrska, 2007).

Figure 3 Methylene dioxymethamphetamine (MDMA)



Source: Byrska B, 2007

1.4.7 Phencyclidine HCL (PCP)

PCP is grouped as a "hallucinogen" compound but it does not appear to cause true hallucinations, as described below. In appearance PCP typically is synthesized as white crystalline powder that is readily soluble in water or alcohol. This drug affects multiple neurotransmitter systems in the brain. For example, PCP inhibits the reuptake of dopamine, norepinephrine and serotonin and also inhibits the action of glutamate by blocking NMDA receptors (Brust, 1993). Some types of opioid receptors in the brain are also affected by PCP. These complex effects on multiple chemical systems in the brain most likely underlie the behavioral effects of PCP.

This compound is classified as a dissociative anesthetic because users appear to be "disconnected" from their environment: they know where they are, but they do not feel as if they are part of it. It is said to act as a stimulant, a depressant, an analgesic (decreasing pain), or a hallucinogen depending on the dose and route of administration (Doweiko, 1996), although recent pharmacological research indicates that does not cause true hallucinations. Rather the sensory experience is more akin to the experience of an illusions, with the user retaining insight. The effects produced by PCP are different from those caused by hallucinogens such as LSD. Rather than producing visual hallucinations, PCP causes changes in body image. At low to moderate doses, physiological effects of PCP include a slight increase in breathing rate and a pronounced rise in blood pressure and pulse rate. At high doses of PCP, blood pressure, pulse rate, and respiration drop. These physiological effects may be accompanied by nausea, vomiting, blurred vision, flicking up and down of the eyes, drooling, loss of balance, and dizziness. High doses of PCP can also cause seizures, coma, and death (though death more often results from accidental injury or suicide during PCP intoxication). High doses can cause symptoms that mimic schizophrenia, such as delusions, hallucinations, paranoia, disordered thinking, a sensation of distance from one's environment, and catatonia. Speech is often sparse and garbled (Doweiko, 1996).

PCP can be mixed easily with dyes and turns up on the illegal drug market in a variety of tablets, capsules, and colored powders. It is normally used in one of three ways: snorted, smoked, or ingested. Intravenous or IM use is rare (Frances, 1998).

1.5 The Hallucinogen Dependence Syndrome

It already has been highlighted that drug compounds in the hallucinogen category apparently do not give rise to a clear withdrawal syndrome upon abrupt discontinuation of sustained use. The idea that hallucinogen drug use might give rise to a more general syndrome of psychic dependence or behavioral dependence surfaced during the 1960s. This idea was formalized in the 10th revision of the World Health Organization's (WHO) International Classification of Diseases (ICD-10), which has been posted by WHO with the label 'European description' (http://www.mentalhealth.com/icd/p22-sb05.html). The hallucinogen dependence syndrome also appears in the Fourth Revision of the Diagnostic and Statistical Manual of the American Psychiatric Association (American Psychiatric Association, 1994), as shown in Table 2.

Hallucinogen dependence has been described as a syndrome cluster of physiological, behavioural, and cognitive phenomena in which the use of hallucinogen takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take hallucinogen (which may or may not have been medically prescribed). There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals.

1.6 Diagnostic Guidelines

A definite diagnosis of dependence should usually be made only if three or more of the following have been experienced or exhibited at some time during the previous year:

A. A strong desire or sense of compulsion to take hallucinogens;

B. Difficulties in controlling hallucinogen-taking behavior in terms of its onset, termination, or levels of use;

C. A physiological withdrawal state when hallucinogen use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for hallucinogen; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;

D. Evidence of tolerance, such that increased doses of hallucinogen are required in order to achieve effects originally produced by lower doses;

E. Progressive neglect of alternative pleasures or interests because of hallucinogen use, increased amount of time necessary to obtain or take the substance or to recover from its effects;

F. Persisting with hallucinogen use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Table 3 DSM-IV Substance Dependence Criteria (APA, 2004)

DSM-IV Criteria for Substance Use Disorders (Substance Dependence)	
Addiction (termed substance dependence by the American Psychiatric Association) is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:	
1. Tolerance	Defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect or (b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal	Manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than intended	
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use	
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	
6. Important social, occupational, or recreational activities are given up or reduced because of substance use	
7. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance	

With respect to the frequency of occurrence of the hallucinogen dependence syndrome, the first nationally representative epidemiological field survey estimates on this topic were published in 1994, and were based upon the National Comorbidity Survey conducted in 1990-92 (Anthony et al., 1994). The survey report was focused upon estimation of the cumulative incidence proportion for having become dependent upon each type of drug by the date of the survey assessment, based upon the experience of survey respondents who had used these compounds extra-medically on one or more occasions. Inspection of the report and its background materials confirms that the NCS report's category of 'psychedelic' drugs corresponds to the NSDUH category of 'hallucinogen' drugs. Anthony and colleagues (1994) found that an estimated 1 in 20 hallucinogen users had developed a hallucinogen dependence syndrome (cumulative over all years of hallucinogen use, and not just in the recent-onset interval).

In a subsequent study of young people growing up in Germany, von Sydow and colleagues investigated the occurrence of hallucinogen drug use and dependence, with a focus upon MDMA users (von Sydow et al., 2002). In that study, it was found that: men used hallucinogens more often than women; the younger birth cohort (1977-1981) tended to start earlier with substance use compared to the older birth cohort (1970-77); use of hallucinogens was associated with increase rates of concomitant use of other drugs; the majority of the life time hallucinogen users without disorder has stopped to use these substances and not consumed them during the 12 months preceding the second follow-up assessment; those who had stopped taking ecstasy and related drugs at follow up also took other illegal drugs less often than those who continued to consume hallucinogens. In a later elaboration of that research project, Lieb and colleagues (2002) investigated

other psychiatric disturbances observed in association with MDMA use and found that an estimated 68% of those reporting at least one ecstasy use had experienced at least one DSM-IV mental disorder. Users of ecstasy and related drugs were more likely to have had an alcohol or other drug disorder than polydrug users or non-drug users. Ecstasy users were more likely than non-drug users to be diagnosed with affective disorders, anxiety disorders, somatoform disorders and eating disorders, and diagnosis with a DSM-IV mental disorder was higher in ecstasy users than polydrug users, though the difference in likelihood of diagnosis with a psychiatric disorder in ecstasy users and polydrug users was less pronounced than differences between ecstasy users and non-drug users. Suicidal ideation was more commonly reported in ecstasy users than in non-drug users (Lieb at al., 2002)

Setting the more immediate stage for the present masters thesis research project, Stone and colleagues borrowed a research approach first introduced by Anthony and colleagues in research on cocaine and cannabis. In specific, this research involves simulating a nationally representative prospective study of the rapid transition from first extra-medical drug use to onset of a drug dependence syndrome, based upon an analysis of cross-sectional survey data from a nationally representative sample. In brief, the method involves identifying individuals who have just started to use the drug (e.g., in the same year as the year of assessment or in the prior year), and investigating whether they might have already qualified for a diagnosis of the drug dependence syndrome within the short span of time since onset of the drug use. When asked to compare estimates from this type of simulation of prospective study data with estimates that might be obtained via a longitudinal follow up and re-assessment of the drug users 1-2 years after onset of their

drug use, Anthony communicated that sample attrition had become a major problem in national prospective studies in the United States, and that sample attrition was a special concern once young people start becoming engaged in extra-medical drug use and in the process of becoming drug dependent (Professor J.C. Anthony, personal communication). A similar logic is conveyed in prior research reports by that research group (e.g., see O'Brien and Anthony, 2002; Chen & Anthony, 2003, 2004, 2005; Anthony et al., 2004).

