

# DARK Side of Amphetamine and Analogues: Pharmacology, Syndromic Manifestation, and Management of Amphetamine Addiction

Abdul Mannan Baig\* 

The Aga Khan University, 78400 Karachi, Pakistan

**ABSTRACT:** The threat imposed by the use of psychoactive, illicit drugs on human health and the cost of rehabilitation of the affected individuals is nothing less than billions of dollars per year. Of the psychoactive substance abuse drugs are amphetamine and its analogues like methamphetamine. This Viewpoint intends to draw the attention of readers toward the neurological basis of “falling a prey” to methamphetamine. Attention has been paid toward a rapid desensitizing attribute that develops shortly after the repetitive use of drugs belonging to sympathomimetic agents of this group. Also summarized are the changes in physical characteristics and behavioral changes that could herald the loved ones around the methamphetamine abuser to seek the help of healthcare professionals before permanent and irreversible neurological damage ensues. A brief pharmacology of methamphetamine also precedes the management of these patients, for which no standard procedures exist at present.

**KEYWORDS:** Methamphetamine, amphetamine, crystal meth, ice, crank, psychoactive drugs, illicit drugs

## INTRODUCTION

As a contribution to the call for DARK Classics in Chemical Neuroscience in 2017, this Viewpoint is to reflect on underlying mechanisms behind the addictive central nervous system (CNS) excitation that rushes in with abuse of amphetamine (APA) and its analogues like methamphetamine (MA) (Figure 1A). As with any other addictive drug and chemical, all that is needed to get an individual hooked to MA is the first experience of its “rush”, an event that is so very likely to occur in gatherings and parties these days. The rest of the job of getting an individual addicted to APA or MA is done by the recalls of the highs by the temporal lobe of the brain, that is known for keeping the virtual memories of such events. These memory recalls are nearly impossible to resist in the near future and could be best referred as the revisit calls which are hard, if not impossible, to resist. The next exposures and the buildup of addiction takes a natural course, with the denials by the individual that “I am not hooked to it at all” and “my use of this is purely occasional.” We as humans would honestly confess that the same rule applies to not so very dangerous, but addictive social drinks like coffee and tea. In the case of MA and similar drugs like cocaine, the addiction builds up over a period of time until it completely grips the user to defy the above-mentioned confident denial and initiates the downward spiral of the most dangerous kind. Briefly, this Viewpoint addresses the

1. Chemistry and sites of amphetamine bindings to induce its CNS action
2. Effects of methamphetamine on organs and tissues
3. The nature of neurochemical imbalance at the level of synapses in amphetamine addiction
4. Management of methamphetamine addiction

## CHEMISTRY AND SITE OF AMPHETAMINE BINDINGS FOR ADDITIVE ACTION

Amphetamine (APA) (racemic  $\alpha$ -phenylisopropylamine) is one of the most potent sympathomimetic amines in inducing an excited state of the CNS (Figure 1A). Of its different isomers, the D-isomer (dextroamphetamine) is 3–4 times more potent than the L-isomer. APA and its analogue methamphetamine (MA) (Figure 1) acts on the CNS to release dopamine (DA) and other biogenic amines and to inhibit neuronal and vesicular monoamine transporters (VMAT2) and monoaminoxidase (MAO).<sup>1,2</sup> The effect of amphetamine as a CNS stimulant, its anorectic effect, and at least an element of its locomotor-stimulating action presumably are mediated by release of noradrenaline from central noradrenergic neurons. Some aspects of locomotor activity and the stereotypical behavior induced by amphetamine probably result from the release of dopamine from dopaminergic nerve terminals in the neostriatum (Figure 1B). Higher doses are required to produce behavioral effects, and disturbances of perception as well as overt psychosis may occur, with the latter being possibly due to release of 5-HT from serotonergic neurons and of dopamine in the mesolimbic system. In low doses, amphetamine increases the concentration of dopamine in the synaptic cleft (Figure 1A) in three ways:<sup>1</sup> (1) Amphetamine can interact with dopamine containing synaptic vesicles, releasing free dopamine into the nerve terminal. (2) It can bind to the presynaptic membrane of dopaminergic neurons and induce the release of dopamine from the nerve terminal. (3) Amphetamine can bind to the dopamine reuptake transporter, causing it to act in reverse and transport free dopamine out of the nerve terminal.

