



# ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

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In Partnership with the UVA Division of Medical Toxicology – Department of Emergency Medicine

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## Ketamine Analogues

### Ketamine

Ketamine is a dissociative anesthetic that is used commonly in human and veterinary medicine for both pain and sedation. Ketamine antagonizes the glutamate N-methyl-D-aspartate (NMDA) receptor to produce its dissociative effects, a mechanism shared with phencyclidine (PCP). Ketamine is increasingly popular as a substance of misuse, and there has been an emergence of novel agents that are analogues of ketamine with similar activity to the parent compound.

### What are ketamine analogues?

Ketamine analogues, used as designer drugs, are substances structurally similar to ketamine, but contain different side chain substitutions. Examples include methoxetamine (MXE) and 3-methoxy-PCP.

These substances produce effects similar to ketamine but vary in potency, duration, and clinical profile. Some agents are more stimulating and PCP-like, while others cause more prolonged dissociation or sedation than the parent compound. Ketamine analogues have gained popularity both because certain compounds are perceived to have stronger or longer-lasting effects and because their legal status may temporarily differ from ketamine. Although some analogues, such as methoxetamine (MXE), are banned in the United States, newly synthesized compounds may remain legally unscheduled for a period of time before regulatory action occurs.

### Pharmacology

PCP, ketamine, and their analogues can be administered orally, via inhalation (smoked or vaporized), intravenously, or subcutaneously and are rapidly absorbed through all these routes. Their primary mechanism of action is antagonism of the NMDA receptor, particularly within cortical and limbic regions of the brain. By inhibiting NMDA-mediated glutamate signaling, they disrupt excitatory neurotransmission and produce dissociative and anesthetic effects. In addition, these substances have also been shown to cause weak catecholamine reuptake inhibition, which is responsible for the excitatory symptoms that can also be seen after PCP and ketamine use.



Image from [Narcanon](#)

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**Clinical Effects**

NMDA receptor antagonism accounts for the analgesic, dissociative, and sedative effects of ketamine and its analogues. Rotary nystagmus is a characteristic clinical finding following exposure to NMDA antagonists. The varying structures of the analogues may contribute to the differences in degree of central nervous system effects between different analogues. However, because these compounds are produced in clandestine settings and used primarily for recreational purposes, human data are limited.

In addition to NMDA receptor blockade, varying degrees of catecholamine reuptake inhibition can lead to sympathomimetic manifestations, such as tachycardia, hypertension, agitation, and mydriasis. These findings are more commonly associated with PCP and PCP-like analogues and are generally less pronounced with ketamine alone. Three analytically confirmed cases found that MXE acute toxicity was associated with a 'dissociative catatonic' state similar to that seen with ketamine, accompanied by sympathomimetic toxicity, with significant tachycardia and hypertension.

**Management**

Identifying intoxication with ketamine analogues can be challenging due to the wide variability in clinical effects among different compounds, as well as differences in individual patient response. Routine diagnostic testing is generally not available or clinically useful. Standard urine drug screens do not detect ketamine or its analogues, and confirmatory testing is rarely available in real-time. As a result, diagnosis is primarily clinical.

Management is supportive and guided by the patient's presentation. Careful assessment of airway protection is essential, particularly in patients with significant agitation or sedation. Benzodiazepines are the first-line treatment for agitation, hallucinations, or significant sympathomimetic effects such as tachycardia or hypertension. Patients with severe agitation should receive prompt chemical sedation to reduce the risk of complications such as hyperthermia or rhabdomyolysis. Because these substances are frequently adulterated with other drugs, clinicians should maintain a high index of suspicion for co-exposures and pursue additional evaluation or treatment if the presentation is atypical. The Blue Ridge Poison Center is available 24 hours a day at 1-800-222-1222 to assist in the management of these complex cases.