

**Amphetamine and methamphetamine induced psychosis: toxicological
findings, comparison with acute symptoms of schizophrenia and
transition of diagnoses**

A clinical investigation

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Table of contents

Abstract.....	1
Sammendrag på norsk	4
Study background	6
Papers	8
1. Introduction	9
1.1 Amphetamines and psychoses	9
1.2 Amphetamine and methamphetamine in Norway.....	11
1.3 Amphetamine and methamphetamine pharmacology	13
2. Objectives	14
3. Material.....	16
3.1 Setting	16
3.2 Study samples	16
3.3 Inclusion and exclusion criteria.....	18
4. Methods.....	19
4.1 measurements	19
4.1.1 Laboratory analyses.....	19
4.1.2 On-site urine testing.....	22
4.1.3 Physician assessment	22
4.1.3 Review of medical records and clinical diagnoses	22
4.1.4 Comparisons of drug levels	23
4.2 Statistical analyses	25
5. Ethical considerations	27
6. Methodological considerations	28
6.1 Study design.....	28
6.2 Internal validity	29
6.2.1 Selection bias.....	29
6.2.2 Information bias	30
6.3 External validity.....	32
7. Results	34
Overview of material	34
Specific aims.....	34
8. Discussion	43
Objectives	49
Clinical implications and final word	51
Reference List	52
Appendices.....	63
Papers I-IV.....	69

Abstract

Background

There is a long-standing debate about the relationship between amphetamines and psychoses. While some have found psychoses induced by amphetamines to be indistinguishable from schizophrenia, others have found that psychoses induced by amphetamines, in contrast to schizophrenia, were characterized by visual hallucinations and lack of thought disorder. It has also been discussed whether there really are sharp boundaries between the two diagnoses, and whether there is a transition between them. Also, there are few studies which investigate the relationship between blood concentrations of amphetamines and clinical presentation, and whether methamphetamine could have a greater potential for generating psychoses than amphetamine.

Objectives

Our main objectives were to investigate whether there are clinically evident differences between psychosis induced by amphetamines and acute symptoms of schizophrenia, and if there is a transition from amphetamine-/methamphetamine induced psychosis to schizophrenia. We also wanted to study the relationship between blood concentrations of amphetamines and clinical presentation, and if methamphetamine was more potent in generating central nervous influence and psychosis than amphetamine.

Methods

The first source of data were from two psychiatric wards at public hospitals, where blood and/or urine samples were collected as soon as possible after admission for 87 individual patients in 2003 and 285 in 2006/2007. Psychotic symptoms were assessed with the positive subscale of the Positive and Negative Symptom Scale (PANSS) for the patients admitted in 2006/2007. The second source of data came from the Norwegian Institute of Public Health (NIPH) where all blood samples from apprehended drivers in Norway are analysed. Blood samples were obtained from 735 apprehended drivers from the same time periods and the same geographical area as the acutely admitted patients. On the basis of blood drug concentrations among patients admitted to psychiatric wards and among apprehended drivers, drug influence was estimated. In 2012, we did a follow-up by reviewing their hospital records of 35 patients who were admitted to one of the two hospitals and were positives for

amphetamines in 2006/2007. From these 12 individual patients received diagnoses specifically related to disorders due to psychoactive substance use (F10-F19 according to the ICD-10 classification of mental and behavioural disorders).

Results

We compared positive PANSS scores for 1) patients who received a diagnosis of schizophrenia and were negatives for amphetamines in blood and/or urine with PANSS scores (N=8), to 2) patients who were positive for amphetamines in blood and/or urine and either received a diagnosis of amphetamine-induced psychosis or psychoses induced by multiple drugs (N=31). We found no differences between the two groups (total PANSS 23.5 vs 22.8, $p=0.783$). With rising blood levels of amphetamines no differences in symptoms, as measured by PANSS, were observed (urine positives only total PANSS 18.0, low/moderate blood concentrations 20.6, high blood concentrations 20.9, $p=0.782$). Having amphetamines in the blood increased the likelihood of being judged clinically to be under the influence of drugs (OR 5, 95% CI 1-17) compared to having other substances in the blood. We found that individuals who had taken methamphetamine had a 3-4 times increased risk of being admitted to an acute psychiatric ward compared to those who had taken only amphetamine (adjusted OR= 4.423 (2.031 – 9.631)). The apprehended drivers were the comparison group here. When we did the follow-up in 2012, four patients who had not been diagnosed with schizophrenia before, now had got this diagnosis, all in the period 2008–2010.

Conclusions

In acute phase, i.e. at the time of admission to acute psychiatric wards, it is not possible to distinguish patients with psychoses induced by amphetamines from patients with schizophrenia. An important clinical implication is that patients with dual diagnosis may be mis-diagnosed as only having a drug-induced psychosis and may not receive the correct treatment). Also, we found no relationship between symptoms and blood concentrations of amphetamines and no strong relationship between being positive for amphetamines and being judged as under the influence of drugs by the physician on call. On the basis of our

main findings, we propose a traditional stress-vulnerable model for understanding the relationship between psychosis induced by amphetamines and schizophrenia.

Sammendrag på norsk

Bakgrunn

Det har lenge hersket uenighet om forholdet mellom amfetaminer (amfetamin og metamfetamin) og psykoser. Mens noen har funnet at psykoser framkalt av amfetaminer var umulige å skille fra schizofreni, har andre funnet at amfetaminutløste psykoser, i motsetning til ved schizofreni, var kjennetegnet av synshallusinasjoner og mangel på tankeforstyrrelser. Det har også vært diskutert om det egentlig fins skarpe skillelinjer mellom de to diagnosene, og om den ene kan gå over til den andre. I tillegg er det få studier som har studert forholdet mellom amfetaminkonsentrasjoner i blod og det kliniske bildet, og om metamfetamin i større grad fører til psykotiske symptomer enn amfetamin.

Forskningsspørsmål

Vårt hovedmål var å studere om det er klinisk viktige forskjeller mellom psykoser utløst av amfetaminer akutte symptomer ved schizofreni, og om en overgang skjer mellom de to. Vi ønsker også å studere forholdet mellom amfetaminkonsentrasjoner i blod og klinisk bilde, og om metamfetamin i større grad enn amfetamin førte til psykotiske og sentralnervøse symptomer.

Metoder

Den første datakilden var fra to psykiatriske akuttavdelinger fra to norske sykehus, der blod- og urinprøver ble tatt så raskt som mulig etter innkommst. Det ble tatt prøver av 87 pasienter i 2003 og fra 285 pasienter i 2006/2007. Psykotiske symptomer ble vurdert ved hjelp av positiv subskala fra Positive and Negative Symptom Scale (PANSS) for de pasientene som ble innlagt i 2006/2007. Den andre datakilden kom fra Nasjonalt folkehelseinstitutt, som analyserer blodprøver fra alle anholdte bilførere i Norge. Derfra kom blodprøver fra 735 bilførere fra samme tidsperiode og fra samme geografiske område som blodprøvene fra sykehusene kom fra. På grunnlag av konsentrasjonene av ulike stoffer i blodprøvene hos begge gruppene, ble graden av ruspåvirkning anslått. I 2012 gjorde vi en oppfølgingsstudie der vi gikk gjennom innleggelsesjournalene til de 35 pasientene som var innlagt på ett av de to sykehusene og som var positive for amfetaminer i 2006/2007. Av disse hadde 12 fått en rusdiagnose (F10-F19 ifølge ICD-10 diagnosene av psykiske lidelser og atferdsforstyrrelser).

Resultater

Vi sammenliknet PANSS-scorene fra 1) pasienter som fikk diagnosen schizofreni og hadde blod- og urinprøver som var negative for amfetaminer (N=8), med 2) pasienter som hadde blod- og urinprøver som var positive for amfetaminer og enten fikk diagnosen amfetaminutløst psykose eller psykose utløst av flere stoffer (N=31). Vi fant ingen forskjeller mellom de to gruppene (total PANSS 23.5 vs 22.8, $p=0.783$). Ved økende blodkonsentrasjoner for amfetaminer fant vi ingen forskjeller i symptomer målt ved PANSS (bare positive urinprøver total PANSS 18.0, lav/middels blodkonsentrasjon 20.6, høy blodkonsentrasjon 20.9, $p=0.782$). Å ha amfetaminer i blodet økte sannsynligheten for å bli klinisk vurdert som ruspåvirket (OR 5, 95% CI 1-17) sammenliknet med å ha andre stoffer i blodet. Vi fant også at de som hadde tatt matamfetamin hadde 3-4 ganger økt risiko for psykiatrisk innleggelse sammenliknet med dem som bare hadde tatt amfetamin (justert OR= 4.423 (2.031 – 9.631). Bilførerne var her sammenligningsgruppen. Da vi gjorde oppfølgingsstudien i 2012, hadde fire pasienter som tidligere ikke hadde hatt diagnosen, fått diagnosen schizofreni i løpet av tidsrommet 2008-1010.

Konklusjon

I akuttfasen, det vil si ved innleggelse i psykiatriske akuttavdelinger, er det ikke mulig å skille pasienter med psykoser utløst av amfetaminer fra pasienter med schizofreni. En viktig klinisk implikasjon er at pasienter med dobbeltdiagnoser kan bli feildiagnostisert til å ha bare en rusutløst psykose og dermed ikke få riktig behandling. I tillegg fant vi ingen sammenheng mellom symptomer og amfetaminkonsentrasjoner i blod, og heller ingen sterk sammenheng mellom å være amfetaminpåvirket og å bli vurdert som ruspåvirket av vakthavende lege. På grunnlag av våre hovedfunn vil vi foreslå en tradisjonell stress-sårbarhetsmodell for å forstå sammenhengen mellom psykose utløst av amfetaminer og schizofreni.

Study background

In 2004, I started working as a ward psychiatrist on the acute psychiatric ward at Lovisenberg Diakonale Hospital in Oslo. The ward had 27 beds and served approximately 100 000 inhabitants. Crisis intervention and diagnostic evaluation were the ward's main activities. Typical problems among admitted patients were suicide risk and acute psychoses. Many were also under the influence of different kinds of drugs, including stimulating drugs, mostly amphetamine. Among those who were admitted with psychotic symptoms, some were already diagnosed with schizophrenia, some had recognized drug use problems, and some had both. A dilemma emerged for the psychiatrists with regard to some of these patients. When a patient was admitted and had both psychotic symptoms and a recognized drug problem, could we assume that the psychotic symptoms were due to drug use alone or could some of these patients have schizophrenia as well? Also, some patients seemed to take longer with each successive admission to recover from their psychotic symptoms. Could some patients who originally presented with drug-induced psychoses be developing schizophrenia?

Similar discussions were taking place at other psychiatric hospitals in Oslo. One hospital refused to accept patients with a drug history and channelled them to drug service units, which at the time were sparse. A major argument from those working at that hospital was that everyone who uses stimulating drugs like amphetamine would eventually develop psychotic symptoms. Was this really the case?

The discussion had implications for treatment as well. If psychotic patients with a history of drug abuse were admitted to acute psychiatric wards, should they be discharged after a slight improvement of symptoms on the assumption that the rest of the symptoms would be gone in a few days? Or would some of these patients have persisting psychotic symptoms? Perhaps some had schizophrenia or developed schizophrenia during the course and were not receiving the correct treatment. There was also uncertainty about treatment. Should drug-induced psychoses in the initial phase be treated with antipsychotics (1;2), benzodiazepines (3) or a combination of the two? There is little knowledge from empirical evidence about which treatment to choose for amphetamine psychoses (4).

We also had the impression that there was an increase in the number of amphetamine-

induced psychoses. We knew that both amphetamine and methamphetamine were available on the drug market in Oslo at the time, but noticed that the patients did not seem able to distinguish between the two and called both of them “amphetamine”. Did methamphetamine slowly replace amphetamine on the market, and was the perceived increase of drug-induced psychoses related to this shift?

