3,4-Methylenedioxymethamphetamine
Ecstasy or MDMA
“... MDMA produces a state of relaxation and euphoria, a state of emotional openness, empathy, reduction of negative thoughts, reduction of inhibitions "

Sounds and colors may appear more intense
Defining Ecstasy
A derivative of amphetamine

MDMA, XTC, E, essence, Adam
Ecstasi (weak base)
Stomach H+
Polar

Gut (alkaline)
Non polar
Brain Areas Affected by Ecstasy

neocortex
basal ganglia
amygdala
hypothalamus
hippocampus

Cognitive functions
Thoughts, Perception

Memory
Stress/anxiety
Emotions
Mood
Acute Effects of Ecstasy

heightened perceptions

reduced appetite

stimulation

rewarding

elevated mood

serotonin
dopamine
Short Term Effects after Ecstasy is Gone

Normal

During Ecstasy
  elevated mood

After Ecstasy
  depression-like feelings, irritability
Adverse Effects of Ecstasy

- Sweating
- Dry mouth
- Tachicardia
- Fatigue
- Muscle contraction

- Clouded thinking
- Hyperthermia
- Disturbed behavior
- Jaw-clenching
Life-Threatening Effects

- hyperthermia
- arrhythmias
- renal failure
# Neuropsychiatric side effects following use of MDMA

<table>
<thead>
<tr>
<th>ACUTE EFFECTS (IN 24 hrs)</th>
<th>SUB-ACUTE EFFECTS (IN 1 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration of decision-making skills</td>
<td>Decrease of sleep</td>
</tr>
<tr>
<td>Decreased desire to perform physical / mental activities</td>
<td>Decrease of appetite</td>
</tr>
<tr>
<td>Difficulty performing mathematical operations</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Panic</td>
<td>Depression</td>
</tr>
<tr>
<td>Flashback</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Irritability</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>Chronic EFFECTS (over 1 month)</td>
</tr>
<tr>
<td>Bruxism</td>
<td>Panic</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Decrease appetite</td>
<td>Flashback</td>
</tr>
<tr>
<td>Intensification of unrest / agitation</td>
<td>Severe depression</td>
</tr>
<tr>
<td>Disorientation / confusion</td>
<td>Memory impairment</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
</tr>
</tbody>
</table>
Ecstasy Damages Brain Areas Controlling Memory

memory impairment

memory impairment
Micro-photographs of sagittal sections of the frontal, parietal and primary visual cortex showing the serotonergic axons:

A, D: controls

B, E: ecstasy 2 weeks before (5 mg/Kg 2vv/day for 4 days)

C, F: ecstasy 7 years before (5 mg/Kg 2vv/day for 4 days)

G, H, I: ecstasy treated monkeys 2 weeks and 7 years before the study.
Methamphetamine
"Ice", "Shaboo" or "Crystal meth"

**Effects**
- The purest form of methamphetamine, clear crystals of d-methamphetamine hydrochloride.
- Increased energy, excitement, euphoria that can lead to violence
- Smoked or injected with effects far superior and more durable than other routes of intake and other amphetamines

**Consequences**
- Anxiety, depression, insomnia
- Inability of social relations
- Paranoia, hallucinations, psychotic behavior with murderous and suicidal thoughts
**Table. Summary of Methamphetamine Pharmacokinetics by Administration Route**

<table>
<thead>
<tr>
<th>Method</th>
<th>Bioavailability</th>
<th>Dose (mg)</th>
<th>T ½ (hr)</th>
<th>Time peak effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>100%</td>
<td>30</td>
<td>9</td>
<td>&lt; 15 min</td>
</tr>
<tr>
<td>Smoking</td>
<td>67%</td>
<td>30</td>
<td>12</td>
<td>20 min</td>
</tr>
<tr>
<td>Oral</td>
<td>67%</td>
<td>30</td>
<td>9</td>
<td>180 min</td>
</tr>
<tr>
<td>Intranasal</td>
<td>79%</td>
<td>50</td>
<td>11</td>
<td>&lt; 15 min</td>
</tr>
</tbody>
</table>

Summed brain images from Baboons for 11C-d-methamphetamine (top row, from 0–90 min) and 11C-l-(2)-cocaine (bottom row, from 0–54 min) in same animal. 11C distribution is widespread over cortical and subcortical brain regions for 11C-d-methamphetamine but is highly localized in striatum for 11C-(2)-cocaine.

Fowler et al., 2007
Criteria of the DMS-V for the diagnosis of: addiction, withdrawal, intoxication

Stimulant use disorder
Stimulant Intoxication

Diagnostic Criteria

A. Recent use of an amphetamine-type substance, cocaine, or other stimulant.

B. Clinically significant problematic behavioral or psychological changes (e.g., euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension, or anger; stereotyped behaviors; impaired judgment) that developed during, or shortly after, use of a stimulant.

C. Two (or more) of the following signs or symptoms, developing during, or shortly after, stimulant use:
   1. Tachycardia or bradycardia.
   2. Pupillary dilation.
   3. Elevated or lowered blood pressure.
   4. Perspiration or chills.
   5. Nausea or vomiting.
   7. Psychomotor agitation or retardation.
   8. Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias.
   9. Confusion, seizures, dyskinesias, dystonias, or coma.

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Specify the specific intoxicant (i.e., amphetamine-type substance, cocaine, or other stimulant).

Specify if:

With perceptual disturbances: This specifier may be noted when hallucinations with intact reality testing or auditory, visual, or tactile illusions occur in the absence of a delirium.
Stimulant Withdrawal

Diagnostic Criteria

A. Cessation of (or reduction in) prolonged amphetamine-type substance, cocaine, or other stimulant use.

B. Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after Criterion A:
   1. Fatigue.
   2. Vivid, unpleasant dreams.
   3. Insomnia or hypersomnia.
   4. Increased appetite.
   5. Psychomotor retardation or agitation.

