The pharmacology of (meth)amphetamine

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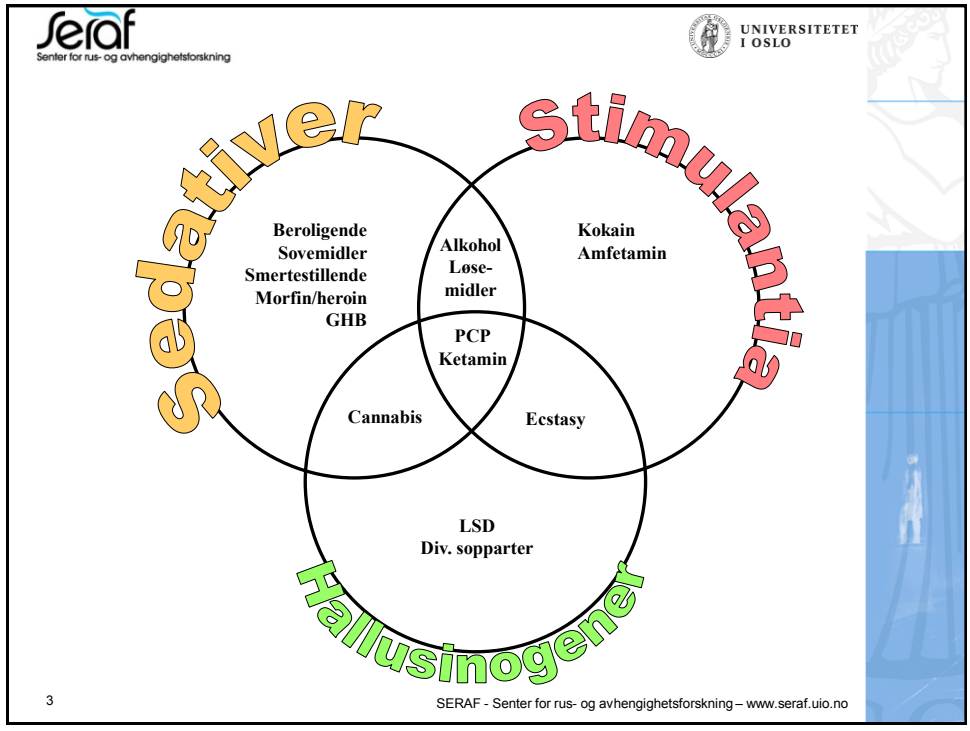
Conflicts of interest

- No conflicts of interest
- The presented research on sponsored by
  - The Norwegian Research Council, Program for Addiction Research
  - Norwegian Center for Addiction Research
  - Norwegian Directorate of Health
  - Lovisenberg Diaconal Hospital, Oslo, Norway



Central stimulants

- Legal
  - Koffein
  - Nikotin
  - Efedrin (hostedempende)
  - Metylfenidat (Ritalin)
- Illegale
  - Amfetamin
  - Metamfetamin (ice)
  - MDA
  - MDMA (ecstasy)
  - MDEA (Eve)
  - Kokain
  - Cathine / cathinon
  - Meskalin