These were questions to which neither I nor my colleagues knew the answers. During 2003 and 2006/2007, researcher Jørgen G. Bramness at the Norwegian Institute of Public Health and, then PhD student, Jon Mordal initiated a study on the ward where I worked at Lovisenberg Diakonale Hospital. The aim was to study dual-diagnosis patients on acute psychiatric wards. As a ward psychiatrist, I became quite involved in the collection of data and had the main responsibility for asking patients to participate in the study. I started seeing the possibility of combining my experience of dual diagnoses as a clinician with my interest in research. Hence, I started my PhD project in 2009 with the aim of studying the amphetamine-positive patients from the study.

Papers

I. A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards (Sigrid Medhus, Jon Mordal, Bjørn Holm, Jørg Mørland, Jørgen G. Bramness)

II. Influence of drugs of abuse and alcohol upon patients admitted to acute psychiatric wards: Physician's assessment compared to blood drug concentrations (Jon Mordal, Sigrid Medhus, Bjørn Holm, Jørg Mørland, Jørgen G. Bramness)

III. Association between methamphetamine versus amphetamine and acute psychiatric symptoms (Sigrid Medhus, Bjørn Holm, Jørg Mørland, Jørgen G. Bramness)

IV. Methamphetamine positive patients admitted to acute psychiatric wards – a follow-up five years later (Sigrid Medhus, Michael Gossop, Bjørn Holm, Jørg Mørland, Jørgen G. Bramness)

1. Introduction

1.1 Amphetamines and psychoses

The use of amphetamine and methamphetamine, here called amphetamines, is widespread (5), particularly in Southeast Asia (6) and North America (7-9), but also in Europe (10), Australia (11;12) and South Africa (13). In Europe, amphetamines are most common in Central and Northern Europe (14). In most of this area, amphetamine is found much more frequently than methamphetamine. The exception is the Nordic and the Baltic countries, and especially Norway, where methamphetamine has obtained an important position (10;15).

Amphetamines use is not common in the general population. The lifetime prevalence of amphetamines in Europe ranges from 0.1% to 3.6% for most European countries. Nearly 3.5% of all Europeans have tried amphetamines at least once, but only 0.7% on average (range 0 – 1.3%) have used it last year (16). In Norway, the lifetime prevalence for amphetamines is 3 - 4% (16-18). However, use of amphetamines is far more frequent among psychiatric patients (19-21). There is a link between the use of amphetamines and psychoses (22-25), and individuals patients who are not receiving psychiatric treatment and have no known primary psychotic disorder can have psychotic symptoms (26;27). When patients who use amphetamines are admitted to acute psychiatric wards, drug-induced psychosis can be difficult to distinguish from other psychotic disorders. Also, these patients often require considerable resources because of agitation and aggression (28-31), and there is a debate about whether they should be treated by psychiatric or drug-misuse services (32), or by integrated teams for dual diagnosis (33). Poly drug use is common; both recreational methamphetamine users and acutely admitted psychiatric patients commonly use tobacco, alcohol, ecstasy, tobacco and cannabis and to a lesser extent opioids and benzodiazepines (19;27;34-38).

There is a long-standing debate about the relationship between amphetamine and methamphetamine on the one hand and schizophrenia and psychosis on the other. Some found that the symptoms of amphetamine-induced psychosis were so similar to the symptoms found in schizophrenia (39;40), that they proposed the first as a model for the

latter (41-43). Others found that amphetamine-induced psychosis, in contrast to schizophrenia, was characterized by visual hallucinations and lack of thought disorder (44-46). Interestingly enough, in two early observational studies the authors noted two different courses among patients with amphetamine-induced psychoses: one group had psychotic episodes that cleared within 10 days, the other had a prolonged course which lasted for months and was very similar to schizophrenia (44;46). Another author noted that a few amphetamine-psychotic patients continued to experience psychotic symptoms long after amphetamine withdrawal (43).

In early experimental studies, amphetamine was given to amphetamine users either orally (40;42;47;48) or as injections (45;49). These studies showed that amphetamine can cause psychotic symptoms such as suspiciousness, delusions of persecution and auditory and visual hallucinations. These early studies also noted that the same dose may induce psychotic symptoms in some individuals but not in others (41;45;47;48), but more individuals develop psychotic symptoms on high doses of amphetamine (41) than on low (47). Some found that all (45;47;50) or nearly all (49) became psychotic after administration of amphetamine, but several of these were recruited from psychiatric wards and had experienced psychoses earlier. Others found that not all individuals developed psychotic symptoms, even at high doses of amphetamine (42;45;48;51). One author notes that "Those who denied formal psychotic experiences with past use tended not to experience them in the course of the experiment" (42).

Later observational studies also have inconsistent conclusions with regard to psychoses induced by amphetamine or methamphetamine versus schizophrenia. Some have found that visual hallucinations are common among methamphetamine users (52-55). Others have found it difficult to distinguish between methamphetamine-induced psychoses and schizophrenia (56-58). Yet others have found visual hallucinations among those who have used high doses of methamphetamine and not among those who have used low doses (59).

The similarities are so pronounced there has been discussion about whether there really are sharp boundaries between the two diagnoses. The western view has been that drugs cannot produce prolonged psychotic syndromes, i.e. according to the ICD-10 classification, the psychotic symptoms must not exceed six months if a condition is to be called psychotic

disorder due to use of drugs (60). The Japanese view, on the other hand, has been that heavy use of amphetamine can precipitate a chronic psychosis indistinguishable from schizophrenia in individuals who would not otherwise have developed a psychotic disease. Japanese researchers describe different clinical courses of methamphetamine psychoses in different patients: some clear up after a short time, some have a protracted course of psychosis, and some develop chronic psychoses (58;61;62). Also, some experience psychotic recurrence even after long-term abstinence, up to five years (31;63-65). During flashbacks, they had psychotic symptoms such as paranoid delusions and auditory and visual hallucinations (66).

In the western psychiatric tradition, psychotic symptoms after several years of abstinence from amphetamines would be regarded as schizophrenia (60;67;68). Some of the later observational studies found that those with methamphetamine-induced psychosis did not have negative symptoms in the acute phase whereas those diagnosed with schizophrenia did (69;70). Others found that methamphetamine-induced psychosis in the acute phase resembled schizophrenia with regard to negative symptoms like affective flattening and psychomotor retardation (3;56;57;71), but as one author notes, these negative symptoms may be due to undetected primary psychoses (56).

The stability of the diagnoses drug-induced psychosis versus schizophrenia has also been discussed. There is considerable overlap between patients who receive a diagnosis of substance-induced psychosis, and those who later receive a diagnosis of schizophrenia (72;73). One study shows that among inpatients who receive a diagnosis of substance-induced psychosis, 25% had received a diagnosis of primary psychosis one year later (74). Another study showed that among patients who were hospitalized because of psychosis and concomitant methamphetamine use, 38.8% had received a diagnosis of schizophrenia due to persistent psychosis at follow-up (75).

1.2 Amphetamine and methamphetamine in Norway

In most of Europe, as opposed to the rest of the world, amphetamine use is more prevalent than methamphetamine (14). However, in the Baltic and Nordic countries, methamphetamine is increasingly dominant (14) as in North America, Mexico and South-

East Asia (5). Previously, most of the supply to Norway was amphetamine produced in the Netherlands or Poland. More recently, smuggling via the “Baltic Route”, i.e. from the Baltic states, mainly Lithuania and to some extent Estonia, has taken over. Here, the traffickers seem to have switched to producing mostly methamphetamine as opposed to amphetamine (14).

Data from several sources show that methamphetamine makes up an increasing proportion of the total use of amphetamine in Norway. While the total number of seizures of amphetamines made by the National Criminal Investigation Service has remained relatively constant, methamphetamine increased from 2% of all amphetamine seizures in 2000 to 64% in 2009 (76). Data from the National Institute of Public Health (NIPH) in Norway which analyses blood samples of apprehended drivers show the same tendency. In 2000, among Norwegian drivers suspected of driving under the influence and testing positive for amphetamines, methamphetamine was found in only 3% of the samples. In 2009, this had risen to 35% (77). In a study of injured patients admitted to a Norwegian emergency department in 2007/2008, methamphetamine was detected in about 80% of patient samples positive for amphetamines (78).

The Division of forensic medicine and drug abuse research at the Norwegian Institute of Public Health has also analysed urine samples from inmates in Norwegian prisons and from post-mortems. All analyses have been carried out using chromatographic-mass spectrometric methods and show the same tendency of increasing use of methamphetamine and decreasing use of amphetamine, while the total amount of the two remains relatively constant (79).

In Europe, methamphetamine is not in crystalline form (ice), but rather a white powder indistinguishable from amphetamine (14) and it is eaten, snorted or injected (79;80). One study suggests that among the marginalized users of amphetamines, injection is very common, as opposed to integrated users who do not inject (38). The prices of amphetamine and methamphetamine are very similar in Europe (10;81). It has been confirmed in studies amongst users of amphetamines that they, most often, do not know what they are buying and using (80). It, therefore, seems unlikely that any group would be selected into using amphetamine or methamphetamine specifically.

1.3 Amphetamine and methamphetamine pharmacology

Both amphetamine and methamphetamine stimulate the central nervous system and can give wanted effects like increased alertness, euphoria with wakefulness and feelings of energy and increased sexual drive (82). These reactions are rewarding and connected to different types of stimuli, meaning development of incentive salience, which motivates further intake (83). Not so sought-after effects include anxiety, aggression, prolonged sleeplessness as well as psychotic symptoms as described above. Amphetamine and methamphetamine can also give side effects like hypertension, tachycardia, dysrhythmia, dyspnea and tachypnea as well as serious condition like seizures, stroke and myocardial infarction (84;85). Both act by releasing synaptic catecholamines, i.e. dopamine, adrenaline and noradrenaline, and inhibiting their presynaptic uptake (86-89).

Methamphetamine has one additional methyl group compared to amphetamine (90). Methamphetamine is, therefore, presumed to be more lipid soluble (91) and more difficult to metabolize than amphetamine (92). Theoretically, this should make methamphetamine act more potently and for longer (89). Methamphetamine is also perceived as a more potent drug of abuse in clinical practice (80). However, both amphetamine and methamphetamine are mostly renally excreted (93) and only metabolized to a lesser extent and, when used therapeutically, amphetamine and methamphetamine are dosed similarly (94). Still, it is reasonable to ask whether methamphetamine could have a greater potential for generating psychoses than amphetamine. It has been difficult to find empirical support for this notion. Small studies in humans showed that subjects perceived the two drugs as very similar (95-97). Several preclinical animal studies have not found methamphetamine to be more potent (98-100) or have found it to be only slightly more potent than amphetamine (101). Other studies suggest that the difference between the two drugs is more qualitative than quantitative, with methamphetamine affecting different regions of the brain than amphetamine (102-104). We have not found any empirical studies supporting the notion that methamphetamine is more potent than amphetamine in generating psychoses.

2. Objectives

- What are the clinically evident differences between amphetamine-/methamphetamine-induced psychosis and acute symptoms of schizophrenia?
- What is the relationship between blood concentrations of amphetamines and clinical presentation?
- Is methamphetamine more potent in generating central nervous influence and psychosis than amphetamine?
- Is there a transition from amphetamine-/methamphetamine induced psychosis to schizophrenia?

Specific research aims:

1. How many patients acutely admitted in a psychiatric ward were positives for amphetamine/methamphetamine? (paper I and III)
2. Which other psychoactive drugs did the amphetamine positives have in their blood/urine? (paper I and III)
3. Which socio-demographic characteristics do the amphetamine-positive patients have? (paper I)
4. What are the symptoms of psychosis induced by amphetamines compared to schizophrenia in the acute phase? (paper I and IV)
5. Is there a relationship between blood concentrations of amphetamines and psychotic symptoms? (paper I)
6. What is the relationship between having positive blood samples for amphetamines and physician's assessment of drug influence? (paper II)
7. Is methamphetamine more prevalent than amphetamine among acutely admitted patients compared to apprehended drivers? (paper III)

8. Are there any differences in concentrations between amphetamine and metamphetamine among psychiatric patients compared to DUI cases? (paper III)
9. How many of those diagnosed with amphetamine-/methamphetamine-induced psychosis later receive a diagnosis schizophrenia? (paper IV)
10. What characterises those who experience this transition? (paper IV)

3. Material

3.1 Setting

Data for this study were taken from two sources. The first source of data were from two psychiatric wards at public hospitals, both with crisis intervention and diagnostic evaluation as their main activities, namely Lovisenberg Diakonale Hospital, Oslo, Norway and Sørlandet Hospital, Arendal, Norway. A pilot was conducted in 2003 and the main study in 2006/2007. In 2012, we did a follow-up of all patients at Lovisenberg Diakonale Hospital who were positives for amphetamine or methamphetamine or both in the main study.

