(Meth)amphetamine and emergency psychiatry

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  - Lovisenberg Diaconal Hospital, Oslo, Norway

Amphetamine psychosis

- Use of (meth)amphetamine can trigger psychosis

  Vincent et al. 1998

- Paranoid experiences: 23-45 %

  Leamon et al. 2010;McKetin et al. 2006

- Acute psychosis last year: 18 %

  McKetin et al. 2006

Table 1 Frequency of METH associated psychosis

Population studied	Time period	% Psychotic symptoms	Psychosis definition	Reference
US gay & bisexual treatment-seeking METH abuse/dependent men 18–65 years	Lifetime	26.5%	SCID	Shoptaw et al. 2003
Australian community METH users >16 years	Past Year	13%	BPRS	McKetin et al. 2006
METH dependent		27%		
Non-METH dependent		8%		
Taiwanese incarcerated adolescent METH users	Past Year	7.5%	K-SADS-E	Yen and Chong 2006
U.S. adults in treatment for METH dependence	Lifetime	36%	MINI	Grant et al. 2007
Rural		45%		
Urban		29%		
US METH dependent adults in treatment (didn't distinguish between METH-induced or primary psychotic disorders)	Past or current	12.9%	MINI	Glasner-Edwards et al. 2008
Rural Australian community volunteers >16 years with METH dependence	Lifetime	46%	Self-reported	Wallace et al. 2009
U.S. community and in-treatment METH dependence	Lifetime	45%	MEQ	Leamon et al. 2010

BPRS Brief psychiatric rating scale; *K-SADS-E* Kiddie epidemiologic version of schedule for affective disorders and schizophrenia; *MEQ* METHamphetamine experience questionnaire

MINI Mini-International neuropsychiatric interview; *SCID* Structured clinical inventory for DSM-IV

Amphetamine psychosis

- Amphetamine is often taken over some days
  - If amphetamine triggers psychosis
    - The acute amount taken?
    - The amount taken over days
    - The length of the ”run”
  - Vulnerability?
  - Sleep deprivation?
  - The concurrent use of other drugs?
    - A ”run”/”binge” is often ended by sedating drugs
      - Opiates
      - Alcohol
      - Benzodiazepines
      - Cannabis

Can amphetamine give psychosis?

- Acute effects on the brain
  - Increased dopamine

Segal and Kuczenski 1997

- Long term use
  - Neuro toxic for serotonin- and dopamine-neurons

Myers et al. 1999

  - Neuro toxic for dopamine transporters

Iyo et al. 2004

  - Changes in the dopamine receptor
  - The changes are larger in vulnerable individuals

Seeman 2010

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Psychoses from central stimulants

- Short schizophrenia like conditions
  - Hallucinations (mainly auditive)
  - Dilutions (usually paranoid)
- Different from schizophrenia
  - Only need for short term use of anti psychotics
- Reported with a variety of central stimulants
- The first rapport on psychosis with central stimulants was 1938

*Young D., Serorille W. B. Paranoid psychosis in narcolepsy and possible dangers of benzedrine treatment. Med Clin North Am 1938; **22**: 637–43.*

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Experimentally triggered psychosis

- Central stimulants can give psychosis in healthy volunteers

Janowsky and Risch 1979

- 50 mg amphetamine/h to healthy volunteers gave psychosis within 7-45 h
- Usually after 100-300 mg amphetamine
- All symptoms subside within 6 days

Angrist 1995, Angrist and Gershon 1970, Bell1973, Griffith 1970

- Triggers and aggravates psychosis in schizophrenics
- On lower doses

Liberman et al 1987

- Effects is blocked by anti psychotics

Espelin and Done 1968

Observationel studies

- Amphetamine psychoses epidemics after WWII in Japan, Germany and US
  - Different from what we have observed with cannabis

Degenhart 2003, Sato 1992

- From clinical studies
  - With different central stimulants

Calello and Osterhoudt 2004, Chen et al 2003, Segal et al 1981, Surles et al 2002