Evidence of this type of sample attrition bias in prospective studies with national samples has been seen in the National Epidemiological Survey of Alcoholism and Related Conditions (NESARC). In NESARC, the follow up participation level has been reported as less than 80% (Grant et al., in press).

When Stone and colleagues applied the "simulated prospective research approach" to estimation of the risk of making a transition from onset of hallucinogen drug use to rapid emergence of a hallucinogen dependence syndrome (as defined in DSM-IV), they found that an estimated 2–3% of these recent-onset hallucinogen users had become dependent on hallucinogens, according to the NHSDA DSM-IV computerized diagnostic algorithm. Stone and colleagues also investigated subgroup variation in the estimated risk of rapid-onset of hallucinogen dependence soon after start of hallucinogen use, finding that an excess risk of developing hallucinogen dependence was present in association with recent-onset use of mescaline; excess risk also was found for recent-onset users of ecstasy and of PCP. In relation to 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; analyses revealed minimal income-related variation in risk of becoming hallucinogen dependent soon after onset of use.

In sum, there now is epidemiological evidence that thousands of young people initiate hallucinogen use each year in the United States, with the largest numbers engaged in the extra-medical use of the mixed stimulant-hallucinogen compound MDMA. If it is true that 2%-3% of these new initiates go on to develop a hallucinogen dependence syndrome, possibly with 4%-6% of the MDMA users developing the syndrome within 24 months after onset of use, then one might forecast a need for public health outreach and early intervention to address the needs of individuals with this psychiatric syndrome.

Although the caseload burden associated with hallucinogen dependence seems to be rather small compared to caseloads associated with other drug dependence syndromes (e.g., involving alcohol, cocaine, cannabis), this analysis provides some evidence of the potential public health significance of hallucinogen dependence in the United States. It was on this basis that this masters thesis research project was undertaken, in an effort to probe into the findings reported by Stone and colleagues, to re-estimate the cumulative incidence proportion for onset of the hallucinogen dependence syndrome soon after onset of use, seeking to learn whether there would be replication of the prior estimates about this rapid transition. This replication research became possible with release of a public use dataset from the NSDUH surveys completed in 2001 and 2002, with newly drawn nationally representative community samples of U.S. residents age 12 years and older. In the process, it also has been possible to study the possible subgroup variation in risk of becoming hallucinogen dependent soon after onset of hallucinogen use, with a specific focus upon (a) the hallucinogen drug compounds that have been consumed, (b) male-

female variations, and (c) variations in relation to other background characteristics (e.g., race-ethnicity of the survey participants).

CHAPTER 2

2. MATERIALS AND METHODS

2.1 Participants

The population under study and the data for this research are from public use data files of the National Survey on Drug Use & Health (NSDUH) from two calendar years, CY2002 and CY 2003 (n= 109,309). The NSDUH now is a cross-sectional survey designed to yield a nationally representative sample of non-institutionalized United States citizens aged 12 years and older (United States, 2003, 2004). Multi-stage sampling procedures have been used to obtain a probability sample of residential and group quarters dwelling units, as well as a probability sample of individuals within each sampled dwelling unit. Study participants always are given the opportunity to decline participation; they provide assent (age 12-17) or consent (age 18+) in accord with protocols approved by cognizant Institutional Review Boards. More details on the NSDUH sampling methods of sample can be found elsewhere (United States Substance Abuse and Mental Health Services Administration, 2003)

2.2 Levels of participation

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 NSDUH 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. For the NSDUH in 2002, a total of 68,126 and for the 2003 a total of 67,784 dwelling units (DU) were sampled; 78.9% for 2002 and 77.3% for 2003 participated. Within participatory

DU, a total of 54,079 designated respondents were sampled for 2002, and a total of 55,230 designated respondents were sampled for 2003 (U.S. SAMSHA, 2002a; 2003)

2.3 Assessment

2.3.1 Key response variables and covariates

The key response variable in this study is occurrence of a dependence syndrome among recent-onset users of the following hallucinogen compounds: LSD, mescaline, peyote, psilocybin, and 'other hallucinogens,' as well as PCP and MDMA. The NSDUH research team bundled several non-hallucinogen compounds into its definition of hallucinogen (e.g., PCP, MDMA).

2.3.2 Hallucinogen dependence

Clinical features of the dependence syndrome were ascertained via 11 questions included in the NSDUH audio computer-assisted self interviews (ACASI); these items tap clinical criteria listed for hallucinogen dependence in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV; APA, 1994). Framed in relation to this specification for 'hallucinogen,' the NSDUH team devised a hallucinogen dependence variable according to a SAMHSA-specified computerized diagnostic algorithm. This algorithm identified respondents who had experienced at least three of the seven DSM-IV clinical features of dependence. In our analyses, respondents who did not meet these criteria for hallucinogen dependence were coded with a '0' value; others were coded with a value of '1'. The DSM-IV criteria are listed in table 2.

2.3.3 Recent- onset hallucinogen users

Recent-onset hallucinogen users can be identified via a NSDUH-derived variable that designates individuals who had started using one or more of the hallucinogenic

compounds within 24 months of the date of assessment. The approach of studying drug dependence among recent-onset users has been described in detail in multiple papers (e.g., Chen and Anthony, 2003, 2004; Storr et al., 2004; O'Brien and Anthony, 2005; Chen et al., 2005). In brief, there are three main reasons to focus upon these recent-onset users. First, this focus approximates and may provide a 'best estimate' for prospective research on the risk of developing drug dependence soon after use. In a true prospective study, drug users may be more likely to drop out (e.g., See Eaton, Anthony and Tepper 1992). If this type of drug-related sample attrition is prominent in a prospective study, its implication would most likely be an "underestimation" of the risk of becoming drug dependent because the attrition process is must likely to be present for drug users who progress to dependence, less likely for those who try the drug one or two times and then stop using it. Second, the focus on the most recent experiences of recent-onset drug users reduces recall and reporting processes that can distort estimates based on recollected information about the long distant past, particularly when the recollection might be disrupted by repeated bouts of drug intoxication, Anthony et al. (1994) drew attention to a major difficulty faced when comparisons of drug experiences are made over long span of developmental or chronological time, including possible changes in the purity or dosage forms of the drug under study, as well as changes in the subgroups recruited into illegal drug-taking. Third, one of the goals of pharmacological research is to develop a comparative picture of drug effects across compounds of interest. To the extent that this research is based upon a common product that also is applied to other psychoactive compounds, it becomes possible, via meta-analysis, or simple data displays, to compare the risk of become drug dependent among recent-onset hallucinogen users with

corresponding risk estimates for recent–onset users of other compounds (e.g., cannabis, cocaine, etc.). This is another important reason to hold constant the research approaches used by others.