The second source of data came from the Norwegian Institute of Public Health (NIPH) where all blood samples from apprehended drivers in Norway are analysed. All DUI cases positive for amphetamine and/or methamphetamine during 2003, 2006 and 2007 were included, i.e. from the same time intervals as the data for the pilot and the main study were collected from the psychiatric wards.

3.2 Study samples

The study sample is summarized in table 1. Paper I consists of data from the main study on the two psychiatric wards at Lovisenberg Diakonale Hospital and Arendal Hospital. Exclusion criteria were dementia or mental retardation. From a total of 462 admissions, 13 (2.8%) did not give blood or urine samples, 84 (18.2%) declined, 16 (3.5%) were excluded because of dementia and 6 (1.2%) were not asked to participate, leaving 343 admissions (74.2%). Because 37 patients were admitted more than once during the project period, this comprised 285 individual patients who were included in the study.

Paper II also consists of data from the main study, but here we included only those who had volunteered blood samples and were assessed by a physician within six hours

of admission. In this paper, 271 admissions comprising 214 individual patients were included.

In paper III, patients from the pilot study of 116 admissions were included in addition to the main study. Again, exclusion criteria were dementia or mental retardation, and we only included those who had given blood samples, giving us a total of 100 admissions and 87 individual patients from the pilot study. In total, 578 admissions, from whom 443 (76.6%) admissions comprising 372 individuals consented to participation in the study and volunteered blood samples within 48 hours. In this article, we also included DUI cases from the Norwegian Institute of Public Health (NIPH). The data were grouped according to county, enabling us to select data from the same geographical area and the same time periods as the patients, a total of 988 cases comprising 735 individuals.

For paper IV, we did a follow-up in 2012 of the 36 individuals, all admitted to Lovisenberg Diakonale Hospital in 2006/2007, who were positive for amphetamine and/or methamphetamine in blood and/or urine in the original study. One withdrew her consent, leaving us with 35 individual patients.

Table 1 Number of admissions included in the study and in the different papers (N).

Setting	Total number of admissions/DUI-cases	Admissions/DUI-cases included in the study	Individual patients/DUI-cases included in the study	Paper I Individuals	Paper II Admissions	Paper III Individuals	Paper IV Individuals
Patients Pilot	116	100	87			87	
Lovisenberg (Oslo)	351	300	247	247	236	238	35
Arendal	111	43	38	38	35	38	
DUI-cases							
Oslo	518	517	378			378	
Arendal	471	471	357			357	

In articles I, III and IV, we studied individual patients, while in article II we studied each admission per se. Even if it would be more statistically correct to do all analyses with

regard to individuals and avoid double counting of individuals, this may have the disadvantage of making type II errors, and we have tried to balance these considerations in the papers.

3.3 Inclusion and exclusion criteria

For patients from the main study (papers I-III), the patients provided written informed consent. They were asked again if they were readmitted during the project period. The patients in the pilot did not give informed consent (paper III), see ethical considerations. Exclusion criteria were dementia and mental retardation, as diagnosed by the ward psychiatrist. The patients included in the follow-up, were sent a letter with information about the study (paper IV). Data from the DUI cases belonged to the criminal ward and were handled anonymously, which left informed consent unnecessary and enabled us to include all cases (paper III).

4. Methods

4.1 measurements

4.1.1 Laboratory analyses

All blood and urine samples were analysed at the Division of Forensic Toxicology and Drug Abuse, Norwegian Institute of Public Health. This laboratory had been accredited since 1996 according to ISO 17025, which is the ISO standard for testing and calibrating laboratories by the Norwegian body for accreditation of laboratories (Norsk Akkreditering, Kjeller, Norway). Samples from the psychiatric wards and from the DUI cases were analysed in the same laboratory using exactly the same procedures.

For all patients admitted to psychiatric wards, the blood and urine samples were collected as soon as possible after admission. For the patients admitted in 2003, the blood samples were taken after 15 minutes (median; range 2 minutes to 24 hours), and for the patients admitted in 2006/2007 30 minutes, (median, range 0 minutes to 48 hours). Samples of whole blood for drug analyses were collected by laboratory staff simultaneously as blood samples for routine laboratory analyses were obtained. For drivers suspected of driving under the influence of alcohol and/or other drugs (DUI cases), blood samples were collected within a few hours after apprehension.

All urine samples were screened for parent drugs and/or metabolites using enzyme multiplied immunoassay technique (EMIT) for benzodiazepines, barbiturates, dextropropoxyphene, opiates, methadone, cocaine, amphetamines (amphetamine, methamphetamine, khat and ecstasy), Lysergic Acid Diethylamide (LSD) and Δ^9 -tetrahydrocannabinol (THC; active ingredient in cannabis), and using a gas chromatographic method for gamma hydroxy butyrate (GHB). Blood samples were screened using EMIT immunological test for morphine, codeine, amphetamines, cocaine and THC (105), and using liquid chromatography-mass spectrometry for benzodiazepines, meprobamate, carbamazepine and methadone (106) and using an enzymatic dehydrogenase method for alcohol (107). All positive screening results in urine and blood were confirmed and quantified using gas or liquid chromatography-

mass spectrometry (108-112) (table 2).

Table 2 Substances included in the study with analytic methods and cut-off values (ng/ml) for screening and confirmation in blood and urine^a

Substance	Blood ^b				Urine ^b			
	Screening		Confirmation		Screening		Confirmation	
	Method	Cut-off	Method	Cut-off	Method	Cut-off	Method	Cut-off
Benzodiazepines	-	-	-	-	EMIT	200	-	-
Diazepam	LC-MS	57	LC-MS	57	-	-	LC-MS	150
Oxazepam	LC-MS	287	LC-MS	287	-	-	LC-MS	144
Flunitrazepam	LC-MS	2	LC-MS	2	-	-	LC-MS	28
Clonazepam	LC-MS	9	LC-MS	9	-	-	LC-MS	32
Nitrazepam	LC-MS	14	LC-MS	14	-	-	LC-MS	25
Alprazolam	LC-MS	9	LC-MS	9	-	-	LC-MS	31
Zopiclone	LC-MS	19	LC-MS	19	-	-	-	-
Opiates	EMIT	85	-	-	EMIT	300	-	-
Morphine	-	-	GC-MS	15	-	-	LC-MS	29
Codeine	-	-	GC-MS	32	-	-	LC-MS	60
Methadone	LC-MS	62	LC-MS	62	EMIT	300	LC-MS	62
Dextropropoxyfen	LC-MS	68	LC-MS	68	EMIT	300	LC-MS	200
Buprenorphine	-	-	-	-	EMIT	5	LC-MS	4
Barbiturates	LC-MS	4640	LC-MS	4640	EMIT	200	-	-
Alcohol ^d	ADH	0.002	HS-GC-FID	0.004	ADH	0.01	HS-GC-FID	0.01
Amphetamines	EMIT	54	-	-	EMIT	300	-	-
Amphetamine	-	-	GC-MS	41	-	-	LC-MS	135
Methamphetamine	-	-	GC-MS	45	-	-	LC-MS	150
Ecstasy	-	-	GC-MS	58	-	-	LC-MS	77
Cannabis	EMIT	9	GC-MS	1	EMIT	20	LC-MS	10
Cocaine	EMIT	91	GC-MS	60	EMIT	300	LC-MS	60

LC-MS indicates liquid chromatography-mass spectrometry; GC-MS, gas chromatography-mass spectrometry;

EMIT, enzyme multiplied immunoassay technique; ADH, alcohol dehydrogenase method for alcohol; HS-GCFID,

Headspace gas chromatographic flame ionisations detection.

a Due to conversion from molar units, some of the numbers in the table may seem odd. Blood concentrations are given and plasma/blood concentration ratios for some drugs are markedly above 1. Cut-off values are given for analyses performed in 2006-7.

b Analyses in blood and urine also included lorazepam, ethylmorphine, isopropanol, methanol and 6-monoacetylmorphine (6-MAM, a metabolite of heroine), and, in blood; carbamazepine, meprobamate, carisoprodol, phenazepam, midazolam, zolpidem, and, in urine; pholcodin, phenacylidine, lysergic acid, diethylamide (LSD) and 2-ethylidene-1.5-dimethyl-3.3-diphenylpyrrolidine (EDDP, a metabolite of methadone).

Urine gamma hydroxybutyrate (GHB) was analysed only on special request and urine creatinine and pH were analysed for all samples.

c Phenobarbital.

d Values given in %.

4.1.2 On-site urine testing

The device already in routine use at Lovisenberg Diakonale Hospital was chosen for urine samples, "Clearview 6 Panel Drug Screen card" (Inverness Medical International, Bedford, UK). Urine samples were obtained by the staff who routinely documented in case notes. The patients were not observed when sampling.

4.1.3 Physician assessment

On admission, all patients were examined and interviewed by the physician on call. As a part of this research project, all physicians on call were also asked to fill in forms where the following was registered:

1. Psychotic symptoms.

The instrument we used to register psychotic symptoms was the positive subscale of the Positive and Negative Syndrome Scale (PANSS) (113), which is a rating instrument which assesses seven different symptoms of schizophrenia. The sub-scale we used, that rates positive symptoms, includes the items 'delusions', 'conceptual disorganisation', 'hallucinatory behaviour', 'excitement', 'grandiosity', 'suspiciousness' and 'hostility'. All items can be rated from 1-7 with 7 as the maximum score, which means all patients could receive between 7 and 49 points. To not make the data collection too extensive, we did not register negative or cognitive symptoms. Information on background, admission and stay were obtained by collecting data from the records after discharge.

2. Assessment of drug influence.

On the basis of all the data available at assessment, the physicians on call completed a study form and answered the following question derived from the Clinical Test for Impairment: "In your opinion, is the patient under drug influence at admission: Not at all, mildly, moderately, markedly or uncertain?" (114)

4.1.3 Review of medical records and clinical diagnoses

Data were also collected from the medical records. At Lovisenberg Diakonale Hospital this was done by Jon Mordal, a then PhD-student, and at Arendal Sykehus by a

research assistant. Data were collected with regard to gender, age, educational level, type of accommodation, employment status, number of previous psychiatric admissions, duration of stay and use of coercion (seclusion, medication without consent and use of mechanical restraints). Information about medication given after admission was also registered. This made us able to exclude patients who had positive laboratory findings with regard to benzodiazepines and opiates because of drugs given in the ward after admission. Global assessment of functioning and symptoms (GAF, split version) (115;116) and ICD-10 diagnoses at discharge (60) were also registered. The diagnoses were routinely stated at discharge or either given by or confirmed by a ward psychiatrist. As a part of the project, 63.2% of the patients at Lovisenberg Diakonale Hospital were interviewed using the Norwegian 16-item version of the Mini-International Neuropsychiatric Interview (MINI) (117) and the 7-item Iowa Personality Disorder Screen (118). These results were registered in the medical records and taken into account when the diagnoses at discharge were given. At Arendal Sykehus, these interviews were not done.

We later grouped the following diagnoses together and called them “psychoses”: mental and behavioural disorders due to psychoactive substance use, psychotic disorder (F1x5), all diagnoses in the chapter schizophrenia, schizotypal and delusional disorders (F20-F29), and the following from the chapter on mood (affective) disorders: *mania with psychotic symptoms (F30.2)*, *bipolar affective disorder, current episode manic with psychotic symptoms (F31.2)*, *bipolar affective disorder, current episode severe depression with psychotic symptoms (F31.5)* and *severe depressive episode with psychotic symptoms (F32.3)*.

