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PREFACE

A number of our Nation's best monitoring systems are detecting alarming increases in the popularity of the drug MDMA (3,4-methylenedioxymethamphetamine), particularly among today's youth. Unfortunately, myths abound about both the acute effects and long-term consequences of this drug, also known as "Ecstasy." In response, on July 19-20, 2001, the National Institute on Drug Abuse (NIDA) convened a national and international cadre of experts to examine the latest scientific findings on MDMA on the NIH campus entitled, "*MDMA/Ecstasy Research: Advances, Challenges, Future Directions."* Attendance at this two-day conference surpassed the Institute's expectations, as over 500 researchers, drug abuse counselors, law enforcement officials, and concerned citizens attended to learn more about MDMA. The conference was also recorded for future playback, and is now available at http://www.nida.nih.gov/Meetings/MDMA/MDMAindex.html.

Conference presenters and participants were asked to discuss both what we know about the patterns and trends of abuse, acute effects, long-term toxicity, and functional consequences of MDMA abuse, as well as to identify areas requiring additional research. This report offers a summation of the research findings presented during the conference.

While we have learned much about how MDMA exerts many of its effects, many questions remain to be answered, particularly about the long-term consequences of MDMA abuse. Studies in animal models have clearly demonstrated long-lasting damage to specific areas of the brain. Evidence is emerging that shows this same type of damage may be occurring in people abusing this drug, and researchers are beginning to identify some of the long-lasting psychological consequences of MDMA abuse. Studies of the functional consequences of MDMA abuse are complicated by the fact that what is sold as ecstasy on the streets may or may not contain MDMA, and may also contain other drugs or drug combinations that can be harmful. Also, as with other drugs of abuse, MDMA is rarely used alone. It is not uncommon for users to mix MDMA with other substances such as alcohol and marijuana. Nevertheless, data are emerging that MDMA is not the benign party drug that it is portrayed to be by some individuals.

In order to provide researchers, practitioners, and policy makers with up-to-date scientific information, the NIDA is pleased to bring you this report on our current understanding of the public health impact of MDMA abuse.

Sincerely,

Acting Director, National Institute on Drug Abuse

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EXECUTIVE SUMMARY

A number of our Nation's best monitoring mechanisms have detected an alarming increase in the popularity of MDMA (3,4-methylenedioxymethamphetamine), particularly among young Americans. Unfortunately, myths abound about both the acute effects and long-term consequences of this drug, also known as "Ecstasy," with many young people believing that MDMA is safe, offering nothing but a pleasant high for the $25 cost of a single tablet. But MDMA is not new to the scientific community, with many laboratories beginning their investigations of this drug in the mid 1980s, and the picture emerging from their efforts paints a much different image of this drug, one that is far from benign.

This report, *Ecstasy: What We Know and Don't Know About MDMA*, represents a scientific review of what research has discovered about how this drug works in the brain and what requires further study to fully understand the consequences of using this illicit substance. This report discusses what scientists know and don't know about MDMA's acute effects on the brain and behavior from laboratory studies in both animals and humans. The report also reviews the long-term effects on the brain, again in both laboratory animals and humans, as well as long-term behavioral consequences detected in chronic MDMA users.

Much of this report is based on a scientific conference – *MDMA/Ecstasy Research: Advances, Challenges, Future Directions* – that was sponsored by the National Institute on Drug Abuse (NIDA) and the National Institutes of Health and held July 19-20, 2001. Information in this report was supplemented by an exhaustive review of the extensive published scientific literature on MDMA, particularly that which has appeared in scientific and medical journals during the past five years.

MDMA, a relatively simple chemical belonging to the amphetamine family of compounds, has properties of both stimulants and hallucinogens. While MDMA does not cause true hallucinations, many people have reported distorted time and perception while under the influence of this drug. The vast majority of people take MDMA orally, and its effects last approximately four to six hours. Many users will "bump" the drug, taking a second dose when the effects of the initial dose begin to fade. The typical dose is between one and two tablets, with each containing approximately 60-120 milligrams of MDMA. However, tablets of what users call Ecstasy often contain not only MDMA but a number of other drugs, including methamphetamine, caffeine, dextromethorphan, ephedrine, and cocaine.

One of the more alarming facts about MDMA is that despite its known detrimental effects, there are increasing numbers of students and young adults who continue to use the drug. Results from the 2000 Monitoring the Future survey indicate that MDMA use

increased among students in the 12th, 10th, and 8th grades. African Americans show considerably lower rates of MDMA use than do either whites or Hispanics. The recent CEWG data showed a large increase in use among Hispanics that may represent an important change.

EFFECTS OF ACUTE DOSES OF MDMA

MDMA works in the brain by increasing the activity levels of at least three neurotransmitters: serotonin, dopamine, and norepinepherine. Much like other amphetamines, MDMA causes these neurotransmitters to be released from their storage sites in neurons, increasing brain activity. Compared to the potent stimulant methamphetamine, MDMA triggers a larger increase in serotonin and a smaller increase in dopamine. Serotonin is a major neurotransmitter involved in regulating mood, sleep, pain, emotion, and appetite, as well as other behaviors. By releasing large amounts of serotonin, and also interfering with its synthesis, MDMA leads to a significant depletion of this important neurotransmitter. As a result, it takes the human brain a significant amount of time to rebuild the store of serotonin needed to perform important physiological and psychological functions.

One hypothesis to explain the long-lasting neurotoxicity of MDMA on serotonergic systems is that MDMA induces both oxidative and metabolic stress in serotonin neurons that, in turn, adversely affect the ability of these neurons to produce serotonin. Support for this hypothesis comes from a variety of studies, including those showing that MDMA perturbs the activity of various antioxidant enzymes; artificially boosting the levels of these enzymes reduces MDMA's effects on serotonin and dopamine neurons. Also, stress appears to increase the oxidative damage caused by MDMA.

It has been difficult to study the effects of MDMA in humans under controlled conditions, and virtually impossible until recently to conduct simultaneous neurochemical studies. However, several groups of researchers have chosen to study the behavioral pharmacology of MDMA in various animal species, showing that MDMA and related compounds produce a unique behavioral profile in rodents. Studies in non-human primates suggests that acute doses of MDMA may have subtle effects on higher cognitive functions, including memory and learning. Other experiments in laboratory animals suggest that MDMA is a drug that humans are likely to abuse, and that humans may develop tolerance to MDMA's reinforcing effects. Limited studies in humans have shown that MDMA negatively impacts short-term performance on a variety of measures of cognitive ability.

Controlled studies in humans have shown that MDMA has potent effects on the cardiovascular system and on the body's ability to regulate its internal temperature. Of great concern is MDMA's adverse effect on the pumping efficiency of the heart – in the presence of MDMA, increased physical activity increases heart rate significantly, but the heart does not respond in its normal manner, which is to increase the efficiency with which it pumps blood. Since MDMA use is often associated with sustained, strenuous activity, such as dancing, MDMA's effects on the heart could increase the risk of heart damage or other cardiovascular complications in susceptible individuals.

Pharmacokinectic studies have shown that MDMA is rapidly absorbed into the human blood stream, but once in the body the metabolites of MDMA inhibit MDMA metabolism. As a result, subsequent doses of the drug produce unexpectedly high blood levels, which could worsen the cardiovascular and other adverse effects of this drug without increasing its ”pleasurable” effects, which tend to peak about two hours after taking an initial dose. MDMA interferes with the metabolism of other drugs, including some of the adulterants in MDMA tablets.

LONG-TERM CONSEQUENCES OF MDMA: NEUROCHEMICAL AND DEVELOPMENTAL

Acute doses of MDMA produce marked changes in both dopamine and serotonin systems within the brain. Though the changes in dopaminergic neurons appear transient, the data suggest that the changes in the serotonergic system are longer-lasting. In addition, examinations of more global brain function have shown that the effects of acute doses of MDMA extend to regions of the brain that are thought to be involved in higher thought processes. These findings have raised concern about possible long-term effects on both infrequent and regular users of MDMA.

Several groups have shown that exposure to MDMA rapidly and persistently destroys a key marker of serotonergic function in regions known to have a high density of serotonin neurons, including the striatum and cortex. More detailed examination of this structural damage shows that MDMA appears to prune, or reduce in number, serotonin axons and axon terminals. Eighteen months after a short course of MDMA, investigators found that some brain regions had substantial loss of serotonin axon terminals, while a few others had more serotonin axon terminals. This pattern is a hallmark of axon pruning, since nerve cells will often grow replacement terminals upstream of the damaged terminals. These results, then, are evidence not only of MDMA’s neurotoxicity, but of the brain attempting to rewire the serotonin system after damage.

Since younger brains may have an increased susceptibility to the neurotoxic effects of MDMA, it may be that the youngest, fastest developing brains – those of a developing fetus – could be particularly vulnerable to the effects of this apparent serotonin neurotoxin. Since most MDMA users are young and in their reproductive years, it is possible that some female users may take MDMA when they are pregnant, either inadvertently or intentionally, because of the misperception that it is a safe drug. Studies in animals have shown that MDMA has little effect on the physical development of the young brain. Behavioral and cognitive studies in laboratory animals, however, have identified significant adverse cognitive effects from pre and neonatal exposure to MDMA. This effect was not due to serotonergic neurotoxicity; the mechanisms underlying the development of these cognitive deficits are not known yet. Though the rodent experiments have predictive value, it is not known whether human fetuses exposed to MDMA when their mothers abuse the drug will develop persistent and learning memory deficits.

LONG-TERM FUNCTIONAL CONSEQUENCES OF MDMA: BEHAVIORAL, MOOD, PSYCHIATRIC, AND COGNITIVE

Because MDMA produces long-term deficits in serotonin function, and because serotonin function has been implicated in the etiology of many psychiatric disorders including depression and anxiety, investigators have suspected that MDMA users may experience more psychopathology than non-users. Indeed, a number of investigators have found that heavy MDMA users experience a constellation of psychiatric changes, scoring significantly higher on measures of obsessive traits, anxiety, paranoid thoughts, and disturbed sleep, among others. One study, aimed at developing reliable measures of diagnosing substance abuse disorders, found that 43 percent of MDMA users met DSM-IV criteria for dependence and 34 percent met the criteria for abuse of MDMA.

There is a large and growing body of evidence from a variety of studies with humans that MDMA use can have long-lasting effects on memory. None of these studies are perfect, as they all have methodological concerns such as concurrent use of other drugs (it is apparently impossible to find but a few MDMA users who do not use other illicit substances, particularly marijuana). In addition, results vary with the assessment used. Nonetheless, the general finding that emerges across all of the studies is that MDMA does impact memory abilities in ways that could adversely affect normal functioning on every day tasks. Moreover, the relationship between memory problems and MDMA use appears to have a dose-dependent relationship, that is, the more MDMA used, the greater the deficit.

Given that numerous studies have shown that the serotonin deficits caused by MDMA are persistent, lasting at least seven years in one study of nonhuman primates, it is important to determine if the psychological and memory deficits associated with even moderate use of MDMA recover after some period of time. This is a particularly important issue with MDMA because of the relatively young age of the majority of people who abuse this drug. So far, the majority of studies have focused on MDMA users who have been abstinent for a period of a few weeks to a few months – longer-term studies have been planned or are underway – and these have shown that the adverse psychiatric and cognitive changes associated with MDMA use are persistent.

In attempting to answer the question of whether MDMA causes permanent damage to human memory abilities, there is no one study that provides a resounding, definitive yes. To be sure, no study provides any evidence that MDMA is a beneficial drug or even that it is safe when taken in moderation. In fact taking MDMA at any dose carries with it the risk of inducing physiological, psychological, and cognitive damage in vulnerable users. Clearly, there is still room to debate the exact nature of the deficits produced by MDMA use. Nevertheless, based on the results from the overwhelming majority of studies conducted so far, the data show that MDMA can be harmful to human health.

METHODOLOGICAL ISSUES

As much as the data collected so far largely supports the proposition that MDMA damages the serotonin system in the brain and produces long-lasting behavioral deficits, researchers agree that methodological issues, such as limited sample size and difficulties

controlling for the possible influence of other illicit substances, have made it difficult to move beyond generalities and unequivocally prove a cause and effect relationship between MDMA use and specific cognitive or psychological damage in humans.

All of the studies reviewed in this report have relied on self-referred MDMA users, recruited through targeted sampling techniques by advertising for volunteers or through word-of-mouth. This introduces an unknown bias into each study since it is possible that such self-referrers are not representative of MDMA users as a whole. There is also the problem of verifying that what users report as Ecstasy is, in fact, solely MDMA. In addition, it is impossible to verify self-reports of past drug use beyond a certain period of time, making it difficult at best to accurately control for prior drug use.

Since there seem to be few, if any, young people who use MDMA without also abusing other drugs, this will continue to be a confounding factor in future studies. Some investigators have tried to accommodate this problem by using a control group comprising individuals who have never used MDMA but who otherwise have closely matched histories of using other drugs of abuse. This type of control has not been used universally, however, and even when it is, it may be difficult to closely match users and controls for prior drug use, as well as on other demographic details such as educational level and age.

Self-reporting also means that it is not possible to determine with complete confidence or accuracy how much a person has consumed, either on a particular occasion or over a lifetime of use. This uncertainty arises for two reasons: MDMA content is not constant across all tablets, and user memory of how much and how often a person took MDMA over many years is far from reliable.

Ideally, researchers would like to be able to study MDMA's effects in drug-naïve humans, and indeed, a limited number of groups in Europe have received approval from the appropriate governmental regulatory agencies and institutional review boards to conduct what would essentially be Phase I safety trials with MDMA in a limited number of humans. However, there is little likelihood of studying the effects of MDMA on large numbers of drug-naïve volunteers. An alternative might be to conduct longitudinal, controlled prospective studies, in which current MDMA users and controls of non-MDMA users are followed for many years to observe changes from some defined baseline.

CHALLENGES AND FUTURE DIRECTIONS

Though the data presented at this conference and in the literature support the hypothesis that MDMA produces acute behavioral and physiological effects, there is still more to be determined about factors that precipitate severe acute toxicity. For example, are there predisposing genetic factors that increase the risk for acute toxicity? Is overall health status important? Which organs and systems are the primary targets of MDMA toxicity? Are interactions with other drugs important? Does MDMA use lead to tolerance, withdrawal, and craving?

Because MDMA is not the only drug taken by young adults, there is a need for more characterization of interactions between these substances and a determination of how those drug interactions may influence acute toxicity. Is the practice of "bumping" or taking sequential doses of MDMA particularly dangerous? How do individual genetic factors influence MDMA metabolism and drug interactions?

One critical piece of missing data is the incidence of acute toxicity among MDMA users. Assembling this database will require improved emergency room reporting of MDMA-associated incidents. In addition, data do not yet exist on the number of people seeking treatment for MDMA-related dependence and behavioral or psychological problems.

One of the key concerns raised at the meeting was the lack of longitudinal studies designed to follow MDMA users, both as they continue to use the drug and after they have stopped using it. Such studies may provide important insight into how age and length of use affect MDMA's acute and long-term neurochemical toxicity. In addition, such studies would allow researchers to determine if deficits appear later in life, long after use stops, or if adverse effects diminish over time. Such studies, if designed with regular assessment intervals, might also allow researchers to develop better measures of MDMA toxicity, and to more accurately determine how much drug is used and in what circumstances.

If conducted with large enough groups of MDMA users and control subjects, both drug naïve and matched for poly-drug use, longitudinal studies could also help identify risk and protective factors for drug use and the deficits that result from continuing exposure to MDMA. The identification of significant risk and protective factors would greatly aid the development of efficacious prevention and rehabilitation approaches. Data from longitudinal studies would also help establish associations between MDMA use and behavioral impairments that researchers have observed in the majority of studies. Longitudinal designs may enable researchers to determine how long such impairments last, whether they are progressive, and if deficits become more evident as MDMA users move into middle and late adulthood or experience other age-related neurologic disorders. Questions about the reversibility of impairments, a concern given the data seen in animal studies and even in some human studies, could also be addressed by such designs. Longitudinal studies should also provide data on critical patterns of MDMA use that may be more or less likely to cause impairments, and can help to determine whether simultaneous abuse of other drugs plays a role in causing behavioral and cognitive damage.

