



Metaphedrone (3-Methylmethcathinone): Pharmacological, Clinical, and Toxicological Profile

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GENERAL INFORMATION

Metaphedrone (3-methylmethcathinone, 3-MMC) is a substance that belongs to a large group of novel psychoactive substances called **synthetic cathinones**. It is a psychostimulant drug and structural isomer of the most famous synthetic cathinone, **mephedrone (4-methylmethcathinone, 4-MMC)**. Synthetic cathinones are derivatives of cathinone, the main psychostimulative substance naturally occurring in the leaves of *Catha edulis* (the khat plant). Metaphedrone became a popular drug after the previous generations of synthetic cathinones became legally controlled. This substance made its first appearance in Sweden in 2012, while the abuse quickly spread to other European countries. The drug is commonly used by younger generations, probably due to its low price. The usual forms are white powder, crystal, tablets, capsules and liquid. The common methods of administration are snorting (insufflation), oral ingestion, intravenous application, inhalation and rectal administration. The reported desired effects are **euphoria, excitement, high energy levels, stimulation, happiness, awareness of senses, unbridled libido, appreciation of music, improved social skills and feeling of empathy**. Metaphedrone has **ADDICTIVE POTENTIAL** (significant psychological dependence can occur).



The leaves of khat plant*



The packages of 3-MMC**

THE AIM

Analysis of the the relevant research on the novel psychoactive substance - metaphedrone, and presentation of its pharmacological, clinical, and toxicological profile.

METHODOLOGICAL APPROACH

The relevant literature was researched using standard search engines (*Google Scholar, PubMed*).

Inclusion criteria: all literature on metaphedrone and its properties.

Exclusion criteria: literature lacking inclusion criteria, recent similar paper, not in English.

CONCLUSION

- There is a growing trend of abuse of metaphedrone among recreational drug users.
- Future studies should focus on pharmacological and toxicological effects of metaphedrone on animals and humans.
- The potential findings might be significant in determining whether the abuse of metaphedrone should be considered a potential public health problem or not.

THIS RESEARCH WORK WAS SUPPORTED BY

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*The picture was taken from: Patel, N.B. (2015) "Natural Amphetamine" Khat: A Cultural Tradition or a Drug of Abuse", *International Review of Neurobiology*, pp. 235–255.

**The picture was taken from: <https://unity.nl/nl/drug/3-mmc/>

***All pictures were taken from the original article.

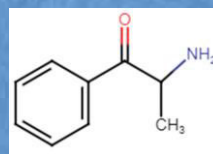
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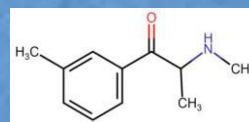
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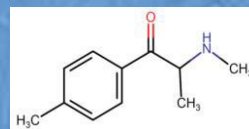
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Cathinone***



3-methylmethcathinone***



4-methylmethcathinone***

PHARMACOLOGICAL PROFILE

Pharmacodynamics

- ✓ Potent **inhibition of the norepinephrine, dopamine, and serotonin transporters** in central nervous system.
- ✓ The drug shows the ability to evoke the **release of norepinephrine and dopamine in the synaptic cleft**.
- ✓ 3-MMC **binds to the serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors**, but it **does not activate 5-HT_{2A} receptors**, suggesting low influence on hallucinatory activity.

Pharmacokinetics

The mean oral bioavailability of 7% suggests metaphedrone undergoes an **extensive first-pass effect**. The distribution into the extravascular tissues is good, with a volume of distribution of 240 L. However, the drug **rapidly eliminates from and does not accumulate in the central nervous system**. The common metabolic pathways of 3-MMC are **β-keto-reduction** and **N-demethylation**. The total clearance value of metaphedrone is 199 L/h; therefore, **the half-life is very short (0.83 h)**.

CLINICAL PROFILE

- **Sympathomimetic side effects (the most common):** tachycardia, chest pain, hypertension, agitation, and perspiration
- **Cardiovascular manifestations:** tachycardia, hypertension, palpitations, chest pain, cardiac arrest
- **Neurological manifestations:** verbosity, stuttering, slurred speech, fatigue, reduced level of consciousness, uncoordinated movements, staggering, tingling, dilated pupils, headache, convulsions
- **Psychiatric phenomena:** concentration difficulties, confusion, disorientation, fear, anxiety, depression, agitation, aggression, paranoid delusions, hallucinations.
- **Other signs and symptoms:** gastrointestinal distress, diaphoresis, dyspnea, tachypnea, dry mouth/throat/nose, hyperthermia, and rhabdomyolysis.

If combined with other substances, more serious side effects and florid clinical pictures can be expected.

TOXICOLOGICAL PROFILE

- The toxic and fatal concentrations of 3-MMC are difficult to determine. Various reported concentrations from blood samples of intoxicated individuals and post-mortem samples support this claim.
- Repeated administrations in a single session escalate the risk of overdose. **Most of the reported deaths associated with 3-MMC were polyintoxications**. Users usually combine metaphedrone with another **novel psychoactive substance(s)** and/or **traditional psychotropic drug(s)** (e.g., amphetamine, buprenorphine, cannabis).
- Several **mechanisms of toxicity** are currently proposed:
 - Metaphedrone can induce **hyperthermia**, which can sometimes be refractory to treatment, leading to **metabolic acidosis** and **renal failure**.
 - **Hepatotoxicity** is proposed by the most current literature. The bioactivation produces metabolites with higher toxicity which may be capable of damaging the liver and the overall homeostasis. Reactive oxygen and nitrogen species lead to the depletion of intracellular glutathione. When liver cells run out of their defensive capabilities, intrinsic, extrinsic, and common apoptotic pathway activation occurs as a consequence.