4.1.4 Comparisons of drug levels

On the basis of earlier epidemiological and experimental studies, the different blood drug concentrations were assessed and given a certain level (114;119-123). Points were given for each interval, enabling us to compare drug levels across different drugs and to add the effects of these drugs (table 3).

Table 3. Blood drug analysis: confirmation methods, detection limits and blood concentration groups that were the basis for estimating drug influence.

Drug(s)	Confirmation method	Detection limit (ng/ml)	Blood concentration intervals (ng/ml) used for the estimation of drug level					
			1 point	2 points	4 points	6 points		
<i>Sedatives and hypnotics</i>								
Alprazolam	LC-MS ¹	9	9-37	38-77	78-117	≥118		
Diazepam and N-desmethyldiazepam	LC-MS	70	70-313	314-654	655-996	≥997		
Flunitrazepam	LC-MS	3	3-6	7-12	13-18	≥19		
Clonazepam	LC-MS	9	9-47	48-49	99-148	≥149		
Nitrazepam	LC-MS	30	30-53	54-110	111-166	≥167		
Oxazepam	LC-MS	140	140-1118	1119-2265	2266-3411	≥3412		
Zolpidem	LC-MS	15	15-105	106-212	213-320	≥321		
Zopiclone	LC-MS	19	19-66	67-136	137-206	≥207		
<i>Opiates/opioids</i>								
Codeine/ethylmorphine	GC-MS ²	32	32-286	287-603	604-920	≥921		
Morphine	GC-MS	15	15-54	55-140	141-284	≥285		
Methadone	LC-MS	62	62-433	434-896	897-1360	≥1361		
THC	GC-MS	1	1-2.8	2.9-4.7	4.8-9.7	≥9.8		
Ethanol (%)	HS-GC-FID ³	0.001	0.001-0.10	0.11-0.15	0.16-0.25	≥0.26		

¹LC-MS indicates liquid chromatography-mass spectrometry

²GC-MS, gas chromatography-mass spectrometry

³HS-GC-FID, Headspace gas chromatographic flame ionisation detection.

4.2 Statistical analyses

Analyses were performed using SPSS versions 16.0, 19.0 and 20.0. Count data were presented as numbers (%). Continuous data with approximate normal distributions were presented as means (SD) and those which did not as medians (range) (124).

Table 4. Statistical packages and statistical analyses used in papers I, II, III and IV.

		Paper number			
		I	II	III	IV
Statistical package	SPSS 16.0		x		
	SPSS 19.0	x		x	x
	SPSS 20.0			x	x
Statistical analyses	Chi-square test	x	x	x	x
	Fisher's Exact probability Test	x			
	Student's t-test	x	x	x	x
	ANOVA	x			
	Mann Whitney U-test		x		
	Pearson's r		x		
	Binary logistic regression		x	x	

The Statistical Package for the Social Sciences (SPSS) versions 16, 19 and 20 were used to analyse the data. Differences between groups were analysed using the χ^2 -test or Fisher's Exact Probability Test for categorical variables and Student's t-test or ANOVA for continuous variables. Binary logistic regression was used to explore the interrelationship between the probability of being admitted to a psychiatric ward, the level of different sedating drugs and amphetamine concentrations. In a second step, a binary logistic regression analysis was performed with the group

(psychiatric patients vs. DUI case) as outcome and as drug concentrations of amphetamines or sedative drug points as confounders. In this analysis, all subjects where a drug was not detected were treated as having a drug level of zero for this drug (table 4).

5. Ethical considerations

Paper I and II: The main study at Lovisenberg Diakonale Hospital and Arendal Hospital in 2006/2007 was conducted in accordance with the Declaration of Helsinki (125) and approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Blood samples were collected on admission, and during the first few days of admission, there was a complete discussion with potential participants, including if they consented to the blood samples' being analysed for drugs. After the discussion, written informed consent was obtained.

Paper III: Data from the acute psychiatric wards in 2006/2007 as described above. The data from the patients admitted to acute psychiatric ward in 2003 were collected anonymously and with no link to individual data like age, gender or diagnoses. Hence, according to the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate no informed consent was needed. With regard to data from the DUI cases, they belonged to the criminal ward and were handled anonymously, which left informed consent unnecessary and enabled us to include all cases.

Paper IV: All patients included in this paper were informed in writing about the follow-up, but no new consent was obtained. The follow-up was also approved by the Regional Committee for Medical Research.

6. Methodological considerations

6.1 Study design

Both the pilot at Lovisenberg Diakonale Hospital in 2003 and the main study at Lovisenberg Diakonale Hospital and Arendal Hospital in 2006/2007 were cross-sectional studies. We used the main study from 2006/2007 to describe characteristics of and to compare symptoms and blood and urine values between different groups of patients acutely admitted to psychiatric wards. This study design does not enable us to say anything about cause-effect relationships because we do not have a time course to determine which factor came first, i.e. in this study, did the psychotic symptoms come before or after the exposure to amphetamines?

A cross-sectional study is appropriate for studying prevalence. At Lovisenberg Diakonale Hospital and the Norwegian Institute of Public Health, we had data from two different time periods, 2003 and 2006/2007, which allowed us to compare how the prevalence of amphetamines changed over time among patients acutely admitted to psychiatric wards and among DUI cases. However, we did not have enough power to find significant differences.

The five-year follow-up at Lovisenberg Diakonale Hospital was a prospective case series study. In a cohort study, information is collected about a group of individuals before a certain outcome, i.e. death or a certain disease. In our study, we collected data about 12 acutely admitted psychiatric patients who were positives for amphetamines in blood/urine and got a diagnosis of either drug-induced psychoses or amphetamine-induced psychosis. We then went through their records five years later to see how many had got a diagnosis of schizophrenia during the follow-up time. Hence, this part of the study can be regarded as a very small cohort-study where the patients who were acutely admitted were their own controls.

6.2 Internal validity

6.2.1 Selection bias

In the main study from 2006/2007, we wanted to study use of drugs among patients who were admitted to acute psychiatric wards. At Lovisenberg, 300 from a total of 351 admissions were included (85%) and from Arendal 43 from 111 (39%). Taken together, 74% of acutely admitted patients were included. When we compared those who were included to those who were not, we found no differences with regard to gender, age or substance-related diagnoses at discharge ($p > 0.2$ for all). Those who did not consent to participation, however, more often received a diagnosis of schizophrenia at discharge (41% vs 25%, $p = 0.037$) and were more often involuntarily admitted (81% vs. 57%, $p = 0.003$). From the 285 patients who were included in the study, 38 received a diagnosis of schizophrenia, and only four of these were positives for amphetamines. It is most likely, therefore, that as more patients with schizophrenia declined, more negatives for amphetamines declined. It is also likely that those who declined had more pronounced symptoms like suspiciousness and hostility than those who consented. This may imply that the PANSS scores among amphetamine negatives with diagnosis of schizophrenia would have been higher if all of them had consented to participate in the study.

A comparison was also made between the included admissions from Lovisenberg in 2006/2007 and data from computerized records of all admissions at the acute psychiatric ward at Lovisenberg in 2006 ($N = 1133$). We found no differences with regard to age, gender, involuntary admissions, length of stay or diagnoses at discharge ($p < 0.2$ for all). We found no significant differences between the patients from Arendal compared to those from Lovisenberg with regard to clinical or laboratory findings.

In papers I, III and IV, we studied individual patients, while we studied the total number of admissions in paper II. When we compared analyses performed with regard to individuals compared to admissions, we got very similar results with no statistical or clinical significance. Because of over-powering when comparing

psychiatric admissions to DUI cases in paper III, only results with $p < 0.01$ have been reported.

Since data from the DUI cases belonged to the criminal ward and were handled anonymously, informed consent was unnecessary and enabled us to include all cases. Therefore, there is no selection bias in the DUI cases.

6.2.2 Information bias

Information bias occurs when the individuals studied give wrong information or information is wrongly registered during the study for other reasons (126).

Laboratory analyses

The use of a two-step process with both screening and confirmation analyses which were used in this study, give high reliability and validity. Also, since the laboratory we used is a forensic laboratory, the cut-offs for all tests are set high to avoid false positives. Still, false negative results are still possible because some substances might have had concentrations below screening cut-off levels. Another possible source of false negatives is urine tampering (127), but the fact that creatinine and pH were within recommended ranges for all samples, indicates that tampering was not common. False negatives may imply that some of the amphetamine/methamphetamine negatives diagnosed with schizophrenia, who were used as a comparison group to amphetamine/methamphetamine positives with drug-induced psychoses, should have been excluded from the comparison. Since the PANSS score between negatives with schizophrenia varied from 7 to 35 points, it is likely that those with higher scores were influenced by amphetamines and that the actual PANSS mean score should have been lower in the schizophrenia group.

In this study, we used blood and urine concentrations of different drugs as an indicator of recent drug use. Earlier a good correlation has been demonstrated between methamphetamine as measured in urine and patient self-report of methamphetamine use (128). However, there are still methodological problems. Some substances have short half-lives and may not have been detected because the intake had occurred too early to be detected in the laboratory tests or because of test delay up to 24 hours. The opposite may also have occurred, i.e.

substances with long half-lives could be detected even if the patient's symptoms were not influenced by the drug at admission, and the intake was not regarded by the physician as "recent". Some of the patients may have been hospitalized during a withdrawal phase for methamphetamine rather than in an intoxication phase (129-131).

Our method of estimating drug influence by grouping different concentrations for the different drugs and giving points for each interval, also poses methodological problems. Even if there is an established relationship on the basis of earlier epidemiological and experimental studies, the different blood drug concentrations were assessed and given a certain level (114;119-123). A given dose of a drug will not give the same blood concentration in all individuals, and the same blood concentration will not lead to the same level of symptoms for all individuals. Also, the same concentrations may give different symptoms at increasing or decreasing blood drug concentration curve. All these factors will contribute to obscuring a dose-response relationship.

Assessment of diagnoses and symptoms

Diagnoses were taken from the records, and for those who had been interviewed with Mini-International Neuropsychiatric Interview (MINI) and the 7-item Iowa Personality Disorder Screen, these interviews were taken into account when the diagnoses were given at discharge. All clinical diagnoses were routinely confirmed by a ward psychiatrist. However, for 37% of the admissions at Lovisenberg and all the admissions from Arendal, structured interviews were not performed. Clinical diagnoses are not always reliable (132), and even when MINI-interviews have been performed, the test-retest reliability was only moderately good (133). One can speculate if this led to an underestimation of how many patients were diagnosed with a primary psychotic disorder. As the wards were crowded, it may have been easier to discharge patients after a few days if they were assessed as having a drug-induced psychosis.

The positive subscale of the Positive and Negative Syndrome Scale (PANSS) was used to assess positive psychotic symptoms. This instrument was developed to

assess psychotic symptoms in patients with schizophrenia (113). As far as we know, no data have been published on its reliability and validity in acute psychiatric settings, but it has been used on acute psychiatric wards among patients with bipolar disorders and schizophrenia without any report of serious validity problems (134).

Global assessment of functioning and symptoms (GAF, split version) was routinely stated at admission and at discharge. The reliability is low when assessing individual patients with GAF (135).

6.3 External validity

I have now discussed internal validity, which is a premise for external validity (126). To which populations can our results be generalized?

We compared our results to data from a national report from 2006 which used data from 19 acute psychiatric wards in Norway (N=3572) collected in 2004/2005, i.e. about the same time period as our study. We found no differences with regard to age, gender, GAF scores, length of stay and disorders not related to substance disorders. However, the patients from Lovisenberg differed in some respects from patients both at Arendal and in the national survey. They were more often of non-Norwegian origin (20% vs 0% in Arendal and 10% nationally), were more often homeless (10% vs 4% and 4%) and more often had a substance use disorder as their discharge diagnoses (45% vs 36% and 22%) (no p-values because we only have aggregated data from the national survey).