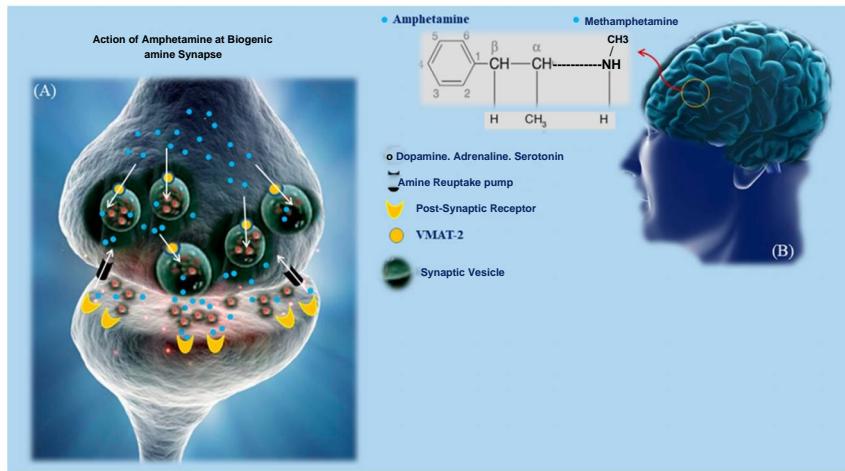
**Special Issue:** DARK Classics in Chemical Neuroscience

**Received:** March 22, 2018

**Accepted:** April 10, 2018

**Published:** April 19, 2018





**Figure 1.** Shows a CNS synapse representative of biogenic amines as neurotransmitters and the sites of action of amphetamine and methamphetamine. Structures of both of these drugs resemble the biogenic amines. APA and MA (blue dots) enter the axonal terminals in different areas of the brain by a reuptake pump that normally transports biogenic amines (A). Within the axonal terminal, VMAT2 [yellow circle] transports APA and MA into the secretory vesicles to replace the biogenic amines in a quantitative manner (A). These biogenic amines like dopamine, adrenaline, noradrenaline, and serotonin escape the axon to reach the synaptic cleft and bind the receptors to produce the CNS stimulation (B) and euphoric effects observed with the use of APA and MA. Chronic use induces a short-developing tolerance called tachyphylaxis in which the vesicles become depleted of the biogenic amines. Amphetamine is released into the synaptic cleft with subsequent nerve discharges and acts as a “false neurotransmitter”.

### EFFECTS OF AMPHETAMINE ON ORGANS AND TISSUES

**Neurological and Behavioral Effects.** Psychic effects of an oral dose of 10–30 mg manifest by causing wakefulness, alertness, and reduced fatigue; mood elevation, with improved self-confidence, ability to concentrate and an increase in speech. APA and analogues often produce elation and euphoria. Performances of mental tasks are noted to improve.<sup>1</sup> Physical performance of sportsmen and athletes gets notably improved, which becomes the basis of it abuse in these professionals. Depression and fatigue often follow during prolonged use or upon using large doses. Many individuals given APA experience headache, palpitation, dizziness, vasomotor disturbances, agitation, confusion, dysphoria, apprehension, delirium, or fatigue. In general, amphetamine extends the period of sufficient performance before fatigue takeover. The need for sleep may be postponed, but it cannot be avoided for an indefinite period.

**Body Weight and Hunger.** Amphetamine has been used for weight loss in obese individuals, and this effect is entirely due to a reduced appetite caused by this drug. Tolerance to the appetite suppression develops quickly in humans.

**Analgesia.** Amphetamine and some other sympathomimetic amines have a miniature analgesic effect that is not therapeutically useful. APA can enhance the analgesia produced by morphine and other related opioids.

**Respiratory Function.** Amphetamine stimulates the respiratory center in the brainstem, increasing the respiratory minute volume by increasing the rate and depth of respiration. However, its action is seen to appreciably stimulate breathing when the center of respiration is under inhibition caused by morphine and hypnotic drugs.