2.3.4 Covariates of central interest

The covariates of central interest here are age, sex, race/ethnicity, level of education, family income, size of metropolitan statistical area (MSA), type of compound used, and the number of drugs used prior to first hallucinogen use (e.g., cocaine, cannabis, alcohol, tobacco).

2.3.5 A guiding conceptual model

The guiding conceptual model for the research is one in which we would expect to see hallucinogen dependence develop among a small proportion of recent-onset users (Stone et al., 2007). Based on these prior estimates, this proportion should be roughly 2%-3%. Some degree of subgroup variation in risk was anticipated, possibly in relation to sociodemographic characteristics such as male-female differences in risk of dependence (e.g, see Wagner and Anthony, 2005) and possibly in relation to the specific hallucinogen compound(s) used (e.g., see Stone et al., 2006;2007), as outlined in the project's aims.

2.3.6 Statistical Analysis

Our statistical analysis involves characterization of the distribution of hallucinogen experience and estimation of the risk of developing dependence among recent-onset users of the listed hallucinogens and related compounds. STATA 8.2 commands use the calculus (Taylor series linearization) together with logistic regression to estimate variances for complex survey data. STATA svylogit was used to regress the logit-transformed probability of becoming hallucinogen dependent on the covariates of

interest. For the analyses except when the results are labeled as "unweighted", the survey estimates are based upon proper survey analyses approaches, with application of the sampling weight and post-stratification adjustment factors (e.g, inverse of the probability of sampling; adjustment factors so as to make the age, sex, and race-ethnicity marginal distribution equivalent to those of the most recent United States Census Bureau values). The specific statistical model for the regression analysis was generalized linear model with the logistic link function because the response variable was binary (0/1) (STATA Corp, 2007) as shown here:

$$E(Y) = \mu = \eta = \beta_0 + \sum_{j=1}^{p} \beta_j x_j,$$

CHAPTER 3

3. RESULTS

3.1 Number of recent-onset users

The NSDUH method identified a total of 2026 respondents who had tried hallucinogens for the first time within 24 months of interview assessment, consisting of 1.8 % of the total constructed 2002-3 survey sample of 109,309 individuals (unweighted). Table 3 offers a sociodemographic description of all persons in the sample and these 'recent-onset hallucinogen users,' showing both unweighted proportions and weighted proportions.

Table 4 Selected sociodemographic characteristics of all persons and recent-onset Hallucinogen users. Data from 2002-2003 National Survey on Drug Use and Health

	All Persons in the sample			Recent-Onset Users of Hallucinogens*		
	n	%uwt	%wt	n	%uwt	%wt
All Persons	109309	100		2026	100	100
Sex						
Male	52723	48.2	48.3	1013	50.0	52.0
Female	56586	51.7	51.7	1013	50.0	48.0
Age at interview (in years)						
12 to 13	12291	11.2	3.5	96	4.7	3.5
14 to 15	12046	11.0	3.5	306	15.1	12.4
16 to 17	11576	10.5	3.4	584	28.8	22.0
18 to 20	14115	12.9	5.2	670	33.0	34.6
21 to 25	21996	20.1	7.9	324	15.9	16.6
26 to 34	11092	10.1	15.0	37	1.8	8.1
35 and older	26193	23.9	61.3	9	0.4	2.4
Race / ethnicity						
Nonhispanic White	73855	67.5	70.1	1487	73.4	72.7
Nonhispanic Black/African American	13528	12.3	11.4	147	7.2	7.9
Hispanic	14542	13.3	12.4	251	12.3	12.3
Other	7384	6.7	5.9	141	7.0	6.9
Education						
College Senior or Graduate	14629	13.3	22.7	73	3.6	7.2
Some College	20552	18.8	22.2	344	17.0	18.9
High School Graduate	25146	23.0	28.6	404	19.9	23.0
Less than High School Graduate	48982	44.8	26.3	1205	59.4	50.7
Family Income						
0 to $19,999	25354	23.1	19.4	552	27.2	26.0
$20,000 to $49,000	41935	38.3	37.8	709	35.0	33.0
$50,000 to $74,999	19446	17.7	18.4	352	17.3	17.8
$75,000 +	22574	20.6	24.1	413	20.3	23.0
Population density						
MSA of 1 million +	39006	35.6	44.8	728	35.9	47.3
MSA < 1 million	40775	37.3	33.1	804	39.6	34.2
Segment not in MSA	29528	27.0	22.0	494	24.3	18.3

*Note: This set of numbers includes all persons, including young individuals with years old enough to attend college.

3.2 Recent-onset and persistent hallucinogen use descriptive analysis

The proportions for 'all persons' are, in a sense, the expected values for the population against which we can compare 'observed' values for recent-hallucinogen users. For example, in the contrast of weighted proportions we see that the male-female ratio in the

total survey population is 48% to 52%, based on US Census values for 12 year old community residents. In the 'recent-onset users' column, we see a male-female ratio of 52% to 48%, an observed slight excess of males, but not appreciably different from the expected values. Moreover, the recent-onset users were slightly younger than 'all persons' in the sample. For example, at the time of survey assessment, looking at weighted values, 22% and 34% of the recent-onset hallucinogen users were 16-17 and 18-20 years old, respectively, as compared to roughly 3% and 5% of 'all persons'. Similar row by row comparisons reveal that members of the study population who designated themselves as Non-Hispanic Whites are somewhat over-represented among the recent-onset hallucinogen users (73%), as compared to the total population. College seniors and graduates are under-represented (3.6%) among the recent-onset hallucinogen users compared to the total population (but this is to same extent, an artifact of NSDUH over-sampling of 12-17 years old). No remarkable differences are evident for social status (gauged via a measure of family income) and size of the metropolitan statistical area (MSA) of residence.

Tables 4 and 5 show estimates pertinent to drug use characteristics of the recent-onset hallucinogen users. For example, an estimated 2.3% of the recent-onset hallucinogen users were found to have developed dependence on hallucinogens as assessed within 24 months after starting hallucinogen use; these users already had fulfilled criteria for DSM-IV hallucinogen dependence, as assessed via the NSDUH survey items and diagnostic algorithms.

Table 5 Selected drug use characteristics of all persons and the subset of recent-onset hallucinogen users

	All Persons			Recent Onset Users of Hallucinogens		
	n	%uwt	%wt	n	%uwt	%wt
All Persons	109309	100	100	2026	100	100
Occurrence of DSM-IV Hallucinogen Dependence Syndrome						
Yes, 3+ Clinical Features	171	0.2	0.1	47	2.3	2.3
No	109138	99.8	99.9	1979	97.6	97.7
Occasions of hallucinogen use (all forms) **in past 12 months.**						
1 to 2 days	1738	1.5	0.7	805	39.7	37.8
3 to 11 days	1338	1.2	0.5	462	22.8	23.3
12 to 100 days	1060	0.9	0.4	259	12.7	12.2
101 or more days	177	0.1	0.0	25	1.2	1.0
Never/not in past year/dk/ref	104996	96.0	98.1	475	23.4	25.4

Examination of the table 4, row by row, reveals that 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. However, 40% of the recent-onset hallucinogen users had consumed hallucinogens on only 1-2 days in the past 12 months, and one may surmise that none of these users had developed dependence.