Along with such studies, researchers need better tools to assess neurotoxicity in human MDMA users and to measure changes of neuronal integrity and possible recovery over time. With such tools, investigators may also be able to address important mechanistic questions, such as how damage to the serotonin system leads to behavioral and cognitive changes, how the brain responds to and compensates for serotonergic damage, and why the dopaminergic system seems to escape lasting damage from MDMA. Such studies might then lead to the development and validation of methods for promoting recovery from MDMA-induced neurotoxicity.

There is also a need for more studies looking at the long-term effects of poly-drug abuse. Such studies will require new analytical tools for detecting multiple drugs of abuse simultaneously in biological samples and for more accurately assessing drug use histories, including the combination and sequencing of drugs used.

There are little data available on whether addiction, dependence or tolerance develops with continued use of MDMA. Though the data from animal studies support this possibility, more studies are needed in humans to determine the degree of abuse liability for this drug and to help develop treatments specific for reducing MDMA addiction. Along the same lines, researchers at this meeting stressed again that there are little data on numbers of drug treatment patients who have used MDMA or who have sought treatment because of MDMA abuse.

Another scientific gap idenitfied at the scientific conference concerns the development of methods for tracking so-called hidden populations of MDMA users; that is, those who don't go to dance clubs or raves, where the majority of volunteer recruiting occurs. At the same time, researchers also stressed the need to better understand the youth party culture that seems to actively promote MDMA use through the use of in-house drug dealers and marketing messages delivered through music and by pop icons.

There is a need to foster interdisciplinary research and dialogue that links epidemiological, ethnographic, clinical and laboratory studies. As this report shows, there is much overlap between these separate fields, and undoubtedly, this area of investigation could benefit from better coordination between disciplines. There is also a need to link local, regional, national, and international supply-side intelligence with demand-side epidemiological and ethnographic research.

Prevention efforts cannot be universal but must be targeted at different groups that use MDMA, particularly since MDMA appears to be a drug whose use is sensitive to and intimately linked with social context and networks. In particular, there is a need to integrate local research, services, prevention and intervention efforts to provide targeted, shared messages. The conference speakers recommended that there be a new focus within youth networks and adult education programs to counter the perception that MDMA is much safer than other drugs. The use of youth-led advocacy and drug prevention programs seems particularly promising for reducing MDMA use among adolescents and young adults.

ECSTASY : WHAT WE KNOW AND DON'T KNOW ABOUT MDMA A SCIENTIFIC REVIEW

CHAPTER 1. INTRODUCTION

In 1912, pharmaceutical scientists created a new chemical derivative of amphetamine, 3,4-methylenedioxymethamphetamine or MDMA, and patented it soon afterwards for use as a versatile chemical intermediate in the synthesis of other pharmaceuticals. For reasons that have been lost over time, the company that invented this compound did little to explore its own properties as a drug. In fact, there was little interest in MDMA until the 1950s, when the U.S. Army studied it as a potential chemical warfare agent that would temporarily disable enemy troops. In the 1970s, despite a lack of any meaningful, controlled clinical trials, many psychotherapists used it as a regular part of therapy, with some even calling it "penicillin for the soul" because of the way that it seemingly enhanced communication in patient sessions and supposedly allowed users to achieve important, healing insights about their problems.[1] However, therapeutic utility of MDMA was not established.

In the 1980s, MDMA got a new nickname, Ecstasy (also XTC and E), given to it by the newest group to experiment with it, our Nation's youth. But at about the same time that MDMA first appeared as a so-called "party" or "club" drug at raves or all-night dance parties, evidence was emerging that this compound was not harmless, and indeed, could cause damaging effects on serotonergic neurons. In fact, in 1985 the U.S. Drug Enforcement Administration added MDMA to the Schedule I list of drugs with no accepted medical use.

Despite MDMA's classification as a Schedule I drug, it continues to be used illegally. In fact, some of the Nation's top drug use monitoring mechanisms, including the Monitoring the Future Survey, the Community Epidemiology Work Group (CEWG), and emergency department episodes as measured by the Drug Abuse Warning Network, are reporting that the use of MDMA is not only on the rise, but may be dramatically so. Unlike encouraging trends for other illicit drugs, where the Nation is seeing a stabilization or decrease in use of drugs such as cocaine and heroin, the data for MDMA use suggest that it is now spreading beyond its most recent association with dance clubs into other settings. MDMA is now being used increasingly in both urban and suburban populations and is reportedly being combined with other drugs, such as marijuana, LSD, Viagra, and methamphetamine. Most alarming, however, are the data showing sharp increases in MDMA use among 12^{th}, 10^{th} and even 8^{th} graders in this country.[2]

Fortunately, our scientific understanding of how MDMA works in the brain, and of the short- and long-term consequences of its use, has improved over the past few years. A recent Medline search of the scientific literature reveals over 1300 scientific papers published in the peer review literature on MDMA/Ecstasy, an astonishing number given that a concerted research effort began only 15 years ago. In fact, in many respects, this is a historic moment in the annals of drug abuse research. Our scientific understanding of

how MDMA works is several steps ahead of its use patterns. This gives us an important opportunity to use sound science as the basis for educating potential users about the dangers of MDMA, and to inform policy makers on the appropriate actions for stemming the drug's illicit use and potential harm.

This report, *Ecstasy: What We Know and Don't Know About MDMA*, provides a scientific review of what we know today about how this drug works in the brain and what we still need to learn to fully understand the consequences of using this illicit substance. In the pages that follow, this report will discuss what scientists know and don't know about MDMA's acute effects on the brain and behavior, particularly on the serotonergic system in the brain, from laboratory studies in both animals and humans and patterns of use from field studies. The report will also review the long-term effects on the brain, again in both laboratory animals and humans, and on the long-term behavioral consequences in chronic MDMA users.

Much of this report is based on a scientific conference – *MDMA/Ecstasy Research: Advances, Challenges, Future Directions* – that was sponsored by the National Institute on Drug Abuse (NIDA) and the National Institutes of Health and held July 19-20, 2001. This conference, the first to bring together an international group of experts on the abuse and effects of MDMA, allowed researchers to present a variety of up-to-date research findings and discuss them among their colleagues and with NIDA staff, with an emphasis on highlighting work that still needs to be done. In addition to the information from this meeting, the following review also benefited from an exhaustive review of the published scientific literature on MDMA, particularly that which has appeared in scientific and medical journals during the past five years.

What should be clear from this report is that we know a great deal about MDMA and its harmful effects on specific neurotransmitter systems in the brain, and that we are beginning to understand the short-term and long-term behavioral consequences of those harmful effects. It will also become clear that there are still voids in our knowledge that researchers are already addressing or are preparing to address. But despite these gaps in knowledge, it should also be apparent that while we shouldn't "demonize" MDMA as the next crack cocaine or methamphetamine, neither should we "deify" it and dismiss it as a cause for concern; indeed, the scientific evidence suggests that MDMA is not a benign drug with magical properties, but one that can have important, deleterious effects on the brain and behavior. This scientific information can serve as the foundation for educational efforts to correct the tremendous misperception that MDMA is benign, and since perception of harm or risk may influence drug use, the fact that the science of MDMA is ahead of its use presents a unique opportunity to change perceptions before a growing drug problem becomes a widespread one.

In attempting to answer the question of whether MDMA causes permanent damage to human memory abilities, there is no single scientific study that provides a resounding, definitive yes. To be sure, no study provides any evidence that MDMA is a beneficial drug or even that it is safe when taken in moderation. In fact, as the work discussed in

this report will show, taking MDMA at any dose carries with it the risk of inducing physiological, psychological, and cognitive damage.

WHAT IS MDMA?

MDMA, a relatively simple chemical belonging to the amphetamine family of compounds, has properties of both stimulants and hallucinogens. While MDMA does not cause overt hallucinations, many people have reported distorted time and perception while under the influence of this drug. MDMA does cause an amphetamine-like hyperactivity in people and laboratory animals, and like other stimulants, MDMA is potentially addictive.

The majority of people take MDMA orally, most often in tablet or capsule form, and its effects last approximately four to six hours. Many users will "bump" the drug, taking a second dose when the effects of the initial dose begin to fade. The typical dose is between one and two tablets, with each containing approximately 60-120 milligrams of MDMA. However, tablets of what users call Ecstasy often contain not only MDMA but a number of other drugs, including methamphetamine, caffeine, dextromethorphan, ephedrine, and cocaine. MDMA is well-absorbed by the gastrointestinal tract, so peak blood levels occur in about an hour or two.

Users of the drug say that it produces profoundly positive feelings and empathy for others, that it eliminates anxiety and that it produces a state of extreme relaxation. MDMA is also said to suppress eating, drinking and sleeping. Thus, users often stay awake through two- to three-day parties, leading to dehydration and exhaustion. Because of its stimulant properties, when used in club or dance settings it is associated with vigorous physical activity for extended periods, which can lead to dangerous increases in core body temperature (hyperthermia), as well as dehydration, hypertension, and even heart or kidney failure in susceptible individuals. MDMA can also cause other adverse effects, including nausea, chills, sweating, involuntary teeth clenching, muscle cramping and blurred vision. MDMA users also report after-effects that include anxiety, paranoia, and depression. MDMA overdose can occur and is characterized by high blood pressure, faintness, panic attack, and in more severe cases, loss of consciousness, seizures and a marked rise in body temperature.

MDMA works in the brain by increasing the activity levels of at least three neurotransmitters (chemicals that nerve cells, or neurons, use to communicate with one another): serotonin, dopamine, and norepinepherine. Much like other amphetamines, MDMA causes these neurotransmitters to be released from their storage sites in neurons, increasing brain activity. Compared to the potent stimulant methamphetamine, MDMA triggers a larger increase in serotonin and a smaller increase in dopamine. Serotonin is a major neurotransmitter involved in regulating mood, sleep, pain, emotion, and appetite, as well as other behaviors. By releasing large amounts of serotonin, and also interfering with its synthesis, MDMA leads to a significant depletion of this important neurotransmitter. As a result, it takes the human brain a significant amount of time to rebuild its stores of serotonin that is needed to perform important physiological and psychological functions.

WHO IS USING MDMA?

One of the more alarming facts about MDMA is that despite its known detrimental effects, there are increasing numbers of students and young adults who continue to use the drug. Results from the 2000 Monitoring the Future survey indicate that MDMA use increased among students in the 12th, 10th, and 8th grades. For 12th and 10th graders, this is the second consecutive year that MDMA has increased, but this is the first year that a significant number of 8th graders have reported using the drug. Among 12th graders, lifetime use increased from 8.0 percent to 11.0 percent – the epidemiological data indicates that one in nine high school seniors have tried ecstasy in their lifetime. African Americans show considerably lower rates of MDMA use than do either Whites or Hispanics. The recent CEWG data showed a large increase in use among Hispanics that may represent an important change.[3]

Ethnographic data from NIDA's Community Epidemiology Workgroup (CEWG) meeting in June 2001 showed that MDMA use is spreading from raves and dance parties to high schools, colleges, and other social settings frequented by adolescents and young adults.[4] Although compared to other drugs the number of cases of MDMA use remains relatively small, the group of epidemiologists, public health officials, and researchers who monitor emerging drug trends found increases in MDMA abuse in 13 of 21 CEWG areas and easy availability in most other areas. In addition, the Drug Abuse Warning Network, maintained by the Substance Abuse and Mental Health Services Administration, has reported that emergency room admissions involving MDMA increased substantially from 1,143 in 1998 to 4,511 in 2000.[5]

Although some MDMA production occurs in the United States, most of the drug is imported from Western Europe. The Netherlands, Belgium, and Luxembourg produce approximately 80 percent of the world's MDMA supply. The retail cost of a single MDMA tablet or capsule ranges from $15 to $40.[6]

CHAPTER 2. EFFECTS OF ACUTE DOSES OF MDMA

MDMA has become a popular illicit drug because of the acute positive subjective effects that a person experiences within an hour or so after taking a single dose. Those effects include feelings of mental stimulation, emotional warmth, empathy toward others, a general sense of well-being, and decreased anxiety. In addition, users report enhanced sensory perception as a hallmark of the MDMA experience.

Though the state of neuroscience is such that investigators have yet to detail all of the specific neural circuits and brain regions involved in producing these acute subjective effects, a substantial body of research has shown that MDMA, like other members of the amphetamine family, works at the molecular level by binding to the transporters for three key neurotransmitters: serotonin, dopamine, and norepinepherine. This binding appears to reverse the normal uptake of these neurotransmitters from the synapse between neurons, resulting in excess release. But unlike amphetamine, MDMA appears to be more selective for the serotonin system compared to its activity on dopamine or norepinepherine systems, and this selectivity appears to have important consequences for MDMA's toxicity. Since MDMA and other amphetamines differ in their abilities to interact with various neurotransmitter systems, it shouldn't be surprising that the drug-induced behavioral effects associated with MDMA differ markedly from those produced by other amphetamines.

Other important aspects of the acute actions of MDMA result from the way in which the human body metabolizes and eliminates this molecule. Again, there are important differences compared to the way in which the human body handles other illicit drugs, including amphetamine, and the data demonstrating these differences raises concerns about MDMA's acute toxicity, particular among users who take subsequent doses of the drug.

Finally, researchers are now beginning to accumulate data on how single doses of MDMA have overall effects on brain function, as well as on other systems within the body. They are also starting to learn more about the acute subjective effects of taking MDMA in controlled laboratory settings, both in animals and humans, which should lead to a better understanding of neurochemical mechanisms that produce MDMA's positive subjective effects, and of the full nature of the negative effects, including depression, that have been reported once the MDMA "high" ends.

PRECLINICAL STUDIES IN ANIMALS

THE INTERACTION BETWEEN SEROTONIN AND DOPAMINE

One of the hallmark observations concerning MDMA's effects on the brain is that it induces marked changes in the release and uptake of serotonin by neurons throughout the brain, and that these alterations persist long after the body has metabolized and cleared the drug. In fact, experiments in rats show that MDMA triggers a rapid release of serotonin in the brain followed by a significant decrease in serotonin levels that persists at least seven days after MDMA administration.[7] These same experiments also show that

MDMA triggers a rapid release of dopamine in the brain, but that the magnitude of this release is smaller than that seen when rats are treated with an equivalent dose of methamphetamine. In addition, dopamine levels return to normal within hours after administration of either MDMA or methamphetamine.[8] Methamphetamine also produces a smaller release of serotonin than does MDMA.

MDMA's effects on the dopamine system may be related to the long-lasting effects on serotonin neurons. Using antisense technology, researchers have been able to reduce levels of the dopamine transporter by 70 percent, which has the effect of significantly attenuating serotonergic neurotoxicity induced by MDMA administered one week later.[9] Presumably, this protective effect results from a decrease in dopamine release following MDMA administration, and suggests that MDMA's interaction with dopamine neurons is involved in the neurotoxicity that this drug produces in serotonin neurons.

Brain serotonin and dopamine systems are intimately connected. For example, serotonin neurons innervate dopamine neurons, that is, they make connections with dopamine neurons and send signals directly to these dopamine neurons. In particular, serotonin neurons connect to dopamine neurons in parts of the brain that are critical in mediating the behavioral effects of many psychostimulants, including MDMA.[10] Researchers have attempted to tease apart a role for these two neurotransmitter systems in MDMA's actions, using chemicals with differential affinities for the two systems. For example, while MDMA binds to both dopamine and serotonin transporters, amphetamine binds primarily to the dopamine transporter and another drug, fenfluramine, interacts almost exclusively with the serotonin transporter. The observation that MDMA and amphetamine evoke hyperactivity while fenfluramine does not, suggests from the behaviors elicited by the MDMA, that the dopamine neurotransmitter system is critical. However, experiments with compounds that are more selective in the ways they interact with these two systems suggest that serotonin release also plays a role in triggering dopamine activity and that serotonin release is necessary for MDMA to produce hyperactivity. This effect may result from serotonin's ability to influence both the manner and magnitude of dopamine release. In fact, several groups have shown that using a chemical to block ability of MDMA to bind to the serotonin transporter, but not the dopamine transporter, markedly reduces the amount of dopamine released upon MDMA administration.[11] Subsequent studies, however, have found that the serotonin system's response to MDMA in the presence of compounds that inhibit various subtypes of either the serotonin transporter or dopamine transporter is unpredictable, given the current state of understanding of how these two systems interact. While researchers have proposed many hypotheses to account for the variable responses that have been observed, this is one area where this is a clear need for further experimentation.

