The Effects of Dissociative Drugs (PCP, Dextromethorphan and Ketamine on Human Performance and Behavior

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Dissociative Drugs

- Prescription drugs:
  - Ketamine (veterinary and human anaesthetic)
  - Tiletmaine (veterinary anaesthetic)
  - Memantine and Amantadine

- Over The Counter Drugs and Quasi-Legal Drugs:
  - Dextromethorphan
  - Nitrous Oxide (Whippets and whipped cream charger):

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Dissociative Drugs

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  - Tiletmaime (veterinary anaesthetic)
  - Memantine and Amantadine

- Over The Counter Drugs and Quasi-Legal Drugs:
  - Dextromethorphan
  - Nitrous Oxide (Whippets and whipped cream charger):

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Dissociative Drugs Cont.…. 

- **Street Drugs:**
  - Ketamine, PCP, Dextromethorphan

- **Research Drugs:**
  - Dizocilpine maleate (MK-801)
Structures

Ketamine

Phencyclidine

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Brief History of PCP

- Synthesized in early 1950’s
  - Potential surgical anesthetic
  - Animal trials showed “cataleptoid” response
- Marketed as veterinary anesthetic Sernyl®
- Human clinical trials started in 1957
  - Based on positive results seen in animals
  - Induced similar anesthetic effects
- Appeared on the street in mid ’60’s in California
- In 1970, PCP placed in Schedule III of the CSA

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Brief History of PCP

- In 1970, PCP placed in Schedule III of the CSA
- In the 1970’s PCP started to be smoked
  - Usually placed on parsley, tobacco or marijuana
  - Allowed user to control dose
- Later in the 70’s, PCP was moved to Schedule II
- In 1978, removed from vet use

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Human trials revealed other properties
- Potential hallucinogenic
- Seemed to induce schizophrenic state in some patients
- Helped uncover repressed memories
- Some patients exhibited “emergence delirium”
Sources

Commercial

There are no commercial sources

Illicit

Clandestine labs from

- piperidine
- cyclohexanone
- bromobenzene
- phenylmagnesium bromide

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Routes of Administration

PCP comes in liquid, crystal, pill or powder form

- Inhalation/Insufflation
- Intravenous injection
- Transdermal absorption (absorbing thru the skin)
- Oral absorption
- Rectal and Vaginal absorption
- Add PCP to cigarettes, marijuana, or herbs to smoke it
PCP Metabolism

Phencyclidine (PCP)

4-(1-Piperidinyl)-cyclohexanol (PPC) 1-(1-Phenylcyclohexyl)-4-hydroxypiperidine (PCHP)

Glucuronide and Sulfate Conjugates

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Pharmacokinetics of PCP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (oral)</td>
<td>50% to 90%</td>
</tr>
<tr>
<td>Peak plasma (oral)</td>
<td>approx. 1.5h</td>
</tr>
<tr>
<td>Peak plasma (smoke)</td>
<td>approx. 5-20 min.</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>5.3-7.5 L/kg</td>
</tr>
<tr>
<td>Fraction plasma protein bound</td>
<td>approx. 0.65</td>
</tr>
<tr>
<td>Half-life</td>
<td>approx. 7-46 h</td>
</tr>
<tr>
<td>Blood/Plasma Ratio</td>
<td>1</td>
</tr>
<tr>
<td>Clearance</td>
<td>approx. 0.14-0.77 mL/KgL/min</td>
</tr>
</tbody>
</table>

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Mechanism of Action of PCP

- Interacts with neurotransmitter systems
  - Cholinergic
  - Adrenergic
  - Dopaminergic
- Interacts with the N-methyl-D-aspartate (NMDA) receptor
- Interacts with the opiate receptors
Pharmacodynamic

- PCP has sedative/analgesic properties
  - Produces ataxia
  - Enhances effects of other CNS depressants like barbiturates and alcohol
- PCP has some properties in common with stimulants
  - Increased blood pressure, heart rate and temperature

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Effects on Behavior

- **User reported depressant effects**
  - Calmness, depression, psychic numbing, anergia, impaired concentration, ataxia

- **User reported stimulant effects**
  - Feelings of euphoria, power, strength, invulnerability, anxiety, insomnia, anorexia