Vulnerability and methamphetmaine psychosis

- Triggers and aggravates psychosis in schizophrenics
- On lower doses

Liberman et al 1987

- This may be related to alterred responsiveness i DRD2 rec

Ujike H 2009, Seeman P 2010

- Even diagnosed as well as possible drug induced psychosis may be wrongly diagnosed

Caton et al 2009

- Several vulnerability factors among those who become psychotic on central stimulants
  - Relatives of methamphetamine users with history of psychosis have 5 times increased risk of schizophrenia

Chen et al 2005

  - Patients with amphetamine induced psychosis have an increased plasma NE compared non psychotic amphetamine users (similar to schizophrenia)

Yui et al 1997 and 2000

  - There are several common vulnerability genes (next slide)

?

- Some Japanese research indicates that these psychosis can become chronic

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Bousman CA 2011

Common vulnerablilty genes with schizophrenia

Table 15.2 Genetic biomarkers for MAP susceptibility

Gene	Location	Gene name	Supporting evidence	
			MAP	SCZ
ARRB2	17p13.2	Beta-arrestin 2	60	–
DAOA/G72	13q33.2	D-amino acid oxidase activator	61	74
DRD2	11q23.2	Dopamine receptor D2	62	74, 81
DTNBP1	6p22.3	Dystrobrevin-binding protien 1 (dysbindin)	56	74
ESR1	6q25.1	Estrogen receptor alpha	63	110
FZD3	8p21.1	Frizzled 3	64	111, 112
GLYT1	1p34.1	Glycine transporter 1	65	–
GRM2	3p21.2	Glutamate metabotropic receptor 2	113	–
GSTT1	22q11.23	Glutathione-related enzyme T1	66	114
HTR1A	5q12.2	5-hydroxytryptamine (serotonin) receptor 1A	75	115
OPRM1	6q25.2	Mu-opioid receptor 1	57	116
SNCA	4q22.1	Alpha-synuclein	58	–
SOD2	6q25.3	Superoxide dismutase	59	–

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The dopamine system and amphetamine or schizophrenic psychosis

- Dopamine system dysregulation by ventral subiculum in both maladies

  Grace AA 2010

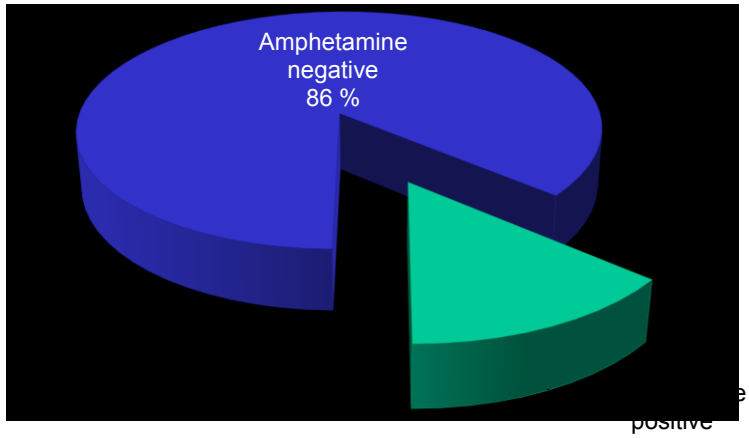
- Genetic variants of D2, but not D3 and D4 dopamin receptor is related to poorer outcome of psychosis

  Ujike H 2009

(Meth)amphetamine in emergency psychiatry

- Clinically a large problem
  - Large
  - Increasing?
- Demanding patients
  - Many readmissions
  - Short term admissions
    - How to medicate?
    - How to give proper follow up?

Avute admission two different wards at two different timepoints (Oslo/Arendal; 2003/2006)



A marginalized group…

- Amphetamine positive were
  - Younger
  - More often male
  - Lower education
  - More often homeless

- More contacts prior to index episode
- More contacts during investigation period

Supports earlier findings
(Gray, Fatovich, McCoubrie, & Daly 2007;Pasic, Russo, Ries, & Roy-Byrne 2007;Srisurapanont, Ali, Marsden, Sunga, Wada, & Monteiro 2003;Yukitake 1983).