In table 6 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 23% of recent-onset users had tried LSD. 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 all persons, (71% versus 6.4%). It is noteworthy that most users had consumed three or more drug compounds

before starting hallucinogen use. Most likely, these drugs were alcohol, tobacco, and cannabis.

Table 6 Selected drug use characteristics of hallucinogenic compounds and the subset of recent-onset hallucinogen users

	All Persons			Recent Onset Users of Hallucinogens		
	n	%uwt	%wt	n	%uwt	%wt
All Persons	109309	100	100	2026	100	100
LSD use in lifetime						
Yes	11302	10.3	10.4	465	22.9	20.5
No	6129	5.6	4.3	1561	77.0	79.4
Never/dk/ref	91878	84.0	85.2	–	–	–
PCP use in lifetime						
Yes	2940	2.6	3.0	165	8.1	6.1
No	14493	13.2	11.7	1861	91.8	93.8
Never/dk/ref	91876	84.0	85.2	–	–	–
Ecstasy use in lifetime						
Yes	7615	6.9	4.4	1160	57.2	1.4
No	9791	8.9	10.2	866	42.7	37.8
Never/dk/ref	91903	84.0	85.2	–	–	–
Mescaline use in lifetime						
Yes	3039	2.7	3.9	59	2.9	2.2
No	14324	13.1	10.7	1962	96.8	97.3
Never/dk/ref	91946	84.1	85.2	5	0.2	0.3
Peyote use in lifetime						
Yes	2028	1.8	2.4	72	3.5	3.2
No	15351	14.0	12.2	1952	96.3	96.5
Never/dk/ref	91930	84.1	85.2	2	0.1	0.1
Psilocybin use in lifetime						
Yes	9564	8.7	8.0	822	40.5	36.8
No	7761	7.1	6.6	1204	59.4	63.1
Never/dk/ref	91984	84.1	85.2	–	–	–
Number of hallucinogenic compounds used						
0	92125	84.2	85.3	–	–	–
1	7010	6.4	5.7	1442	71.1	74.1
2	4437	4.0	3.6	392	19.3	17.6
3	3206	2.9	2.6	134	6.6	6.0
4	1546	1.4	1.5	43	2.1	1.4
5	765	0.7	0.8	11	0.5	0.4
6 or more	220	0.2	0.2	4	0.2	0.1
# of drugs used prior to first hallucinogen use						
0	92928	85.0	86.0	44	2.1	2.2
1	1407	1.2	1	124	6.1	5.8
2	2802	2.5	2.4	268	13.2	12.4
3	12172	11.1	10.4	1590	78.4	79.4

3.3 Risk and relative risk estimates

Tables 7 and 8 present relative risk estimates (RR) without statistical adjustment, then RR estimates statistically adjusted for the other listed covariates. For example, according to unadjusted estimates being female, age at which hallucinogen use first started, education, and race/ethnicity are associated with becoming dependent on hallucinogens within the first 24 months after the onset of use. Female recent-onset users were an estimated 1.8 times more likely to have become dependent on hallucinogens soon after onset, as compared to male recent-onset users, an association at the margin of the conventional frequentist standard of $p < 0.05$ (estimated relative risk, RR=1.8; 95% CI=0.98, 3.3; p=0.05). As noted elsewhere, the RR estimate for education is misleading, in that the reference group includes a large number of 12-17 years olds who had not yet complete highs school. This issue is addressed in a separate analysis, as described in Section 4.5.

Table 7 Relative risk estimates for becoming hallucinogen dependent among recent-onset hallucinogen users, without statistical adjustments for listed covariates

	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases		Estimated Risk of Becoming Dependent without statistical adjustment		
			%	RR	95% CI	p value
All Persons	2026	47	2.3%	–	–	–
Sex						
Male	1013	17	1.7%	1.0	–	–
Female	1013	30	3.0%	1.8	0.9-3.3	0.05
Age at first hallucinogen use						
10 to 15	571	21	3.6%	2.1	1.02-4.6	0.046
16 to 17	590	14	2.4%	1.3	0.6-3.1	0.43
18 to 20 (ref)	580	10	1.7%	1.0	–	–
21 to 25	247	1	0.4%	0.2	0.02-1.8	0.16
26 and older	38	1	2.6%	1.5	0.1-12.3	0.68
Race/ethnicity						
Nonhispanic White	1487	31	22.0%	1.0	–	–
Nonhispanic Black	147	2	1.4%	0.6	0.1-2.7	0.55
Hispanic	251	7	2.8%	1.3	0.5-3.0	0.48
Others	141	7	5.0%	2.4	1.06-5.6	0.03
Education						
Less than High School Grad	1205	39	3.2%	1.0	–	–
High School Graduate	404	4	1.0%	0.2	0.1-0.8	0.02
Some College	344	4	1.2%	0.3	0.1-0.9	0.04
College Senior or Graduate	73	0	0.0%	–	–	–
Family income						
0 to $19,999	552	11	2.0%	0.7	0.3-1.4	0.34
$20,000 to 49,000 (ref)	709	20	2.8%	1.0	–	–
$50,000 - $74,999	352	7	2.0%	0.6	0.2-1.6	0.42
$75,000 or above	413	9	2.2%	0.7	0.3-1.7	0.51
Population density						
MSA of 1 million +	728	14	1.9%	0.8	0.4-1.6	0.55
MSA < 1 million (ref)	804	19	2.4%	1.0	–	–
Segment not in MSA	494	14	2.8%	1.2	0.5-2.4	0.60
# of drugs used prior to first hallucinogen use						
None or 1	168	1	0.6%	0.2	0.1-1.8	0.17
2	268	9	3.4%	1.4	0.6-3.0	0.31
3 or above	1590	37	2.3%	1.0	–	–

Note: Estimated RR adjusted are based on odds ratios from logistic regression with unweighted data and taylor series linearization for variance estimation to estimate 95% confidence intervals (CI), and associated p-values. See text (Sections 4.3 and 4.5) a discussion of the education RR estimates)

Among the 580 recent-onset hallucinogen users who were age 18-20 years old at the time of first use, an estimated 1.7% had developed hallucinogen dependence within 24 months after onset, not appreciably different from the 2.4% estimate derived for 16-17 year HU (Table 4). When the 10-15 year old HU are combined into a subgroup and compared to the 18-20 years old, there is excess risk in association with starting hallucinogen use before age 16 (RR=2.1; 95% CI=1.02, 4.6; p=0.046).

3.4 Race ethnicity

Recent-onset users who designated themselves as belonging to the "Other" race ethnicity category were an estimated 2.4 times more likely to have become dependent on hallucinogens soon after onset of use as compared to Non-Hispanic White recent-onset users (RR=2.4; 95% CI=1.06, 5.6; p=0.03). The composition of the 'others' category mainly includes Native Americans and Pacific Islanders. As seen in table 7, these associations remained statistically robust even when other listed covariates were held constant via regression models (sex, race/ethnicity, family income, and number of drugs used prior to first hallucinogen use).