- **User reported hallucinogenic effects**
  - Slowed time perception, visual illusions, paranoia, religious experiences, bizarre behavior
Effects on Behavior

**Observable manifestations**

- Bank stare, illogical speech, peripheral analgesia, grimacing facial expression, mild impairment of eye-hand coordination, horizontal and vertical nystagmus, mild increase in blood pressure and heart rate

**As dosage increases, these effects become more severe**

- Continue to delirium, confusion, agitation, violent or bizarre behavior, seizures, muscle rigidity, dilated pupils with eyes open

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Effects on Performance

- *Studies with “street” doses have not been performed*
- *Can gain some insight from arrest records*
- *No independent studies of the effects of PCP on driving have been performed*
Dextromethorphan (DXM)

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Dextromethorphan

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Dextromethorphan

- Nonopioid, antitussive
- over-the-counter in the US, and other parts of the world:
  - “Maximum Strength” Robitussin Cough Syrup® and Vick’s 44 (US), and Contac Coughcaps (Canada)

- potent psychoactive drug when taken in sufficient quantities.
  - dissociative drugs
  - hallucinogen.

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Pharmacokinetics of DXM

- Within 30 minutes absorbed
- Plasma half-life: 3 to 4 hours
- Peak plasma level: 2 hours
- Elimination:
  - The main metabolite, dextrorphan, is eliminated renally.
Primary psychological symptoms:

- Euphoria;
- CNS stimulation;
- Increased perceptual awareness;
- Altered time perception;
- Feelings of floating;
- Tactile, visual, and auditory hallucinations.
## Recreational Doses

<table>
<thead>
<tr>
<th>Category</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold</td>
<td>80-90 mg</td>
</tr>
<tr>
<td>Light</td>
<td>100 - 200 mg</td>
</tr>
<tr>
<td>Common</td>
<td>200 - 400 mg</td>
</tr>
<tr>
<td>Strong</td>
<td>300 - 600 mg</td>
</tr>
<tr>
<td>Heavy</td>
<td>600 - 1500 mg</td>
</tr>
<tr>
<td>Risk of Death</td>
<td>2500 - 20000 mg</td>
</tr>
</tbody>
</table>

* Duration: 4-8 hours

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Recreational Doses (cont.)

<table>
<thead>
<tr>
<th>Plateau</th>
<th>Dosage (mg/Kg)</th>
<th>For 75 Kg adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1.5 - 2.5</td>
<td>115 - 185 mg</td>
</tr>
<tr>
<td>Second</td>
<td>2.5 - 7.5</td>
<td>185 - 560 mg</td>
</tr>
<tr>
<td>Third</td>
<td>7.5 - 15</td>
<td>560 - 1125 mg</td>
</tr>
<tr>
<td>Fourth</td>
<td>&gt; 15</td>
<td>&gt; 1125 mg</td>
</tr>
</tbody>
</table>
Recreational DXM (cont.)

| First Plateau (1.5-2.5 mg/Kg) | • Light intoxicating stimulant, like being a little drunk;  
|                              | • Music and movement are pleasurable;  
|                              | • Colors seem richer. |
Recreational DXM (cont.)

| Second Plateau (2.5-7.5 mg/Kg) | • Intoxicating, a “stoning” similar to that of marijuana or nitrous oxide;  
|                               |  
|                               | • Occasional visual hallucinations, especially if in dark room (or with closed eyes);  
|                               | • Short-term memory and physical impairment;  
|                               | • Double-vision.  

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Recreational DXM (cont.)

| Third Plateau (7.5-15 mg/Kg) | - Altered state of consciousness, psychometric effects take over;  
|                            |   - Logical and causality breakdown;  
|                            |   - Very easy to become delusional and extremely disoriented. |
Any Comments/ Questions?

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Special K: It's Not Just Cereal Anymore

The illegal use of ketamine is increasing at an alarming rate among teenagers and young adults in the United States, Europe, and Asia. On the street, ketamine is known as Special K, Vitamin K, K, Kit Kat, Ket, Cat Valium, Keller, Super C, New Ecstasy, Psychedelic Heroin, Super K, and probably more creative names of which we are not aware. A combination of ketamine and cocaine is called "CK". Ketamine in combination with other drugs, including MDMA, heroin, methamphetamine, or benzodiazepines, is referred to as "Trail Mix."