MDMA PRODUCES OXIDATIVE AND METABOLIC CHANGES IN SEROTONIN NEURONS

One hypothesis to explain the long-lasting neurotoxicity of MDMA on serotonergic systems is that MDMA induces both oxidative and metabolic stress in serotonin neurons that, in turn, adversely affect the ability of these neurons to produce serotonin. Support for this hypothesis comes from a variety of studies, including those showing that MDMA perturbs the activity of various antioxidant enzymes, including superoxide dismutase,

catalase, and glutathione peroxidase, and that artificially boosting the levels of these enzymes reduces MDMA's effects on serotonin and dopamine neurons.[12] To examine this possibility further, investigators have measured the production of hydroxyl radicals, which are strong oxidants, within the brains of rats given MDMA. The researchers found that following MDMA injection there is an immediate rise in hydroxyl radical, as measured by two different techniques, in the vicinity of serotonin neurons in the striatum (a brain region rich in serotonin neurons). However, when the researchers administered the antidepressant fluoxetine – a compound that inhibits the serotonin transporter –an hour prior to the administration of MDMA, they observed a dramatic reduction in both hydroxyl radical formation and in the amount of serotonin released in the striatum; MDMA-induced dopamine release in the striatum was also suppressed.[13] The same effect was seen even when fluoxetine was administered four hours after MDMA, suggesting that the neurotoxic effects of MDMA occur more slowly than the pleasurable behavioral effects, and that these neurotoxic effects involve MDMA's actions at the serotonin transporter. As will be discussed later in this chapter, this particular result may have important implications for adverse events in humans who take multiple, sequential doses of MDMA over the course of a single day.

Subsequent experiments also showed that MDMA administration reduced levels of the antioxidants ascorbic acid and vitamin E in the same microenvironment of the striatum, further supporting the hypothesis that MDMA increases oxidative stress in the region of serotonergic neurons. The natural follow-up experiment was to see if administering ascorbic acid into this same microenvironment would prevent hydroxyl radical formation after MDMA injection, and in fact, this is exactly what investigators found.[14] But in addition, the simultaneous administration of both MDMA and ascorbic acid also prevented a constellation of behavioral changes known as the "serotonin syndrome" – forepaw treading, head weaving, and low body posture – that MDMA usually produces. MDMA also produces hyperthermia, or a significant rise in body temperature, in rats, and this, too, was suppressed when ascorbic acid was injected at the same time as MDMA. These results strongly suggest that MDMA is indeed producing oxidative stress in the serotonin system and that this oxidative stress is directly involved in the behavioral and physiological effects of MDMA.

The same investigators have also looked at the effect that MDMA has on metabolic stress in the rat striatum. To do this, the researchers measured cytochrome oxidase activity, a key indicator of metabolic activity. Two hours after MDMA administration, cytochrome oxidase activity is markedly reduced, not just in the striatum but throughout the brain. This effect persisted for at least 24 hours, and was still measurable in some brain regions seven days after administration.[15] Further experiments showed that MDMA decreased brain glycogen, the most important energy store in the brain, and increased extracellular concentrations of glucose in the striatum, reflecting the breakdown of glycogen, which is a polymer of glucose.[16] However, reducing or blocking the MDMA-induced hyperthermia, either with chemical inhibitors of the serotonin transporter or by physically chilling the animals, prevented the MDMA-induced breakdown of glycogen. By way of comparison, other amphetamine analogs that produce hyperthermia, including methamphetamine, also enhanced the brain's breakdown of glycogen. These results

support the view that MDMA promotes energy disregulation, and that hyperthermia may play an important role in MDMA-induced alterations in cellular energetics.

Researchers have found evidence, however, that the effect of MDMA on the body's ability to regulate internal temperature depends on ambient temperature.[17,18] Rats housed at 17° C and given MDMA experienced a fall in body temperature, while those housed at 22° C became hyperthermic, as expected. Both sets of animals showed signs of improper thermoregulation at both four weeks and 14 weeks after receiving MDMA, suggesting that the drug's adverse effects on thermoregulation are long-lasting.

STRESS AND MDMA-INDUCED NEUROTOXICITY

Several teams of investigators have looked at the interactive effects of MDMA and environmental stress on neurotransmitter functions and neurotoxicity. One group, for example, found that giving rats MDMA prior to subjecting the animals to an environmental stressor blocked the normal stress-induced release of serotonin in the prefrontal cortex and significantly reduced serotonin release in the hippocampus. MDMA-pretreatment also blunted the normal stress-triggered releases of the neurotransmitter dopamine in the cortex and of the neuromodulator glutamate in the hippocampus. However, prior administration of MDMA had no effect on the release of corticosterone, one of the major hormones involved in the body's overall response to stress. MDMA, therefore, has a very specific effect on certain aspects of the brain's response to stress and not on the overall stress response.[19]

Another group of researchers examined the effects of both acute and chronic stress on how MDMA influences dopamine neurons in the striatum in mice.[20] By itself, MDMA produced a dramatic decrease in dopamine and levels of the key enzyme involved in synthesizing dopamine in the mouse striatum. MDMA administration also resulted in a marked increase in molecular indicators of neuronal damage in the striatum. But when the investigators added acute stress, in the form of restraining the animal, placing it in a room chilled to 15° C, or giving it alcohol, they found that any of these stressors actually protected against neurotoxicity in dopamine neurons. In contrast, repeated exposure to stress caused a loss of this protective effect, possibly related to chronic elevations in circulating levels of corticosterone.

BEHAVIORAL EFFECTS OF ACUTE MDMA ADMINISTRATION IN ANIMALS

It has been difficult to study the effects of MDMA in humans under controlled conditions, and virtually impossible until recently to conduct simultaneous neurochemical studies. As a result, several groups of researchers have chosen to study the behavioral pharmacology of MDMA in various animal species. MDMA and related compounds produce a unique behavioral profile in rodents that includes locomotor hyperactivity, reductions in exploratory behavior, and deficits in both habituation and prepulse inhibition of startle – a measure of how an animal becomes less sensitive to a startling stimulus when it is given soon after an initial stimulus (the prepulse). Prepulse inhibition of startle is regarded as an operational measure that reflects the ability to filter cognitive or sensory information.

Acute doses of MDMA, for example, increase locomotor activity in rats in a dose dependent manner, as does amphetamine, but on other behavioral measures, including rearing, MDMA induces a smaller effect compared to that induced by amphetamine. In addition, rats given MDMA and placed in a closed environment tend to spend less time in the center of the "room" than do amphetamine-treated rats. This indicated that anxiety levels induced by an open environment are decreased. However, MDMA-induced changes are significantly smaller in knockout mice that lack either the serotonin-1B receptor or the serotonin transporter, which supports the hypothesis that MDMA-triggered release of serotonin produces a characteristic behavioral pattern that differs from that produced by amphetamine.[21] Acute MDMA also disrupts the prepulse inhibition of startle in rats, as well as an animal's habituation to startle. This effect, too, is blocked when MDMA is given with compounds that interfere with the serotonin transporter.

Several groups have also conducted experiments in animals that together strongly suggest MDMA is a drug that humans are likely to abuse. For example, MDMA causes rats to develop a conditioned place preference; it also decreases the threshold for rewarding electrical stimulation. Other studies have shown that rats who receive repeated administration of MDMA exhibit enhanced hyperactivity, which the researchers who conducted these experiments term a "behavioral sensitization." Withdrawal from the sensitization regimen then produced further changes in behavior and hyperactivity, akin to the response that humans show when they stop taking a drug of abuse after repeated dosing.[22]

Experiments in non-human primates have taken these results a step further by showing that MDMA acts a reinforcer in intravenous self-administration experiments, although not as powerfully as cocaine. In other words, animals will work fairly hard to receive MDMA, though not as hard as they will to receive cocaine infusions.[23,24] However, chemicals that block the serotonin transporter eliminate MDMA's reinforcing activity. The reinforcing effects of MDMA also faded when monkeys self-administered MDMA for approximately two years, suggesting that tolerance may develop to MDMA's reinforcing effects.

Other studies in non-human primates have examined the acute behavioral effects of MDMA administration. In rhesus monkeys that had never received MDMA, administration of low doses of the drug had more of an effect on tests that required learning and the ability to estimate time than on tasks that depend on short-term memory and visual discrimination.[25] Also sensitive to MDMA were tasks that assess motivation to work for food, possibly reflecting MDMA's anorectic properties. Animals that had been repeatedly exposed to high or escalating doses of MDMA also performed poorly on tests associated with complex brain function, such as short-term memory, learning, and time estimation, when subsequently challenged with a low dose of the drug.

CONTROLLED CLINICAL STUDIES IN HUMANS

MDMA HAS POWERFUL EFFECTS ON THE HUMAN CARDIOVASCULAR SYSTEM

Several groups of researchers have begun studying the acute effects of MDMA in humans in controlled laboratory settings.[26,27] Though such studies are just beginning, they are laying the groundwork for a more detailed understanding of how MDMA elicits its effects in humans.

In the first set of experiments conducted by one group, the investigators began by measuring blood pressure responses to MDMA in 12 volunteers who ranged from 18 to 40 years of age and who had a history of MDMA use. The results, according to the researchers, were somewhat startling in that only moderate doses of MDMA produced large increases in both systolic and diastolic blood pressure that were far greater than those seen when the same volunteers received amphetamine. This rise occurred in a dose-dependent manner and was so substantial that the investigators chose not to test some of the higher doses that they had planned to use – doses that are within the range of those taken by humans in real-life settings – and for which they had received regulatory clearance prior to beginning their studies. Participants also experienced substantial increases in heart rate that were greater than those seen with amphetamine administration. The researchers concluded that MDMA is a very powerful physiological arouser.

Echocardiography studies have also demonstrated powerful and potentially dangerous cardiovascular effects of MDMA. Again, this study was performed on a small group of healthy volunteers who had a history of MDMA use, only in this case the investigators compared MDMA's cardiovascular effects to those produced by dobutamine, a drug that cardiologists use in certain types of cardiovascular stress tests. These researchers also found that moderate doses of MDMA produced substantial and sustained increases in heart rate and blood pressures, as well as myocardial oxygen consumption, in a manner similar to dobutamine. But the echocardiogram results showed an important difference between the action of dobutamine and MDMA. Normally, when the heart beats faster, it also pumps blood more efficiently, a phenomenon known as ionotropy. Dobutamine produces this effect, but MDMA does not.[28] In the absence of inotropy, incremental increases in the rate at which the heart beats produces a proportional increase in the force applied to the wall between the heart's chambers, and this, in turn, increases myocardial oxygen consumption to a far greater extent than would be expected from the observed changes in heart rate and blood pressure.

Since MDMA use is often associated with sustained, strenuous activity, such as dancing, MDMA's effects on the heart could increase the risk of heart damage or other cardiovascular complications in susceptible individuals. In addition, in the event that emergency treatment is needed for MDMA-induced cardiac instability, physicians may need to alter the normal therapeutic regimen. Standard care for such vascular instability would be to give a β-blocker, and indeed, such drugs would be an attractive choice because they would directly counteract some of the physiological changes that MDMA induces. However, because of the way in which β-blockers work, there is at least a theoretical risk of further complications, which can be mitigated by also treating the patient with a vasodilator such as nitroglycerine.

How does MDMA trigger these cardiovascular effects? The answer appears to be at least partially through the drug's interaction with the serotonin system. When investigators administered MDMA in combination with an inhibitor of the serotonin transporter, MDMA did not trigger the expected increases in blood pressure, heart rate or body temperature.[29]

MDMA EXHIBITS NONLINEAR PHARMACOKINETICS

One of the most basic parameters that influences how a drug behaves in the body is its pharmacokinetics – how quickly it appears in the blood stream, how much accumulates in the blood stream for a given dose, and how long it remains in circulation before it is metabolized and excreted. A drug's pharmacokinetic characteristics are straightforward to measure and provide the foundation on which to build other physiological studies.

Investigators have now determined the pharmacokinetic profile for MDMA at two different oral doses – 0.5 milligrams/kilogram, a relatively low dose, and 1.5 mg/kg, a moderate dose – in eight healthy volunteers, each of whom had had at least four prior experiences with the drug over the previous three years.[30] One unique aspect of this study was that the researchers repeated the experiment using the two different enantiomers of MDMA, known as the R(-) and S(+) forms. MDMA, like many other legal and illicit drugs, exists in two optical forms; on the street, MDMA is sold as a mixture of the two, since that is what results from the chemical methods used to synthesize the drug. Often, the body's reactions to the two enantiomers of a drug are identical, but this is not always the case. And in fact, MDMA is one of those cases, at least as far as pharmacokinetics are concerned.

Plasma measurements following oral doses of MDMA showed that the drug is rapidly absorbed into the blood stream. At both dose levels, peak blood levels of both enantiomers occurred about two hours after administration. However, blood levels of the R(-) form were substantially higher than for the S(+) form at both dose levels. In addition, the R(-) form remained in circulation longer than the S(+) form: at 1.5 mg/kg, for example, circulating levels of the S(+) enantiomer had returned to zero approximately 24 hours after administration, while measurable levels of the R(-) form remained in circulation at 36 hours. Quantitative measurements revealed that nearly three times more of the R(-) form accumulated in circulation compared to the S(+) form and that the R(-) enantiomer was cleared from circulation some 35 percent more slowly than the S(+) form. These results suggest that the R(-) enantiomer may accumulate with repeated dosing.

Another worrisome finding from this pharmacokinetics study was that MDMA does not behave in a simple, linear dose-dependent manner. Though the measurements varied among the eight patients, a common occurrence in such trials reflecting individual differences in drug metabolism and absorption, the consistent finding was that the 1.5 mg/kg dose produced unexpectedly high circulating blood levels when compared against the 0.5 mg/kg dose. In fact, the rate of elimination of the drug from circulation decreased with increasing dose. Prior *in vitro* data suggest that MDMA metabolites bind to and inactivate a critical enzyme known as CYP2D6, which is involved in metabolizing many

drugs. As a result, higher doses of MDMA may inactivate more of this enzyme, making less of it available for metabolizing the drug. Nonlinear pharmacokinetics would be the end result.

There are several implications of these findings. First, it may be that MDMA makes everyone a so-called "poor metabolizer," which would increase the number of adverse consequences seen even in very small groups of patients who take any number of prescription drugs. Since MDMA is often taken in conjunction with other drugs, the consequences due to decreased metabolism of the many prescription drugs metabolized by CYP2D6 could be significant. More certain, however, is that small increases in oral doses of MDMA will produce dramatic increases in circulating levels of the drug, which may explain some of the acute toxicities seen at higher doses when MDMA users "bump" or take another pill before the first dose clears the body.

NEUROENDOCRINE EFFECTS OF MDMA

As part of an approved Phase I clinical trial of MDMA, the first step toward larger, systematic studies of MDMA's behavioral and physiological effects, one research team has measured circulating levels of a variety of neuroendocrine hormones.[31] Eighteen volunteers who had not used MDMA for an average of 6 months took oral doses of MDMA at doses ranging from 0.25 mg/kg to 2.5 mg/kg. The volunteers tolerated the experience without evidence of psychological distress or physical discomfort, though two subjects did experience transient episodes of high blood pressure. Little effect was seen at the lowest doses, but circulating levels of the stress-related neuroendocrine hormones ACTH, cortisol, and prolactin did rise in a dose-dependent manner, with a threshold dose of between 0.5 mg/kg and 0.75 mg/kg. Body temperature also rose in a dose-dependent manner.

BRAIN ACTIVITY CHANGES OCCUR AT MODERATE DOSES OF MDMA

Neuroscientists have at their disposal several tools that can give them a view of global activity changes within the brain. One group of European researchers has used positron emission tomography to measure regional cerebral blood flow, an indicator of which parts of the brain are more active than others at a given moment, in 16 volunteers given MDMA who had no history of prior MDMA use.[32] The volunteers were also given several tests to measure cognitive activity and assessments of mood and perception in order to obtain information on the possible neural circuits that might be involved in the MDMA-induced psychological experience.