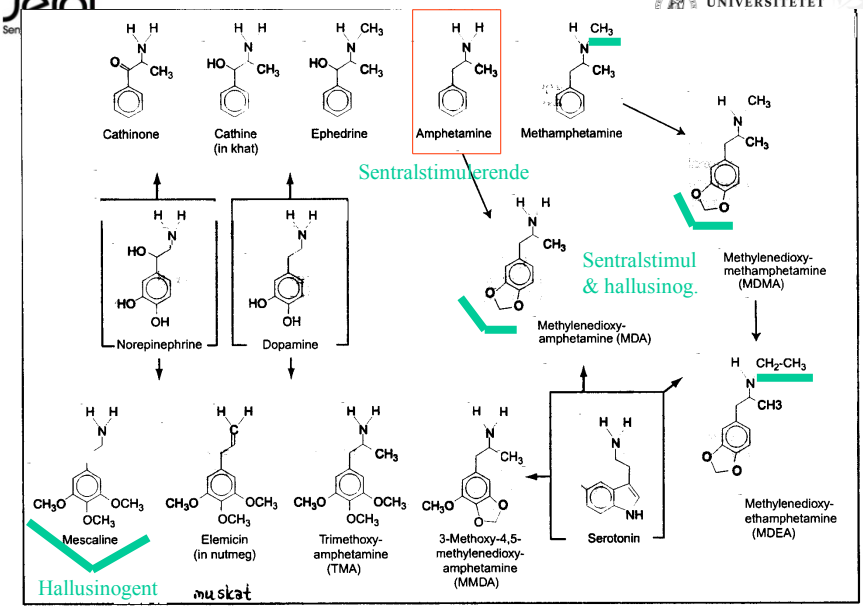


Fig. 1: Chemical structures of MDMA, MDEA and related drugs compared with those of the monoamine neurotransmitters. Arrows do not represent pathways of synthesis or metabolism; they merely indicate the closest resemblances of structure.

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Methamphetamine more potent than amphetamine?

- Methyl group
  - more lipid soluble
  - more difficult to metabolize
- More potent and a longer duration of action

de la Torre R 2004

- Larger potential for generating psychoses?
- Difficult to find empirical support for this
- A small human study: subjects perceived the two as very similar

Lamb RJ 1994

- Animal studies: methamphetamine is not more potent

Balster RL 1973, Kuhn DM 1974, Yokel RA 1973

- Or only slightly more potent than amphetamine

Hall 2008

- Is the difference more quantitative than qualitative
  - Methamphetamine affecting other brain regions than amphetamine

Kuczenski R 1995, Segal DS 1997, Shoblock JR 2003

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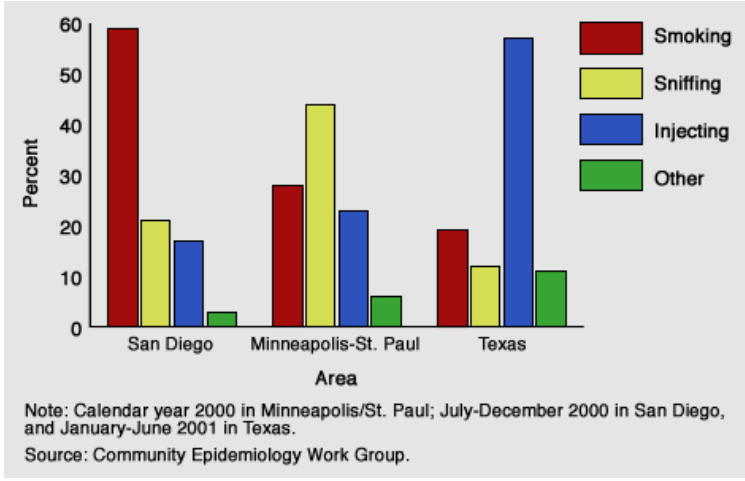

Note: Calendar year 2000 in Minneapolis/St. Paul; July-December 2000 in San Diego, and January-June 2001 in Texas.

Source: Community Epidemiology Work Group.

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”Designer drugs”

- Ring substituted molecules: shares the effects of (meth)amphetamine and mescaline
- Illegally produced synthetic derivatives with mixed effects (also often more potent)
- Produced to evade the law (US)

- Amphetamine like drug increases the effects of signal substances in the brain
  - **Norepinephrine** (physical eff.)
  - **Dopamine**
  - **Serotonin**
    - Sleep/wakefulness, mood, senses, appetite, temperature, sexual function

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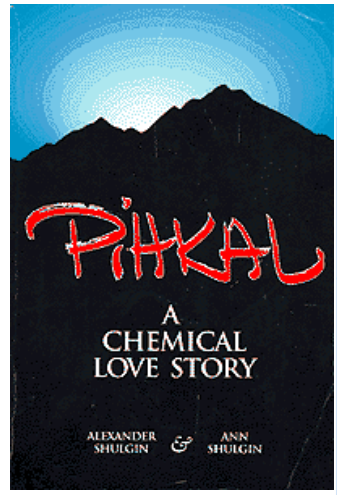
XTC and history

