

# **Club Drugs: They're All the Rave: A Review of Use and Abuse: Effects of MDMA, Methamphetamine, and Gamma-Hydroxy-Butyrate (GHB) on Memory**

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## **The Amphetamine Epidemic**

In 2005, the National Center on Addiction and Substance Abuse (NCASA) reported an alarming increase (212%) in the abuse of controlled prescribed drugs among the 12- to 17-year-old age group from 1993-2003. Among these abused drugs are the amphetamines, specifically the illicit drugs methamphetamine (meth) and structurally related 3,4-methylenedioxy methamphetamine (MDMA). Meth and MDMA drug abuse is a growing epidemic worldwide. According to one study, 6.2% of high school seniors used meth in 2004 (National Institute on Drug Abuse). An estimated 35 million people regularly use amphetamines, compared to 15 million users of cocaine (Rassool, Gonzales, & Bretten, 2002; Rawson et al. 2002; Thompson, Hayashi. & Simon. 2004). An 87% increase in meth-related arrests was observed over the past 3 years at 500 law enforcement agencies across 45 states; law enforcers consider meth to be the most significant drug problem in America as printed recently in the *New York Times* (Zernike, 2005). The United Nations International Drug Control (UNIDC) estimated that there are 250 million abusers of psychoactive

abusers of psychoactive drugs worldwide posing a significant public health problem (Rawson et al., 2002). The statistics described above demonstrate the widespread effects that such abused drugs can impose on our country community and society. Along the same line, recent publications have discussed the role of meth and MDMA in causing different psychobiological effects leading to memory deficits and cognitive impairment, which will be discussed later (Roques & Noble, 2003).

## **Methamphetamine as a Club Drug**

Meth (also known as ice, crank, speed, crystal meth) is an addictive psycho stimulant belonging to the amphetamine family, which was originally introduced as an appetite suppressant and a treatment for attention deficit disorder (Robbins & Everitt, 1999; Sulzer, Sonders, Poulsen, & Galli, 2005; Tellier, 2002). Meth was used during WWII by Japanese kamikaze pilots for energy and bravery (Taylor, 2005). Meth can also be useful in treating narcolepsy due to the energy boost it provides (Goetz, 2003). It is the most widely spread illicit drug because it is easy to prepare and cheap to obtain. Meth can be smoked, inhaled, or injected leading to a variety of social behaviors with a feeling of euphoria and increased self-esteem, with the effects lasting up to 15 hours. Amphetamines are sympathomimetics that act by increasing the amount of dopamine, nor epinephrine, and epinephrine neurotransmitters available in the brain. As a result, the user may experience a heightened sense of awareness and paranoia. The average meth dose may cause the user to experience mydriasis (dilated pupils), hypertension, tachycardia (increased heart rate), and hyperthermia (Moore & Jefferson, 1996). Other indicators of meth use include auditory hallucination, visual hallucinations often involving bugs, agitation, insomnia, anxiety, nausea, and vomiting. Upon meth overdose, psychosis, myocardial infarction, seizures, and even death may occur.

## **Methamphetamine Neurotoxicity**

Meth is a psychostimulant that is known to mediate addictive behavior by acting on the monoaminergic system leading to an increase in the dopamine (DA) and serotonin (5-HT) levels in certain brain regions (Fleckenstein, Gibb, & Hanson, 2000; Robbins & Everitt, 1999). Several human and non-human primate studies

have indicated that the meth monoaminergic effect can lead to neurotoxic effects, which are associated with neurocognitive impairments involving memory deficits (nonspatial and working memory) (Gonzalez et al., 2004; Schroder, O'Dell, & Marshall, 2003). Long-term meth use induces dopaminergic and serotonergic axonal terminal damage that is coupled with neuronal degeneration of specific population of neocortical neurons (Schroder et al., 2003), and is attributed to the lipophilic nature of meth, which facilitates crossing of the blood brain barrier (BBB) and access to different brain regions (Nordahl, Salo, & Leamon, 2003). Upon entering the monoaminergic system, meth binds to the plasmalemmal dopamine transporter (DAT) and alters its function by blocking the re-uptake of DA and overloading the synapse (Baucum, Rau, Riddle, Hanson, & Fleckenstein, 2004; Robbins & Everitt, 1999). Meth also diffuses via the DAT into the neuronal terminal where it acts as a substrate for a number of neuronal structures, including the dopamine vesicular transporter (VMAT) that contributes to increased cytosolic DA. Afterward, neuronal function is altered leading to a reduction in DAT activity and the dysfunction of tyrosine hydroxylase (TH) and dopamine vesicular transporter (Nordahl et al., 2003). Furthermore, the oxidizing environment of the cytosol can lead to DA oxidation