Since Oslo is the largest city in Norway and also the capital, the composition of the population is different. The proportion of immigrants is higher in Oslo, and it has been reported that non-western immigrants have lower drug use levels than the rest of the population, both in the population in general (136) and among acutely admitted patients (137). On the other hand, substance use is more common in Oslo than in rural areas (138).

All in all, our results are probably representative for patients admitted to the two hospitals included in the study, but are probably not representative for the entire country or for other countries (139).

With regard to DUI cases, we got very similar results when we analysed all cases for the entire country compared to the cases from the same geographical area as the two hospitals. The DUI cases were chosen because they involved analysis of a large group at the same laboratory, with the same analytical repertoire and in the same time period. However, we do not know the extent to which the DUI cases are representative for all users of amphetamines in Norway or if the DUI cases were a suitable comparison group to psychiatric patients. The conclusion that methamphetamine is more likely to cause psychosis than amphetamine is based on the assumption that individuals who have been arrested will have fewer or less severe psychotic symptoms than those who are admitted to acute psychiatric wards. We cannot totally exclude the possibility that any of the apprehended drivers were psychotic, but the drivers had been subject to a short clinical examination, increasing the chance that they were not psychotic. Neither can we exclude the possibility that some of the drivers were later taken to psychiatric wards after apprehension and would, therefore, have been counted in both groups. However, since the number of DUI cases ($n = 988$) was so much larger than the number of patients ($n=51$), this would, at worst, have affected a very small number of cases.

7. Results

Overview of material

The number of patients is summarized in table 1. In the pilot study from 2003 which had 87 acutely admitted patients with a total of 100 admissions, 63% (95% CI 54%-73%) of the admissions and 61% (51%-71%) of individual patients had psychoactive drugs in their blood or urine or both. We did not register if any of them were given psychoactive drugs after admission and before sampling of blood and urine tests.

From the main study in 2006/2007, 64% (59%-69%) of the 331 admissions and 63% (58%-69%) of the 285 individual patients had psychoactive drugs in their blood or urine or both when we corrected for those who had received psychoactive drugs between admission and blood sampling. Fifteen different substances were found in blood and/or urine: amphetamine, methamphetamine benzodiazepines (alprazolam, clonazepam, diazepam, flunitrazepam, nitrazepam), zopiclone, methadone, codeine, morphine, 6-MAM (from heroin), cocaine, THC (from cannabis) and ethanol.

Specific aims

Aim 1: How many patients acutely admitted to a psychiatric ward were positive for amphetamine/methamphetamine (paper I and III)?

In the pilot study from 2003, we found that of 87 individual patients, 17 (20%, 95% CI 11%-28%) were positives for amphetamines in blood and/or urine. Among the 285 patients included in the main study from 2006/2007, 38 (13%, 95% CI 9%-17%) were amphetamine positive in blood and/or urine, and 35 (92%, 95% CI 84%-101%) of these were also positive for methamphetamine in blood and/or urine.

Aim 2: Which other psychoactive drugs did the amphetamine positives have in their blood/urine (paper I and III)?

Of the 17 patients who were positives for amphetamines in the pilot, 13 (76%, 95% CI 56%-97%) had at least one psychoactive drug in their blood/urine in addition to amphetamine and methamphetamine. The 17 patients had a median of 1 (SD 0.862,

range 1-3) of psychoactive drugs including amphetamines in blood/urine at admission. Of the 38 patients who were positives for amphetamines in the main study, 33 (87%, 95% CI 76%-98%) were also positives for psychoactive drugs including amphetamines with a median of 4 (SD 2.2, range 1-10) of psychoactive substances in blood/urine at admission. The following drugs were found in addition to amphetamines: benzodiazepines (alprazolam, clonazepam, diazepam, flunitrazepam, nitrazepam), zopiclone, methadone, codeine, morphine, 6-MAM (from heroin), cocaine, THC (from cannabis) and ethanol.

With regard to the 735 apprehended drivers in our study, we only had blood samples, not urine samples, and all of them were positive for amphetamines. Of these, 623 (84%, 95% CI 82%-87%) had at least one other psychoactive drug in their blood with a median of 3 (SD 1.151, range 1-10) drugs including amphetamines. Of the patients 38 patients who were positive for amphetamines in their blood, 28 (74, 95% CI 60%-88%) had at least one other psychoactive drug in their blood with a median of 2 (SD 1.599, range 1-7) including amphetamines. Among the apprehended drivers, we found the same drugs as among the patients, in addition to ecstasy, carisoprodol/meprobamate, ethylmorphine, oxazepam and zolpidem.

Aim 3: Which socio demographic characteristics do the amphetamine-positive patients have (paper I)?

Compared to those who were negatives for amphetamines, we found that those who were positives for amphetamines were more often male, 71% (95% CI 57%-85%) vs. 45% (95% CI 38%-51%), more often had fewer than 9 years of education, 71% (95% CI 57%-85%) vs. 49% (95% CI 42%-55%), more often lived alone, 87% (95% CI 76%-98%) vs. 64% (95% CI 58%-70%) or were homeless, 26% (95% CI 12%-40%) vs. 6% (95% CI 3%-9%) and were more often involuntarily admitted, 63% (95% CI 48%-78%) vs. 47% (41%-53%). None of the amphetamine/methamphetamine positives cared for children, 0% vs. 13% (95% CI 8%-17%). During their stay, these patients were also more often subjected to coercive measures than amphetamine/methamphetamine negative patients, 34% (95% CI 19%-49%) vs. 17% (95% CI 12%-22%).

Aim 4: What are the symptoms of psychosis induced by amphetamines compared to schizophrenia in the acute phase (paper I and IV)?

We compared PANSS scores at the positive subscale for those 1) patients who received a diagnosis of schizophrenia and were negatives for amphetamines in blood and/or urine with PANSS scores to 2) patients who were positive for amphetamines in blood and/or urine and either received a diagnosis of amphetamine-induced psychosis or psychoses induced by multiple drugs. Nine patients were in the group with amphetamine/drug-induced psychoses, and from these 8 individual patients had PANSS scores for all seven items at the positive subscale. 33 individuals were diagnosed with schizophrenia, and from these 31 had PANSS scores for all seven items. We found no differences in PANSS scores between the two groups (paper I). We also did an ANOVA to compare the PANSS scores between the same two groups and got very similar results; those positive for amphetamines with drug-induced psychoses had a total PANSS-score of 22.8 and the negatives with schizophrenia 23.5 ($p = 0.783$). For each sub-scale of PANSS, we also got very similar results when we did ANOVA, which showed the same trends as Student's T-test. We also carried out a post-hoc analysis where we excluded all patients who were positive for any sedating drug, i.e. benzodiazepines, THC, ethanol and/or opiates/opioids. The patients with schizophrenia, who were negative for all drugs ($N = 17$) had a mean PANSS score of 24.8. Only two patients with drug/amphetamine-induced psychosis were positive for amphetamines and no sedating drugs, and only one of these had a total PANSS score, positive subscale. This one person had a score of 28.0 ($p = 0.671$). We found similar non-significant results for all the subscales of PANSS.

When we corrected for being positive for sedating drugs, both for individual drugs and taken together, we found a tendency towards slightly higher PANSS scores among those with amphetamine or drug-induced psychoses (table 5).

Table 5. PANSS (positive subscale total score) for amphetamine/methamphetamine negatives diagnosed with schizophrenia versus amphetamine/methamphetamine positives diagnosed with amphetamine-induced psychoses. Statistical analysis is Student's T-test. Values given as mean and 95% confidence intervals (95% CI).

	Number of patients with schizophrenia and total PANSS scores N=31	Number of patients with amphetamine induced psychoses and total PANSS scores N=8	Total PANSS score among amphetamine/methamphetamine negatives diagnosed with schizophrenia	Total PANSS score among amphetamine/methamphetamine positives diagnosed with psychoses induced by amphetamines or by multiple substances	p-value
All bzd positives excluded	31	8	mean (95% CI) 23.5 (20.9-26.1)	22.8 (17.3-28.2)	0.783
All opiate/opioid positives excluded	19	3	mean (95% CI) 25.1 (21.7-28.4)	28.0 (8.1-47.9)	0.596
All THC positives excluded	29	6	mean (95% CI) 23.2 (20.5-26.0)	23.2 (15.2-31.1)	0.983
All ethanol positives excluded	30	3	mean (95% CI) 23.7 (21.0-26.4)	22.3 (8.7-36.0)	0.720
All with sedating drugs excluded	17	1	mean (95% CI) 24.8 (21.0-28.5)	23.7 (17.8-26.3)	0.958
				28.0 (-)	0.671

Aim 5: Is there a relationship between blood concentrations of amphetamines and psychotic symptoms (paper I)?

With rising blood levels of amphetamine/methamphetamine only very marginal differences in symptoms, as measured by PANNS, were observed. We found that individuals who were positives for amphetamines in urine only (N=9) had a PANSS score at 18.0 (95% CI 8.9-27.1). Those who were positives in blood with low/moderate concentrations of amphetamines (≤ 270 ng/ml) (N=15) had a PANSS score of 20.6 (95% CI 15.5-25.7) and those with high concentrations of amphetamines (271-1052 ng/ml) (N=8) had a PANSS score of 20.9 (95% CI 14.1-27.7), $p=0.782$. For the seven individual items of PANSS, similar tendencies were found (table 6).

Table 6. Different blood concentrations of amphetamines. All patients positive for amphetamines with PANSS-scores. Statistical analysis, Analysis of variance (ANOVA). Values given as mean and 95% confidence intervals (95% CI).

Amphetamine and methamphetamine blood concentration intervals (ng/ml) (detection limit 41 ng/ml) N=32					
		None (urine positives only) N = 9	Low/moderate (≤270) N = 15	High (271-1052) N = 8	p-value
PANSS (positive subscale total score)	mean (95% CI)	18.0 (8.9-27.1)	20.6 (15.5-25.7)	20.9 (14.1-27.7)	0.782
Delusions (1-7)	mean (95% CI)	3.1 (1.3-4.9)	3.4 (2.3-4.5)	3.5 (2.4-4.6)	0.912
Conceptual disorganisation (1-7)	mean (95% CI)	3.1 (1.3-5.2)	3.7 (2.6-4.9)	4.1 (2.3-5.9)	0.655
Hallucinatory behaviour (1-7)	mean (95% CI)	2.7 (1.3-4.0)	2.7 (1.6-3.8)	3.3 (1.7-4.9)	0.752
Excitement (1-7)	mean (95% CI)	2.7 (1.7-3.7)	3.8 (2.6-5.0)	3.5 (2.2-4.8)	0.339
Grandiosity (1-7)	mean (95% CI)	1.8 (0.5-3.1)	1.6 (1.0-2.2)	1.8 ((0.6-2.9)	0.941
Suspiciousness (1-7)	mean (95% CI)	2.6 (1.3-3.8)	3.0 (2.0-4.0)	2.6 (1.2-4.0)	0.795
Hostility (1-7)	mean (95% CI)	2.1 (0.8-3.4)	2.1 (0.7-3.6)	2.3 (1.7-2.9)	0.898

Aim 6: What is the relationship between having positive blood samples for amphetamines use of amphetamines and physician's assessment of drug influence? (paper II)

Of the 271 admissions included, 27 (10%) had positive blood samples for amphetamines. All of these were assessed by the physician on call as being under the influence of amphetamines. Three admissions with no drugs detected in their blood samples were judged by the physician as being under the influence of amphetamines. For these patients, recent use of amphetamines was reported. When adjusted for age, gender, psychotic symptoms and blood drug concentration scores, having amphetamines in the blood were associated with an increased likelihood of being judged clinically to be under the influence of drugs (OR 5, 95% CI 1-17) compared to other substances in the blood.

Aim 7: Is methamphetamine more prevalent than amphetamine among acutely admitted patients compared to apprehended drivers (paper III)?