These experiments showed that MDMA produced significant, reproducible, bilateral increases in regional cerebral blood flow in a variety of brain regions that included parts of the prefrontal cortex and the entire cerebellum. MDMA also decreased regional cerebral blood flow in other brain regions, again bilaterally. Though the connections between brain activity, as measured by regional cerebral blood flow, and the various psychological changes induced by MDMA were small, the investigators did calculate that heightened mood correlated positively with regional cerebral blood flow in the right parietal cortex and negatively in the caudate nucleus, while three different measures of altered states of consciousness each correlated with cerebral blood flow changes in other

distinct regions. For example, a measure known as "oceanic boundlessness" correlated positively with regional blood flow changes in the right lateral prefrontal cortex, the right supramarginal gyrus, and the right lingual/fusiform gyrus. Perhaps the most relevant finding was that cerebral blood flow decreased in a region known as amygdala in the left hemisphere, a change that had previously been found to correlate with feelings of euphoria during controlled experiments with other mood-altering drugs. The investigators caution, however, that these results should be regarded as purely descriptive, though they can serve to generate anatomically oriented hypotheses for future studies. Nevertheless, those areas found to correlate with the mood changes observed among volunteers are richly interconnected, and there is growing evidence that they form a functional network for the regulation of mood and emotion.

PSYCHOLOGICAL EFFECTS OF MDMA IN A CONTROLLED SETTING

One of the difficulties in understanding the effects of any illicit drug is making sense of subjective reports from users either during the course of their experience in the real-world setting or by relying on recollections of their experiences long after the drug experience is over. It is encouraging, then, that several groups of researchers, with the approval of the appropriate regulatory agencies and institutional review boards, have been studying acute psychological effects that MDMA produces in a controlled clinical setting. In the United States, these studies rely on healthy volunteers who have used MDMA at some point but who have abstained for some significant period of time. In Europe, a limited number of investigators have been allowed to conduct such studies on healthy volunteers who have never used MDMA.

One group examined the effect MDMA had on self-reported measures of intoxication, insightfulness, and closeness to others and found that MDMA produced elevations in each of these three measures in a dose-dependent manner.[33] In fact, the researchers concluded that MDMA produced mostly pleasurable effects, but the increase in self-reported feelings of closeness to others, supposedly one of the hallmark benefits of MDMA, was not significant.

These positive effects peaked at about two hours, though concurrent measures of blood levels showed that circulating levels of MDMA did not peak until three hours and remained substantially elevated for another two to three hours after that. The two hour mark is when users in the club setting will often take a second dose of the drug, evidently seeking to maintain maximum positive psychological effects. But since plasma concentrations remain high, the likely result of this "bumping" may be to enhance mood elevation, but at the expense of dramatically increasing plasma concentrations of the drug. Based on earlier discussions in this chapter concerning MDMA's effects on cardiovascular performance, additional doses of MDMA may be increasing stress on the heart in a manner disproportionate to the pleasurable subjective effects that the user experiences. In other words, there may not be much of a psychological reward for the considerable risk of adverse cardiovascular effects produced by subsequent doses of MDMA.

Another group used the Addiction Research Center Inventory Scale to compare MDMA's acute psychological effects with those produced by amphetamine and the serotonin releasing agent m-chlorophenylpiperazine (mCPP).[34] This study showed that MDMA produced a large stimulant effect, greater even than amphetamine at the doses tested, a drug which is known for its stimulant properties. In addition, volunteers scored high on measures of "hallucinatory effects," as they did when given the serotonin releasing agent mCPP. The effect on "hallucinatory effect" ratings from taking amphetamine were no different than from placebo on this measure. And while the investigators noted that MDMA produced some perceptual changes, they were not of the same magnitude as seen with true hallucinogens. Euphoric effects were large in volunteers taking MDMA, but not with the other drugs. MDMA was not as powerful at producing anxiety as mCPP.

Perhaps a more meaningful result from this study, however, was the finding that MDMA scored very high on a scale of "drug liking," duplicating results seen in a similar study.[35] According to the researchers, people like MDMA, which suggests that campaigns urging adolescents and young adults to "just say no" are going to meet some resistance. In a follow-up to these results, investigators found that volunteers were willing to pay more than twice as much to obtain MDMA as they were willing to pay for amphetamine, a powerful statement of how pleasurable the MDMA experience is for users. In addition, the results of the psychological measures taken together show that MDMA was highly reinforcing for all the participants in the study, suggesting that its abuse potential would also be high.

MDMA, SEROTONIN AND PSYCHOLOGICAL EFFECTS IN HUMANS

Data from the study of neurons grown in tissue culture, combined with the results from studies in laboratory animals, show that MDMA exerts effects by altering the activity of the serotonin neurotransmitter system and, at least to some extent, the dopaminergic system. Testing this hypothesis in humans, however, has only recently begun; nevertheless, the data from these early studies lend support to these hypothesized mechanisms.

For example, investigators have administered the serotonin transporter inhibitor citalopram and the dopamine antagonist haloperidol along with MDMA administration in healthy volunteers, in much the same way that similar compounds have been used as tools in animal studies to tease out relative contributions of the serotonin and dopamine activity to MDMA's effects.[36] In these experiments, the investigators measured startle reflexes in human subjects to probe MDMA's effects on the serotonin and dopamine systems, measuring prepulse inhibition much as other investigators have done with rodents. In humans, deficits in prepulse inhibition of startle occur in patients with schizophrenia, schizotypal personality disorder, obsessive-compulsive disorder, and Huntington's disease, while in animals, MDMA has been found to decrease the prepulse inhibition of startle as well as the habituation to startle.

In humans, however, MDMA appears to have the opposite effect, as the investigators found in their study involving 44 healthy volunteers. That is, when the volunteers received a preliminary pulse some period of time before the "test" pulse, those on

MDMA were less startled than those who received placebo – the prepulse had a bigger effect under the influence of MDMA. Though the increase in prepulse inhibition was moderate, it was statistically significant. Equally as important, the researchers found a series of significant correlations between psychological changes brought about by MDMA and the MDMA-induced increase in prepulse inhibition of startle and habituation to startle, a measure of how the subject becomes used to the startle event. Probing this finding further, the investigators found that citalopram, the most selective inhibitor of serotonin uptake known, attenuated MDMA's effect on prepulse inhibition in their human volunteers, while haloperidol did not alter MDMA's effect on prepulse inhibition. As a result, the investigators concluded that despite the different direction of the effect in humans and rodents, the data support the hypothesis that MDMA interacts strongly with the serotonin system in humans.

MDMA'S ACUTE EFFECTS IN A REAL-LIFE SETTING

Studies of MDMA's effects on healthy volunteers in a controlled setting are making an important contribution to the overall understanding of this drug. But the setting in which most users take MDMA is far from controlled – dance clubs and raves are hot, noisy and crowded, and those taking the drug are bombarded with external sensory stimuli. Therefore, studies of the psychological effects of MDMA in uncontrolled situations, though difficult and with their own limitations, are also important.

One such study compared the performance on measures of mood and cognitive performance among three groups of volunteers ages 19 to 30 years old: 15 who were regular MDMA users with a history of MDMA use on ten or more occasions, 15 novice users who had taken the drug on fewer than 10 occasions, and 15 controls who had never taken MDMA. Each subject completed a series of tests during a drug-free period, then again at a Saturday night dance, and at two and seven days after the dance.[37] During the evening of the dance, regular MDMA users took an average of nearly two tablets, the novices took an average of nearly 1.5 tablets, and the controls mostly drank alcohol. Some of the participants also took cocaine or smoked marijuana, but use was similar among all three groups. This study was the first to compare the acute effects of MDMA self-administration upon mood and cognitive performance before, during and after drug use.

All three groups reported positive moods at the dance club, with the somewhat surprising finding that controls were as "happy" as were those taking MDMA. The current study did find borderline trends for less sadness or depression among the MDMA users, and the controls were less sober as a result of their greater consumption of alcohol. However, two days afterwards, the MDMA users felt significantly more depressed, abnormal, unsociable, unpleasant and less good-tempered, a constellation of psychological after effects referred to as "terrible or suicide Tuesdays." These after effects may result from post-use serotonin depletions that have been observed in many of the animal studies reported earlier in this chapter. Over the course of the week following MDMA use, feelings of depression, sadness, calmness, pleasantness, and sociability fluctuated markedly in the MDMA user groups, but were stable over time in the controls.

Cognitive performance on two different tasks – verbal recall and visual scanning – was significantly reduced the night of drug use in both user groups. Verbal recall was also significantly impaired in drug-free MDMA users at two and seven days post-drug, with regular MDMA users showing the worst memory scores compared to the other two groups, at every test session. On the Saturday night, for example, both groups of MDMA users recalled only 60 to 70 percent of the words remembered by controls. Again, this may result from MDMA's effects on serotonin, as this chemical is an important neurotransmitter in the hippocampus, one of the most critical brain regions involved in memory formation. Memory impairment in the drug-free state may indicate that damage to the serotonin neurotransmission is persistent, a subject that the next chapter will discuss in great detail. MDMA can impair information processing both during and after the drug experience, emphasizing the risks of undertaking skilled activities, such as driving a car, while under the influence of this drug.

Another group of investigators examined in more detail the after-effects of MDMA use on mood during the subsequent week after taking the drug.[38] The researchers enrolled 24 volunteers at a London dance club, 12 who reported having taken MDMA and 12 who reported that they only drank alcohol and took no other drug apart from caffeine or nicotine. The volunteers were assessed for mood the evening of their drug experience, and then again two days and five days after the dance. MDMA users scored high on mood ratings the evening of the dance, but scored significantly low on day five, with some of the MDMA users scoring within the range for clinical depression. The investigators speculate that the low mood seen days after MDMA is taken may result from depletion of serotonin that occurs after taking MDMA.

ECSTASY DEATHS – IS MDMA RESPONSIBLE?

Between 1974 and 2000, 160 deaths attributed to MDMA have been reported worldwide in the scientific literature, a number that is almost certain to under-represent the total number of deaths attributed to MDMA self-administration. But at least some researchers and public health officials have wondered if MDMA is to blame for any or all of these deaths, since in the real world, "Ecstasy" and MDMA are not always synonymous.

Reports from Europe, for example, have demonstrated that "Ecstasy" commonly contains substances other than MDMA[39], and one study from the United States found the same.[40] In the U.S. study, conducted between February 1999 and March 2000, 107 pills received anonymously by the organization DanceSafe, which offers an Ecstasy tablet analysis service, were analyzed by gas chromatography-mass spectroscopy. By region, 45 percent of the pills were from California and southwestern states, 17 percent from the South, 16 percent from both New England and the Mid-Atlantic, 3 percent each from the Pacific Northwest and Midwest, and 1 percent from Hawaii. The analysis showed that 63 percent contained some MDMA, while 29 percent contained other identifiable drugs, but no MDMA. The most common drug identified other than MDMA was dextromethorphan, the active ingredient in over-the-counter cough syrups, at an average content of 136 milligrams, some 4.5 to 9 times higher than the usual therapeutic dose. At doses ranging from 300 to 480 milligrams, dextromethorphan can cause tachycardia and other adverse side effects, including phencyclidine-like psychosis and dysphoria. In addition, since

dextromethorphan, like MDMA, inhibits the drug metabolizing enzyme CYP2D6 (see **MDMA EXHIBITS NONLINEAR PHARMACOKINETICS** above), taking both drugs together could produce unexpected adverse side effects. For example, it is known that other inhibitors of CYP2D6 increase the incidence and severity of adverse reactions to dextromethorphan. Other identifiable drugs found in the tested tablets included caffeine, ephedrine, pseudoephedrine and aspirin.

Because of results such as these, investigators in Australia decided to look more closely at MDMA overdoses reported in Adelaide, a city of about 1 million people on the country's south coast.[41] As their U.S. counterparts did, the Australian team assayed "Ecstasy" pills obtained on the street and found that they contained an even wider variety of other compounds, including dextromethorphan as well as the illicit drugs methylenedioxyamphetamine (MDA) and para-methoxyamphetamine (PMA) – both members of the amphetamine family. Other drugs found in the sample included LSD, GHB and ketamine. In fact, only 40 percent of the "Ecstasy" pills contained any MDMA at all, and many contained only PMA, which appears more likely than MDMA to produce serious acute adverse reactions.

Although the number of fatalities examined so far are small, two cases in particular in the Australian survey stand out. Though both have been attributed to MDMA, analysis of the blood samples from the victims revealed no circulating MDMA, surprising given MDMA's long circulating half-life. However, both victims had significant levels of PMA in their blood, and one victim also had fairly high levels of amphetamine and methamphetamine.

The researchers then looked at known PMA overdoses and compared symptoms and vital signs between those patients and emergency room cases attributed to Ecstasy. Based on cardiovascular, temperature and neurological measures, the investigators concluded that most severe "Ecstasy" overdoses, at least in Adelaide, Australia, result from PMA self-administration. Subsequent animal studies with PMA showed that it produces dramatic hyperthermia at street doses, meaning it profoundly disrupts thermoregulation. In addition, there was evidence that PMA can induce potentially dangerous cardiac abnormalities. This is not to say that MDMA is not dangerous, or that it is safer than PMA, only that physicians should look for the presence of other drugs as well when patients come to the emergency room and the cause is a suspected MDMA overdose.

CHAPTER 3. LONG-TERM FUNCTIONAL CONSEQUENCES OF MDMA: NEUROCHEMICAL AND DEVELOPMENTAL

MDMA's potential neurotoxicity is of great concern because more of our Nation's youth are trying this illicit drug each year. Data from NIDA's Monitoring the Future Survey has shown that lifetime exposure of young adults and adolescents to MDMA/Ecstasy has been rising significantly over the past several years.[42] Survey data released at the end of 2000 showed that lifetime use by adolescents had risen in all age groups surveyed, from 13 year olds (8th graders) to 28 year olds. The percentage of 8th graders who have reported that they have used MDMA at least once in their lives was 4.3 percent in 2000, up from 2.7 percent in 1999. Similar increases occurred among 10th graders – 6.0 percent in 1999 to 7.3 percent in 2000 – and 12th graders – 8.0 percent in 1999 to 11.0 percent in 2000. Among 19 to 28 year olds, 11.6 percent have used MDMA at least once during their lifetimes, while among college students, lifetime use jumped from 8.4 percent in 1999 to 13.1 percent in 2000. These data are of particular concern given that the use of other illicit drugs among our Nation's youth appears to be leveling off or dropping over the same period.

One statistic about MDMA from the Monitoring the Future Survey showing a positive trend was that attitudes concerning this drug are showing slight changes for the better. When researchers asked 12th graders if there was a risk of harming themselves if they used MDMA only once or twice, almost 38 percent said there was a "great risk," up from 35 percent in 1999. Among young adults, those percentages are higher, with nearly 50 percent of 23 to 26 year olds and 27 to 30 year olds acknowledging that there was great risk from even limited exposure to MDMA.

That rising concern is certainly warranted. As the discussion in the previous chapter showed, acute doses of MDMA produce marked changes in both dopamine and serotonin systems within the brain. Though the changes in dopaminergic neurons appear transient, the data suggest that the changes in the serotonergic system are longer-lasting. In addition, examinations of more global brain function have shown that the effects of acute doses of MDMA extend to regions of the brain that are thought to be involved in higher thought processes. These findings have raised concern about possible long-term effects on users who have had only a few experiences with MDMA, as well as for those who are more regular users.

This chapter will discuss studies that have been conducted to address the issue of MDMA's long-term effects on humans, and as this discussion will show, it appears that there is good cause for concern. The studies presented in this chapter have been conducted in both animals and humans, and they focus on identifying and characterizing physiological damage to the brain from even moderate cumulative doses of MDMA. The next chapter will discuss studies that have been cataloguing the behavioral and functional changes that may result from those physiologic insults.