Clinical findings

- Among the psychotic patients
  - Few differences between those with and without amphetamine
- Among those without psychosis
  - Amphetamine positive patients have more symptoms (PANSS)
    - delusions
    - disorganization
    - agitation
    - hostility
  - But the amphetamine positive have a shorter length of stay
- The amphetamine positive look like the psychotics in the acute phase!

Drug screening

	Number of drugs Mean (SD)
Amphetamine negative (N=406)	0,83 (1,22)
Amphetamine positive (N=56	3,73 (1,97)

- Most amphetamines were methamphetamine
- All were positive for more drugs
- Often opiates (methadone) or benzodiazepines
  - Diverted methadone and benzodiazepines to end ”runs”?
  - Eller amphetamine use in OMT patients?

- There are100dreds possible substances
- We tested for the most common 56

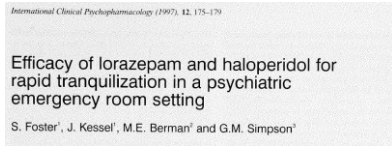
What had they taken?

- Most amphetamines was methamphetamine
- Everybody had more than one drug
- Often sedating drugs
  - Methadone and benzodiazepines diverted form legal sources to “land”
  - Or amphetamine abusing OMT-patients?
- There are100s of possible substances: vi tested for the 56 most common
- No correlation between symptom level and drug level

SENSITISATION?
- Did the concentrations go down in consecutive admissions?
  - Adjusted for PANNS score
  - Adjusted for time from PANNS to blood sampling

What pharmaco therapy?

- Benzodiazepines
  - Can be efficient
  - Beware of interactions with other drugs
  - Often use and failed by the patient
  - But not enough?



International Clinical Psychopharmacology (1997), 12, 175–179

Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting

S. Foster[1], J. Kessel[1], M.E. Berman[2] and G.M. Simpson[3]

"Given the potential for severe extra pyramidal symptoms developing hours or days after a single dose of haloperidol, lorazepam may provide an excellent alternative for the rapid tranquilization of the acutely agitated psychotic patient in the emergency room setting"

Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP; Expert Consensus Panel for Behavioral Emergencies 2005. The expert consensus guideline series. Treatment of behavioral emergencies 2005. J Psychiatr Pract 2005; 11 (suppl 1): 5-108

Introduction: Methods, Commentary, and Summary

MICHAEL H. ALLEN, MD
GLENN W. CURRIER, MD, MPH
DANIEL CARPENTER, PhD
RUTH W. ROSS, MA
JOHN P. DOCHERTY, MD

Objectives. Due to inherent dangers and barriers to research in emergency settings, few data are available to guide clinicians about how best to manage behavioral emergencies. Key constructs such as agitation are poorly defined. This lack of empirical data led us to undertake a survey of expert opinion, results of which were published in the 2001 *Expert Consensus Guidelines on the Treatment of Behavioral*

"…these guidelines suggest that the SGAs are now preferred for agitation in the setting of primary psychiatric illnesses but that BNZs are preferred in other situations"

Use of antipsychotics

- Antipsychotics are far better than placebo
- Treat the psychotic symptoms
  - One Cochrane review
  - 2 case series
- No studies have look on relapse of drug abuse
  - Anhedonia
  - Cue craving
- It may not be important what antipsychotic to use to treat the psychosis, but maybe to prevent relapse

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What antipsychotic drug to use?