leading to the generation of nitrogen, oxygen, and metabolic reactive species that trigger dopaminergic terminal degeneration and subsequently cause necrotic cell death (Baucum et al., 2004; Davidson, Gonzalez, Gow, Lee, & Ellinwood, 2001). In addition, it has been shown that meth can diffuse into other neuronal organelles, such as the mitochondria where it causes perturbation in the mitochondrial electron gradient leading to mitochondrial mediated apoptotic cell death- Oxidative stress mediated injury is exacerbated by increased glutamate levels, which in turn can activate NMDA receptors producing more reactive oxygen species leading toward excitotoxicity.

Neuronal degeneration is not confined to the monoaminergic system but can include other neocortical cells in a dopamine independent pathway. In a study by Cadet, Ordonez, and Ordonez (1997), it was demonstrated that an immortalized neuronal cell line when treated with meth exhibited an apoptotic cell death phenotype. These results were strengthened by other findings showing that neocortical cells were killed by meth treatment and showed increased expression of apoptotic markers and apoptotic family proteins (Stumm et al., 1999). Newly published work from our research has shown that an acute meth neurotoxic regimen (4,40 mg/kg) in rats causes neuronal injury in both the cortex and the hippocampus mediated by calpain and caspase activation that is suggestive of neuronal cell death (Warren et al., in press).

## **Neuropsychobiological Effect of Methamphetamine on Memory Deficits and Cognition**

Coupled to meth-related toxicity observed in DA neurons, it has been shown using positron emission test (PET) imaging that DA reduction is correlated with memory deficits observed in heavy meth users (Fleckenstein et al., 2000; Hanson, Rau, & Fleckenstein, 2004). Daberkow, Kesner, and Keefe (2005) further evaluated meth induced memory deficits in rats. Meth was administered at 2-hour intervals for 5 hours; then 10 days later, the rats were tested using a radial arm maze with free access for 5 days. Three weeks after exposure to meth, the rats were trained in the maze for 5 days using food rewards. Afterward, the maze pattern was changed. Meth exposed rats took longer to complete the maze and spent more time in its center. These rats also made fewer direct moves on the last day. This shows a likely decrease in procedural memory in meth-exposed rats. The meth-exposed rats had decreased DA and SHT in the striatum, an area of the brain involved with cognition. The more the DA was depleted, the fewer direct moves were made by the rats, indicating that DA in the striatum may be at least partially responsible for procedural learning.

To further explain meth-mediated memory impairment, Schroder et al. (2003) demonstrated a novel approach to evaluate the neurotoxic effects of meth, in which treated rats were evaluated in nonspatial memory (i.e., object recognition) and spatial memory (i.e. Morris water maze) hippocampal associated tasks. Rats were exposed to meth for one day and presented with a novel and a familiar object. The amount of time spent investigating the new object compared with the time spent on the familiar object is indicative of the rats' memory of the old object. Meth-treated rats consistently had poorer memory of the old object at 90 minutes, 24 hours, one week, and three weeks post meth exposure. In contrast, the results of the Morris water maze spatial memory test showed that at one week post-treatment, there was

no difference between the meth-exposed and control groups; however, after sacrifice it was found that there was a significant decrease in DAT and serotonin transporter (SERT) in the striatum and hippocampus, respectively. One major finding of this research is that a single meth treatment can cause long lasting selective hippocampal dependent memory deficits attributed to damage of the hippocampus monoaminergic terminals (Schroder et al., 2003).