MDMA IS A POTENT SEROTONERGIC NEUROTOXIN

The serotonin neurotransmitter system is one of the most widespread in the central nervous system, extending from the brain stem and lower brain regions to virtually every region throughout the rest of the brain, except the cerebellum. Brain serotonin neurons have been shown to be involved in mood regulation, memory and cognition, impulse control, aggression, appetite and thirst control, sexual function, body temperature, sleep and hormonal control. As the discussion in the previous chapter showed, it takes very little exposure to MDMA to trigger a dramatic release of serotonin by neurons, which results in substantial serotonin deficits that can last two weeks or longer. This appears to occur through some oxidative stress. It appears, however, that this oxidation-triggered release and depletion of serotonin is only the tip of the iceberg for MDMA's effects in the brain, for the very enzyme that synthesizes serotonin is destroyed by oxidation, and this effect may have longer-term consequences.[43]

Neurons synthesize the neurotransmitters they use near the terminals of their axons. In the case of dopamine, the key synthetic enzyme is tyrosine hydroxylase, while for serotonin the critical enzyme is tryptophan hydroxylase. Since tyrosine hydroxylase is found in dopaminergic neurons and tryptophan hydroxylase is present only in serotonergic neurons, researchers have used these two enzymes as surrogate markers for the health of these respective neurotransmitter systems. As early as the 1970s, for example, investigators showed that four doses of methamphetamine produced a rapid and permanent destruction of much of the tyrosine hydroxylase activity in dopamine neurons, which caused at least some of these neuron terminals to die. Further research has shown that neurons deprived of their neurotransmitters do suffer damage over time.

Several groups have since shown that exposure to MDMA – 10 milligrams/kilogram given every six hours for five times, for example – rapidly and persistently destroys tryptophan hydroxylase in several brain regions known to have a high density of serotonin neurons, including the striatum and cortex.[44] And although MDMA is known to influence dopamine function, this compound does not affect levels of tyrosine hydroxylase, supporting the hypothesis that MDMA is a neurotoxin specifically for serotonin neurons. Subsequent studies have shown that levels of the major metabolite of serotonin – 5-hydroxyindoleacetic acid (5-HIAA) – and the serotonin transporter also decrease markedly after MDMA exposure, and that these additional markers of the status of serotonin neurons also remain low for months after exposure. Even single doses of MDMA produce dramatic reductions in levels of serotonin, tryptophan hydroxylase, and 5-HIAA in a matter of minutes. Two weeks later, only minimal recovery had occurred.

A study in Rhesus monkeys found that a 4-day course of twice daily injections of a moderate dose of MDMA produces long-lasting effects on the serotonergic system.[45] The MDMA-treated animals showed a four-to-five-fold reduction in cortical serotonin levels 17 months after exposure. However, cognitive assessments, using standard tests such as delayed non-matching to sample and self-ordered spatial search, found only minor reductions in performance at 17 months, even though the treated animals were markedly affected immediately after treatment. Similar findings have been found by other researchers.

Histological studies have provided more dramatic evidence for the serotonin neurotoxicity produced by MDMA. Two weeks after receiving 20 mg/kg of MDMA twice daily for four days, brain tissue taken from rat brain showed a substantial decrease in neurons containing serotonin – in fact, the axons of these neurons appeared to be missing. More recently, investigators have published data from similar studies in squirrel monkeys showing that the loss of serotonin axons from four days exposure to MDMA was severe 18 months after exposure and persists seven years later, though there was some evidence of minimal recovery in some brain regions.[46]

More detailed examination of this structural damage revealed that MDMA appears to prune, or reduce in number, serotonin axons and axon terminals.[47] One line of evidence comes from studies on the transport of the amino acid proline – a well-established marker of health and function of the serotonin neuronal system. Investigators treated rats with either minimal doses of MDMA or a known serotonin neurotoxin. As a control, the investigators treated another group of rats with a drug that damages other neurons but not those that use serotonin. There was no change in proline transport in the control animals, showing the specificity of this measurement for serotonin neurons, while the animals given MDMA showed identical changes to those seen in the animals that received the known serotonin neurotoxin.

Further studies using a radioactive label for the serotonin transporter revealed the neuronal pruning that occurs in the brains of squirrel monkeys; the serotonin transporter is present only in axon terminals, so its presence or absence is a good marker of the density of axon terminals. Eighteen months after a short course of MDMA, investigators found that some brain regions had substantial loses of serotonin axon terminals, while a few others, such as the amygdala, had more serotonin axon terminals. This pattern is a hallmark of axon pruning, since nerve cells will often grow replacement terminals upstream of the damaged terminals. These results, then, are evidence not only of MDMA's neurotoxicity, but of the brain attempting to rewire the serotonin system after damage. The functional consequences produced by this damage have yet to be uncovered.

Given that MDMA triggers the production of reactive hydroxyl radicals, as detailed in the previous chapter, and that this causes an acute depletion of brain serotonin, researchers asked the logical question of whether MDMA-triggered oxidation is also involved in producing long-term deficits. Indeed, investigators have found that MDMA-induced oxidation rapidly destroys tryptophan hydroxylase, which causes a long-term depletion of serotonin in affected neurons, and eventual cell death.[48] Moreover, this oxidation is triggered by MDMA binding to the serotonin transporter and by MDMA-induced release of dopamine. Blocking either dopamine release or MDMA binding to the serotonin transporter blocks the production of free radicals and the destruction of tryptophan hydroxylase. Neurotoxic effects of dopamine may result from the fact that dopamine can itself form oxidizing free radicals. In addition, researchers have shown that the formation of reactive oxygen triggered by MDMA and other amphetamine derivatives increases with body temperature which explains observations that hyperthermia increases MDMA-induced toxicity.

RELEVANCE TO HUMAN NEUROTOXICITY

Though mechanistic studies regarding MDMA's serotonin neurotoxicity have largely been performed in non-human primates and rodents, there is good reason to believe that they are applicable to humans. As one example, an autopsy study of one heavy MDMA user, found that serotonin levels in the striatum were significantly reduced.[49]

Investigators have also examined the effect of MDMA on human serotonin neurons grown in culture.[50] In a dose-dependent manner, MDMA was neurotoxic to serotonin neurons, but not to dopaminergic neurons; this toxicity was blocked by imipramine, a selective inhibitor of the serotonin transporter. Further study showed that MDMA induced DNA fragmentation and cell cycle alterations in serotonin neurons, and that these lethal changes were blocked by inhibiting the intracellular synthesis of nitric oxide, which is both an important intracellular messenger and can generate free radicals. MDMA, it was then shown, regulates the activity of the enzyme that synthesizes nitric oxide. Additionally, the researchers found that adding dopamine – but not serotonin - increased MDMA's toxicity.

Researchers also argue that MDMA neurotoxicity – not merely reduced serotonin levels, but measurable changes in the number of axons on serotonergic neurons – occurs in every species studied, including rats, guinea pigs, squirrel monkeys, rhesus monkeys, cynomegalus monkeys, and baboons. Some have questioned the relevance of the dosing schedules used in animal studies compared to patterns of use in humans, but researchers have reported that a single, moderate dose of MDMA produces a significant effect on the axons of brain serotonin neurons in two of five brain regions examined in one rhesus monkey. Moreover, these changes persisted for at least two weeks.

As far as the relevance of doses are concerned, investigators have relied on interspecies relationships for scaling drug doses, a technique developed and tested at length by the pharmaceutical industry. Based on this accepted methodology, the typical 5 mg/kg dose used in non-human primate studies corresponds to 1.5 mg/kg for a human, well within the range of the amount taken by humans in real-life settings. In addition, at least one group of investigators has tested the street dose of 2 mg/kg on non-human primates and found that after three such doses at three-hour intervals – not uncommon in the dance club setting – squirrel monkeys experienced a 60 to 70 percent drop in serotonin levels that persisted for at least___weeks and was uniform throughout the brain, while at the same dose and frequency, baboons registered an 80 to 90 percent reduction in brain serotonin.[51] Animal studies such as these have led the majority of researchers to conclude that MDMA is not a safe drug.

NEUROIMAGING STUDIES OF NEURONAL HEALTH IN THE HUMAN BRAIN

Though it is difficult to perform detailed neuroanatomical and neurochemical studies on human subjects at the same level of detail as is possible in laboratory animals, researchers can use various neuroimaging technologies to study human brain activity in ways that are not possible with other species. These studies, using tools such as magnetic resonance

spectroscopy and positron emission tomography, have allowed investigators to begin examining the adverse effects of MDMA on brain function in living humans.

The technique known as magnetic resonance spectroscopy allows researchers to measure the concentrations of a few individual brain chemicals – and record how these concentrations change – in real-time throughout single "slices," or transverse sections, in a single region of the human brain at a time. Two neurochemicals of particular interest are N-acetyl-aspartate and myo-inositol, which are specific markers for the two major cell types of brain cells, neurons and glial cells respectively. Measuring the concentration of these two chemicals provides a good estimate of the density of these two cells types, which in turn, yields information on neuronal damage – neuronal density usually decreases in brain injury, while glial cell density usually increases.

In one such study, investigators recruited an older group of volunteers who had used MDMA for an extended period of time and were relatively infrequent users of other drugs.[52] When compared to a group of control subjects with no history of drug use, the MDMA users had increased concentrations of myo-inositol, but there were no significant changes in N-acetyl-aspartate levels. Changes in myo-inositol concentrations correlated with cumulative lifetime use of MDMA, suggesting that MDMA use had triggered glial cell expansion, often a sign of past neurotoxicity, but also suggesting that neuronal recovery may have occurred.

This same research team also examined regional cerebral blood flow in much the same group of recreational MDMA users, although there were fewer women volunteers, perhaps because this technique involves the use of radioactive tracer molecules. These investigators found that MDMA use did not correlate with global or regional cerebral blood flow in abstinent MDMA users, though there were decreases in brain volume that did correlate with the duration of MDMA use.[53] However, there were significant decreases in regional cerebral blood flow three weeks after these MDMA users were given acute MDMA in the laboratory, and these decreases were more pronounced in volunteers who received a higher dose.

Another method of assessing brain function uses magnetic resonance imaging is to detect changes in blood oxygen levels within specific brain regions. This technique relies on the assumption that oxygen use within a discrete brain region will correlate with the activity level of the neurons in that region. Using this technique, known as fMRI BOLD, investigators found in one small study that male MDMA users showed less brain activity in the visual cortex following a light flash than did non-drug-using control subjects.[54] Female subjects did not show a clear pattern of decreased light-induced activation. Having validated this technique, the researchers plan to conduct a more detailed study involving more subjects.

POSITRON EMISSION TOMOGRAPHY REVEALS MORE SUBSTANTIAL BRAIN CHANGES

Though the results from magnetic resonance techniques found only minimal changes in the brains of MDMA users, researchers using positron emission tomography have obtained more conclusive evidence that MDMA use does in fact damage the brain at a

level beyond damage to the axons of individual serotonin neurons. In one study, for example, investigators determined the density of serotonin axon terminals, as measured by the density of serotonin transporters, in human brains using a radioactively labeled compound designed to bind specifically to the serotonin transporter.[55,56] Another group assayed brain activity by tracking glucose metabolism;[57] increased energy use, as measured by the amount of glucose being metabolized, is taken as a surrogate measure of neuronal activity, since more active neurons use more energy than inactive neurons.

The group using PET to determine serotonin transporter density, and thus the density of serotonin axon terminals, started by using baboons to successfully validate that changes measured using PET reflected actual neuronal damage and that this damage correlated with MDMA use. Having completed this part of their study, the researchers then enrolled 14 users of MDMA and 15 controls who had never used the drug. MDMA users, who were abstinent for at least three weeks prior to the PET studies, had taken the drug an average of more than 200 times over the previous five-year period. Data from this study showed clearly that the density of the serotonin transporters was significantly less in the MDMA user group than in the control volunteers, indicating that there were fewer serotonergic axon terminals present in the brains of MDMA users. Furthermore, the amount of decrease in serotonin transporter density correlated with the extent of prior MDMA use. These changes were seen in every region of the brain examined during the study.

The group measuring glucose metabolism also found marked decreases in the brains of MDMA users, specifically in brain regions that are densely populated with serotonin neurons. One important finding was that glucose metabolism was significantly more affected in MDMA users who began taking the drug before age 18. The investigators are now attempting to follow-up this observation in a larger number of subjects.

MDMA'S EFFECTS ON THE DEVELOPING BRAIN

Since younger brains may have an increased susceptibility to the neurotoxic effects of MDMA, it may be that the youngest, fastest developing brains – those of a developing fetus – could be particularly vulnerable to the effects of this apparent serotonin neurotoxin. Since most MDMA users are young and in their reproductive years, it is possible that some female users are pregnant when they take MDMA, either inadvertently or intentionally because of the misperception that it is a safe drug.

MDMA use has not been widespread enough for a long enough time for there to be large numbers of "MDMA babies" for study, in the way that there was a significant number of children born of mothers who used cocaine during the height of the crack epidemic. Researchers have, however, begun examining the effects that MDMA has on the developing rat brain, both during gestation and in the period immediately following birth. These developmental periods are analogous to human brain development during the third trimester of pregnancy. As of yet, there have been no studies on whether MDMA crosses the placenta and reaches the developing fetus. However, it is a molecule of low molecular weight and high lipid solubility, which suggests that it should cross the placenta. In

addition, the structurally similar drugs methamphetamine and fenfluramine have been shown to cross the placenta.

In one study of MDMA's effects during pregnancy, rats were injected twice daily with 20 mg/kg of MDMA on days 14-17 of gestation (rat gestation typically lasts 21 days).[58] This dosing regimen produced marked hyperthermia in the mothers and a decrease in body weight, perhaps resulting from MDMA's known appetite suppressing properties. The pups were delivered normally, though litter size was approximately 20 percent smaller in the treated animals compared to controls that had received saline injections. A week after birth, the brains of the mothers showed a substantial decrease in both serotonin content and serotonin axon terminals, as expected. However, the cerebral content of serotonin in the pups was normal, suggesting that MDMA was not toxic to the fetal rat brain's serotonergic terminals.

One possible explanation for the difference between MDMA's effects on the adult versus its effects on the fetal brain is that fetal brain may have a greater capacity to destroy free radicals. In the case of MDMA, whose neurotoxic effects likely stem from its ability to trigger free radical formation, this could protect against the neurotoxicity seen in the adult brain. To test this hypothesis, the researchers measured lipid oxidation in brain tissues by a method that can detect the products of such free-radical-triggered oxidation reactions. In adult brains, there was extensive lipid oxidation following MDMA, but neonatal brains showed no elevation of the measured reaction products. Thus, it appears that the neonatal brain has a much higher capacity to scavenge and inactivate free radicals than does the adult brain. Support for this hypothesis comes from other studies of free radical production in the rodent neonatal brain.

The absence of gross brain changes does not mean that more subtle injury might not occur in the developing brain. To explore this possibility, investigators have examined the effects of administering MDMA on learning and memory abilities early in life.[59,60] To model the effects that MDMA might have on human brain development early and late in the third trimester of pregnancy, the researchers administered MDMA to rat pups either during days 1 through 10 after birth – the early group – or days 11 through 20 – the late group. MDMA exposure had no effect on survival, and while it did affect body weight gain during treatment, body weight largely recovered after treatment stopped.

Approximately 60 days after birth, the animals were put through a variety of standard tests designed to measure learning and memory function in rats. In a simple test of learning to swim a straight channel, MDMA had no effect on performance. On a harder water maze test of sequential learning, animals in the late group made significant numbers of errors, while the early group performed as well as untreated controls. Tests on even harder water maze tests designed to measure spatial learning, in addition to memory, again showed marked deficits in the late group but not in the early group. Finally, after the tests were completed, the investigators measured brain serotonin, dopamine, and norepinepherine levels, finding only small differences in only two brain regions –the frontal cortex and hippocampus – among the three groups, nothing close to the magnitude seen when MDMA is administered to adult animals.

The results of these experiments show that MDMA exposure during a late stage of brain development disrupts both sequential and spatial reference memory-based learning. These learning deficits reflect a developmentally specific vulnerability in that they were selective, affecting only those animals treated on days 11 through 20 after birth. The effects were also long-term in that they were seen in animals after they had reached adulthood. Also, the changes were not related to any long-term changes in neurotransmitter content, suggesting that MDMA exposure during development may induce learning and memory deficits through mechanisms other than through injury to serotonin axon terminals. Because of the experimental design used in these studies, the investigators were able to rule out confounding factors such as maternal rearing, nutritional status, differences in handling, and stress as possible causes of the cognitive deficits observed.