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Specify the specific substance that causes the withdrawal syndrome (i.e., amphetamine-type substance, cocaine, or other stimulant).

Diagnostic Features

The essential feature of stimulant withdrawal is the presence of a characteristic withdrawal syndrome that develops within a few hours to several days after the cessation of (or marked reduction in) stimulant use (generally high dose) that has been prolonged (Criterion A). The withdrawal syndrome is characterized by the development of dysphoric mood accompanied by two or more of the following physiological changes: fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, and psychomotor retardation or agitation (Criterion B). Bradycardia is often present and is a reliable measure of stimulant withdrawal.

Anhedonia and drug craving can often be present but are not part of the diagnostic criteria. These symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion C). The symptoms must not be attributable to another medical condition and are not better explained by another mental disorder (Criterion D).
THERAPY

- Methylphenidate (reduces craving, does not affect compulsion)
- Modafinil (reduces cocaine intake)
- Slow release methamphetamine (reduces cocaine use)
- Antidepressants (reduce cocaine consumption, but no craving)
- Dopamine receptor antagonists (not effective)
- Vaccination
Caffeine
CAFFEINE

1 cup (60-100 mg caffeine) (5 µM)

1-10 cups antagonism adenosine receptors $A_1/A_2A$ receptors

10-20 cups: inhibition cAMP and phosphodiesterase (100 µM); release of $Ca^{2+}$ (1 mM)

CAFFEINE (thè, cola, cocoa)
Theophylline (thè)
Theobromine (cocoa)
Europe's Top Ten Coffee-Drinking Nations

Cups of coffee consumed per capita on average in 2015

1. Finland: 1,310
2. Sweden: 1,070
3. Netherlands: 1,004
4. Denmark: 863
5. Germany: 675
6. Italy: 658
7. Estonia: 635
8. Austria: 623
9. France: 482
10. Portugal: 482

Chart 5: Caffeine — Mg/day by age group (2010-2011)

Source: International Life Sciences Institute
Figure 1: Various drinks in their caffeine concentration. Note red horizontal line specifies the FDA imposed limit of 71 mg caffeine/12 fl oz soda.

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https://cheatdaydesign.com/caffeine-in-energy-drinks/
Caffeine is an **antagonist** of the adenosine receptors.
ADENOSINE

- Formed either intra-extra cellularly from ATP
- Homeostatic modulator (sleep, pain, arousal, hypoxia/ischemia, seizures)
- Neuromodulator (release, receptor interaction)
- Acts through specific metabotropic receptors (A1, A2A, A2B, A3)
Methylxanthines

• Caffeine and theophylline produce psychomotor stimulant effects.
• Average caffeine consumption from beverages is about 200 mg/day.
• Main psychological effect is reduced fatigue and improved mental performance, without euphoria. Even large doses do not cause stereotyped behaviour or psychotomimetic effects.
• Methylxanthines act mainly by antagonism at purine A₂-receptors, and partly by inhibiting phosphodiesterase, thus producing effects similar to those of β-adrenoceptor agonists.
• Peripheral actions are exerted mainly on heart, smooth muscle and kidney.
• Theophylline is used clinically as a bronchodilator; caffeine is not used clinically.

contractility  
diuresis  
Gastric secretion  
HCl
Caffeine

- Pharmacokinetics
  - CNS and all organs
  - Placenta, breast milk
  - Metabolized liver, excreted urine

Common Side Effects of Caffeine:
- Shakiness and jittery, anxious feeling
- Trouble sleeping
- Headaches and dizziness
- Dehydration
- Rapid heart rate

High doses: cardiac arrhythmias, convulsions
Withdrawal crisis: headache, irritability
Caffeine Withdrawal

Diagnostic Criteria

A. Prolonged daily use of caffeine.
B. Abrupt cessation of or reduction in caffeine use, followed within 24 hours by three (or more) of the following signs or symptoms:
   1. Headache.
   2. Marked fatigue or drowsiness.
   3. Dysphoric mood, depressed mood, or irritability.
   4. Difficulty concentrating.
   5. Flu-like symptoms (nausea, vomiting, or muscle pain/stiffness).
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The signs or symptoms are not associated with the physiological effects of another medical condition (e.g., migraine, viral illness) and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.
More than 95% of $A_{2A}$ receptors are located in striatal dopamine-enriched areas.
ADENOSINE AND DOPAMINE RECEPTORS INTERACT IN AN OPPOSITE WAY

A

Adenosine & Dopamine

Adenosine receptor

Dopamine receptor

$\text{ADO}$

$\text{DA}$

$\pm$

Effects

Normal condition

B

Agonist

Stimulation of adenosine receptors

C

Antagonist

Blockade of adenosine receptors
Caffeine has both positive effects that contribute to widespread consumption of caffeine-containing beverages and adverse unpleasant effects if doses are increased. Caffeine has weak reinforcing properties, but with little or no evidence for upward dose adjustment, possibly because of the adverse effects of higher doses. Withdrawal symptoms, although relatively limited with respect to severity, do occur, and may contribute to maintenance of caffeine consumption. Health hazards are small if any and caffeine use is not associated with incapacitation.
In general, caffeine is not considered a substance of abuse, but several studies have reported that caffeine consumption is often a correlate in drug abuse (Istvan and Matarazzo, Psychol Bull, 1984; Swanson et al., Addict Behav 1994)

Studies in experimental animals and humans suggest that the effects of caffeine may share some similarities with those elicited by certain substances of abuse and that, accordingly, caffeine could function as a trigger for drug abuse