Some research on meth has been performed in humans. Thompson et al (2004) utilized magnetic resonance imaging (MRI) to evaluate different brain alterations associated with chronic meth abuse in human subjects. In brief, 22 human subjects with a chronic history of meth abuse were subjected to MRI and compared to healthy subjects.

Interestingly, this study revealed three important findings related to chronic meth abuse: (1) Cortical maps revealed severe gray matter deficits in three separate cortical areas in the meth abusers compared to the control group, (2) Meth subjects showed significant hippocampal volume reduction (7.8% decrease) compared to the control subjects, and (3) hippocampal mapping was correlated with memory performance evaluated via word recall test. It was shown that chronic meth abusers caused selective cerebral damage contributing to the memory deficits observed (Blakeslee, 2004; Thompson et al., 2004).

## **MDMA**

MDMA also known as ecstasy, XTC, E, and X, is one of the most commonly used and abused drugs. Ecstasy, as the name suggests, is taken to induce euphoria, a sense of well-being, and a good mood, with its effects lasting for 4 hours (DEA, 2001). At \$20 to \$30 dollars per dose, MDMA is a profitable industry, with 4% of American high school seniors reported to have used the drug in 2004, down from an all-time high of 9.2% in 2001 (National Institute on Drug Abuse, 2004).

## **Signs of MDMA Intoxication**

Like other club drugs, MDMA has physiological consequences other than those for which the drug is taken. MDMA can cause tachycardia, hypertension, and hyperthermia, which can lead to heat stroke (DEA, 2001; Moore & Jefferson, 1996; National Institute on Drug Abuse, 2005). Deaths have occurred due to body temperatures reaching 109° F while under the influence of MDMA. As a result, many clubs have cool down rooms or spray patrons with cool water (DEA, 2001). Trismus, clenching of teeth, may occur, which is why it is common for ravers to chew gum or use pacifiers (DEA, 2001; Moore & Jefferson, 1996)- MDMA also produces increased energy levels, which allows users to attend extended parties.

## **MDMA and Memory**

Research has provided insight into the neurotoxicity caused by MDMA especially in regards to the serotonergic system (Obrocki et al., 2002). A significant amount of research has been done to study the long-term effects of MDMA on cognition. A pilot study of MDMA users found 5-HT injury in the occipital cortex. It also found a relationship between memory deficits and the amount of neuronal injury (Reneman, Booij, Schmand, Van Der Brink, & Gunning, 2000). In order to evaluate

the effects of long-term intermittent use as is common among MDMA users, one study administered MDMA in this fashion to rats and then tested their working memory and anxiety-like behavior one week later. This study found that there was a significant decrease in working memory as seen in novel object recognition tests in MDMA-exposed rats. The study also found that there was a decreased anxiety-like behavior as evident by increased open arm exploration in an elevated maze test, which should induce natural anxiety. They also noted a reduction in serotonin transporters in the hippocampus, an area of the brain involved in memory. Decreased SERF density was related to decreased anxiety-like behaviors (Piper & Meyer, 2004). An additional study compared cognition in heavy MDMA users with moderate MDMA users and non-user& There was increased reaction time with more MDMA use. Also, memory span was larger in non-users than users (Verkes et al., 2001).

## **Gamma-Hydroxy-Butyrate (GHB)**

Gamma-hydroxy-butyrate (GHB) is often termed a date rape thug due to its sedative and amnestic qualities; however, it has become an increasingly popular drug of abuse among American teenagers. It is classified as a club drug due to its popularity at raves. The annual prevalence of GHB use in 2004 was estimated to be 2% among high school seniors (National Institute on Drug Abuse, 2004). GHB, whose pseudonyms include G, liquid ecstasy, Georgia Home Boy, and fantasy, just to name a few, is a naturally occurring short chain fatty acid in human brains (Snead & Gibson, 2005). GHB's popularity may relate to its motto "euphoria without the hangover" (Ford, 2001). CHB is intentionally taken due to its effects of "mild euphoria, disinhibition, and increased libido" (Jacobson & Jacobson, 2001). GHB is also marketed as a supplement for body builders (Cecil, Goldman, Ausiello, 2004).