Another approach to modeling MDMA's effects on the developing brain is to use a sophisticated tissue culturing assay system known as reaggregate tissue culture. This system provides a method for the *in vitro* reconstruction and development of specific neuronal projections with circuitry similar to that in the intact brain. In this culture system, known numbers of dissociated fetal cells from various subdivisions of the brain can be placed in rotary culture, where they collide and adhere to one another to form reaggregates. Neurons contained within reaggregates develop both biochemically and structurally in a manner that is similar to that observed *in vivo* and demonstrate characteristic responses to pharmacological and toxicological agents. These reconstructed neuronal projections can thrive for up to a year, giving researchers an opportunity to monitor drug-induced effects during the entire developmental history of neurons from the fetal to the adult stage.

Researchers have formed such aggregates from fetal mouse neurons harvested after the mothers had received either saline or MDMA injections from days six to 13 of gestation. Neurons from the MDMA-exposed fetuses formed reaggregates with significantly higher levels of markers of both serotonin and dopamine development, suggesting that these neurons were experiencing accelerated development.[61] This enhanced development and metabolism persisted for at least 36 days, suggesting that acute exposure to MDMA during early- to mid-gestation may result in more active serotonergic and dopaminergic neurons in mature animals.

CHAPTER 4. LONG-TERM FUNCTIONAL CONSEQUENCES OF MDMA: BEHAVIORAL, MOOD, PSYCHIATRIC, AND COGNITIVE

The dozens of studies discussed in the preceding two chapters provide extensive support for two hypotheses: that MDMA can be a potent and selective neurotoxin that induces long-lasting damage to serotonin neurons after only brief exposure, and that acute doses of MDMA can produce significant changes in brain function, as well as cognitive and behavioral deficits. That leaves the question of whether there are long-term cognitive and behavioral consequences of MDMA use, and this is the subject of the following discussion in this chapter.

NEUROPSYCHOPATHOLOGY ASSOCIATED WITH MDMA USE

GENERAL PSYCHIATRIC DISORDERS

Because MDMA produces long-term deficits in serotonin function, and because serotonin function has been implicated in the etiology of many psychiatric disorders including depression and anxiety, investigators have suspected that MDMA users may experience more psychopathology than non-users. Indeed, at least one study, discussed in Chapter 2 (see **MDMA'S ACUTE EFFECTS IN A REAL-LIFE SETTING**), found that MDMA users suffered significant mood depression, even to the point of clinical depression, in the week following a one-night use of the drug. Numerous studies in the early 1990s also suggested that MDMA users experience flashbacks, chronic psychoses, major depressive disorder, panic disorder, and mixed anxiety and depression.

More recently, a number of investigators have found that heavy MDMA users experience a constellation of psychiatric changes. In a pilot study in a small town in Ireland, where MDMA use is common among young adults, one group of researchers enrolled 16 light MDMA users and 12 heavy MDMA users – defined as having used MDMA fewer than 20 times or more than 20 times, respectively. The investigators also enrolled 22 non-MDMA-using controls to test the validity of a self-reporting assessment technique, known as SCL-90, normally used with psychiatric outpatients to determine clinical symptoms of psychiatric disorders.[62] All of the volunteers, however, were conspicuous consumers of a wide variety of illicit substances, so even the controls were polydrug users, save for MDMA. Nonetheless, the results of the assessments showed that the heavy MDMA users displayed a range of psycological problems, scoring significantly higher on measures of somatisation (the conversion of mental experiences or states into bodily symptoms), obsessive traits, anxiety, hostility, phobic anxiety, paranoid thoughts, psychotic behavior, poor appetite, and restless or disturbed sleep.

These same researchers then conducted a much larger study of 768 young people at dance clubs in four major European cities. In this study, researchers found that social anxiety scores were significantly higher among light and heavy MDMA users than among non-drug-using controls and among those who used other illicit drugs.[63] While some might argue that people who suffer from phobic anxiety might take MDMA as a form of self-medication, it is unlikely since those who suffer from social anxiety, almost by definition, would not be found among the patrons of the dance clubs that were sampled.

In the same study, other relevant psychiatric conditions, including psychotic behavior, obsessive-compulsive behavior, and general anxiety were significantly higher among the MDMA users than in controls, though the difference with other types of drug users was not significant. Interestingly, there were no differences in positive mood states among any of the groups including the non-drug-using controls, suggesting that the positive experiences associated with MDMA may have as much to do with expectations of having a good time as they do with drug-induced effects. Heavy MDMA users, however, were more than three times as likely to report a loss of sexual interest or pleasure compared to non-drug-using controls. Sleep patterns were also significantly impaired among the heavy MDMA users.

SLEEP DISORDERS

Another group has specifically examined MDMA's effects on sleep. The serotonergic system plays a central role in sleep, though the details of that involvement have yet to be elucidated. In animal studies, pharmacological depletion of brain serotonin leads to dramatic decreases in non-REM sleep, with less dramatic decreases in REM sleep. In humans, serotonin neurons become progressively less active as sleep progresses from stage 1 through stage 4 sleep, becoming nearly silent in the deepest stages of non-REM sleep.

In one early study of MDMA's effects on sleep in humans, researchers compared the sleep of abstinent MDMA users to that of non-drug using controls and found that MDMA users had decreased total sleep time.[64] Based on these results, the same group performed an all-night sleep study on MDMA users and obtained the opposite results – MDMA subjects spent significantly more time asleep.[65] In particular, the MDMA users spent more time in stage 3 and stage 4 sleep than did control subjects. The investigators were unsure why the two studies gave conflicting results except that the two groups of MDMA users tested in the two studies differed in the extent of MDMA use, the amount of time since last MDMA use, and the duration of time since the first use of MDMA.

IMPULSIVENESS

Investigators have also studied MDMA's effects on the personality traits known as impulsiveness and sensation seeking. The earliest study in this area found that heavy MDMA users scored lower on measures of impulsivity. However, all subsequent studies have found either no differences between MDMA users and non-users, or increased scores on impulsivity measures among the heaviest MDMA users.

In one of the larger studies to examine this issue, investigators measured impulsivity in three groups of volunteers: MDMA users who had also used other drugs, other drug users who had never used MDMA, and controls who had not taken any illicit drugs.[66] This study found that the MDMA group had more psychological problems and were more impulsive than the other two groups, based both on their own self-reports and on more formal clinical assessments. In addition, the users who had consumed the most MDMA over the course of their lives had the highest trait impulsiveness scores. This change may reflect an effect from MDMA-induced serotonin deficits, since reduced serotonin levels

have been shown to be associated with increased impulsivity in humans. Another explanation may be that those who are more impulsive for other reasons may be those who use the most MDMA.

ADDICTION

Several studies in both humans and animals suggest that the abuse liability of MDMA is significant and that users may develop addiction. One group, which has been conducting a larger research project aimed at developing and testing reliable measures for diagnosing substance abuse disorders, has examined whether adolescent and young adult MDMA users meet the diagnostic criteria for abuse and dependence as detailed in the fourth version of the Diagnostic and Statistical Manual (DSM-IV).[67] In this study, the investigators recruited 173 adolescents and young adults and interviewed them two times, one week apart, to determine the reliability of their responses. Just over 30 percent of the volunteers reported using MDMA, nearly all of whom had used it recently. Almost two-thirds of those who were using the drug reported "continuing to use despite knowledge of physical or psychological harm."

Of the 52 young adult users who had reported using MDMA, almost 60 percent reported symptoms of withdrawal, including feeling tired, sleepy or weak, having a change in appetite, feeling depressed, and having trouble concentrating. To the surprise of the researchers, 43 percent of the MDMA users met DSM-IV criteria for dependence on MDMA awith or without abuse nd 34 percent met the criteria for abuse only. Twenty-three percent met neither criteria. Furthermore, all of the dependent users had symptoms of tolerance, withdrawal or both.

MDMA AND MEMORY PERFORMANCE

There is a large and growing body of evidence from a variety of studies with humans that MDMA use can have long-lasting effects on memory. None of these studies are perfect, as they all have methodological problems such as concurrent use of other drugs – it is apparently impossible to find but a few MDMA users who do not use other illicit substances, particularly marijuana. In addition, results vary with the assessment used. Nonetheless, the general finding that emerges across all of the studies is that MDMA does impact memory abilities in ways that could adversely affect normal functioning on every day tasks. Moreover, the relationship between memory problems and MDMA use appears to have a dose-dependent relationship, that is, the more MDMA used, the greater the deficit.

GENERAL MEMORY DEFICITS

Several studies have shown that MDMA users have trouble on recall tests compared to users of other drugs and control subjects who do not use any illicit substances. In one study of MDMA users, volunteers were asked to listen to a brief audio-taped news story of five sentences and 65 words and then write down as much of what they had heard as possible, word for word, immediately after the story and again 40 minutes later.[68] Members of the MDMA group, all of whom had taken the drug on at least 20 occasions, but were abstinent from all psychoactive drugs (including alcohol) on the day of the

study, scored substantially worse than either the polydrug group or non-drug group on both immediate recall and delayed recall. Though the analysis found that there was no correlation between the amount of MDMA taken over a person's lifetime and memory performance, there was a trend suggesting that the immediate recall abilities might be related to the average dose taken per occasion.

The results of this study suggest the possibility that memory impairment associated with recreational MDMA use is a long-lasting phenomenon, since users who reported having abstained for 6 months still perform poorly on the recall tests. There was, however, tentative evidence of recovery of memory performance in a small group of three MDMA users who had been assessed earlier and who not taken the drug for more than 6 months.

Another study compared 20 heavy and 20 light MDMA users to 20 non-MDMA-using control subjects on memory performance while also measuring serotonergic function. Both heavy and light MDMA users performed significantly worse than controls on recall tests.[69] Although the researchers found significant associations of chronic ecstasy use with impairment of memory and serotonergic neuroendocrine function, they cautioned that the clinical relevance of the deficits could not be easily determined, but also noted that these results are worrisome given that they were seen in such a small sample of MDMA users.

A web-based study of memory function among users of a variety of drugs also turned up evidence of memory deficits in MDMA users.[70] Separate groups of MDMA users and marijuana users both scored poorly on general memory tests, but MDMA use, accounting for all other drug use, predicted decrements seen on measures of long-term prospective memory. In other words, based on these results, MDMA users would have greater difficulty than users of other drugs remembering that they had something to do at some point in the future. This suggests that MDMA users have deficits in memory storage and retrieval of new information.

Since serotonin is thought to be involved in both memory and learning functions, several groups have begun attempting to determine if there is a correlation between poor performance on memory and learning tasks in humans and changes in serotonin activity in the brains of MDMA users. In one such pilot study, investigators used a technique known as single photon emission computed tomography (SPECT) to assess the density of serotonin receptors and determine if this measure could be related to performance on memory tasks.[71] Though the study examined only five volunteers with a history of heavy MDMA use and nine control subjects who had never used MDMA or any illicit drug, the researchers did find a significant correlation between a decrease in receptors, as compared to controls, and poor performance on the memory tests among the group of MDMA users. Overall, the MDMA users had significant deficits in delayed memory tasks, consistent with the findings of other research groups.

VERBAL AND VISUAL MEMORY DEFICITS

Two decades of research have shown clearly that as far as the brain is concerned, "memory" cannot be reduced to a unitary process, but instead probably comprises many

specialized processes that together work to create what we experience in everyday life as memory. One of the most consistent findings across many studies on MDMA is that this drug causes problems in the verbal memory system.[72] One study, for example, compared the memory skills of 24 abstinent MDMA users and 24 control subjects chosen to have the same drug-use history except without prior MDMA use.[73] The investigators decided to use this group as the control because most MDMA users have also experimented with other recreational illicit drugs, making it difficult to attribute group differences to MDMA use rather than to drug use in general.

The main finding of this study was that the MDMA user group, who on average had not taken MDMA for four weeks, had deficits in tasks of both assessing both verbal and visual memory. In addition, higher average monthly doses of MDMA were associated with poorer scores on the memory tests. The researchers also measured levels of the serotonin metabolite 5-HIAA in the cerebral spinal fluid of volunteers and found that levels of this metabolite were also lower in the MDMA users, consistent with findings from many other studies indicating that MDMA use causes lasting deficits in brain serotonin levels. Correlation analysis also showed that reduced 5-HIAA levels predicted lower scores on verbal and visual memory tests, adding support to the hypothesis that changes in serotonin levels have functional consequences on cognitive function.

With the large number of studies being conducted on MDMA's behavioral effects, the possibility exists to combine the results of these studies using what researchers call a meta-analysis. Though there are methodological difficulties involved in conducting meta-analyses, at least one group of investigators has attempted to undertake this challenge with MDMA.[74] The researchers identified 21 studies that had examined MDMA's effects on cognition and selected six for inclusion in their meta-analysis. The criteria for including studies in the analysis were that each study had to contain a statistical test of the relationship between MDMA and cognition, that study participants were not using MDMA at the time of the study, and that the studies had to control for age and amount of education. Based on the subsequent analysis, the strongest finding was that MDMA users exhibited significant impairments in verbal learning and memory when compared to non-MDMA using controls. The analysis also showed smaller deficits in nonverbal learning and memory, executive functioning and visuospatial skills that nonetheless fell within the "normal" range of performance.

WORKING MEMORY DEFICITS

One important memory component, and one considered a sign of higher cognitive functioning, is the ability to store and use information as further information continues to pour in. Reading a long sentence, for example, requires holding the ideas from the beginning of the sentence in some form of memory storage until the sentence is completed. This is called working memory, and it seems vulnerable to damage by MDMA.

In a small study of 12 MDMA users and 12 alcohol-using controls who were enrolled on the evening of drug use, investigators found significant impairments on a task designed to assess working memory and attention. Examining both of these cognitive tasks is

important because the two go hand-in-hand – you have to pay attention for information to make it into working memory.[75] The deficit measured by this test worsened over the next two days and was still significant five days after drug use.

Another study looked further at this finding by comparing working memory performance among 10 current and 10 former MDMA users and a control group of 10 volunteers who did not use MDMA or any other drug.[76] MDMA users found the memory task difficult, and in fact, two users found the task so unpleasant that the investigators did not make these two subjects complete the most challenging part of the test. Both groups of MDMA users, current and former, showed deficits in working memory function compared to controls, supporting the idea that MDMA has long-lasting effects on cognition. The data also suggest that this is not a function of the speed at which MDMA users can process information, which was also measured, but was solely a matter of working memory deficits.

As suggested earlier in this report, polydrug abuse is common in MDMA using populations, raising the possibility that some of the effects seen on learning and memory tasks may result from this polydrug use. To begin addressing this issue, one group has examined the effect that marijuana may play as a confounding factor in examining MDMA's adverse effects on memory.[77,78] These investigators enrolled three groups of volunteers: 28 MDMA users who were not ever regular users of other recreational drugs except for marijuana, 28 marijuana users who had never used MDMA and were never regular users of other recreational drugs, and 28 healthy volunteers who had never taken MDMA and were never regular users of other drugs. No participants had a history of heavy alcohol use, which is known to impair memory. MDMA users, on average, took 3.5 tablets per month, which is considered an occasional rather than a heavy use of MDMA.

After administering a comprehensive cognitive test battery, the researchers found that all three groups performed within the normal range. However, the MDMA users performed worse than one or both control groups in several of the more complex attention and memory tests. Poorer performance in working and verbal memory, as well as in divided attention tasks, were associated with heavier MDMA use and heavier marijuana use. These results raise the concern that MDMA use, even in typical moderate recreational doses and possibly in conjunction with marijuana use, may lead to a decline in working and verbal memory in otherwise healthy young adults, albeit a decline that would not be considered pathological under normal testing conditions. A pilot study of men who have sex with men and who use MDMA (MDMA is a very popular drug in this group) in addition to marijuana and cocaine obtained similar results.[79] Data from other studies suggest, though, that deficits in working memory may grow more severe with increased MDMA use.[80]

There are several caveats to these studies. Most of the tests that researchers have used to assess memory function are designed to test severe brain damage, not the subtle damage that is likely to result from MDMA use. And even when more sensitive tests are used, the results may not indicate specific brain injury. For example, though researchers have

identified verbal memory as being sensitive to MDMA use, verbal memory can be influenced by a variety of factors, and as such, it is not possible to definitely determine that MDMA has a specific influence on the neuronal mechanisms responsible for verbal memory. It is perhaps more useful to view verbal memory as a "canary in the mineshaft," i.e., as a sensitive early warning signal that something is amiss. The challenge of future studies will be to take advantage of more refined cognitive assessments that are able to parse out the specific processes impaired by MDMA.