Table 8 Relative risk estimates for becoming hallucinogen dependent among recent-onset hallucinogen users, with statistical adjustments for all listed covariates

	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases		Estimated Risk of Becoming Dependent with statistical adjustment		
			%	RR	95% CI	p value
All Persons	2026	47	2.3%		–	–
Sex						
Male	1013	17	1.7%	1.0	–	–
Female	1013	30	3.0%	1.8	0.9-3.3	0.06
Age at first hallucinogen use						
10 to 15	571	21	3.6%	2.2	1.0-4.6	0.05
16 to 17	590	14	2.4%	1.3	0.5-3.1	0.47
18 to 20 (ref)	580	10	1.7%	1.0	–	–
21 to 25	247	1	0.4%	0.2	0.02-1.7	0.14
26 and older	38	1	2.6%	1.2	0.1-10.2	0.83
Race/ethnicity						
Nonhispanic White	1487	31	2.0%	1.0	–	–
Nonhispanic Black	147	2	1.4%	0.9	0.2-4.0	0.92
Hispanic	251	7	2.8%	1.3	0.5-3.1	0.48
Others	141	7	5.0%	2.4	1.1-5.7	0.03
Family income						
0 to $19,999	552	11	2.0%	0.8	0.3-1.7	0.60
$20,000 to 49,000 (ref)	709	20	2.8%	1.0	–	–
$50,000 - $74,999	352	7	2.0%	0.7	0.3-1.8	0.59
$75,000 or above	413	9	2.2%	0.8	0.3-1.9	0.72
# of drugs used prior to first hallucinogen use						
None or 1	168	1	0.6%	0.1	0.01-1.1	0.06
2	268	9	3.4%	1.1	0.5-2.4	0.71
3 or above	1590	37	2.3%	1.0	–	–

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

Note: in the final logistic regression model we limited the array of covariates to exogenous characteristics to avoid possible reciprocal relationships operating between suspected determinants and hallucinogen dependence, like education and area of residence

3.5 Social Status

To assess the association between social status and hallucinogen dependence we analyzed data from the survey measure of family income. Both unadjusted and adjusted analyses showed minimal income-related variation in risk of becoming hallucinogen dependent soon after onset of use. An alternate variable, sometimes used to assess social status is level of education. In a subsidiary analysis, we restricted the sample to individuals who were 18 years and older (i.e., old enough to have completed high school) and found, according to unadjusted estimates, that recent-onset users with higher educational level (some college) were less likely to become dependent on hallucinogens as compared to recent-onset users with less than a high school diploma (RR= 0.3; 95% CI=0.1, 0.9; p=0.04). In the same manner, individuals with a high school graduate were less likely to become dependent on hallucinogens as compared to recent-onset users with less than a high school diploma (RR= 0.2; 95% CI=0.1, 0.8; p=0.02)..

3.6 Specific compounds

In Tables 9 and 10, we present unadjusted and adjusted estimates for risk of developing hallucinogen dependence in association with the use of each specific hallucinogenic compound, in reference to individuals who had just used LSD and/or one of the not otherwise specified (NOS) hallucinogens. According to both crude and adjusted estimates, the use of ecstasy was associated with increased risk of developing hallucinogen dependence as compared to the risk experienced by the LSD/NOS subgroup of users. The association with psilocybin was at the margin of conventional "statistical significance, with p=0.05

Table 9 Crude relative risk estimates for becoming hallucinogen dependent among recent- onset hallucinogen users in relation to hallucinogenic compound used

	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases	%	Unadjusted Estimates* Unweighted Estimated Risk of Becoming Dependent RR	95% CI	p value
All Persons	2026	47	2.3%	–	–	–
Lifetime Hallucinogen Use						
LSD	465	16	3.4%	1.0	–	–
PCP	165	9	5.5%	2.9	1.3-6.2	0.01
Ecstasy	1160	33	2.8%	2.2	1.1-4.2	0.02
Mescaline	59	3	5.1%	1.4	0.4-5.3	0.58
Peyote	72	1	1.4%	0.4	0.05-3.3	0.40
Psilocybin	822	22	2.7%	1.7	0.9-3.1	0.10
Number of Hallucinogenic compounds used						
1	1442	22	1.5%	1.0	–	–
2	392	13	3.3%	2.2	1.1-4.4	0.025
3	134	8	6.0%	4.1	1.8-9.4	0.001
4 or more	58	4	6.9%	4.8	1.5-14.4	0.005

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 but not the other listed drugs. The estimates are adjusting for other hallucinogens used, but not adjusting for other covariates

Table 10 Adjusted relative risk estimates for becoming hallucinogen dependent among recent- onset hallucinogen users in relation to hallucinogenic compound used

	Number of Recent-Onset Hallucinogen Users	Number of Hallucinogen Dependence Cases	%	Adjusted Estimates* Unweighted Estimated Risk of Becoming Dependent RR	95% CI	p value
All Persons	2026	47	2.3%	–	–	–
Lifetime Hallucinogen Use						
LSD	465	16	3.4%	1.0	–	–
PCP	165	9	5.5%	2.1	0.9-4.7	0.08
Ecstasy	1160	33	2.8%	2.3	1.1-4.4	0.02
Mescaline	59	3	5.1%	1.6	0.4-6.0	0.46
Peyote	72	1	1.4%	0.5	0.06-3.6	0.46
Psilocybin	822	22	2.7%	1.9	1.0-3.7	0.05
Number of Hallucinogenic compounds used						
1	1442	22	1.5%	1.0	–	–
2	392	13	3.3%	2.1	1.0-4.3	0.036
3	134	8	6.0%	3.9	1.6-9.1	0.002
4 or more	58	4	6.9%	4.8	1.5-15.2	0.007

*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.

The magnitude of increased risk seems not to vary markedly across the different types of hallucinogen compounds. For example, the risk for becoming hallucinogen dependent within 24 months after starting use is an estimates 2.2 times greater for those who used MDMA as compared to the risk of developing dependence for those in the LSD/NOS reference subgroup (RR= 2.2; 95% CI=1.1,4.2; p=0.02). For recent-onset users of PCP, there is an estimated 2.9 fold excess risk of becoming dependent as compared to recent-onset users in the LSD/NOS subgroup in the crude analysis (RR=2.9; 95% CI=1.3, 6.2; p=0.01), but not in the covariated adjusted analysis (p=0.08). No excess risk was observed for mescaline or for peyote. In a separate regression analysis, we studied the extent to which risk of becoming hallucinogen dependent might depend upon the number of hallucinogen compounds used. The resulting estimates indicate that recent-onset users who have tried a greater number of hallucinogens are more likely to have developed hallucinogen dependence as compared to recent-onset users who have used only one hallucinogen. For example, recent-onset users who have tried four or more hallucinogens are an estimated 4.8 times more likely to have developed hallucinogen dependence as compared to recent-onset users who have used only one hallucinogen (RR=4.8; 95% CI=1.5, 15.2; p=0.007). These associations remained strong even when other listed covariates were held constant via regression models.