- 1956 MDA patented cough medicine
- 1961 anorectic
- Prohibited in 1970
- MDMA meant to be an anorectic.
- 1985 illegal in US
- 1986 illegal in Norge.
- Since1990-ties increasing popularity as party drug



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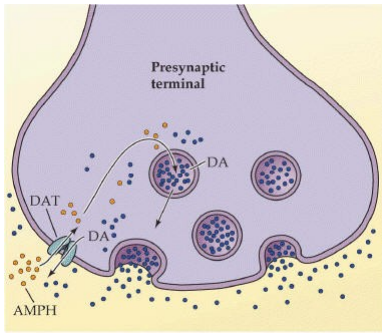
(Meth)amphetamine increases dopamine in several ways



- Enters dopamine vesicles in nerve terminal → increased release of dopamine
- Reverses DA-uptake via DAT
- Dopamine in nerve terminal can be neurotoxic
- MAOA in inhibited
- Neurotoxic to serotonin, norepinephrine and dopamine neurons

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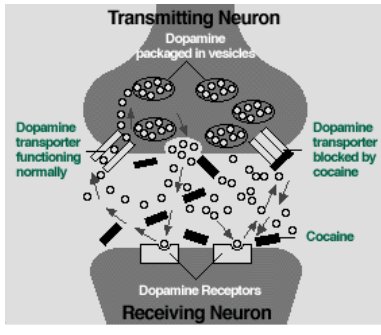
Cocaine increases dopamine by fewer means



- Stops reuptake of DA by blocking DAT
- The most efficient way of increasing DA availability
- Gives increased DA available

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"Tweaking" refers to fine-tuning or adjusting a complex system

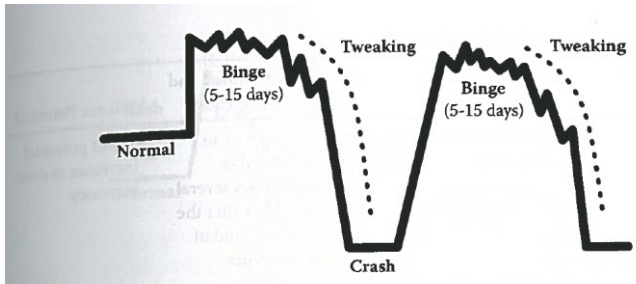

Figure 5.1 High-intensity pattern of abuse cycle.

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Eufori.....

- .....er et medisinsk uttrykk som betyr opprømthet, løftet sinnsstemning på grunn av rusmidler eller visse sykdommer. Ordet kommer opprinnelig fra gresk via latin og er brukt i psykiatrien som beskrivelse av en tilstand av lykke hos mentalt syke pasienter

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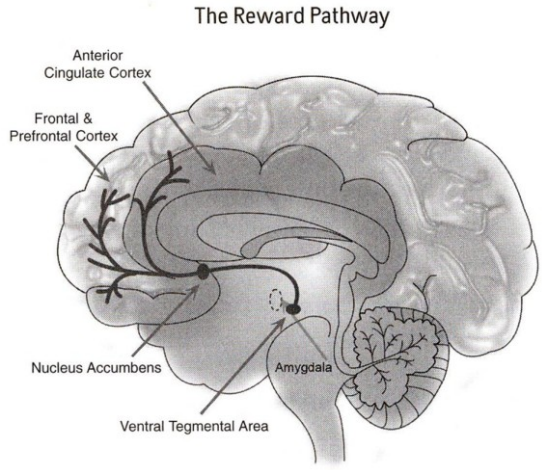
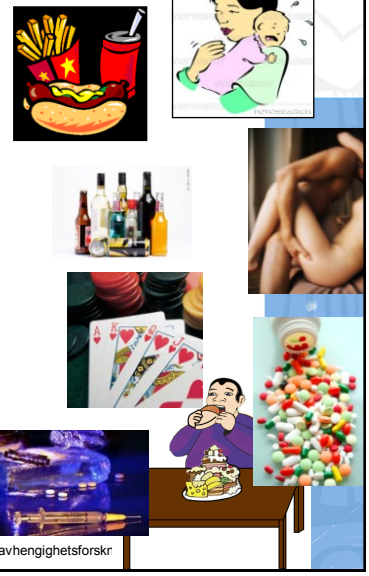
Det mesolimbiske dopaminerge belønnings- og motivasjonssystemet