### AMPHETAMINE ADDICTION ASSOCIATED SIGNS AND SYMPTOMS

APA and MA are powerful CNS stimulants, that produce a high that can last up to 12 h. Both of these drugs exert an appetite

suppressing effect that has made them appealing, particularly among women interested in losing weight. The crystallized form of MA, often referred to as “speed”, “ice”, “crank”, or simply “meth”, is a powerfully addictive synthetic drug which is typically snorted, injected, or swallowed. MA is often administered several times over the course of many days in runs or binges.<sup>2</sup> However, tolerance and eventually tachyphylaxis to APA and MA occur rapidly, causing the addicts to take increasing amounts or more frequent doses as they chase a diminishing high (an effect that is not possible because of tachyphylaxis). Severe addiction invariably takes hold at this point. Because of the process by which this form of MA is manufactured, crystal meth is full of punitive chemicals, filth, and additives that make this form of the drug so very dangerous.

MA abusers often have pupillary dilation, their heart rate increases, and they may show signs of physical exertion (sweating and increased body temperature). They may seem particularly frantic, edgy, or angry without a reasonable cause. Because it has CNS stimulant effects, users will often go for extended periods, even days at a time, without sleep with a markedly diminished appetite. Looking bony, drawn, or starved may be the first clue toward MA addiction, but when coupled with other neurological and cardiovascular symptoms of MA abuse these signs should be taken very seriously. Over long periods of addiction, the harsh chemicals in the drug cause oral cavity erosions and deterioration of the gums and teeth. Eventually, psychosis follows and clinically symptoms of induced by amphetamines are very similar to those of acute schizophrenia.

**Cognitive Deficits.** With chronic exposure to APA and MA, deficits in learning, memory, perception, and problem solving are seen. The exact mechanism is unknown. As mentioned in sections below, impairment of the functions of parallel running neurotransmitter systems also may occur in APA and MA abusers. Such a parallel neurotransmitter system includes the cholinergic pathway, and studies have shown that,



**Figure 2.** Shows the deadly downward spiral of methamphetamine addiction. What begins as a party drug with occasional use, like any other addictive drug its use becomes more frequent with time. Skin, teeth, muscles, and eyes start exhibiting the features of an emaciated individual. Insomnia is usual and an accidental or deliberate overdose causes death. Incidences of stroke and myocardial ischemia are reported to be high in amphetamine addicts.

with the abuse of MA, a central cholinergic impairment in cholinergic system, related enzymes and receptors occurs during embryonal development of the brain in rats that become permanent.<sup>3</sup> With the addiction trends in early teenage kids (when the brain development still continues), this may provide the explanation of the permanent loss of some cognitive functions seen even years after the complete rehabilitation of some MA addicts.

**Skin and Mucosal.** Fanatical skin-picking often causes methamphetamine users' faces to be covered in small sores and scar tissue, the result of a common sensory hallucination of germs crawling beneath the skin. Facial skin with weight loss gives them a gaunt, hollowed-out appearance (Figure 2).

**Meth Mouth.** Oral cavity findings are caused by several factors: tooth enamel is dissolved by the harsh irritant nature of the drug, the blood vessels contained in healthy gums and teeth shrink, increasing the rate of tooth decay, and the production of saliva diminishes (Figure 2).

**Psychosis.** Psychotic episodes are seen in MA addicts that have been observed with short-term use as well as in chronic heavy MA users.<sup>2</sup> Neurotoxic damage to the serotonergic and dopaminergic neurons has been proposed<sup>2,4</sup> for psychosis

resembling schizophrenia. The latter group has also been implicated to be addiction prone in several studies. Chronic use is very commonly associated with paranoid features that are a sign of what is referred to be the "rock bottom" of the downstream spiral of MA abuse.

**End Organ Damage and Death.** Stroke, heart attack, and accelerated hypertensive states necessitates hospitalization, and death from overdose is common in MA and APA abusers.

