Pharmacology of MDMA, Ketamine and Methamphetamine

By

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Pharmacology of MDMA, ketamine and methamphetamine:
1. Mechanism of action and pharmacokinetics
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MDMA

- Full name: 3,4-methylenedioxyamphetamine
- Street names: Adam, E, Ecstasy, M&M, XTC, “Fing Tao” etc
- A “rave-party” drug
- Pharmacological classification: a phenylethylamine compound structurally related to amphetamine with CNS stimulation and hallucinogenic effects
- Legal classification in HK: Dangerous Drug
Pharmacology

- Major mechanism of action: by central stimulation and a rapid and brief liberation of noradrenaline from peripheral adrenergic terminals → sympathomimetic effects
- Recent findings: mechanism of action could be related to a serotonin-depletion effect* → “serotonin syndrome”

* Fleckenstein, Gibb, Hanson, Eur J Pharmacol, 2000
  Wallace, Gudelsky, Vorhees, Psychopharmacol, 2001
Pharmacology (cont’d)

- Pharmacokinetics:
  - absorption: oral
  - onset of action: 20 min
  - duration of effect: up to 8 hours or more
  - excretion: renal
Toxicity and Adverse Effects

- Class effects of the amphetamine group
  - acute and chronic
- MDMA-specific effects
  - acute and chronic
Toxicity and Adverse Effects

• General amphetamine effects:
  I. Acute:
    - CNS: restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, tenseness, irritability, weakness, insomnia, fever, euphoria (sometimes), fatigue and depression after stimulation
- Psychotic effects: paranoid hallucinations, panic states, suicidal or homicidal tendencies, aggressiveness, changes in libido, anxiety, delirium

- Cardiovascular effects: pallor, flushing, palpitation, arrhythmias, anginal pain, hypertension, circulatory collapse
- GI: dry mouth, metallic taste, anorexia, nausea & vomiting, diarrhoea, abdominal cramps

- fatal poisoning → convulsions, coma, cerebral haemorrhages, cardiovascular collapse
II. Chronic effects:

- Weight loss, psychotic reaction with vivid hallucinations and paranoid delusions, incipient schizophrenia
- Recovery usually rapid after discontinuation of drug
MDMA-specific Adverse Effects

1. “Serotonin Syndrome”:
   - Diagnostic criteria: mental status changes (confusion, hypomania), agitation, myoclonus, hypereflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination, fever
"Serotonin Syndrome" (cont’d)

- Manifestations:

1. Cognitive and behavioral changes – disorientation, hallucinations, dizziness etc
2. Autonomic dysfunction – tachycardia, hypertension, flushing, salivation, hyperthermia etc
3. Neuromuscular effects: muscle rigidity, bruxism, trismus
4. Disseminated intravascular coagulopathy (DIC), rhabdomyolysis, renal failure, acute respiratory distress syndrome (ARDS) etc
2. Acute symptomatic hyponatraemia with the syndrome of inappropriate antidiuretic-hormone secretion (SIADH)
- cause: MDMA-induced increased secretion of vasopressin $\rightarrow \downarrow \text{Na}$
- if fluid intake increased $\rightarrow \downarrow \downarrow \text{Na}$ $\rightarrow$ hyponatraemic coma
MDMA-specific Adverse Effects (cont’d)

3. Others :
   - “flashbacks”
   - parkinsonism
   - chronic paranoid psychosis
   - jaundice
   - subarachnoid haemorrhage
   - cerebral infarction

4. Drug-drug interactions : with monoamine oxidase inhibitors, other anti-psychotic agents
Abuse of MDMA

- Forms: mostly as round tablets of various colours with different logos, less often powders and capsules
- Hallucinogenic dose: 50-150mg
- Adulterants: “Ice”, methaqualone, ketamine, phenobarbitone, caffeine, benzodiazepines, paracetamol
- Serious risk for uninformed users
### Phenethylamine-type Stimulant Tablets

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Ketamine

- Full name: Ketamine hydrochloride
- Street name: Special K, “K”
- Pharmacological classification: anaesthetic agent for minor human and veterinary surgical procedures
- Legal classification: Dangerous Drug
Pharmacology

- Mechanism of action: by blocking activation of non-competitive N-methyl-D-aspartate (NMDA) receptors → a state of "dissociative anaesthesia" → sensory loss, analgesia, amnesia but without actual loss of consciousness
Pharmacology (cont’d)

• Pharmacokinetics:
  - onset of action: IV – seconds
    IM – 4 min
  - duration: 15-30 min
  - excretion: renally excreted after liver metabolism
Toxicity and Adverse Effects

• Emergence reactions: common during recovery, include unpleasant dreams, confusion, hallucinations and irrational behaviour (children less susceptible), reduced by prior administration of a benzodiazepine

• “out-of-body” state/experience: a psychological dissociation, “near death experience”

• “flashbacks”
Toxicity and Adverse Effects (cont’d)

- Hyper- and hypotension, arrhythmias, brady- or tachycardia
- Respiratory suppression, apnoea
- Long term effects: impaired memory, learning and attentional mechanisms; compulsive repeated use
- Drug-drug interactions: with other anti-psychotic agents
Abuse of Ketamine

- Forms: powder for snorting, injection for liquid
- Adulterants: often mixed with MDMA, “Ice”, benzodiazepines etc
- Hallucinogenic dose: 30mg po
Methamphetamine

• Full name: methamphetamine/methylamphetamine hydrochloride
• Street names: crank, “Ice” for the high-purity crystalline smokeable form
• Pharmacological classification: amphetamine-type CNS stimulant with hallucinogenic effects
• Legal classification: Dangerous Drug
Pharmacology

- Mechanism of action: similar to MDMA
- Medical uses: appetite-suppressant, hyperactivity, narcolepsy
- Pharmacokinetics:
  - well absorbed orally and through mucous membrane of respiratory tract (inhalation)
  - instantaneous “high” after IV (a “rush”) or inhalation
  - duration of action: 8-24 hrs
  - excretion: renal excretion after hepatic metabolism
Toxicity and Adverse Effects

- Instant “rush” after inhalation or injection
- “crashing” after drug effect wears off: profound sleep
- Depression and fatigue, sometimes suicidal
- Tendency to progress to compulsive use
- Tolerance after prolonged use
Toxicity and adverse effects (cont’d)

- Hyperthermia, hypertension, tachycardia, dysrhythmias
- CNS effects: insomnia, auditory hallucinations, confusion, delusions, paranoia, aggressive behaviour, suicidal
- High doses: extreme suspiciousness, overt paranoid psychosis → unpredictable violent behaviour
- Drug-drug interactions: with MAOIs, other anti-psychotic agents
Abuse of Methamphetamine

- Forms: by inhalation of the vapourized crystals, by IV injection
- Adulterants: often with MDMA, ketamine, or benzodiazepines
- Hallucinogenic dose: 20-25mg
- Tolerance develops after prolonged use
Methamphetamine

Fake (Alum)  Genuine

Hookahs

[Images of fake and genuine methamphetamine, and hookah equipment]
Summary

- MDMA, ketamine and methamphetamine have high potential for abuse
- Tolerance and dependence are common
- Combined use poses high risk of fatal poisoning