Journal of Neurochemistry, 2001, 78, 1094–1103

Overexpression of dopamine D2 receptors reduces alcohol self-administration

Panayotis K. Thanos,* Nora D. Volkow,* Paul Freimuth,† Hiroyuki Umegaki,‡ Hiroyuki Ikari,‡ George Roth,§ Donald K. Ingram§ and Robert Hitzemann¶

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More DRD_2 available gives less craving and less drug use

Don't block all DRD_2

Newer antipsychotics blocks DRD_2 the older

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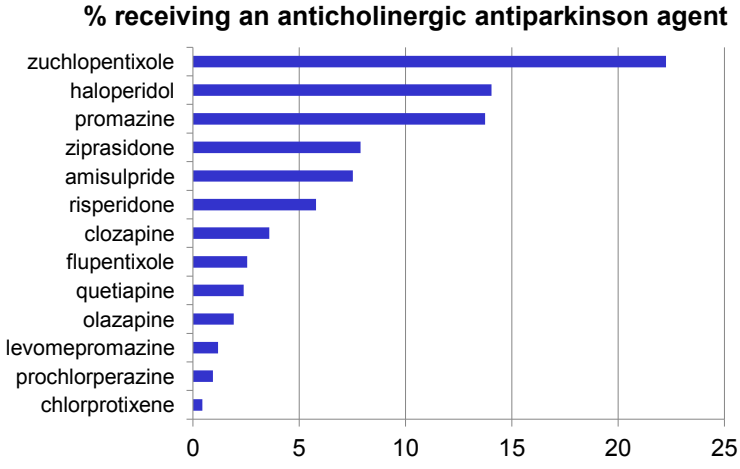
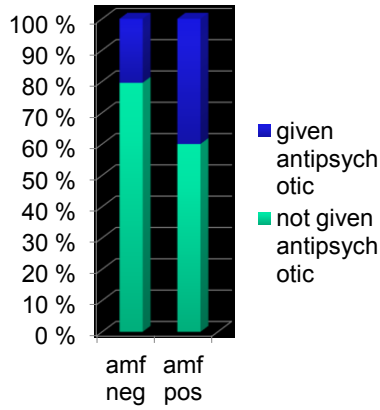
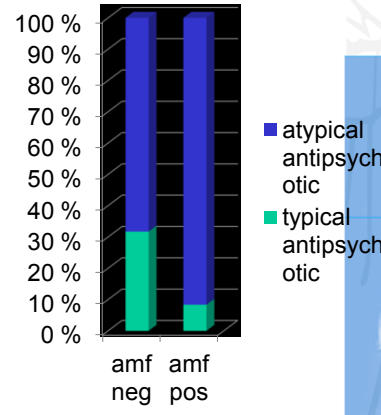
Can DRD2 affinity of drugs tell?

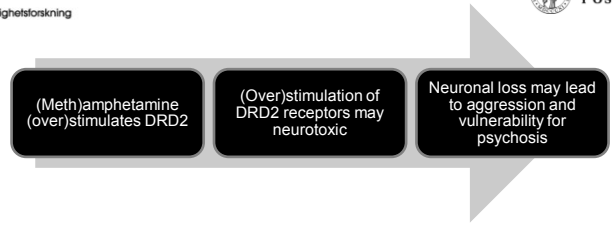


Gjerden, Slørdal og Bramness. Eur J Clin Pharmacol 2009

What antipsychotics did they get?







Dopamine D2-receptor knockout mice are protected against dopaminergic neurotoxicity induced by methamphetamine or MDMA

Noelia Granado [a,c], Sara Ares-Santos [a,b], Idaira Oliva [d], Esther O'Shea [c], Eduardo D. Martin [d], M. Isabel Colado [c], Rosario Moratalla [a,b,*]