ARE MDMA-INDUCED COGNITIVE CHANGES REVERSIBLE?

Given that numerous studies have shown that the serotonin deficits caused by MDMA are persistent, lasting at least seven years in one study of nonhuman primates, it is important to determine if the psychological and memory deficits associated with even moderate use of MDMA recover after some period of time. This is a particularly important issue with MDMA because of the relatively young age of the majority of people who abuse this drug.

So far, the majority of studies have focused on MDMA users who have been abstinent for a period of a few weeks to a few months, though longer-term studies have been planned or are underway. One group of investigators, for example, has been following former MDMA users who have been abstinent for at least six months, with the average time since last MDMA experience being two years.[81] This study is being conducted in England, where an estimated 750,000 MDMA tablets are consumed each weekend. The investigators enrolled 18 current MDMA users, 15 ex-users of the drug, 16 poly-drug control subjects and 15 drug-naïve controls who smoke cigarettes and drink moderate amounts of alcohol.

The results of this study showed that there were no differences between the groups on scores rating general health, impulsiveness, adventuresomeness, empathy, hostility or psychotic symptoms. There were, however, significant group differences between the MDMA users and the two control groups on an overall measure of psychopathology, as well as for anxiety, phobic anxiety, depression and other psychological problems. Moreover, the scores of the two MDMA groups on global psychopathology were what are typically seen among an inpatient psychiatric population. And though the current MDMA users had the highest measures of global psychopathology, the difference between the current and former users was not significant.

On memory tests, both groups of MDMA users scored particularly poorly compared to both control groups. More importantly, the group of former MDMA users did even worse than current users on tests of immediate and delayed recall. The assessment instrument employed, known as the Rivermead Behavioral Memory Test story recall, is considered to probe the most common type of memory task performed in every day life. A correlation analysis showed that performance on the immediate recall test portion of the Rivermead was predicted by the estimated cumulative lifetime dosage of MDMA consumed. In fact, a form of analysis known as stepwise regression found that the extent of past consumption of MDMA predicted most of the cognitive deficits identified in this

study; in contrast, recent marijuana consumptions predicted deficits in psychopathology The lead investigator of this study concluded that the cognitive deficits resulting from MDMA use do not recover with time, and noted that one of the dangers of this drug is that most of the deficits in higher-order cognitive functions may not be noticeable until substantial damage has already been done.

A PROSPECTIVE STUDY OF MDMA USE AND MEMORY DEFICITS

One piece of information that has been lacking from knowledge about MDMA concerns the progression of deficits with continued MDMA use. In other words, it is unclear whether continued MDMA use induces progressive impairments over time. One study has begun addressing this issue by following a group of 15 MDMA users in Toronto, Canada, for over one year of continued MDMA use.[82] At the beginning of the study, and again after a year, participants completed a brief neuropsychological test battery, a general intelligence test, and a detailed memory test. On average, the participants used MDMA approximately 2.4 times per month and had actually increased the average dose they took over the course of the year. In contrast, use of other recreational drugs appeared to remain constant during this sampling period.

Over the one-year period, test scores either declined or remained stable, but none improved. There were large declines in a score of overall memory performance as well as on the Rivermead Behavioral Memory Test of story recall, which asks the subjects to listen to a short story and then recall as much of it as possible immediately and again after a delay. Other memory tests, such as the ability to remember names and vocabulary, also declined in relationship to the amount of MDMA consumed.

A CAVEAT

In attempting to answer the question of whether MDMA causes permanent damage to human memory abilities, there is no one study that provides a resounding, definitive yes. To be sure, no study provides any evidence that MDMA is a beneficial drug or even that it is safe when taken in moderation. In fact, as the work discussed above shows, taking MDMA at any dose carries with it the risk of inducing physiological, psychological, and cognitive damage.

Clearly, there is still room to debate the exact nature of the deficits produced by MDMA use. Nevertheless, based on the results from the overwhelming majority of studies conducted so far, and given some of the methodological concerns that will be addressed in Chapter 6, the data show that MDMA can be harmful to human health.

CHAPTER 5 . THE HUMAN FACE OF MDMA: PATTERNS AND TRENDS OF MDMA ABUSE AND THEIR IMPLICATIONS FOR PREVENTION

In contrast to the encouraging downward trend seen for the abuse of most other illicit substances, MDMA use in the United States among our Nation's youth has been increasing since 1998. Indeed, despite the evidence presented in the preceding chapters that MDMA is not a harmless drug, there are increasing numbers of students and young adults who continue to use MDMA increasingly higher doses. Results from the 2000 Monitoring the Future survey indicate that MDMA use increased among students in 12th, 10th, and 8th grade. For 12th and 10th graders, this is the second consecutive year that MDMA has increased, but this is the first year that a significant number of 8th graders have reported using the drug. Among 12th graders, lifetime use increased from 8.0 percent to 11.0 percent – one in nine seniors have tried ecstasy in their lifetime. African Americans show considerably lower rates of MDMA use than do either Whites or Hispanics – 1.3 percent compared to 7.6 percent and 10.6 percent, respectively. [83]

Ethnographic data from NIDA's Community Epidemiology Workgroup (CEWG) meeting in June 2001 showed that MDMA use is spreading from raves and dance parties to high schools, colleges, and other social settings frequented by adolescents and young adults.[84] Although compared to other drugs, the overall (all ages) number of cases of MDMA use remains relatively small, epidemiologists, public health officials, and researchers who monitor emerging drug trends in the United States report increases in MDMA abuse in 13 of 21 CEWG areas and easy availability in most other areas. In addition, the Drug Abuse Warning Network, maintained by the Substance Abuse and Mental Health Services Administration, has reported that U.S. emergency room admissions involving MDMA increased substantially from 1,143 in 1998 to 4,511 in 2000.[85]

These statistics paint an overall picture of the prevalence of MDMA use, but for prevention efforts to succeed, researchers need more detailed information on who is using MDMA and in what settings. This research is the province of ethnographers, who attempt to put a human face on the drug use by studying specific populations, often in natural settings. Each population studied is unique, and thus, it would be inappropriate to draw general conclusions about all MDMA users from the results of any one study. However, many researchers are now looking at different populations of MDMA users, and when their results are taken together with statistics from Federally sponsored surveys such as the Monitoring the Future and the CEWG, it should allow for a more comprehensive picture of who is using MDMA in what settings and provide information that can be used to educate users about the dangers of this drug.

SOME PATTERNS AND TRENDS OF MDMA USE

One of the aims of ethnographers is to find out how young people learn about MDMA and in what settings they use the drug. To gather such information, researchers in Ohio have conducted a pilot study in Dayton and Columbus, Ohio, starting with two focus groups with 16 people. Researchers then audio-taped individual interviews with 12 additional subjects.[86] Overall, the participants in these studies ranged from 18 to 31 years

old, with an average age of 22.5. There were 15 women and 13 men, all Caucasian and heterosexual, and half were college undergraduates. The length of MDMA use ranged from six months to over three years, and the number of times MDMA was used ranged from two to over 100. The typical dose per occasion was between 1 to 2.5 tablets, and the frequency of use varied significantly, from once a week to once every 1 to 6 months.

The major conclusion of this small study is that there was great variation in drug use seen in these youth. Factors impacting the frequency of use included the cost of MDMA – about $20 to $30 per tablet – and individual tolerance of the drug. As one subject recounted, *"I try to keep it to about once a month that I would do [MDMA] because if you do it a lot, it loses a lot of its effect. I built up a big tolerance to it, and then it doesn't affect you the same."*

Some users experienced negative side effects, while others stopped using, citing responsibilities that they felt came first. *"I haven't done any [MDMA] yet this school year, just 'cause I've been so busy with school and stuff, but last summer I used it a couple of times,"* stated another subject.

There was also a tremendous range of experience with other drugs. For example, three participants who were not taking college classes injected heroin, while the use of alcohol, marijuana, psilocybin, and LSD was common to all subjects. Over time, however, participants report "learning" not to combine MDMA with other drugs, including alcohol to minimize the potential for overdoses, but at the same time, the quantity and frequency of alcohol use in the participants self-reports was often extremely high – the researchers reported that it was not uncommon for men and women to consume 12 or more 12-ounce cans of beer at a single setting while using MDMA. Many users reported smoking marijuana to help "come down" after using MDMA. About a third of the participants had used other "club drugs," including GHB and ketamine. Other drugs used by participants, though less commonly, included flunitrazepam, methamphetamine, cocaine, alparazolam, and oxycodone.

The researchers found that there were several ways of categorizing MDMA users. One was by the preferred venue of use – so-called "club heads" versus "ravers." Club heads may be described as more "recreational" users of MDMA, as generally they are not committed to a drug-using lifestyle as some "ravers" appear to be.

Among the college students interviewed, going to a club and using MDMA was highly valued as a means to celebrate, and some people only used MDMA in this social setting. "Clubbing" can be quite expensive, with a typical evening running $200 per couple including MDMA, cover charge, drinks, taxis, and other expenses. However, MDMA use at clubs was not limited to college students. Raves appear to be attended mostly by younger and less educated MDMA users. The "ravers" who participated in this study often traveled to places like Indianapolis, Cleveland, Cincinnati, Detroit and Chicago.

House parties were another popular MDMA use venue. These ranged from long-term planned events made similar to dance club settings to typical "kegger" parties, sometimes

called rolling parties. In addition, small group settings appear to becoming more popular. A 22-year-old woman reported, "*Before, [MDMA] was mainly a club drug. Now, there are different groups of people who are becoming aware of it. It's more mainstream…very popular in high schools.*"

Friends and siblings were major sources of information, as were television news reports. A 21-year-old woman said, "*Before I took it the first time, I talked to my older brother about it, and he pretty much said it's fun and you'll be alright. I asked him what should I expect, how much should I take.*" The internet was only a minor information source within this group, though more important for some people. The government was recognized as a source of information but was largely ignored. "*When you think about drugs from a government standpoint, it's different. I wouldn't listen to it as much as if a person like a social worker was tellin' me about it face-to-face,"* said a 21-year-old woman in the study.

The investigators identified that there were several important reasons that the study participants initiated MDMA use. As expected, peer influence was important, sometimes as a subtle influence – participants saw their friends using it and having fun and decided to join in. Other times, peer influence was more direct, with a friend or acquaintance just handing out some to try. Boyfriends giving the drug to girlfriends for the first time was common. Some tried MDMA because they wanted to feel part of a scene, to not feel left out among a small circle of friends. As a 20-year-old woman said, "*It makes you sad if you're at a club and everyone else is having all this fun [using MDMA] and you're not. If all the people are doing it, it makes you want to do it."*

Curiosity was also an important reason to initiate MDMA use. Some participants said they had heard about the good experiences that others had with the drug and decided to try it for themselves. Also, some individuals reported a general desire to take drugs because they like the effects. And for some, rebelliousness was important, particularly among young "ravers."

Perhaps the most varied responses came in discussing users' expectations for their MDMA experiences. Users expected to have fun and feel good, to have more energy for dancing, and to enhance the sensual experience of the evening. A 22-year-old man said, "*All the touchy-feely stuff while you're blowin' it up that happens a lot, and that's why I do it, for that very reason is the touchy-feely trip*." Users claimed that MDMA broke down social barriers and allowed them to feel closer to people, strangers and friends alike. Some said it reduced their inhibitions, increasing their opportunities to pick up a date. Said one 21-year-old man, "*If I'm on [MDMA] and I go to a club, I can hook up with a good looking girl no matter what, every time. Something about it gives you that confidence, and you know exactly what to say.*"

The participants in this study largely saw MDMA as a relatively benign drug despite the occasional story in the media about the negative consequences of MDMA use, including overdoses and deaths. The researchers concluded that such stories may dissuade people from using other drugs in conjunction with MDMA, but not from using MDMA itself.

Only one participant personally knew someone who visited the emergency room or used other health services as a result of MDMA use, and only one participant suffered what might be considered a serious adverse consequence. In her words, "*I took one tablet and came home and smoked some pot, and I wake up the next morning and I just literally felt I wanted to stay in bed all day and cry. It was a terrible, terrible feeling. To the point I was thinking something is really wrong and I need to go to the doctor. Finally, it went away.*" None of the participants believes MDMA had negative consequences for them in terms of employment, education or personal relationships. None mentioned negative effects of MDMA use on cognition or memory.

The biggest concern among users was fear of what adulterants might be added to what they expect to be MDMA. Participants reported that they took care to obtain or purchase MDMA from friends who have used similar tablets before. Most participants were unaware that MDMA test kits do not identify the presence of adulterants.

Based on the information obtained in this pilot study, the researchers concluded that better drug abuse prevention education is needed in high schools and as part of college campus orientation. Sadly, college students and college-age youth are significant markets for MDMA and other illegal drugs, which suggested to the researchers that each incoming freshman class represents potential "fuel to feed" the MDMA epidemic. Another approach to reaching this age group might be through the radio with appropriately crafted MDMA prevention messages. A peer-driven network approach to prevention may also be effective since MDMA is often used among relatively small friendship networks.

Another general ethnographic study of young adult MDMA users in Atlanta, Georgia, found that MDMA use has spread beyond the club and rave setting in that city.[87] This ethnographic study of 76 active illicit drug users found that 28 were active MDMA users. The researchers found that this group displayed significant diversity in the settings in which they used MDMA and reasons for using it. However, they found two disturbing similarities among MDMA users. First, most of the participants, regardless of their background, age or education, thought of MDMA as just another pill in a sea of many. Second, most users described developing a tolerance of MDMA that often led them to seek out other drugs in order to achieve a better high. As one user reported, "*The tolerance to MDMA was really hard to take 'cuz that was like really my favorite drug in the world and when [the high] went away, I had to have another drug to replace it.*"

THE DIFFUSION OF MDMA USE AMONG URBAN YOUTH

Once viewed exclusively as a "club" or "rave" drug, MDMA now appears to be used among some networks of urban youth in a broad range of settings. These youth have limited access to accurate sources of information, and thus, have higher levels of exposure to the risks associated with use and selling of MDMA. To gain a better understanding of how this diffusion from downtown clubs, with mixed urban and suburban clientele, into urban neighborhoods is occurring, a group of researchers in Connecticut has observed participants in urban party and club settings in Hartford, Connecticut, and collected survey data using targeted sampling from urban youth ages 16

to 24 to examine diffusion of MDMA through street youth networks and the ways in which urban youth are introduced to MDMA through attendance at regular and after-hours clubs.[88]

This MDMA research was conducted as part of a larger research project aimed at examining pathways to high risk drug abuse among urban youth. The research team began their study with four hypotheses: that drug use sequencing is not linear, that social networks contribute more than vulnerability to drug use transitions, that the diffusion of MDMA from clubs to street use enhances sexual risk in urban youth, and that formal and informal drug economies are inextricably intertwined in urban neighborhoods. To test these hypotheses, the investigators conducted two surveys, 15 months apart, involving 400 adolescents and young adults, and an ethnographic study, involving in-depth interviews, with the same group. Eligibility criteria for participation included use of alcohol or marijuana and one other drug within the past 30 days. The mean age of the group was 19 years old; 71 percent of the participants were male; 45 percent were Puerto Rican, 38 percent were African American, 9 percent were other Latino, and 6 percent were White, Native American and Asian combined. Nearly everyone reported regular marijuana use, and nearly 12 percent reported having used MDMA.