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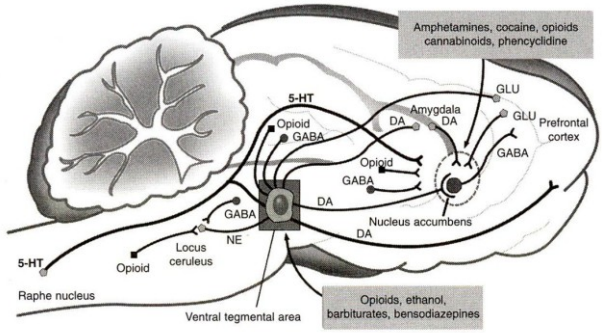
Det mesolimbiske dopaminerge belønnings- og motivasjonssystemet

Interactions Among Subareas of the MDS in the Rat Brain



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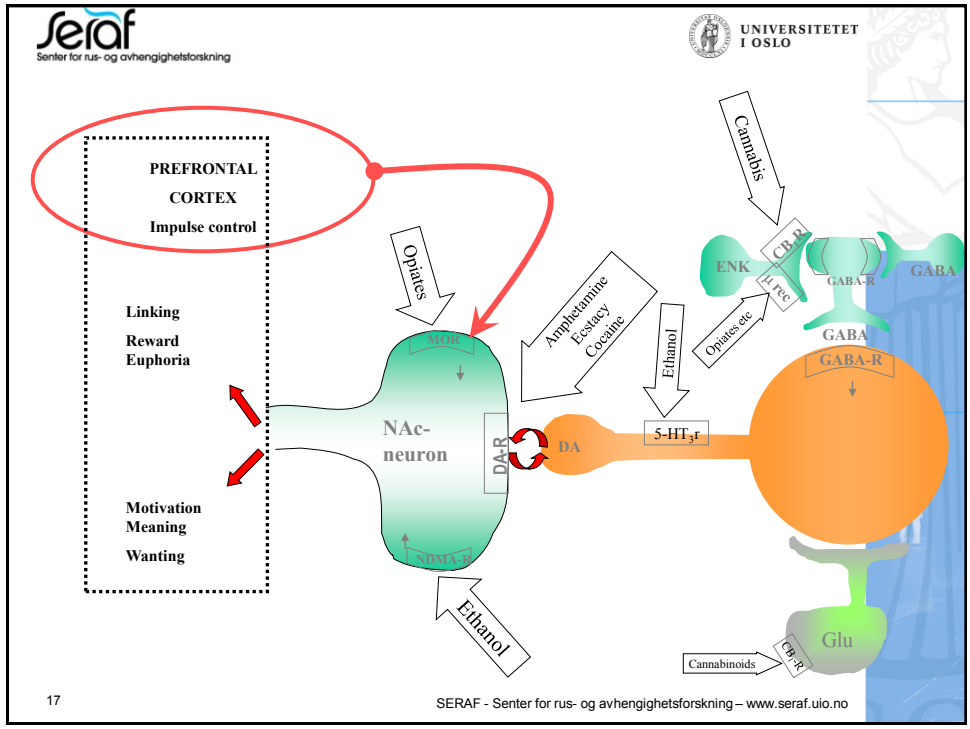
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PREFRONTAL
CORTEX
Impulse control
Linking
Reward
Euphoria
Motivation
Meaning
Wanting
Opiates
Amphetamine
Ecstacy
Cocaine
Ethanol
Cannabis
Opiates etc
Ethanol
ENK
CB-R
GABA-R
GABA
GABA
GABA-R
MOR
NAc-
neuron
D1-R
DA
5-HT3r
NDMA-R
Ethanol
Glu
Cannabinoids
CB1-R
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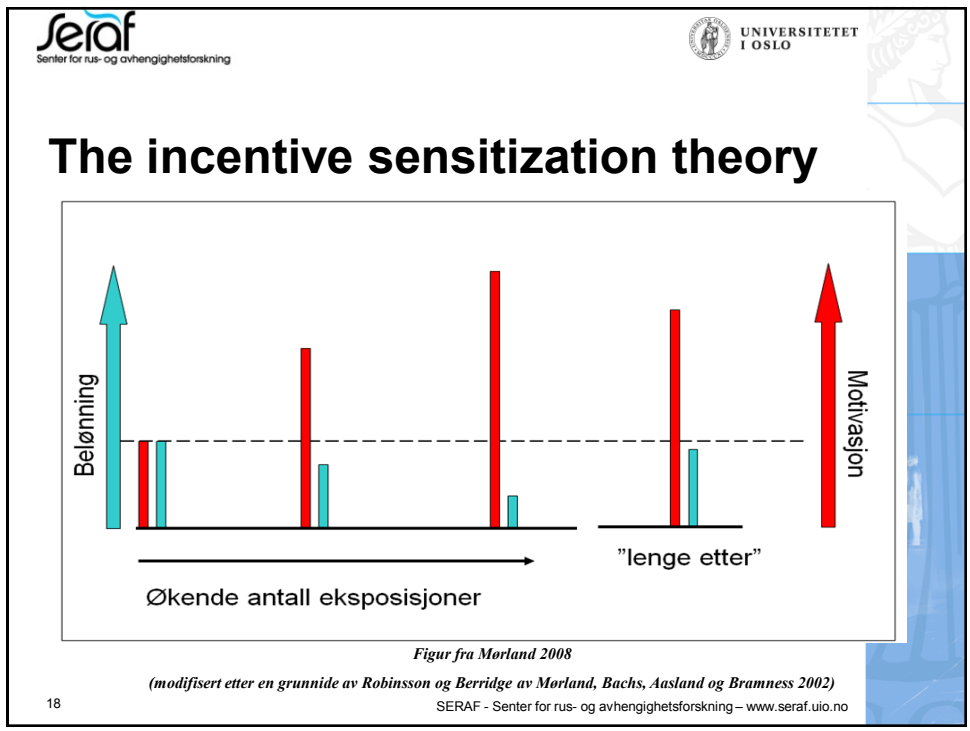