#### THE NATURE OF NEUROCHEMICAL IMBALANCE AT THE LEVEL OF SYNAPSES IN ADDICTS OF AMPHETAMINE AND ITS ANALOGUES

**Understanding the Differences between Tolerance and Tachyphylaxis.** In cases of drugs that follow the rationale of drug tolerance, increasing the dose of the drug often produces the euphoria that the patients are addicted to, but with APA and MA this is not possible after a shorter period of addiction. Central to the understanding of the addiction of drugs that act by doctrine of false neurotransmitters in the CNS synapses (Figure 1A), is their ability to hit the tachyphylaxis benchmark in a short period of time. Drugs like amphetamine, ephedrine, and their derivatives belong to the tachyphylaxis

**Table 1. Practice in Diverse Rehabilitation Centers<sup>a</sup>**

syndromes and lifestyle	management, drugs recommended	exceptions
<b>neurological signs and symptoms</b>	cerebral stimulant replacement therapy should not be used to combat the acute phase of methamphetamine addiction	in approved and supervised clinical trials
excessive sleepiness	armodafnil and analogue that block biogenic amine reuptake in tachyphylaxis inducing drugs like amphetamines is undesirable	under clinical supervision if sleepiness persists many weeks after the withdrawal symptoms
depression	risperidone is recommended particularly when associated with mania; olanzapine has been suggested; <sup>5</sup> SSRI-class drugs are not recommended; tricyclic antidepressants are considered to increase the retention rate	
paranoid schizophrenia and amphetamine associated psychosis	among neuroleptics, haloperidol <sup>6</sup> has been used for combating amphetamine associated psychosis and acute paranoia in Pakistan	supervised continuation of neuroleptics if psychosis persists 4–6 months after withdrawal
anxiety disorders	no specific drug class recommended; olanzapine has been suggested <sup>5</sup>	treatment needed if persists for periods beyond 24 weeks
<b>rebound overeating and weight gain</b>	no specific drug class recommended	drugs of the class H2 blockers and proton pump inhibitors if heartburns become problematic
<b>healthy routine</b>	mild exercises, healthy eating, and sports like swimming are recommended	
<b>prevention of relapses</b>	all attempts should be made to change the prehab surroundings that includes the room, toilets, and company of friends involved in amphetamine abuse in group	
<b>motivation and reward</b>	patient should be accoladed for their success, and behavioral therapy should continue even after 26 weeks of abstinence from amphetamine	

<sup>a</sup>Selection of the drugs and management may vary from country to country, as approved by the qualified psychiatrists. For details of management and drug selection in the United States, refer to <https://www.drugabuse.gov/drugs-abuse/methamphetamine>.

exhibiting class of drugs.<sup>1</sup> Initial stoichiometric displacement of the biogenic amines occurs at the synaptic vesicles (Figure 1A) followed by the storage of the amphetamine within the granules. After synaptic replacement, the next nerve impulse releases the amphetamine instead of the native biogenic amine (dopamine, adrenaline, noradrenaline), resulting in a partial agonistic effect on postsynaptic receptor. Eventually, the disturbed physiological functions of these biogenic amines gets the abusers into a mayhem, resulting in severe behavioral and cognitive abnormalities that become clinically evident in MA addicts. The synaptic cross talk in the human brain is a complex phenomenon, as many of the human behavioral, cognitive, and motor functions are not the result of the function of a signal neurotransmitter, but are due to a balance between them and several parallel neurotransmitters functioning in concert. A reduced functional performance of one of the neurotransmitters is reflected clinically as a syndrome because of the shifting of the neurochemical balance toward a functionally opposite neurotransmitter. Parkinsonism is one known example of such a neurotransmitter imbalance between dopamine and acetylcholine.<sup>1</sup> Contributing therefore toward the disorganized cerebral functions of amphetamine abusers is not only the deficit of the functional biogenic amines, but also an antagonistic effect of other parallel running neurotransmitters. Understanding the concept of this neurotransmitter interplay is expected to improve the treatment protocols in the rehabilitation centers that are striving to understand the biological basis of amphetamine addiction. Prolonged use is associated with neuronal loss like in substantia nigra<sup>4</sup> and serotonin secreting neurons.<sup>2</sup>