3.7 Weighted analysis

The sequence of regression analyses was repeated with a population weighting feature, and it produced estimates and conclusions not appreciably different form unweighted analyses.

CHAPTER 4

4. DISCUSSION

4.1 Overview of Results

The main findings of this study may be summarized succinctly. First, it appears that approximately 2%-3% of recent-onset hallucinogen and related compounds under study had developed a dependence syndrome assessed within 24 months after onset of use. This estimate is consistent with the 2%-3% estimate reported by Stone and colleagues. Second, there is evidence of a modest (but statistically non-robust) male-female difference regarding risk of dependence among these recent-onset users, (RR=1.8; 95% CI=0.98, 3.3; p=0.05). Third, individuals who begin using hallucinogens before mid adolescence, prior to age 16 may be at greater risk of transitioning rapidly to dependence than those who start hallucinogen use at later age. Fourth, individuals who self-designated themselves as being of a race/ethnicity other than Non-Hispanic White, African American or Hispanic may experience a rapid transition to hallucinogen dependence (RR=2.5; 95% CI=1.1, 5.7; p=0.03). Finally, we confirmed an MDMA-associated excess risk of developing hallucinogen dependence, but not the excess risk associated with PCP or with mescaline that previously was reported by Stone and colleagues.

As we noted, that the SAMHSA (NSDUH) "hallucinogen" drug class includes a very heterogeneous set of compounds. Therefore, we conducted a post-hoc analysis in an attempt to study those who used PCP only, ecstasy only, or just PCP and ecstasy only, but no other hallucinogens. We found that the NSDUH sample, despite its size, included

no such hallucinogen use; all used at least one other hallucinogen (e.g., tow or more hallucinogens total). In these data, these subgroups represent empty sets (n=0).

4.2 Selected limitations

It is important to keep in mind several of the more important study limitations. With respect to the study design, the NSDUH is a cross-sectional survey, and is not a prospective study. 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 advancing hallucinogen dependence might induce 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).

Of course, there are disadvantages in the use of this 'simulation' approach with respect to the interpretation of the resulting study associations. For example, in a prospective study, education would be measure at base line, and so it would be not be affected by onset of drug use. Here, there is a probability that the drug use trigger drop outs and it will not allow us to measure education in a reliable way.

With respect to the sampling and recruitment approach, roughly 25% of individuals eligible to participate in the NSDUH declined participate 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. (One presumes that any prospective research of this type also might be affected thus kind of sample attrition at the time of recruitment.)

Another limitation deserves attention of anyone were to design a new research project on this topic – namely, the issue of elapsed time since onset of hallucinogen use. For example, the NSDUH does not gather data on how many days have passed since onset of use. This variable (elapsed time) cannot be controlled, and it might be important. For example, a person who first uses LSD the day before the assessment could not ever become dependent in that one day interval.

Notwithstanding limitations such as these, the present study confirms the prior estimates on the risk of becoming dependent on hallucinogens shortly after the onset of hallucinogen use i.e., 2%-3% within median elapsed time of 12-13 months. These findings of modestly excess risk of hallucinogen dependence among female recent-onset users is intriguing and merits attention in future and more probing research on male-female differences in development of hallucinogen dependence, but the claim of excess risk cannot now be asserted as a fact. It should be confirmed via replications that probe into the issue of statistical robustness. The observed race-ethnicity issue also is intriguing, and will become a topic for a separate report. Pooling across many NSDUH years, it might be possible to sort out the specific 'other' subcategory that is experiencing excess risk (e.g., Native American; Pacific Islander).

Another direction for future research involves a stratification of the recent-onset users by the number of occasions of hallucinogen use, and to estimate risk of becoming dependent for users at each level of drug use frequency,

CHAPTER 5

5. CONCLUSIONS AND MAIN DIRECTIONS FOR FUTURE RESEARCH

Several conclusions can be made about the risk of a hallucinogen dependence syndrome soon after onset of hallucinogen use based on these analyses of the NSDUH from two calendar years, CY2002 and CY 2003:

1. The evidence of this study confirms the prior estimates on the risk of becoming dependent shortly after the onset of hallucinogen use. An estimated 2%-3% became dependent within 24 months after first use .

2. The results of this study show a non-robust male-female difference in risk of dependence soon after onset of hallucinogen use (p=0.05), but Stone et al., found no male-female difference. More evidence is needed.

3. In this study's evidence and in the work by Stone et al., the users in the 'Other' race-ethnicity subgroup seemed to be at excess risk of dependence soon after onset of use. This is an intriguing lead that can be pursued in future research.

4. The other confirmed associations were with respect to the MDMA, who seem to be at excess risk of becoming dependent soon after onset of use of these compounds, relative to the experience of others in the sample.

5. We did not replicate the apparent excess risk associated with mescaline use that was previously reported by Stone and colleagues, although it is noteworthy that the psilocybin association was at the margin of statistical significance with p=0.05.

6. The higher risk status of adults lacking the high school diploma also is a note worthy near finding that merits attention in future research.

7. The results from this study suggest that individuals who begin to use hallucinogens early in adolescence may require more 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.

Overall, 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.

In sum, the evidence from this research work 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.

APPENDICES

Appendix 1

STATA Code

tab irsex if (ecstasy==1 & pcp==1) & (lsd==0 & peyote==0 & mesc==0 & psilcy==0 & halnolst==0)

tab ecstasy if lsd==0 & peyote==0 & mesc==0 & psilcy==0 & pcp==0 & halnolst==0

tab pcp if lsd==0 & peyote==0 & mesc==0 & psilcy==0 & ecstasy==0 & halnolst==0

Gender
tab irsex
tab irsex if halcat2==1
tab irsex if reconset==1
svyprop irsex
svyprop irsex, subpop (halcat2)
svyprop irsex, subpop (reconset)

Age at interview

tab catag7
tab catag7 if halcat2==1
tab catag7 if reconset==1
svyprop catag7
svyprop catag7, subpop (halcat2)
svyprop catag7, subpop (reconset)

Race
tab newracew
tab newracew if halcat2==1
tab newracew if reconset==1
svyprop newracew
svyprop newracew, subpop (halcat2)
svyprop newracew, subpop (reconset)

Education
tab refeduc
tab refeduc if halcat2==1
tab refeduc if reconset==1
svyprop refeduc
svyprop refeduc, subpop (halcat2)
svyprop refeduc, subpop (reconset)

Income

tab income4
tab income4 if halcat2==1
tab income4 if reconset==1
svyprop income4
svyprop income4, subpop (halcat2)
svyprop income4, subpop (reconset)

Pden
tab pden
tab pden if halcat2==1
tab pden if reconset==1

Occurrence of DSM IV Hallucinogen dependence syndrome (DEPNDHAL)
tab DEPNDHAL
tab DEPNDHAL if halcat2==1
tab DEPNDHAL if reconset==1
svyprop DEPNDHAL
svyprop DEPNDHAL, subpop (halcat2)
svyprop DEPNDHAL, subpop (reconset)