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The incentive sensitization theory
Belønning
Motivasjon
"lenge etter"
Økende antall eksposisjoner
Figur fra Mørland 2008
(modifisert etter en grunnide av Robinsson og Berridge av Mørland, Bachs, Aasland og Bramness 2002)
18
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Cues; begrepet ”salience”

Adverse (negative) effects of
Methamphetamine

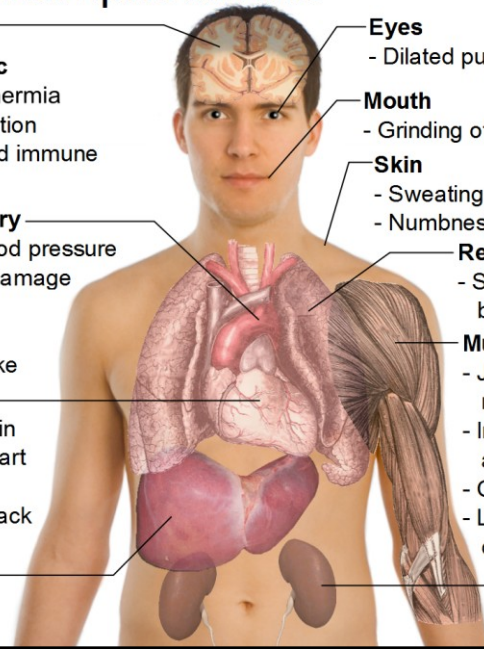
Psychological
- Insomnia
- Aggressive behavior
- Paranoia
- Incessant conversations
- Decreased appetite
- Increased alertness
- Irritability
- Slurred speech
- Dizziness
- Confusion
- Hallucinations
- Obsessive behaviors
- Depression
- Panic attacks