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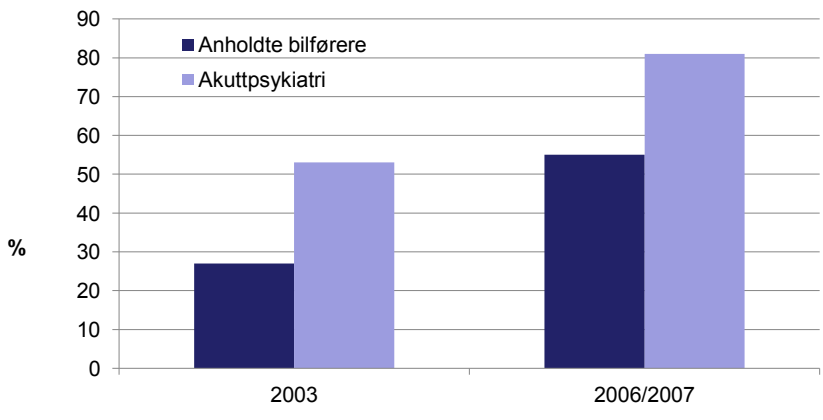
"In fact, drugs that block DA protect against methamphetamine neurotoxicity"

Yudko et al 2009

Does methamphetamine precipitate psychosis more often than amphetamine?

Share methamphetamine positive among amphetamine positive apprehended drivers vs. amphetamine positive acute emergency psychiatric patients



Risk of becoming a psychiatric patient

Medhus S et al 2011

	Unadjusted	Adjusted[a] ([a]age, gender and significant other variables)
	OR (95% CI)	OR (95% CI)
[(Meth)amphetamine]$_{blood}$	0.82 (0.71 - 0.94)	
Sedative hypnotics influence	0.39 (0.23 - 0.68)	0.71 (0.58 – 0.86)
Ethanol influence	1.09 (0.69 - 1.74)	
Opiate-/opioide influence	1.79 (1.34 - 2.40)	1.89 (1.37 – 2.62)
THC influence	0.47 (0.23 - 0.96)	0.49 (0.24 – 0.99)

”Drug induced psychosis” ..... a sin of omission

- Too many keep the diagnosis of drug induced psychosis too long!
- Why is it seemingly easier to give a diagnosis of drug induced psychosis than primary psychosis?
  - Patients with primary psychosis more often take drugs
  - Do we increase period of untreated psychosis and place patients at risk?
- Can a drug induced psychosis become primary?
- Does it matter?
  - Treat with antipsychotics either way?

What to do?

- Vær oppmerksom på de overveldende symptomene
- Ha avdelinger som kan håndtere dette
- Bruk antipsykotika til å behandle psykosen!
- Bruk et antipsykotikum med lav DRD2 affinitet
  - Depot kan være vanskelig?
- Husk at pasienten kommer igjen
  - ”be patient with the patient”
  - Points of disappointment or windows of opportunity?

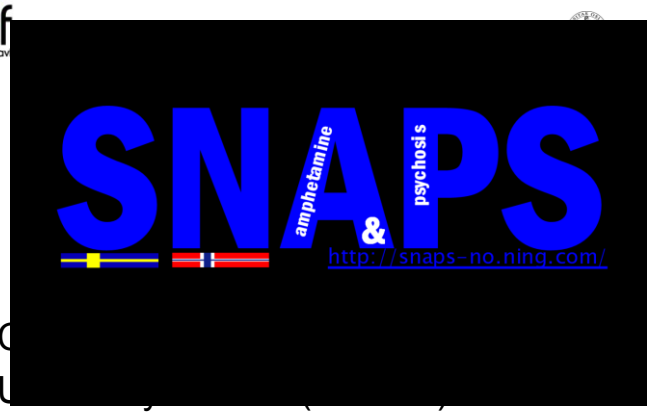
- Naltrekson depot?
- ADHD-medikasjon er antagelig ikke effektivt!

Conclusion

- Amphetamine may precipitate schizophrenia like psychoses
  - Difficult to differentiate from other schizophrenia like psychoses
  - They pass more quickly
  - Probably a dynamic relationship between exposure to amphetamines and vulnerability

- Methamphetamine is probably more potent in producing psychosis

- Can everybody become psychotic if they take enough amphetamine?
- Can acute amphetamine psychosis become chronic?
- Can only vulnerable individual become psychotic?
- What is vulnerability?
- Is it the same vulnerability as for schizophrenia?



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