## **Signs of GHB Intoxication**

GHB intoxication may present in a variety of behaviors. The complexity of diagnosis of GHB intoxication is magnified due to the frequency of co-intoxication, especially with alcohol (Zvosec & Smith, 2005). Some indications of GHB intoxication may include ataxia (impaired gait) (Cecil et al., 2004), impaired judgment, and nystagmus (a rapid, jerking movement of the eyeball) (Jacobson & Jacobson, 2001). Although GHB is often thought of as sedating, Zvosec and Smith (2005) found that 64% of GHB emergency department visits presented with agitation and sometimes aggression. They witnessed bizarre behavior such as "summersaults," "snapping lips," "hugging trees," self-injurious behavior as well as "Zombie-like" behavior (Zvosec & Smith, 2005). GHB is a central nervous system depressant, and as a result, it can produce respiratory depression, somnolence, and coma (Cecil et al., 2004). One clinical finding that can help in forming suspicion of GHB intoxication is coma that lasts only 2 to 3 hours with rapid recovery (Ford, 2001). GHB intoxication can cause clonus (rapid contractions of a muscle) and seizure activity, though the mechanism is not fully understood (Ford, 2001).

## **GHB and Its Effects on Cognition**

The amount of literature available regarding the effects of GHB on cognition is limited (an online search of the National Institutes of Health Pub-Med for "GHB and Memory" yielded only six results, while the search for "MDMA and Memory"

yielded 112 results). In one study by Sircar and Basak (2004), rats were injected with three doses of GHB for 5 consecutive days, after which their spatial learning and memory was tested with a water maze test, and the number of NMDA GABA receptors were counted. The study showed that the rats treated with GHB had significant difficulty with spatial learning and memory, and the difficulty with spatial memory was correlated with the down-regulation of NMDA receptors in the frontal cortex (Sircar & Basak, 2004).

Counter intuitively, some studies have found that GHB can act as a neuroprotectant when administered after an ischemic insult by diminishing cognitive impairment (Ottani et al., 2004; Stumm et al., 1999). Clearly further research regarding the long term cognitive effects of GHB abuse is needed.

## Conclusion

As evident from the rise of club drug usage, METH, MDMA, and GHB are a considerable problem among American teenagers. These drugs increase the likelihood of neurotoxic events, which may be discernible or quite subtle. Brain science tells us that cells are lost, but the young person may appear normal. Age-related memory decline may occur earlier and be more severe in people with pre-existing drug use as a result of hippocampal and other cell loss. Similarly, patients may have cognitive and behavioral effects years later when they are under stress or when aging, which become manifest because of the lost cell reserve. While this is conjecture, we know that cells, once lost, are lost forever. It is unlikely, that the brain could be prepared by a higher being or evolution for drug use and cell loss to the extent we see in laboratory animals given doses of club drugs used by college students and even high school students whose brains are not yet developed. No one suggests that these drugs are memory medications or good for memory.

The main question is how much function is lost and how much of a decrement from baseline is seen. The search for euphoria, free love, and heightened energy levels comes with risky side effects including neuronal loss and even death. Because of ethical standards, it is unrealistic to study the effects of repeated or large doses of drugs on the human brain. We also cannot study the effects of multiple drugs taken at the same time. While this is the typical pattern of use among the young, we have limited ability to prospectively study them and rather, retrospectively report of the effects of experimentation, poisoning, or predators. In many instances, what we have learned comes from emergencies, addiction treatment referrals, and case reports of self-intoxication. Clearly, all medications must be used safely and under physicians' instructions. Drugs of abuse are manufactured by amateur chemists or brought from foreign countries, and use patterns are lost to the current users. If one dose does not work with the desired effect, another and another are taken. Club drugs have been linked to traffic accidents, increased chance of medical emergency, or death as well as other morbidities.

The diversity of meth and MDMA research supports their role in neurotoxicity and cognitive impairment; GHB has only limited evidence for involvement in neurotoxicity and long-term cognitive deficits, but it can clearly cause dependence and abstinence including a fatal syndrome that looks like alcoholic delirium tremens. More research is necessary to determine the extent of its effects and safe window for therapeutics. Perhaps as more basic research is conducted and reported and

Information regarding the extensive risks of drug use becomes available in popular media; their use among America's youth will decline.

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