Systemic
- Hyperthermia
- Malnutrition
- Impaired immune system

Circulatory
- High blood pressure
- Vessel damage in brain
- Clotting and stroke

Heart
- Chest pain
- Rapid heart rate
- Heart attack

Liver
- Damage



Eyes
- Dilated pupils

Mouth
- Grinding of teeth

Skin
- Sweating
- Numbness

Respiratory
- Shortness of breath

Muscular
- Jerky movements
- Increased activity
- Convulsions
- Loss of coordination

Kidneys
- Damage

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Amfetamin: Akutte effekter psykiske

- Angst/nervøsitet
- Opplevelse av økt energi
- Følelse av velvære
- Målrettete tanker og oppgaveløsning
- Repeterende atferd
- Økt oppmerksomhet
- Følelse av makt og overlegenhet
- Emosjonell ustabilitet
- Lett å trekke opp
- Snakkesalig
- Paranoid
- Psykose

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Amfetamin: Akutte effekter somatiske

- Nedsatt appetitt
- Økede/forvrengte inntrykk
- Hyperaktivitet
- Utvidede pupiller
- Rødming
- Uro
- Tørr munn
- Erektil dysfunksjon
- Hodepine
- Tachykardi
- Tachypnoe
- Hypertensjon
- Feber
- Svette
- Diaré
- Forstoppelse
- Sløret syn
- Inkongruent tale
- Svimmelhet
- Repetitive, ukontrollerte bevegelser eller risting
- Søvnløshet
- Nummenhet
- Palpitasjoner
- Arytmier

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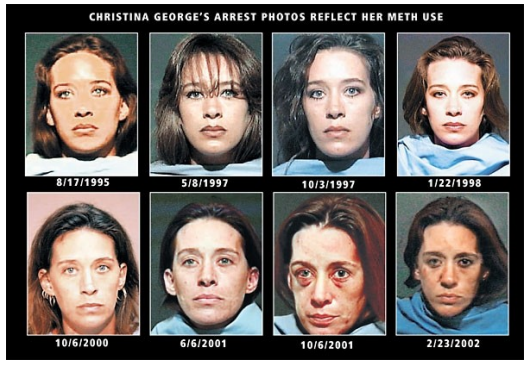

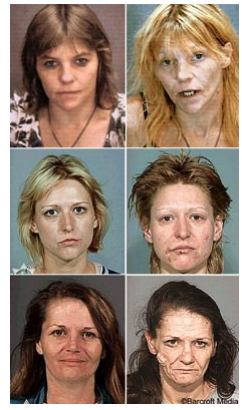

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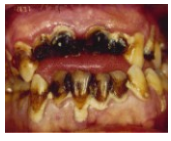
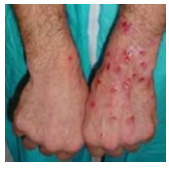
Medical consequences of (meth)amphetamine use





- ”Meth mouth”
  - Xerostomi
  - Acid saliva
  - Poor dental hygiene
  - Bruxisme (grinding of teeth)
- Skin changes
  - Unsterile needles
  - Poor hygiene
  - Obsessive (psychotic?) skin picking/scratching
- Sexual behaviour
  - Increased libido and uncritical behavior
  - Increased stamina
  - Delayed ejaculation
  - Trauma to sexual organs
  - SDS

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Causes of death with methamphetamine use

Table 2 Direct cause of death.

Cause of death (%)	*Male (n = 285)*	*Female (n = 86)*	*All (n = 371)*
Methamphetamine toxicity	17	16	17
Combined drug toxicity	51	53	51
Cardiovascular	15	11	14
Cerebrovascular	4	13*	6
Injury	9	8	9
Pulmonary	5	4	5
Hanging	5	4	5
Other	7	6	7

*$P < 0.05$.