Ketamine (Ketaset®, Ketal Ketaject®) is a powerful nonbarbiturate anesthetic CNS depressant. It alters perception of sight and sound and produces feelings of detachment from the environment. These mind altering effects are considered true hallucinations like LSD produces, this class of drugs labeled "dissociative" anesthetics. Other drugs in the dissociative category are PCP, dextromethorphan, and nitrous oxide of which are abused.

In 1962, Calvin Stewart formed an American pharmacists working for Parke-Davis Pharmaceuticals, in an attempt to find a replacement for I
History of Ketamine

Used to induce “near-death” experiences
- Has a large number of street names
- Is currently appearing in combination with other drugs and sold as Ecstasy at raves
- Becoming a popular hallucinogen
  - Users deem effects superior to PCP or LSD
- $40-50/half gram
History of Ketamine

- Smoked, injected, or snorted
- Synthesized in 1962 at Parke-Davis
  - Goal – PCP-like anesthetic properties without the emergence delirium
  - Anesthesia verified in studies 1962-1965
- Marketed as anesthetic Ketalar® in Europe and Asia, 1966
  - Vet version Ketaset® and Vetalar®
- Extensive clinical trials 1967-1970
  - Mostly in Germany

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History of Ketamine

- FDA approval for use in humans, 1970
- Within 5 years, use had spread worldwide
  - Both legitimate and recreational
  - Used in Europe and Asia as aid in regression therapy
- Publications about personal recreational use appeared in 1978
- In 1995, added to DEA’s emerging drugs list
- Became a Schedule III controlled substance in 1999

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Structures

S-(+)-Ketamine

R-(-)-Ketamine
Sources

Commercial

Mexico, Veterinary anesthetics Ketaset® and Vetalar

Illicit

Difficult to synthesize

Home synthesized versions not seen

Diverted from legitimate sources

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Ketaset®
Ketamine HCl INJ., USP

Equivalent to:
100 mg/mL
Ketamine
10 mL

Store at controlled room temperature.
Infuse at 1 mL/min.
Follow all precautions. This product is not sterile.

Not for intravenous administration.

Avoid excessive use, overuse, or long-term use.
Consult the package insert for complete information.

DOE 025-2003. Approved by FDA.
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Ketamine powder in paper packets
Ketamine Inhaling device
Dosage

- Normal dose is 2-6 mg
  - Lethargy, disorientation, loss of coordination, hallucinations
- Heavier doses (7.5 mg)
  - Produce staggering gait, ataxia, memory impairment
- Even heavier doses (8-9 mg)
  - Marked analgesia
- Still heavier doses (15 mg)
  - Prostration, collapse, total analgesia
Routes of Administrations

- Absorbed rapidly
- Common routes of administration
  - Insufflation
  - Intramuscular
  - Oral ingestion
  - Rectal absorption
- Intravenous used rarely
Metabolism

- Urinary Metabolites
  - Norketamine
  - Dehydronorketamine

- About 2% excreted as unchanged drug
  - Most labs look for parent and norketamine
    - Metabolites are probably active

- Rapidly excreted
  - Half-life 3-4 hours
  - Detectable in urine about 3 days
Ketamine Metabolism

Ketamine → Norketamine → Dehydronorketamine

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Pharmacology

- Ketamine has sedative/analgesic properties
  - Produces ataxia
  - Enhances effects of other CNS depressants like barbiturates and alcohol
- Ketamine has some properties in common with stimulants
  - Increased blood pressure, heart rate and cardiac output
## Pharmacokinetics of Ketamine

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-Life of ketamine</td>
<td>3-4 h</td>
</tr>
<tr>
<td>half-life of norketamine</td>
<td>approx. 4.21h</td>
</tr>
<tr>
<td>half-life of dehydronorketamine</td>
<td>approx. 7.21h</td>
</tr>
<tr>
<td>Volume of Distribution</td>
<td>3-5 L/kg</td>
</tr>
<tr>
<td>Peak Plasma Level at 5 min after 4 mg/kg of administration</td>
<td>6.3 µg/mL</td>
</tr>
<tr>
<td>Clearance</td>
<td>81 mL/Kg/min</td>
</tr>
</tbody>
</table>