In Connecticut, MDMA goes by many names – E, X, the pill, ecstasy, and candy, to name a few – and the tablets themselves come in a variety of colors and stamped with numerous logos such as Playboy, Calvin Klein, Batman, 007, VW, and seashells that are used both to identify source of the drug and as marketing tools. MDMA is also marketed by means of positive messages in magazines, popular literature, and music lyrics, as well as by club disc jockeys and even some famous music artists. The cost per tablet ranged from $20 to $25 apiece, or three for $50, and could be purchased at clubs, specific streets, and through friendship networks. MDMA was used at parties, for having sex, or for hanging around before, during and after school. It was often mixed with other drugs, particularly alcohol and marijuana. Users reported that MDMA enhanced sensations and triggered euphoria, loss of memory, dehydration, depression and fear of disappointment. MDMA users got their information about MDMA from social networks and at raves.

This study tapped into the Hartford club drug scene seemingly at the moment when MDMA use began skyrocketing in the region. Over the course of 15 months, regular MDMA use among the study participants rose from 11.9 percent of those participants to 53.8 percent, while the use of all other drugs in the survey remained constant or declined slightly. Some 27 percent of users who at the beginning of the 15 months had never tried MDMA had converted to MDMA use at the end of the study period.

The researchers found that drug exchanges in Hartford occurred in a variety of settings, including clubs, raves, house parties and street settings. Drug selling groups on street corners and at main avenues were important urban drug sources. So, too, were porches on side streets, in the back rooms of local shops, and in alleyways. There were also private distribution networks accessed through beepers and cellular phones. The researchers suggested that because of its cost, MDMA was becoming a big business in urban drug settings.

The researchers also identified a number of factors that were associated with 30-day MDMA use in urban Hartford. For example, the investigators found that MDMA use was associated with users driving a car while intoxicated with drugs or alcohol, involvement in selling drugs, younger age of initiation of drug sales, previous incarceration, and more frequent incarceration. In addition, MDMA use in this urban setting was associated with being a gang member, trying to hurt or kill oneself, being a victim or perpetrator of violence, having more sex partners in the past 30 days, and trading sex for money.

MDMA use in this group was not associated with the use of drugs such as heroin or cocaine. However, in the urban setting, there are connections between the MDMA distribution network and the heroin and cocaine drug distribution network, which could bring MDMA users into greater contact with those who deal drugs such as heroin and cocaine. The investigators did find that over the course of the 15 months study, MDMA users became more aware of the potential risks associated with taking this drug.

Based on their results, the researchers concluded that media and club-rave marketing expanded the market for MDMA, and that the drug then diffused from suburban and urban youth networks through mixed (suburban and urban) clientele. Urban distributors, seeing the potential for increased income, began meeting the demand in the urban, largely Latino population. Popular music and media may influence the diffusion of MDMA into urban African American youth networks. To stem this diffusion, the researchers suggest the use of activist-oriented prevention programs integrated into other after-school youth development efforts, as well as youth-led advocacy and drug prevention initiatives.

PATTERNS OF MDMA USE AMONG MEN WHO HAVE SEX WITH MEN

Club drug use among men who have sex with men, including the use of MDMA, is the topic of a research study being conducted in Boston and New York City.[89] The study is being conducted in three phases: 1) a community assessment process, 2) an ethnographic study of club drug-using men, and 3) a structured survey of club drug-using men. Preliminary results from 93 participants in the Phase 2 ethnographic study offer insights into patterns of MDMA use in this population. Men were included in the ethnographic sample if they reported sex with a man in the previous 12 months and reported the use of MDMA, methamphetamine, GHB, ketamine or inhaled nitrites in the three months previous to interview or as key informants if they were extremely knowledgeable about club drug use. Men enrolled in the study are interviewed one to six times about their knowledge of club drug use patterns, their patterns of drug use over time, HIV risk behaviors, life histories and other topics. The interviews are taped and transcribed for narrative analysis.

In the sample collected so far, 62 percent of the men are White, 14 percent Latino, 13 percent African-American and 10 percent reporting either a multiracial or other race/ethnicity; 88 percent identify themselves as gay; with an average age of 35. Out of the 93 participants, 55 report current use of MDMA; with current use defined as used in the three months previous to interview. Among the MDMA users, none reported the sole

use of MDMA, and all reported the current use of at least one other drug; 76 percent of current MDMA users had smoked marijuana, 69 percent had used ketamine, 56 percent had used methamphetamine, 55 percent had used cocaine, and 53 percent had inhaled nitrates. Significantly, in this relatively young group, 38 percent reported the current use of Viagra. GHB, anabolic steroids, LSD, and mushrooms were other drugs reported currently used. Eleven percent reported the current injection of drugs (primarily anabolic steroids) and fifteen percent reported enrolling in a drug treatment program at some time in their lives.

In this population, MDMA is taken orally, intranasally using an inhaler known as a bumper, and via anal insertion. According to the investigators, most of the men reporting the current use of MDMA consider MDMA as a "base" or social drug with other drugs added, often in a time-ordered sequence or menu of pills and doses, to achieve specific effects. One menu might be appropriate for dancing, and another might be used for sex. Researchers also found the emergence of a new pattern of drug use which is user manufactured powdered mixtures of various drugs, generally custom combinations of MDMA with ketamine, cocaine, methamphetamine and sometimes powdered Viagra. "Trail Mix," for example, is a popular name for the combination of MDMA, ketamine, and either cocaine or methamphetamine.[90]

The researchers found three general use patterns in this population of men. "Ragers", the least common use pattern, were men who engage in uncontrolled, high frequency drug use and may use high doses of MDMA. The most prevalent pattern is "structured" use, where men may use multiple drugs but structure their drug use to avoid anticipated problems, taking breaks from drug use when problems arise. Finally, there was a significant group of "infrequent" users, who restricted their MDMA use to special events such as parties or traveling. Each type of use pattern may require a different type of intervention in order to reduce or prevent MDMA use.

Some men in the study reported negative consequences of MDMA use. Current MDMA users in the study report accidental drug overdoses, although users attributed these events to either other drugs or poorly mixed combinations of drugs. Nearly a quarter of the MDMA users in this study are infected with HIV. Unprotected sex was prevalent in association with drug use, but it was almost always attributed to the use of other drugs such as methamphetamine. Two men in the study reported unwanted sexual attention or sex in the context of MDMA use.

The investigators found that prevention messages about MDMA have been largely unheard among men in the study. Current MDMA users discounted recent reports of MDMA-related harms and saw other drugs, such as GHB, as far more dangerous. GHB-related overdose deaths have been widely reported in both New York City and Boston, and thus, while MDMA was not necessarily perceived as a safe drug, it is seen as much safer than other drugs. With differing patterns of MDMA use, new drug combinations, and geographic variations in use, researchers concluded that this will be a difficult population to reach and will require specifically targeted intervention approaches.

CHAPTER 6. MDMA RESEARCH: FUTURE DIRECTIONS

When NIDA staff was organizing what was to become the first international scientific conference on MDMA – MDMA/Ecstasy Research: Advances, Challenges, Future Directions – they decided to ask invited speakers to not only address what is known about this drug, but to also discuss what questions still need answering. While almost every speaker presented data supporting the conclusion that MDMA is not a safe drug, and that its use carries with it risks of both physiological damage and at least some adverse effects on cognitive function and psychological well-being, it became clear over the course of the two-day meeting that there is still much that investigators do not yet know about how this drug is affecting human users. Indeed, it was obvious that the presenters took their charge seriously and gave careful consideration to areas that need further attention in regard to understanding what MDMA does to the human brain and what the consequences of these changes are for behavior.

METHODOLOGICAL ISSUES

As much as the data collected so far largely supports the proposition that MDMA damages the serotonin system in the brain and produces long-lasting behavioral deficits, there was universal agreement among the presenters that methodological issues, such as limited sample size and difficulties controlling for the possible influence of other illicit substances, have made it difficult to move beyond generalities and unequivocally prove a cause and effect relationship between MDMA use and specific cognitive or psychological damage in humans.

All of the studies reviewed in this report have relied on self-referred MDMA users, recruited through targeted sampling techniques by advertising for volunteers or through word-of-mouth.[91] This introduces an unknown bias into each study since it is possible that such self-referrers are not representative of MDMA users as a whole. There is also the problem of verifying that what users report as Ecstasy is, in fact, solely MDMA.

In addition, it is impossible to verify self-reports of past drug use beyond a certain period of time, making it difficult at best to accurately control for prior drug use. Since there seem to be few, if any, young people who use MDMA without also abusing other drugs, this will continue to be confounding factor in future studies. Some investigators have tried to accommodate this problem by using a control group comprising individuals who have never used MDMA but who otherwise have closely matched histories of using other drugs of abuse. This type of control has not been used universally, however, and even when it is, it may be difficult to closely match users and controls for prior drug use, as well as on other demographic details such as educational level and age.

Self-reporting also means that it is not possible to determine with complete confidence or accuracy how much a person has consumed, either on a particular occasion or over a lifetime of use. This uncertainty arises for two reasons: MDMA content is not constant across all tablets, and user memory of how much and how often a person took MDMA over many years is expected to be far from reliable.

In addition, because of a paucity of prospective studies, and the ethical issues involved in conducting such studies, it is a challenge to determine which came first – MDMA use or pathology as assessed in moderate and heavy MDMA users. As several of the speakers noted, any differences between MDMA users and non-users could indicate either a long-lasting effect of using MDMA or pre-existing differences between the two groups. For example, you would expect impulsiveness to be a trait that is more common among youth who use drugs than among those who do not. Thus, people with low serotonin levels might be naturally more impulsive and likely to use MDMA and other drugs. However, MDMA use by someone who is already at the low end of normal in terms of serotonin level might further exacerbate a serotonin deficit. Though it is unlikely that damage to the serotonin system seen in animals does not occur in humans, the possibility of pre-existing differences adds an additional level of complexity to interpreting MDMA effects observed in humans.

Ideally, researchers would like to be able to study MDMA's effects in drug-naïve humans, and indeed, a limited number of groups in Europe and the U.S. have received approval from the appropriate governmental regulatory agencies – the Food and Drug Administration and the Drug Enforcement Agency in the U.S., for example – and institutional review boards to conduct what would essentially be Phase I safety trials with MDMA in a limited number of humans. However, there is little likelihood of studying the effects of MDMA on large numbers of drug-naïve volunteers. An alternative might be to conduct the type of longitudinal, controlled prospective study that was discussed in Chapter 4, in which current MDMA users and controls of non-MDMA users are followed for many years to observe changes from some defined baseline.

CHALLENGES AND FUTURE DIRECTIONS

EFFECTS OF ACUTE DOSES OF MDMA

Though the data presented at this conference and in the literature support the hypothesis that MDMA produces acute behavioral and physiological effects, there is still more to be determined about factors that precipitate severe acute toxicity. For example, are there predisposing genetic factors that increase the risk for acute toxicity? Is overall health status important? Which organs and systems are the primary targets of MDMA toxicity? Are interactions with other drugs important?

Since MDMA is used most often in the noisy, overheated, highly stimulatory environment of dance clubs and raves, researchers want to know more about how environmental factors influence acute toxicity. Is overheating a critical factor in reports of MDMA toxicity? Does stress play an important role?

Important issues were raised about the unusual pharmacokinetics of MDMA in the human body and the relationship between the way in which the body metabolizes this drug and the presence of other drugs, both legal and illicit. Because MDMA is not the only drug taken by young adults, there is a need for more characterization of interactions between these substances and a determination of how those drug interactions may influence acute toxicity. Is the practice of "bumping" or taking sequential doses of

MDMA particularly dangerous? How do individual genetic factors influence MDMA metabolism and drug interactions? Certainly, animal studies will go a long way toward answering these questions, but the participants at the meeting felt that it is essential that human studies be conducted to confirm animal data on acute MDMA toxicity.

One critical piece of missing data is the incidence of acute toxicity among MDMA users. Assembling this database will require improved emergency room reporting of MDMA-associated incidents. In addition, data do not yet exist on the number of people seeking treatment for MDMA-related dependence and behavioral or psychological problems

LONG-TERM CONSEQUENCES OF MDMA: NEUROCHEMICAL AND DEVELOPMENTAL

One of the key concerns raised at the meeting was the lack of longitudinal studies designed to follow MDMA users, both as they continue to use the drug and after they have stopped using it. Such studies would give important insight into how age and length of use affect MDMA's acute and long-term neurochemical toxicity. In addition, such studies would allow researchers to determine if deficits appear later in life, long after use stops, or if adverse effects diminish over time. Such studies, if designed with regular assessment intervals, might also allow researchers to develop better measures of MDMA toxicity, and to more accurately determine how much drug is used and in what circumstances.

Researchers need better tools to assess neurotoxicity in humans MDMA users and to measure changes of neuronal integrity and possible recovery over time. With such tools, investigators may also then be able to address important mechanistic questions, such as how damage to the serotonin system leads to behavioral and cognitive changes, how the brain responds to and compensates for serotonergic damage, and why the dopaminergic system seems to escape lasting damage from MDMA. Such studies might then lead to the development and validation of methods for promoting recovery from MDMA-induced neurotoxicity.

There is also a need for more studies looking at the long-term effects of poly-drug abuse. Such studies will require new analytical tools for detecting multiple drugs of abuse simultaneously in biological samples. In addition, researchers need to develop better assessment tools to more accurately determine past histories for individual subjects.

LONG-TERM FUNCTIONAL CONSEQUENCES OF MDMA: BEHAVIORAL, MOOD, PSYCHIATRIC, AND COGNITIVE

Again, researchers stressed the need for longitudinal studies, both to establish baseline measures of cognitive function and psychological health and to more completely describe changes that occur over time with MDMA use. Such studies, if conducted with large enough groups of MDMA users and control subjects, both drug naïve and matched for poly-drug use, could also help identify risk and protective factors for both drug use and the deficits that result from continuing exposure to MDMA. The identification of significant risk and protective factors would greatly aid the development of efficacious prevention and rehabilitation approaches.

Data from longitudinal studies would also help establish associations between MDMA use and behavioral impairments that researchers have observed in the majority of studies. Longitudinal designs will enable researchers to determine how long such impairments last, whether they are progressive, and if deficits become more evident as MDMA users move into middle and late adulthood. Questions about the reversibility of impairments, a concern given the data seen in animal studies and even in some human studies, could also be addressed by such designs. Longitudinal studies should also provide data on critical patterns of MDMA use that may be more or less likely to cause impairments, and if the simultaneous abuse of other drugs plays a role in causing behavioral and cognitive damage.

One issue on which there is little data available is whether addiction, dependence or tolerance develops with continued use of MDMA. Though the data from animal studies support this possibility, studies need to be conducted in humans to determine the degree of abuse liability for this drug and to help develop treatments specific for reducing MDMA addiction. Along the same lines, researchers at this meeting stressed again that there are little data on numbers of drug rehabilitation patients who have used MDMA or who have sought treatment because of MDMA abuse.

PATTERNS AND TRENDS OF MDMA ABUSE AND THEIR IMPLICATIONS FOR PREVENTION

One of the gaps that needs addressing, according to presenters at the scientific conference, is development of methods for tracking so-called hidden populations of MDMA users; that is, those who don't go to dance clubs or raves, which is where the majority of volunteer recruiting occurs. On the other hand, researchers also stressed the need to better understand the youth party culture that seems to actively promote MDMA use through the use of in-house drug dealers and marketing messages delivered through music and by pop icons.

Researchers agreed that there is a need to foster interdisciplinary research and dialogue that links epidemiological, ethnographic, clinical and laboratory studies. As this report shows, there is much overlap between these separate fields, and undoubtedly, this area of investigation could benefit from better coordination between disciplines. Also, there is a need to link local, regional, national, and international supply-side intelligence with demand-side epidemiological and ethnographic research.

In the area of prevention, the speakers stressed that such efforts cannot be universal but must be targeted at different groups that use MDMA, particularly since MDMA appears to be a drug whose use is sensitive to and intimately linked with social context and networks. In particular, there is a need to integrate local research, services, prevention and intervention efforts to provide targeted, shared messages. The speakers also recommended that there be a new focus within youth networks and adult education programs to counter the perception that MDMA is much safer than other drugs that already carry a "safety" stigma. The use of youth-led advocacy and drug prevention programs seems particularly promising for reducing MDMA use among adolescents and young adults.

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