Kaye S. Addiction 2008

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Urine analyzes/drug testing

- Amphetamines can usually be detected up to 2-4 days after intake
  - Maybe longer after larger intakes
- Alkaline urine will delay the process
- Methamphetamine will be like amphetamine

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Bagøien and coworkers. J Clin Psychopharmacology, 2009

TABLE 2. Group by Group Comparisons of the Results From the On-Site Screening Test and the Chromatographic Analyses (n = 262)

	On-Site Screening Test, Drug Group				
	AMP	BZO	COC	OPI	THC
No. true negatives*	248	149	262	227	215
No. true positives†	6	77	0	21	27
No. false positives‡	0	7	0	10	17
No. false negatives§	8	29	0	4	3
Sensitivity, %	42.9	72.6	—	84.0	90.0
Specificity, %	100.0	95.5	100	95.8	92.7
Positive predictive value, %	100.0	91.7	—	67.7	61.4
Negative predictive value, %	96.9	83.7	100	98.3	98.6
Accuracy, %	97.0	86.3	—	94.7	92.4

*Negative on-site test and chromatographic analysis results for a substance within the same group.

†Positive on-site test and chromatographic analysis results for a substance within the same group.

‡Positive on-site test result and negative chromatographic analysis result for a substance within the same group.

§Negative on-site test result and positive chromatographic analysis result for a substance within the same group.

TRADE-OFF

- In the legal system you would like to choose low sensitivity and high specificity instead of the opposite
  - A false positive is worse than a false negative
  - You are often testing in populations were use is common
- In treatment you would prefer high sensitivity and low specificity instead of the opposite
  - A false negative is worse than a false positive
  - You don't want to miss people that could benefit from treatment

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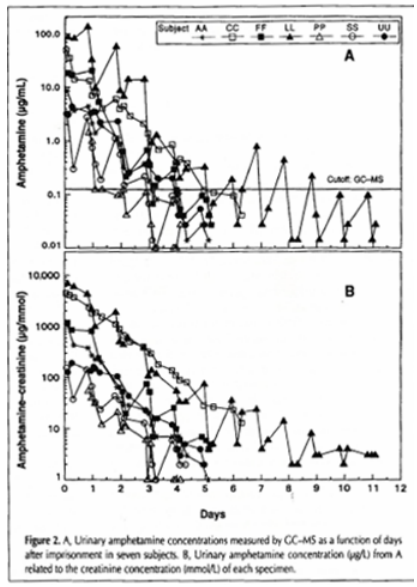

Figure 2. A, Urinary amphetamine concentrations measured by GC–MS as a function of days after imprisonment in seven subjects. B, Urinary amphetamine concentration (µg/L) from A related to the creatinine concentration (mmol/L) of each specimen.

Smith-Kielland and coworkers

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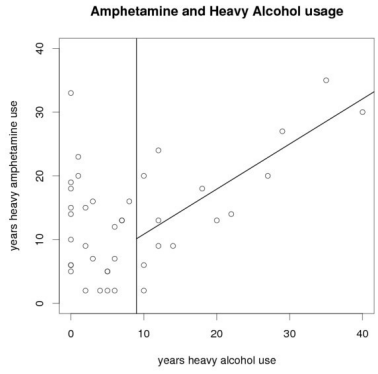
Lawyer G, Bjerkan PS, Hammarberg A, Jayaram-Lindström N, Franck J Agartz I. Amphetamine Dependence and Co-Morbid Alcohol Abuse: Associations to Brain Cortical Thickness. BMC Pharmacol 2010



- Methamphetamine is toxic to dopaminergic and serotonergic neurons
- Methamphetamine is not toxic to NA, colinergic and GABA neurons

  Yudko, Hall and McPherson 2009
- Blocking DA-receptors protects against neurotoxicity