We studied the proportion of methamphetamine positives among all patients and DUI cases with positive blood samples of amphetamines. In 2003, 5 (45 %) of the psychiatric patients (N=11) were positive for methamphetamine. In the same year, 85 (29 %) of the DUI cases who were from the same area (N=294), were positives for methamphetamine. In 2006/2007, 23 (85 %) of the psychiatric patients (N=27) were methamphetamine positives. Among the DUI-cases in the same area and time period, 257 (58 %) were methamphetamine positives (N=441). Taken together across the two time periods 28 (74%) of the psychiatric patients (N=38) were positive for methamphetamine and 342 (47%) of Norwegian DUI cases from the same area (N=735).

We did a binary logistic regression where we compared the odds for being admitted to an acute psychiatric ward compared to being apprehended in traffic. When we adjusted for gender, age, being methamphetamine positive, concentration of the sum of amphetamine and methamphetamine and influence of sedating drugs, we found that individuals who had taken methamphetamine had a 3-4 times increased risk of being admitted to an acute psychiatric ward

compared to those who had taken only amphetamine (adjusted OR= 4.423 (2.031 – 9.631)).

Aim 8: Are there any differences in concentrations between amphetamine and metamphetamine among psychiatric patients compared to DUI cases? (paper III)

The mean methamphetamine concentration was 1.3ng/ml (SD 1.7) among psychiatric patients and 1.3 ng/ml (SD 2.8) among DUI cases (Student's T-test, p-value = 0.961). The patients with psychiatric diagnoses, compared to the DUI cases, had lower mean concentrations of amphetamine (0.9 ng/ml vs. 2.6 ng/ml; $p < 0.001$, Student's T-test) and hence a lower total concentration of amphetamines together (2.2 ng/ml vs. 3.9 ng/ml, $P < 0.001$, Student's T-test). Fewer patients with psychiatric diagnoses were positive for sedatives and hypnotics than among the DUI cases, 18 (47 %) vs. 520 (717 %) ($p < 0.01$, χ^2 -test).

Aim 9: How many of those diagnosed with amphetamine/methamphetamine-induced psychosis later received a diagnosis of schizophrenia? (paper IV)

Of the 35 amphetamine positives included from the original study, seven had a diagnosis from the chapter schizophrenia, schizotypal and delusional disorders (F20-F29 according to the ICD-10 classification of mental and behavioural disorders). 10 moved out of the hospital's catchment area. Six were dead. This left us with 12 individual patients who received diagnoses specifically related to disorders due to psychoactive substance use (F10-F19 according to the ICD-10 classification of mental and behavioral disorders). From these 12 patients, two received the diagnosis *F19.5 Psychotic disorder, amphetamine-induced* and two the diagnosis *F19.7 Multiple and late-onset psychotic disorder, amphetamine-induced*. One got the diagnoses *F90.0 Hyperkinetic disorder, disturbance of activity and attention* and *F60.31 Emotionally unstable personality disorder, borderline type*. The remaining seven got drug-related diagnoses when first included in the study in 2006/2007.

When we scored the original admission records, we also found that three patients had visual hallucinations. Two received a diagnosis of *Schizoaffective disorder (F25.1 and F25.2, respectively)*, and the last one a diagnosis of *F60.3 Emotionally unstable*

personality disorder. One saw colours, the two others “saw people” and did not change diagnosis before moving out of the catchment area later in 2007.

When we did the follow-up in 2012, four patients had been re-diagnosed with schizophrenia, three of these with *F20.0 Paranoid schizophrenia* and one with *F20.3 Undifferentiated schizophrenia*.

Aim 10: What characterises those who experience this transition? (paper IV)

With regard to baseline characteristics, we found small differences between those who had been re-diagnosed with schizophrenia (change group) and those who had not. The change group had less dramatic symptoms on admission measured by PANSS compared to the stable group, 16.7 vs 22.5 points (student’s T-test, $p = 0.580$). For the different sub-scores of PANSS, the largest difference between the two groups was in hallucinatory behaviour, 3.3 vs 1.0 points (student’s T-test, $p = 0.023$). As scored by SAPS-CIP, one person in the stable group had auditory hallucinations (“People talking to subject”), two had persecutory delusions (“Someone is going to harm the subject”), and one had somatic persecutions (felt body was “changed”). In the change group, one person had had persecutory delusions (“Someone is going to harm the subject”). The stable group had more pronounced baseline symptoms with regard to suspiciousness, hostility and hallucinatory behaviour measured by PANSS, the difference regarding hallucinations being the only significant result ($p=0.023$).

The change group had a lower level of function at admission and even more at discharge, as measured by GAF, and the improvement in function was less for the change group than for the stable group, 5 vs 12 points (student’s T-test, $p=0.165$).

The concentration of amphetamine and methamphetamine taken together was higher among the change group than in the stable group, 1.7 mmol/L vs 0.9 mmol/L (student’s T-test, $p=0.663$). The total number of drugs detected were slightly lower in the change group, 4.0 vs 4.9 ($p=0.468$). Sedating drug influence among those who were positives for any sedating drug, was also slightly lower in the change group, 1.6 points vs 1.3 points ($p=0.370$).

8. Discussion

The results will first be discussed in line with the aims. Then the objectives at a higher level will be discussed.

1. Admissions related to amphetamines took up a large proportion of the beds in acute psychiatric wards.

We found that 20% of individuals (95% CI 11%-28%) in the pilot study from 2003 and 13% (95% CI 9%-17%) in the main study from 2006/2007 were positives for amphetamines in blood and/or urine. This indicates a fairly stable pattern of amphetamine use. In the pilot study, blood samples were also collected among medical admissions at Lovisenberg Diakonale Hospital. From these (N=106), 3 (3%) were positives for amphetamines (108). Thus, patients admitted to an acute psychiatric ward were much more likely to have amphetamines in their blood and/or urine than a comparison group from the same time period and catchment area. This higher use of amphetamines among psychiatric inpatients is in line with other studies from Norway (140;141) and elsewhere (19;20;20;28;142;143).

2. The majority of amphetamine positives acutely admitted to psychiatric wards had high rates of recent intake of other psychoactive substances.

In the pilot, 76% (95% CI 56%-97%) had at least one psychoactive drug in their blood/urine in addition to amphetamine and methamphetamine with a median of 1 (SD 0.862, range 1-3) psychoactive drug including amphetamines in blood/urine at admission. In the main study, 87% (95% CI 76%-98%) of the amphetamine positives were also positive for psychoactive drugs including amphetamines with a median of 4 (SD 2.2, range 1-10) psychoactive substances in blood/urine at admission (paper I). Again, the results from the pilot were replicated three years later and show a stable pattern of drug use. Other studies have also found frequent poly drug use among users of amphetamines (144;145). In our study, the substances which were found in addition to amphetamines were all sedating.

It can be debated whether the pattern found on admission to acute psychiatric wards is representative of poly drug use among amphetamine users. Amphetamines are

often taken in “runs” where users stay awake for several days (19;27;27;146-148). These “runs” often end with the intake of sedating drugs like THC, ethanol, opioids or benzodiazepines. Those individuals included in our study may have been admitted after trying, unsuccessfully, to self-medicate with sedating drugs. It is not, therefore, unlikely that we might find a higher percentage of poly drug use in our study compared to users of amphetamines in other settings.

3. Amphetamine users who were admitted to acute psychiatric wards were socially marginalized compared to other patients acutely admitted to psychiatric wards.

We found that those who used amphetamines and were admitted to acute psychiatric wards, compared to other patients admitted to the same wards in the same time period, were younger and more often male, more often had fewer than 9 years of education, more often lived alone and were homeless. This is in line with other studies (52;75;149).

4. Patients who had taken amphetamines and had a diagnosis of psychotic disorder induced by methamphetamine or multiple substances did not show different symptoms from patients with schizophrenia who had not taken amphetamines.

We found the positive psychotic symptoms of the two groups, as measured by PANSS, to be very similar. Despite difficulties in comparing different studies which use different symptom measures, this confirms earlier studies which have reported problems in distinguishing methamphetamine-induced psychosis from primary psychoses, be it in experimental studies where amphetamine was given (45;47) or later observational studies of methamphetamine users (56;57;71).

A limitation was that we did not register symptoms of visual hallucinations and were, therefore, not able to compare with studies which found that visual hallucinations characterized amphetamine-induced psychosis as opposed to schizophrenia (44;54). It is also possible that the more vivid symptoms of amphetamine/methamphetamine-positive patients were masked by the concomitant use of sedating drugs. Almost all the patients were poly drug users, which may be a confounding factor.

5. We found no clinically or statistically significant relationship between blood amphetamine/methamphetamine levels and symptoms.

A cardinal sign of causality in pharmacology is a concentration-effect relationship. We found no statistically significant relationship between blood amphetamine/methamphetamine concentrations and the intensity of positive psychotic symptoms, and this is in agreement with two earlier studies (48;150).

This lack of a relationship between symptoms and blood concentration may be because the development of psychosis is related more to vulnerability than to methamphetamine exposure. We know that methamphetamine users are more likely to develop psychosis if they have first degree relatives with schizophrenia (151) or pre-morbid schizoid/schizotypal personality. There is also evidence to suggest shared genetic components between methamphetamine induced psychosis and schizophrenia and to suggest (152) that individuals with some genetic variants of the dopamine receptor, subtype 2 (DRD2) are more likely to have rapid onset, prolonged duration and spontaneous relapse of methamphetamine psychosis (153;154). Another possible explanation is sensitization to the effects of methamphetamine (155-157). A chronic course of methamphetamine psychoses is associated with frequent use (52) and early onset of methamphetamine use (52;75). A third explanation may be related to the fact that almost all the patients were poly drug users which has probably obscured the relationship between blood concentrations and symptoms. Those individuals included in our study may be admitted after trying, unsuccessfully, to self-medicate. Lastly, some of the patients may have been hospitalized during a withdrawal phase for methamphetamine rather an intoxication phase (129;130;131). Some may also have been in the intoxication or withdrawal phase of drugs other than methamphetamine.

6. When adjusted for age, gender, psychotic symptoms and blood drug concentration scores, amphetamines were associated with an increased likelihood of being clinically judged to be under the influence of drugs.

Patients who were positives for amphetamines had an increased chance of being judged by the physician as influenced by drugs. The association was, however, only moderately strong. A study where blood values of amphetamine and clinical assessment among acutely poisoned patients were compared also showed moderate agreement (158). The lack of a

strong relationship between blood concentrations of amphetamines and the chance of being judged as influenced, is probably due to many of the same factors as described above, under aim 5, about why there is no relationship between blood levels of amphetamines and symptoms, i.e. individual differences in personal vulnerability, possible sensitization to the effects of amphetamines (155-157) and poly drug use (19;27) and the fact that some may have been in a withdrawal phase rather than in an intoxication phase for amphetamines (129-131) or other drugs or both. Three patients were judged as being influenced by amphetamines when they had negative blood and urine samples. This may indicate that some *regular* substance users were misinterpreted as being under the influence at the time of admission, or that symptoms of withdrawal were perceived as being influenced by drugs. Also, because of sampling delay and the fact that amphetamines may have been taken several days before admission, clinicians may have seen influence that was confirmed by history taking, but not by analyses.

7. Methamphetamine was more prevalent than amphetamine among acutely admitted patients compared to apprehended drivers.

The observed increase in the share of methamphetamine in both groups over time is in line with seizure statistics from the National Crime Investigation Service (76), which shows a steady increase in the availability of methamphetamine in Norway between 2000 and 2010. However, the patients with psychiatric diagnoses were more often methamphetamine-positive than apprehended drivers both in 2003 and in 2006/2007. Since most users will not be aware of which they are taking (80), the difference between the groups was probably not due to preference. Our findings could, therefore, point to methamphetamine being a more potent drug in producing psychiatric symptoms like psychosis. The finding that methamphetamine was more prevalent among the patients admitted to acute psychiatric wards, and the lack of a concentration-effect relationship may support earlier findings that methamphetamine has a mode of action which is qualitatively different from that of amphetamine (102-104).

8. The blood drug concentrations both for amphetamine alone and for the total concentrations of amphetamines (i.e. amphetamine and methamphetamine) were lower among those who were admitted to acute psychiatric wards than in DUI cases.