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Pharmacology

Blood levels

- Not much data on street use
- During anesthesia, blood levels of 2-3 µg/mL are used
- Levels in fatalities have ranged from 2-27 µg/mL
- Reasonable to assume that recreational users attain levels less than 1 µg/mL
Experimental legitimate uses

- Chronic pain in stroke victims
- “Phantom” pain in amputees
- Morphine-refractive pain in advanced cancer
- Fibromyalgia
- Migraine
- Depression
- Epilepsy
Mechanism of Action of Ketamine

Acts on the amino acid neurotransmitters (EAAs) receptors
- Such as N-methyl-D-aspartate (NMDA) receptor
- Non-competitive NMDA antagonist
  - Binds within the ion channel thus interfering with calcium flow
- Also effects on the opiate receptors
- 10-50 times less potent than PCP in blocking NMDA

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The Effects of Ketamine

- A Sense of well-being
- Hallucinations
- Feeling of alternate consciousness
- Expanded awareness
- “Out-of-body” experience
- Rapture
- Paranoia
Identification

- **Field Tests**
  - Turns red with Lieberman’s reagent
  - Turns blue with Mandelin’s reagent

- **Lab Tests**
  - No commercial immunoassay kits
  - In body fluids by GC/MS or GC/NPD
  - Identified in solid dose forms by color test and by GC/MS
    - Sometimes TLC, FTIR or other instrumental methods

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Common Methodologies for Ketamine

- GC/NPD
- GC/ECD
- GC/MS(EI)
- GC/MS(PI CI)
Effects on Behavior

- **Observable manifestations**
  - Mild increase in blood pressure and heart rate, slurred speech, ataxia, muscle rigidity, perhaps a slow nystagmus

- **May proceed to**
  - Amnesia, catalepsy, indifference to pain, hallucinations, paranoia, aggressive behavior
One study, 20 ER patients with ketamine overdose

- Anxiety, chest pain, palpitations, tachycardia
- Nystagmus in only 3 of the 20
Evaluation Clues

- Horizontal Gaze Nystagmus: Present
- Vertical Gaze Nystagmus: Present
- Non-Convergence: Present
- Romberg: Fast
- Walk and Turn: Anesthesized
- One Leg Stand: Anesthesized
Evaluation Clues ----

- Pulse: Up
- Pupil Size: Normal
- Pupil Reaction to Light: Normal
- Blood Pressure: Up
- Temperature: Up
- Muscle Tone: Rigid; flacid
Summary

- Rapid absorption
  - Poor bioavailability orally - need higher doses
- Detectable 24 hours in blood; 48 hours in urine
- Causes analgesia, **hallucinations**, dizziness, irrational behavior, nausea, and hypotension, amnesia, loss of consciousness (anesthesia)
- “Conscious sedation”
  - Awake but dissociated
- Magnifies dance floor reactions/hallucinations

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Drugs in Driver Cases

HCME 2001

- Total Cases 4102
- Drivers 266
  - Positive for alcohol and drugs 158
    - Alcohol 120
    - Other drugs (Carisoprodol, Cocaine, THC, Dextromethorphan, Diphenhydramine, Sertraline, Alprazolam, Propoxyphene, …………
Drugs in Driver Cases
HCME 2002

- Total Cases 4284
- Drivers 69
  - Positive for alcohol and drugs 38
    - Alcohol 31
    - Other drugs (Carisoprodol, Cocaine, THC, Dextromethorphan, Diphenhydramine, Sertraline, Alprazolam, Propoxyphene, ……...
Drugs in Homicides Victims
HCME 2001

- Total Cases (4102)
  - Homicides (363)
  - positive drug/alcohol (231)
    - Alcohol (162)
    - Cocaine (48), CE (23), BE (58)
    - THC (17), THC-COOH (60)
    - GHB (1)
    - Morphine (6), 6-MAM (3)
    - PCP (9)

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Drugs in Homicides Victims
HCME 2002