Occasions of hallucinogen use in the past 12 months (dayshal)
tab dayshal
tab dayshal if halcat2==1
tab dayshal if reconset==1
svyprop dayshal
svyprop dayshal, subpop (halcat2)
svyprop dayshal, subpop (reconset)

LSD

tab dlsd
tab dlsd if halcat2==1
tab dlsd if reconset==1
svyprop dlsd
svyprop dlsd, subpop (halcat2)
svyprop dlsd, subpop (reconset)

PCP
tab dpcp
tab dpcp if halcat2==1
tab dpcp if reconset==1
svyprop dpcp
svyprop dpcp, subpop (halcat2)
svyprop dpcp, subpop (reconset)

Ecstasy
tab decstasy
tab decstasy if halcat2==1
tab ecstasy if reconset==1
svyprop decstasy
svyprop decstasy, subpop (halcat2)
svyprop decstasy, subpop (reconset)

Mescaline
tab dmesc
tab dmesc if halcat2==1
tab dmesc if reconset==1
svyprop dmesc
svyprop dmesc, subpop (halcat2)
svyprop dmesc, subpop (reconset)

Peyote
tab dpeyote
tab dpeyote if halcat2==1
tab dpeyote if reconset==1
svyprop dpeyote
svyprop dpeyote, subpop (halcat2)
svyprop dpeyote, subpop (reconset)

Psilocybin
tab dpsilcy
tab dpsilcy if halcat2==1
tab dpsilcy if reconset==1
svyprop dpsilcy
svyprop dpsilcy, subpop (halcat2)
svyprop dpsilcy, subpop (reconset)

Number of hallucinogen compounds use
tab refnumhal
tab refnumhal if halcat2==1
tab refnumhal if reconset==1
svyprop refnumhal
svyprop refnumhal, subpop (halcat2)
svyprop refnumhal, subpop (reconset)

# of drugs used prior to first hallucinogen use
tab xdub4XXX
tab xdub4xxx if halcat2==1
tab xdub4xxx if reconset==1
svyprop xdub4xxr

svyprop xdub4xxr, subpop (halcat2)
svyprop xdub4xxr, subpop (reconset)

Sex
xi: logistic depndhal i.irsex if reconset ==1, or
xi: svylogit depndhal i.irsex, subpop (reconset) eform

AGE at first hallucinogen use
xi: logistic depndhal i.refagecat if reconset ==1, or
xi: svylogit depndhal i.refagecat, subpop (reconset) eform

Race
xi: logistic depndhal i.newracew if reconset ==1, or
xi: svylogit depndhal i.newracew, subpop (reconset) eform

Income
xi: logistic depndhal i.refincome if reconset ==1, or
xi: svylogit depndhal i.refincome, subpop (reconset) eform

Education
xi: logistic depndhal i.refeduc if reconset ==1, or
xi: svylogit depndhal i.refeduc, subpop (reconset) eform

Refpden

xi: logistic depndhal i.refpden if reconset ==1, or
xi: svylogit depndhal i.refpden, subpop (reconset) eform

# of drugs used prior to first hallucinogen use

xi: logistic depndhal i.refdrugb4 if reconset ==1, or
xi: svylogit depndhal i.refdrugb4, subpop (reconset) eform

Adjusted
Unweighted
xi: logistic depndhal i.irsex i.refagecat i.newracew i.refincome i.refdrugb4 if reconset ==1, or

xi: logistic depndhal i.irsex i.ahalage2 i.refeduc i.newracew i.refincome i.refppden i.xdub4XXX if reconset ==1, or (cannabis paper and hall- restricted to reconset)

Logistic regression models for the different drugs

Crude
Unweighted
xi: logistic DEPNDHAL i.apcp i.aecstasy i.amesc i.apeyote i.apsilcy if reconset ==1, or

Adjusted
Unweighted
xi: logistic depndhal i.irsex i.refagecat i.newracew i.refincome i.refdrugb4 i.apcp i.aecstasy i.amesc i.apeyote i.apsilcy if reconset ==1, or

Number of hallucinogenic compound use (refnumhal)

Crude
Unweighted
xi: logistic depndhal i.refnumhal if reconset ==1, or

Adjusted
Unweighted
xi: logistic depndhal i.refnumhal i.irsex i.refagecat i.newracew i.refincome i.refdrugb4 if reconset ==1, or

REFERENCES

1. Abraham, H.D., Aldridge, A.M. and Gogia, P., *The psychopharmacology of hallucinogens.* Neuropsychopharmacology, 1996. 14: 285-298.

2. American Psychiatric Association.1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. American Psychiatric Association (APA), 2005 Washington DC:

3. Anthony, J.C., Warner, L.A., Kessler, R.C., *Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Study.* Experimental and Clinical Psychopharmacology, 1994 2(3): 244-268.

4. Byrska, B Zuba, D. *Profiling of 3,4-methylenedioxymethamphetamine by means of high-performance liquid chromatography.* Anal Bioanal Chem.,2007

5. Blum, R and Associates, Utopiates., *The Use and Users of LSD-25 NY*, 1965,Atherton Press.

6. Reid, D.A., *A monograph of the Australian species of Amanita Person ex Hooker (Fungi).* Australian Journal of Botany, 1980. Supplementary Series

7. Brust, J.C.M., *Neurological Aspects of Substance Abuse*, Boston, 1993: Butterworth-Heinemann

8. Callaway, J.C. and Grob, C.S., *Ayahuasca preparations and serotonin reuptake inhibitors: a potential combination for adverse interaction.* Journal of Psychoactive Drugs, 1998 30(4): 367-369

9. Chen, C.Y., Anthony, J.C., *Possible age-associated bias in reporting of clinical features of drug dependence: epidemiological evidence on adolescent-onset marijuana use.* Addiction, 2003 98(1):71-82.

10. Chen, C.Y., Anthony, J.C., *Epidemiological estimates of risk in the process of becoming dependent upon cocaine: cocaine hydrochloride powder versus crack cocaine.* Psychopharmacology, 2004172, 78-86.

11. Chen, C.Y., O'Brien, M.S., Anthony, J.C., *Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000-2001.*Drug Alcohol and Dependence. In press for 2005.

12. Cohen, S. *Drugs of hallucination: The uses and misuses of lysergic acid diethylamide (in English).* London: Secker & Warburg, 1965. 224-225.

13. Cottler, L.B., Womack, S.B., Compton, W.M., Ben-Abdallah, A., *Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria.* Human Psychopharmacology, 200116(8): 599-606.

14. Doweiko, H. E., *Concepts of Chemical Dependency. Pacific Grove, CA*: 1996. Brooks/Cole Publishing Company

15. Eaton W.W, Anthony J.C., Tepper S., Dryman A., *Psychopathology and attrition in the epidemiologic catchment area surveys.* Am J Epidemiol., 1992. May 1;135(9):1051-9

16. Eugster CH, Müller GFR, Good R., *Active principles from Amanita muscaria: ibotenic acid and muscazone*, 1965. Tetrahedron Letters 6: 1813–1815.