A concentration-effect relationship would have strengthened a hypothesis of causality between the use of amphetamines and psychiatric and psychotic symptoms. We found, however, that the concentrations of both amphetamine alone and the total concentration of amphetamine plus methamphetamine were lower among patients with psychiatric diagnoses than in the control group. This could suggest that the psychiatric symptoms and psychosis were caused not only by the use of the drugs, but that some individuals are more vulnerable to psychiatric and psychotic symptoms (159). However, a concentration-effect relationship may have been obscured by other factors commonly associated with the use of amphetamines. We may have measured the concentration of amphetamines among the patients in the withdrawal phase for amphetamine rather than in an intoxication phase (129). Like previously mentioned, amphetamines are often taken in “runs” (19;27;146-148) where users at the end of a run, self-medicate by sedating drugs. The apprehended drivers were, in fact, more influenced by sedating drugs than the psychiatric patients. This may reflect a greater degree of “success” among apprehended drivers in treating their amphetamine induced “high” than those who are acutely admitted to a psychiatric ward. With our current results, it is difficult to conclude whether the psychiatric problems were due to the intake of amphetamines, or due to personal vulnerability. It is likely, though, that there is a continuum of personal vulnerability between the two groups with hospitalization in a psychiatric ward as a more likely outcome for the most vulnerable.

9. One third of those diagnosed with amphetamine/methamphetamine-induced psychosis have received a diagnosis of schizophrenia five years later. (paper IV)

This is in line with the few other studies in the field, which have also found that some patients who are diagnosed with substance-induced psychosis (74) or methamphetamine psychosis (75) are later diagnosed with schizophrenia. There were few differences with regard to baseline characteristics between those who changed diagnosis and those who did not.

10. What characterises those who experience this transition? (paper IV)

Even though the differences were small and not statistically significant, we are able to see some tendencies. The change group had a lower level of function compared to the stable group as measured by PANSS and the level of function improved to a lesser extent during the stay. All but one were homeless as opposed to none in the stable group, and all of the individuals in the change group had previous psychiatric admissions. These results may suggest that, at the time of our study, they were showing negative symptoms of schizophrenia. Our finding that three of the amphetamine-positive patients had visual hallucinations is in line with earlier studies (52-54).

Objectives

Our first objective was to investigate whether there were clinically evident differences between psychosis induced by amphetamines and acute symptoms of schizophrenia. According to our results, there are few differences in the acute phase, i.e. at the time of admission to acute psychiatric wards (paper 1). This is in line with some other studies (42;43;56;57) which found it hard to distinguish between the two groups. However, others have found visual hallucinations to be more common in psychosis induced by amphetamines (44;45;52-54). It was one of the limitations of our original study that we did not examine visual hallucinations. When we did the follow-up and scored the original admission records of patients positive for amphetamines we found that three patients had visual hallucinations. Visual hallucinations were not common, however, and we still think it is very difficult to distinguish between psychosis induced by amphetamines and schizophrenia in the acute phase. It is possible that there is a dose-response relationship between use of amphetamines and visual hallucinations, i.e. that most individuals will develop other symptoms like delusions, hostility and suspiciousness first, and visual hallucinations later as a high-dose response (144). What constitutes a high dose will, however, vary between individuals.

Our next objective was to investigate if methamphetamine was more potent in generating psychosis than amphetamine. We found that individuals who had taken methamphetamine had a 3-4 times increased risk of being admitted to an acute psychiatric ward as opposed to be apprehended by the police compared to those who had taken only amphetamine. We also found that the mean methamphetamine concentration was the same in the two groups, but the concentrations of amphetamine alone and hence the total concentration of amphetamine plus methamphetamine, were lower among patients with psychiatric diagnoses than among the DUI-cases. This could suggest that the psychiatric symptoms and psychosis were caused not only by the use of the drugs, but that some individuals are more vulnerable to psychiatric and psychotic symptoms (paper III). We found no relationship between symptoms and blood concentrations of amphetamines within the patient group (paper I) and no strong relationship between being positive for

amphetamines and being judged as under the influence of drugs by the physician on call (paper II).

Finally, we wanted to investigate whether there is a transition from psychosis induced by amphetamines to schizophrenia and found that one third of the patients admitted to an acute psychiatric ward with amphetamines in blood/urine and who did not get a diagnosis of primary psychosis at that time, were diagnosed with schizophrenia during the five year follow-up. This was a case series and hence, our results were not statistically significant (paper IV).

On the basis of our main findings, we propose a model for understanding the relationship between schizophrenia and psychoses induced by amphetamines. It is known that having first degree relatives with schizophrenia (151) or pre-morbid schizoid/schizotypal personality (52) increase the risk of developing psychosis when exposed for amphetamines. ADHD (160) and other neurological disorders during childhood (161) may also play a role. A chronic course of methamphetamine psychoses is associated with frequent use (22;52;162) and early onset of methamphetamine use (52;75;163;164) as well as injection as the preferred route of administration (144). Those who inject may have more high-dose related symptoms because injection of amphetamines is connected to higher doses (59;165). Individual differences in vulnerability to developing psychoses explains why some individuals seem not to develop psychotic symptoms at all when using amphetamines (42;45;48;51), others develop symptoms when exposed for larger doses and some for smaller doses (41;47). We believe that the relationship between psychosis induced by amphetamines and schizophrenia can be understood within a traditional stress-vulnerable model (151;159;166;167). The endpoint here is schizophrenia, which the individuals most vulnerable to psychoses develop without any exposure to amphetamines or other stimulants. A stress-vulnerability model may also explain why some individuals develop a more chronic psychotic condition when exposed for amphetamines (31;44;52;62;168).

Clinical implications and final word

My time as a PhD student is now over and I am back to clinical practice. Diagnostic entities now seem more uncertain to me than ever. When patients are acutely admitted, it is not possible to assess from the symptoms whether they have a primary psychotic disorder like schizophrenia or a drug-induced psychosis alone or a combination of the two. The physician's assessment of whether the patient is under the influence of drugs like amphetamines is burdened with uncertainty. I have learned that a diagnosis is not final, but may change over time – either because the patient is misdiagnosed with drug-induced psychosis in the first place or because patients who initially have a drug-induced psychosis may develop schizophrenia over time. It saddens me to see how difficult the living conditions are for patients positive for amphetamines and how poor their prospects are in many respects. A few years on, some of our patients initially diagnosed with amphetamine-induced psychosis have been re-diagnosed with schizophrenia and several of the amphetamine positives are dead (paper IV).

An important clinical implication of our results is that patients with dual diagnosis may be mis-diagnosed as only having a drug-induced psychosis. They may not receive the correct treatment or get social benefits they otherwise would have been entitled to. This should have consequences for how services for dual-diagnosis patients are organized, whether specialist teams for dual-diagnosis are established (32), or health care workers in the existing systems receive better training (33).

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Vil du delta i forskningsprosjektet

”Rus i akuttpsykiatrien”?

Kjære nyinnlagte pasient!

Mange psykiatriske pasienter bruker eller har brukt rusmidler. Sammenhengen mellom rus og psykisk helse er et viktig og komplisert felt hvor det ønskes mer kunnskap. Derfor spør vi om du vil bli med i et forskningsprosjekt hvor vi skal undersøke dette nærmere. Vi ønsker å kartlegge psykisk helse og rusvaner hos alle nyinnlagte pasienter ved akuttpsykiatrisk avdeling. Det er viktig at både pasienter som bruker og ikke bruker rusmidler deltar. Ved din deltakelse vil du gi et verdifullt bidrag til et forskningsprosjekt som ønsker å bidra til bedre utredning og behandling i akuttpsykiatrien.

Studieinnhold

- 1) Vi ber om tillatelse til å hente opplysninger fra din journal til bruk i forskningsprosjektet.
- 2) Vi ber om tillatelse til å intervju deg om din psykiske helse og dine rusvaner. Intervjuene varer cirka en time og gjøres i løpet av oppholdet her.
- 3) Ved innleggelsen ble det rutinemessig tatt blodprøve og urinprøve. Vi ber om tillatelse til å analysere prøvene med hensyn til rusmidler.

Datasikkerhet

- 1) Medarbeiderne i prosjektet har taushetsplikt, og all informasjon om deg vil bli behandlet konfidensielt. Personlige opplysninger vil kun brukes til forskning og vil ikke kunne kobles til deg.
- 2) Blodprøvene og urinprøvene analyseres og oppbevares ved Nasjonalt Folkehelseinstitutt. Der opprettes det en egen biobank for dette prosjektet, som divisjonsdirektøren er ansvarlig for. Prøvene er ikke tilgjengelig for noen andre. Analysene tar noe tid, og svarene vil kun brukes til forskning. Prøvesvarene blir derfor ikke tilgjengelig for deg, din behandler eller din journal.
- 3) Intervjuene med deg vil også gi viktig informasjon. Du har rett til å få innsyn i disse opplysningene og til å få noe endret hvis det er feil. Denne informasjonen legges i journalen din, og kan være nyttig for din behandling.



Informasjon og samtykke

Forespørsel om deltakelse i forskning
Lovisenberg Diakonale Sykehus
Nasjonalt Folkehelseinstitutt

Risiko og nytte

Det er ingen risiko eller ubehag ved å delta i prosjektet. Mange pasienter vil oppleve utredningen som nyttig.

Frivillighet

Deltakelsen er frivillig og du behøver ikke bestemme deg med det samme. Du kan trekke deg fra prosjektet når som helst uten å oppgi grunn og uten at det får noen følger for behandlingen din. Da vil det biologiske materialet bli destruert og opplysningene om deg vil bli slettet, så lenge de ikke allerede er inngått i vitenskapelige arbeider.

Prosjektslutt

Noen pasienter vil bli kontaktet om et halvt år for en etterundersøkelse. Prosjektet avsluttes 31.12.2009. Da vil alle prøvene bli destruert og alle sensitive persondata slettet. Resultatene av studien vil bli publisert som gruppedata, uten at den enkelte kan gjenkjennes.

Prosjektledelse

Prosjektet er et samarbeid mellom Lovisenberg Diakonale Sykehus og Nasjonalt Folkehelseinstitutt. Det er finansiert av Helse Øst, og har ingen kommersielle formål. Forsker er lege Jon Mordal. Avdelingen kan formidle kontakt med ham når som helst ved spørsmål eller uklarheter.

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Divisjonsdirektør
Nasjonalt Folkehelseinstitutt

Prosjektet er tilrådd av Regional komité for medisinsk forskningsetikk og av Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

Samtykkeerklæring – prosjektet "Rus i akuttpsykiatrien":

Jeg har mottatt skriftlig og muntlig informasjon om prosjektet og sier meg villig til å delta.

Oslo, dato: _____

Signatur: _____

Plassér
pasientetiketten
her



Spørsmål til mottagende lege:
Skal besvares for alle nyinnlagte pasienter

(Se viktig informasjon helt nederst)

Plasser pasientetikett her

Eventuelt skriv med blokkbokstaver:

Pas. navn: _____

F. nummer: _____

Dato og tidspunkt for
innkomstundersøkelse

På bakgrunn av alle tilgjengelige data ved innkomstvurdering

1) I løpet av den siste uken og ved innkomstvurdering: I hvilken grad har pasienten hatt positive symptomer?

(Markér høyeste score i denne perioden, se PANSS –veil. på baksiden)

Vrangforestillinger	1	2	3	4	5	6	7
Tankemessig desorganisering	1	2	3	4	5	6	7
Hallusinasjoner	1	2	3	4	5	6	7
Uro / agitasjon	1	2	3	4	5	6	7
Storhetsidéer	1	2	3	4	5	6	7
Mistenksomhet / forfølgelsesidéer	1	2	3	4	5	6	7
Fiendtlighet	1	2	3	4	5	6	7

2) Opplysninger om aktuelt inntak av rusmidler (kryss av)

- | | | |
|--|--|---|
| <input type="checkbox"/> Alkohol | <input type="checkbox"/> Amfetamin | <input type="checkbox"/> Organisk løsemiddel |
| <input type="checkbox"/> Benzodiazepiner | <input type="checkbox"/> Kokain | <input type="checkbox"/> Annet rusmiddel: _____ |
| <input type="checkbox"/> Cannabis | <input type="checkbox"/> Morfin / heroin | <input type="checkbox"/> Ingen opplysninger |

Hvis opplysninger om dette:

Stoff, mengde, tidspunkt, inntaksmåte: _____

3) I hvilken grad opplever du at pasienten er påvirket av rusmidler ved innkomst? (kryss av)

- | | | |
|--|---|---|
| <input type="checkbox"/> Ikke påvirket | <input type="checkbox"/> Moderat påvirket | |
| <input type="checkbox"/> Lett påvirket | <input type="checkbox"/> Tydelig påvirket | <input type="checkbox"/> Ikke mulig å bedømme |

4) Hvordan vurderer du rusmidlers betydning for innleggelsen?