- Total Cases (4284)
  - Homicides (617)
  - positive drug/alcohol (231)
    - Alcohol (208)
    - Cocaine (77), CE (30), BE (92)
    - THC (41), THC-COOH (108)
    - Morphine (9), Codeine (11), Hydrocodone (7), 6-MAM (1)
    - Methadone (1), Rx - Benzodiazepines (13)
    - Miscellaneous (19)
HARRIS COUNTY MEDICAL EXAMINER

11,762 Medical Legal Cases for 2002

Harris County - 11,317
Out of County - 445

434 Homicides 4%
437 Suicides 4%
9,021 Naturals 77%
1,227 Accidents 10%
592 Pending 5%
36 Undetermined 0%
15 Non-Human 0%
15 Non-Human 0%
Drugs in DUI D Cases

HCME 2001

- Ethanol 48%
- Cocaine metabolites 22%
- Meprobamate 20%
- THC-COOH 19%
- Carisoprodol 16%
- Hydrocodone 16%
- Alprazolam 13%
- Acetaminophen 9%
- Hydromorphone 7%
- Cocaine 7%
- Temazepam 5%
- Codeine 5%
- PCP 5%
- Promethazine 5%
- MDMA 5%
- Ephedrine/Pseudoephedrine
- THC 4%
- Nordiazepam 4%
- Others
  - Chlorpheniramine
  - GHB
  - Propoxyphene
  - Venlafaxine
  - Sertraline
  - Citalopram
  - Naproxen
  - Other
Drugs in DUI Cases
HCME 2001

- Ethanol 48%
- Cocaine metabolites 22%
- Meprobamate 20%
- THC-COOH 19%
- Carisoprodol 16%
- Hydrocodone 16%
- Alprazolam 13%
- Acetaminophen 9%
- Hydromorphone 7%
- Cocaine 7%
- Temazepam 5%
- Codeine 5%
- PCP 5%

- Promethazine 5%
- MDMA 5%
- Ephedrine/Pseudoephedrine
- THC 4%
- Nordiazepam 4%
- Others
  - Chlorpheniramine
  - GHB
  - Propoxyphene
  - Venlafaxine
  - Sertraline
  - Citalopram
  - Naproxen
  - Other
Drugs in DUI D Cases
HCME 2002

- Ethanol 24%
- Cocaine metabolites 8.9%
- Cocaine 5.5%
- Meprobamate 0%
- THC 1%
- THC-COOH 6%
- Amphetamines 0.3%
- Hydrocodone 3%
- PCP 0.72%
- Ketamine 0.11%
- GHB 0.11%
- Hydromorphone 0.18%
- Codeine 0.8%
- Opiates 10%
- Rx Drugs 22%
- Others
  - Morphine
  - Oxycodone
  - Methadone
  - 6-MAM
  - Other

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PCP

St. Louis, 1981-1986

- 104 deaths involving PCP
- 81 were victims of homicide
  - 13 suicides, 4 OD, 6 accidental

PCP in HCME

- Harris County, Tx, 1999
  - 24 deaths involving PCP
    - 17 homicide, 5 accident, 2 suicide

- Harris County, 2001
  - 363 total homicides
    - 9 PCP (2.5 %)
    - 57 Cocaine (16.5%)
    - 144 Alcohol (41.7%)
    - 59 THC (17.1%)

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PCP Study

- 18 cases DUI D, DRE
- Age:
  - 18-49 Y, 16 male, 2 female
- Blood conc.
  - 100-600 ng/mL in 9 cases
- Attitude
  - Cooperate, Polite (13), Excited (1), Talkative (1), Incoherent (1), Cocky (1), Paranoid (1)
- Arrest
  - Accident (8), driving on wrong side of road (2), driving badly (8)
- Other drugs:
  - THC-COOH (3), BE (1), Alcohol (3)

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PCP - Is the hype hype?

Review of the literature for reports of PCP and violence:

- Data analyzed by standard techniques
  - Corroborated events?
  - PCP detected in body fluids?
  - Presence of other drugs excluded?

- Concluded that “clinical and forensic assumptions about PCP and violence are not warranted”

Summary
Ketamine, Dextromethorphan and PCP

- All relatively uncommon
- All have physiological effects that might reasonably be assumed to impair driving
- Effects detectable in DRE examination
- Ketamine and Dextromethorphan not routinely looked for by many labs