**Addiction Management of Amphetamine and Analogues.** A 2017 world drug abuse report has shown that the users of amphetamines has increased, reaching the figure of 37 million globally. Studies of drug addiction and abuse in the United States indicate that MA addiction is a substantial public health concern that is growing at an alarming rate. According to the National Household Survey on Drug Abuse done in 2012, approximately 1.2 million people reported use of MA in 2011. APA and MA are now thought to be more of concern than any of the other drugs (including alcohol) and causes the most

drug-related deaths in Australia. There remains no standard treatment of MA addiction. In-house managements often fail due to reduced patient compliance. Management of the syndromic presentation (Table 1) includes drug therapy, psychotherapy that encourages the patients to hold on to the motivation that had brought them to the rehabilitation center. MA induced psychosis, depression, excessive sleeping anxiety, and several related symptoms have to be treated at the same time. No single drug has been effective in combating these signs and symptoms when used alone. The drugs used to combat the withdrawal symptoms have proven to be of help, but despite some of them having an influence on craving, none of the treatment regimens has remained effective on abstinence. Understanding that the tachyphylaxis has no easier way to be combated remains a major problem in the treatment of patients with MA addiction. Replenishment of the neurotransmitters coupled with normalization of the parallel running synaptic neurotransmitters is needed at the molecular level before any clinical improvements could be expected. Antipsychotics have been used, and drugs like olanzapine and haloperidol effectively improved psychotic symptoms due to amphetamines in the short-term.<sup>5</sup> A drawback of using antipsychotics could be that such drugs have a tendency to block the dopamine receptor type-2, potentially increasing anhedonia that could, in turn, cause a greater vulnerability to relapse into drug abuse.<sup>2</sup> Olanzapine has such action on the dopamine type 2 receptor, but has the advantage of being effective because it combats anxiety and depression that may be correlated with its impact on the serotonergic 5HT2A receptor.<sup>5</sup>

## CONCLUSION

The experience of exposure to a euphoric addictive drugs like APA and its analogues is perceived as casual and amusing. The highs (euphoria) caused by these illicit drugs have the potential of getting stored as memory and the subsequent compulsion to re-experience the euphoria. Naivety, therefore cannot be an excuse for the first use of any euphoric drug in general, and MA/APA in particular, users should know that the cycle of use—denial—reuse repeats itself to eventually convert a casual user to a compulsive addict. The management of MA addiction

with an effective drug regimen remains elusive and requires multiple drug therapies. The ominous dangers of chronic APA and MA addiction are irreversible cognitive dysfunction and psychosis caused by neurotoxicity that results in permanent neuronal loss.<sup>3</sup>

## AUTHOR INFORMATION

### Corresponding Author

\*Mailing address: Neuroscience Section, Department of Biological and Biomedical Sciences, Aga Khan University, Medical College, Stadium Road, 78400, Karachi, Pakistan. E-mail: [abdul.mannan@aku.edu](mailto:abdul.mannan@aku.edu). Phone: +923332644-246.

### ORCID®

Abdul Mannan Baig: [0000-0003-0626-216X](https://orcid.org/0000-0003-0626-216X)

### Notes

The author declares no competing financial interest.

## REFERENCES

- (1) Brunton, L. L., Chabner, B. A., and Knollmann, B. C. (2011). Goodman & Gilman's 'The Pharmacological basis of Therapeutics', 12th ed., The McGraw-Hill Companies, Inc, New York.
- (2) Bramness, J. G., Gundersen, O. H., Guterstam, J., Rognli, E. B., Konstenius, M., Loberg, E.-M., Medhus, S., Tanum, L., and Franck, J. (2012) Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable. *BMC Psychiatry* 12, 221.
- (3) Siegel, J. A., Craytor, M. J., and Raber, J. (2010) Long-term effects of methamphetamine exposure on cognitive function and muscarinic acetylcholine receptor levels in mice. *Behav. Pharmacol.* 21 (7), 602-614.
- (4) Rumpf, J. J., Albers, J., Fricke, C., Mueller, W., and Classen, J. (2017) Structural abnormality of substantia nigra induced by methamphetamine abuse. *Mov. Disord.* 32 (12), 1784–1788.
- (5) Xue, X., Song, Y., Yu, X., Fan, Qy Tang, J., and Chen, X. (2018) Olanzapine and haloperidol for the treatment of acute symptoms of mental disorders induced by amphetamine-type stimulants: A randomized controlled trial. *Medicine (Baltimore)* 97 (8), e9786.