17. Frances, R.J., Miller, S. I., *Clinical Textbook of Addictive Disorders.* New York: 1998. The Guilford Press.

18. Goodman & Gilman's, *The Pharmacological Basis of Therapeutics*, 11th Edition.1995. Laurence L. Brunton, editor-in-chief John S. Lazo and Keith L. Parker, Associate Editors

19. Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, Stoll M, Stock C, Obradovic M, Kovar KA. *Psychological effects of (S)-ketamine and N,N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers,* 2005. Pharmacopsychiatry. Nov;38(6):301-11.

20. Greer, G., Tolbert, R., *Subjective reports of the effects of MDMA in a clinical setting,* 1986. J Psychoactive Drugs. (18) 319-27.

21. Haddad, L.M., *Management of Hallucinogen abuse,* 1976. 14 (1): 82-87

22. Jacobs, B.L., *How hallucinogenic drug work,* 1987. American Scientist, 75,386-392

23. Julien, R.M., *Psychedelic Drugs: Mescaline, LSD and other "mind- expanding",* 1995hallucinogen, chapter 12, p.301-329. In Julien, R.M The primer of drug action, 7th ed., WH Freeman & Co, NewYork

24. Kögl F, Salemink CA, Shouten H, Jellinek F., *Über Muscarin III. Recueil des Travaux Chimiques des Pays-Bas,* 1957. 76:109–127

25. Lieb R, Schuetz CG, Pfister H, von Sydow K, Wittchen H, *Mental disorders in ecstasy users: a prospective-longitudinal investigation,* 2002. Drug Alcohol Depend 68: 195-207.

26. Martinez, J.M., Carmen del Rio, M., Lopez, N., Alvarez, F.J., *Illegal drug-using trends among students in a Spanish University in the last decade (1984-1994),* 1999. Subst. Use Misuse 34 (9), 1281-1297.

27. Maclean, J.R.; Macdonald, D.C.; Ogden, F.; Wilby, E.1967. *"LSD-25 and mescaline as therapeutic adjuvants."* In: Abramson, H., Ed., *The Use of LSD in Psychotherapy and Alcoholism,* Bobbs-Merrill: New York, 1967, pp. 407–426; Ditman, K.S.; Bailey, J.J., *"Evaluating LSD as a psychotherapeutic agent,"* pp.74–80; Hoffer, A., *"A program for the treatment of alcoholism: LSD, malvaria, and nicotinic acid,"* pp. 353–402

28. Miller, N.S., *Comprehensive handbook of drug and alcohol addiction,* 1991. Marcel Dekker, Inc. New York.

29. James W., *The varieties of religious experience,* 1902. New York, American Modern Library.

30. Jenkins, JB. *Tyndale House Pub.,* 1999. Left behind text.

31. Johnston, L.D., O'Malley, P.M., & Bachman, J.G., *Monitoring the Future: National Survey Results on Drug Use, 1975–2002,* 2003. Volume II: College students and adults ages 19-40. NIH Publication No. 03-5376. Bethesda, MD: National Institute on Drug Abuse

32. Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E., *Monitoring the Future National Results on Adolescent Drug Use: Overview of key findings, 2005,* 2006. NIH Publication No. 06-5882. Bethesda, MD: National Institute on Drug Abuse.

33. O'Brien, M. S. &, Anthony, J. C., *Risk of Becoming Cocaine Dependent: Epidemiological Estimates for the United States, 2000-200,* 2005. Neuropsychopharmacology, 1-13

34. Parrot A.C., Laski, J., *Ecstasy (MDMA) effects upon mood and cognition, before and after a Saturday night dance* 1988. Psychopharm 139: 261-8.

35. Peroutka, S.J., Pascoe, N.,Faull, K.F., *Monamine metabolites in the cerebroespinal fluid of recreation users of 3,4 methylenedioxymethamphetamine (MDMA; 'Ecstasy'),* 1987. Res. Commun. Subst. Abuse 8, 125-138.

36. Ray, O.S., *Drugs, Society and human behavior,* 1972.

37. Samorini G., *The oldest representations of hallucinogenic mushrooms in the world (Sahara desert, 9000–7000 B.P.),* 1992. Integration: Journal of Mind-Moving Plants Culture 2/3: 69–78.

38. Schultes R. and Hofmann, A., *The botany and chemistry of hallucinogens,* 1980. Springfield, IL, Thomas.

39. Schuster, P., Lieb R., Lamertz C., Wittche H.U., *In the use of ecstasy and hallucinogens increasing? Results from a community study,* 1998. Eur Addict Res. Mar; 4 (1-2); 75-82

40. StataCorp, *Stata Statistical Software: Release 7.0.* 2001. College Station, TX: Stata Corporation.

41. Stone, A.L., O'Brien, M. S., De La Torre, A, Anthony, J.C., *Who is becoming hallucinogen dependent soon after hallucinogen use starts?* 2007. Drug Alcohol Depend., 87 (2-3).

42. Substance Abuse and Mental Health Services Administration. Office of Applied Studies. *Results from the 2004 National Survey on Drug Use and Health: National Findings (NSDUH Series H-28).* DHHS Pub. No. (SMA) 05-4062. SAMHSA, 2005.

43. Substance Abuse and Mental Health Services Administration. Office of Applied Studies. *Drug Abuse Warning Network, 2003: Interim National Estimates of Drug-Related Emergency Department Visits.* DAWN Series D-26, DHHS Publication No. (SMA) 04-3972. Rockville, MD 2004.

44. Turner, D.M. *Mescaline: Peyote and San Pedro cactus. Shamanic Sacraments.* Retrieved on April 8, 2004.

45. United States Substance Abuse and Mental Health Services Administration, 2002a. *Results from the 2002 National Household Survey on Drug Abuse: Volume II. Technical appendices and selected data tables* (Office of Applied Studies, NHSDA Series H-18, DHHS Publication No. SMA 02-3759). Rockville, MD.

46. United States Substance Abuse and Mental Health Services Administration, 2002b. *Results from the 2002 National Household Survey on Drug Abuse: Volume III. Detailed Tables* (Office of Applied Studies, NHSDA Series H-19, DHHS Publication No. SMA 02-3760). Rockville, MD.

47. United States Substance Abuse and Mental Health Services Administration, 2003. *Results from the 2003 National Household Survey on Drug Use and Health: Summary of National Findings* (Office of Applied Studies, NHSDA Series H-22, DHHS Publication No. SMA 03-3836). Rockville, MD.

48. Vollenwieder, Franz X. et al., *Psilocybin induces schizophrenia-like psychosis in humans via a serotonis-2 agonist action.* 1998. NeuroReport 9. 3897-3902.

49. Von Sydow, K., Lieb, R., Pfister, H., Hofler, M., Wittchen, H.U., *Use abuse and dependence of ecstasy and related drugs in adolescents and young adults- a transient phenomenon? Results from a longitudinal community study.* 2002. Drug and Alcohol Depend. 66, 147-159.

50. Webb, E., Ashton, C.H., Kelly, P., Kamali, F., *Alcohol and drug use in UK university students, 1996.* The Lancet 348, 922-925.