- | | |
|--|---|
| <input type="checkbox"/> Ingen betydning | <input type="checkbox"/> Stor betydning |
| <input type="checkbox"/> Moderat betydning | <input type="checkbox"/> Ikke mulig å bedømme |

Dato og tidspunkt: _____

Signatur, mottakende lege: _____

Rekvirere blodprøver så snart som mulig (ø-hjelp, "prosjekt"). Obs! Trengs suppl. undersøkelser?
Du skal ikke informere om prosjektet i innkomstsituasjonen. Dette gjøres senere. Legg ferdig utfyllt skjema i medisinkardex for aktuelle pasient, og kryss av i "sjekklister". TAKK FOR SAMARBEIDET!

PANSS positiv subskala

Det kan lønne seg å lese skalaene nedenfra og oppover før du scorer

Vrangforestillinger

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - Forekomst av en eller to vrangforestillinger som er vage, ikke utkrystalliserte og som ikke fastholdes iverdig. Vrangforestillingene påvirker ikke pasientens tenkning, sosiale relasjoner eller atferd.
- 4 **Moderate** - Forekomst av en brokete samling av diffuse, vagt utformede, ikke stabile vrangforestillinger eller av noen vel utformede som av og til påvirker tenkning, sosiale relasjoner eller atferd.
- 5 **Middels alvorlige** - Forekomst av talrike vel utformede vrangforestillinger som pasienten iverdig fastholder og som av og til påvirker tenkning, sosiale relasjoner eller atferd.
- 6 **Alvorlige** - Forekomst av en stabil samling vrangforestillinger som er utkrystalliserte, muligens systematiserte og som pas. iverdig holder fast ved og som klart påvirker tenkning sosiale relasjoner og atferd.
- 7 **Ekstreme** - Forekomst av en stabil samling vrangforestillinger som enten er uttalt systematiserte eller meget talrike og som dominerer viktige områder av pasientens liv. Dette resulterer ofte i upassende, ansvarslose handlinger som også kan medføre risiko for pasientens eller andres sikkerhet.

Tankemessig desorganisering

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - Tenkningen er omstendelig, på siden av temaet eller med tvisomt logikk. Der er til dels vanskeligheter med å bruke tenkningen målrettet, og springende assosiasjoner kan komme frem når pas. blir utsatt for press.
- 4 **Moderate** - Klarer å fokusere tankene når kommunikasjonen er kortfattet og strukturert, men tankeprosessen blir til dels usammenhengende eller irrelevant ved en mer komplisert samtale, eller ved minimalt press.
- 5 **Middels alvorlige** - Har stort sett vanskelig for å organisere sine tanker, slik at dette blir tydelig pga. ofte forekommende irrelevante svar, manglende sammenheng, løse assosiasjoner selv når pas. ikke er under press.
- 6 **Alvorlige** - Tenkningen er i stor grad sporet av med manglende indre sammenheng, som resulterer i påtagelig irrelevant og usammenhengende tenkning som finnes nesten hele tiden.
- 7 **Ekstreme** - Tankeprosessen er helt usammenhengende. Høy grad av tankeflukt som umuliggjør kommunikasjon (ordsalat eller mutisme).

Hallusinasjoner

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - En eller to klart uttrykte, men ikke ofte forekommende hallusinasjoner eller flere diffuse unormale perseptuelle opplevelser som ikke forvrenger tenkningen eller atferden.
- 4 **Moderate** - Hallusinasjonene opptrer ofte, men ikke hele tiden og pasientens tanker og atferd påvirkes bare i mindre grad.
- 5 **Middels alvorlige** - Hallusinasjonene forekommer ofte, kan omfatte mer enn en sansesmodalitet og har tendens til å forvrenge tenkningen og/eller påvirke atferden. Pas. kan svare på dem emosjonelt og av og til også verbalt.
- 6 **Alvorlige** - Hallusinasjoner forekommer nesten hele tiden, og forårsaker stor forstyrrelse av tenkning og atferd. Pas. oppfatter disse som virkelige sanser opplevelser, og funksjonsnivået er preget av hyppige emosjonelle og verbale reaksjoner på dem.
- 7 **Ekstreme** - Pas. er så og si fullstendig opptatt av hallusinasjoner, som nesten helt dominerer tenkning og atferd. Hallusinasjonene tolkes gjennom fastlåste vrangforestillinger og kommer til uttrykk gjennom tale og atferd, også slik at pas. adlyder imperativ hallusinoser.

Uro / agitasjon

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - Pas. er noe agitert med økt aktsomhet, dvs. med økt tendens til raskt å innrette seg på nye inntrykk, eller med tendens til lett uro gjennom hele intervjuet, men uten klare agitasjonsepisoder eller påtagelige humørsvingninger. Noe øket tælerenhet.
- 4 **Moderate** - Pas. er klart agitert og urolig under hele intervjuet, og dette påvirker tale og motorikk eller pas. har sporadiske utbrudd som kommer av og til.
- 5 **Middels alvorlige** - Betydelig hyperaktivitet eller ofte forekommende utbrudd av motorisk aktivitet som kan observeres, og dette gjør det vanskelig for pas. å sitte stille i lengre tid enn noen minutter av gangen.
- 6 **Alvorlige** - Uttalt uro dominerer intervjuet, og begrenser pasientens oppmerksomhet og påvirker til en viss grad naturlige funksjoner som spising og søvn.
- 7 **Ekstreme** - Uttalt uro som i stor grad hindrer pas. fra å spise og sove, og som gjør kontakt med andre personer nesten helt umulig. Øket talestrøm og økt motorisk aktivitet som resulterer i manglende sammenheng og utmattelse.

Storhetsidéer

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - Virker noe ekspansivt eller skrytende, men uten storhetsidéer.
- 4 **Moderate** - Urealistisk følelse av påtagelig overlegenhet i forhold til andre. Noen diffus formulerte vrangforestillinger om å ha en spesiell posisjon eller spesielle evner kan forekomme uten at det fører til handlinger.
- 5 **Middels alvorlige** - Pas. uttrykker klare vrangforestillinger som gjelder spesielle evner, posisjon eller styrke som påvirker holdningen men ikke atferd.
- 6 **Alvorlige** - Pas. uttrykker klare vrangforestillinger om bemerkelsesverdig overlegenhet som involverer mer enn et område (rikdom, kunnskap, berømmelse o.l.), som påtagelig påvirker samspillet med andre og som kan føre til utagering fra pasientens side.
- 7 **Ekstreme** - Tenkningen og samspillet med andre og atferden domineres av multiple vrangforestillinger om fantastiske evner, helse, kunnskap, berømmelse, styrke og/eller moralsk høyverdighet som kan få bisarre uttrykk.

Mistenksomhet / forfølgelsesidéer

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - Fremtrer med en forsiktig eller åpen mistenksom holdning, men tenkning og samspill med andre og atferd er minimalt påvirket.
- 4 **Moderate** - Uttalt mistenksomhet er klart fremtredende og forstyrrer intervjuet og/eller atferden, men det er ikke tegn på vrangforestillinger om å bli forfulgt. Alternativt kan det finnes løst formulerte vrangforestillinger om å bli forfulgt, men de synes ikke å påvirke pasientens holdninger eller forhold til andre.
- 5 **Middels alvorlige** - Pas. viser uttalt mistenksomhet som fører til store problemer i forhold til andre mennesker eller det finnes klare vrangforestillinger om å bli forfulgt som har begrenset innflytelse på forholdet til andre og atferd.
- 6 **Alvorlige** - Klare og mer varige vrangforestillinger om å bli forfulgt som kan være systematiserte og som i betydelig grad påvirker pasientens forhold til andre.
- 7 **Ekstreme** - Et nettverk av systematiserte vrangforestillinger om å bli forfulgt som dominerer pasientens tenkning, forhold til andre og atferd.

Fiendtlighet

- 1 **Mangler** - Symptomet, slik det er definert, er ikke tilstede.
- 2 **Minimale** - Tvisomt patologisk. Kan være en ekstrem normalvariant.
- 3 **Lette** - Indirekte eller kontrollert sinne slik som sarkasmer, manglende respekt, fiendtlighet og perioder med irritabilitet.
- 4 **Moderate** - Pas. fremviser en klart fiendtlig holdning, blir ofte irritable og gir direkte uttrykk for sinne.
- 5 **Middels alvorlige** - Pas. er svært irritable og bruker av og til ukvemsord Eller er truende.
- 6 **Alvorlige** - Er ikke samarbeidsvillig, bruker ukvemsord eller truer, og dette forstyrrer i stor grad intervjuet og påvirker i stor grad forhold til andre. Pas. kan bli voldsom og destruktiv, men er ikke fysisk voldsom mot andre.
- 7 **Ekstreme** - Uttalt raseri som resulterer i ekstrem uvilje til samarbeid, utelukker kontakt med andre eller resulterer i episoder med fysisk vold mot andre.



Informasjon om forskningsprosjekt

Oslo, 13. august, 2013

«Rus i akuttpsykiatrien»

I perioden september 2006 til mai 2007 var du med i et forskningsprosjekt ved psykiatrisk akuttavdeling ved Lovisenberg Diakonale Sykehus. Prosjektet gikk ut på at det ble tatt en ekstra blodprøve av alle ved innkomst, og hos dem som ga skriftlig tillatelse til det, ble denne blodprøven analysert for rusmidler. En del av dem som sa ja, avga også urinprøver, fylte ut spørreskjemaer om rusbruk og ble intervjuet om psykiske symptomer. Disse dataene ble behandlet anonymt der hver pasient ble tildelt et ID-nummer. Alle blod- og urinprøver er nå blitt destruert i forbindelse med prosjektets avslutning.

Det viste seg at 64 % av alle som ble lagt inn, hadde én eller annen form for rusmiddel i blodet eller urinen på innleggelsestidspunktet, og 15 %, det vil si 36 personer, hadde amfetamin i blod og/eller urin.

Da du sa ja til å delta i prosjektet, sto det i informasjonsskrivet at noen dem som sa ja til å delta, ville bli kontaktet på nytt for en etterundersøkelse. Vi har valgt ikke å oppsøke personlig noen av dem som ble lagt inn den gangen. I stedet har vi fått tillatelse av Regional etisk komité til å gå inn i journalene til alle dem som var positive for amfetamin for å gjøre en etterundersøkelse på denne måten. Vi har ønsket å se på om noen av dem som fikk diagnosen rusutløst psykose, senere fikk en annen diagnose. Vi anser dette som viktig fordi andre diagnoser kan gi flere rettigheter i forhold til blant annet tjenester fra bydel, trygdeytelser og hjelp til å finne bolig.

Du får nå dette brevet fordi du var én av de 36 personene som var amfetaminpositive ved innleggelsen i 2006/2007, og som samtykket til å være med i studien. Jeg har gått gjennom alle journalene på Lovisenberg Diakonale Sykehus for disse 36 pasientene. Når undersøkelsen er ferdig, vil jeg slette forskningsdata med navn, fødselsdato eller

personnummer/fødselsnummer. Det gjør at man ikke senere kan knytte dataene i studien opp mot bestemte personer. Resultatene av studien vil kun bli publisert som gruppedata uten at den enkelte kan gjenkjennes.

Dersom du har spørsmål eller kommentarer, er du velkommen til å ta kontakt med meg på tlf 23 22 60 00.

Med vennlig hilsen

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