  Richaurte 1984

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Gustavsen and Bramness on blood amphetamines concentrations and increase i risk of impairment

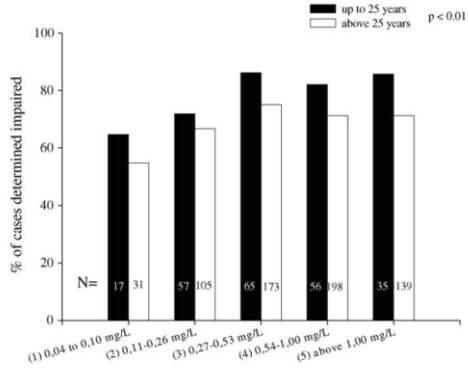

Fig. 2. The percentage of suspected drugged drivers judged impaired by the police physician related to their blood amphetamines concentrations. The drivers were divided in two groups related to age (below or above 25 years-of-age).

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Mørland and co-workers 2010 on traffic related fatalities

Table 4
Crude and adjusted odds ratios for fatally injured driver in single vehicle accident associated with alcohol or drug use.

Factors	Crude OR	95% CI	Adj. OR[b]	95% CI
Alcohol and/or drugs	39.4	24.1–64.3	37.5	21.9–64.2
Alcohol >0.2 g/l	284.0	156.9–514.1	414.4	181.5–946.5
Alcohol only	130.5	68.1–250.1	185.2	76.4–449.1
Alcohol and drugs	803.7	170.0–3799.7	766.6	119.1–5064.3
Two or more substances	59.2	29.4–119.3	64.8	27.4–153.4
Psychoactive medicinal drugs	7.8	3.8–16.0	9.6	4.4–21.2
Two or more medicinal drugs[a]	NC			
Only a single medicinal drug[a]	0.8	0.1–5.5	1.0	0.1–7.1
Benzodiazepines	13.2	6.2–28.5	16.5	7.1–38.6
Only benzodiazepines[a]	NC			
Diazepam	14.2	5.5–36.5	19.1	6.7–55.0
Only diazepam[a]	NC			
Opioids	NC			
Codeine	NC			
Only codeine[a]	NC			
Zopiclone	2.3	0.3–17.1	3.1	0.4–24.7
Only zopiclone[a]	2.4	0.3–17.6	2.8	0.3–21.9
Illegal drug(s)	38.1	18.4–78.9	21.4	9.1–50.5
Two or more illegal drugs[a]	NC			
Only a single illegal drug[a]	4.0	0.5–29.4	2.0	0.2–16.0
THC	18.9	6.5–54.6	9.0	2.7–30.3
Only THC[a]	NC			
Amphetamine/methamph.	76.0	30.4–190.3	49.2	16.5–146.9
Only amphetamine/metamph[a]	13.3	1.7–103.7	10.8	1.3–93.5

OR, odds ratio; CI, confidence interval; NC, no cases.
[a] No other drugs or alcohol.
[b] Adjusted for time period, season, gender, and age group.

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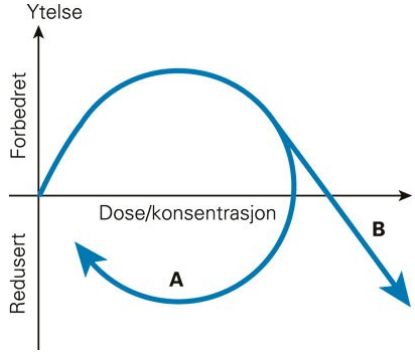
Figur 1
Hysteresekurve for dose-/konsentrasjonsavhengig ytelses-/prestasjonsnivå under påvirkning av amfetamin eller metamfetamin, først foreslått av Ellinwood & Nikaido (8). Kurveforløpet tilbake til origo (A) kan illustrere begrenset bruk, mens en ytterligere prestasjonsforverring som funksjon av dose eller konsentrasjon (B) kjennetegner protrahert bruk over lengre tid



Lia, Spigset, Slørdal. Tidsskr Nor Legeforen 2009; 129: 105-8

tidsskriftet.no