Self-poisonings in Oslo: Epidemiology, substance use, psychosocial factors and prognosis

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ABSTRACT

Background: The majority of self-poisonings treated at emergency departments are the result of suicidal behaviour (suicide attempts or acts of appeal) and substance use. Both of these groups exhibit aspects of self-destructive behaviour. However, most studies focus on subgroups such as suicide attempters, non-fatal drug overdoses, etc. Knowledge of this patient group is therefore fragmented with respect to toxic agents, extent, common features and prognosis. Despite this, there are well-known interactions because substance use is known to be a risk factor for suicidal behaviour, and affective and personality disorders are commonly seen among substance users. The evaluation of intention can be difficult in an acute setting because of reduced consciousness, unwillingness to report the use of illicit drugs and even instability in the wish to die. The overlap between patient groups may therefore be considerable. The long-term prognosis for different subgroups has been documented in terms of increased mortality and a high number of suicides. More information about socio-demographic, psychiatric and toxicological factors is needed for this patient group, as well as risk factors for death and suicide. Furthermore, treatment options need to be documented, both in the acute setting and in referral to follow-up services.

Research questions: The aim of this thesis is to study patients with self-poisonings who have been treated at the Emergency Department as a single risk group. The pattern of toxic agents, the extent of substance use and the psychosocial risk factors among these patients need to be investigated. The long-term prognosis, as well as the treatment offered, will be studied. The thesis attempts to answer six main research questions.

1. What are the patterns of toxic agent usage, especially for drugs of abuse, according to age, gender and suicidal intention for all patients admitted to medical departments in Oslo for acute poisoning over a one-year period? (Papers I and II)
2. What is the concordance between the clinical assessments by the physicians on duty and drug analyses in patients treated for acute poisonings? (Paper II)
3. What kind of treatment are patients offered in the acute setting, and to what extent are the patients referred to follow-up services at discharge? (Papers III and VI)
4. Are there differences in psychosocial factors, substance use and referral to follow-up services at discharge according to the intention of the self-poisoning? (Paper VI)
5. Compared with the general population, what are the 20-year overall and cause-specific mortality rates for all patients admitted to medical departments for self-poisoning in Oslo in 1980, in particular for hospital-treated opioid addicts? (Papers IV and V)

6. What factors might differentiate those who died in the follow-up period from those who survived, and what factors might predict suicide or other causes of death? (Paper IV)

Material and methods: This thesis, which consists of six papers, includes five different samples of acute poisonings and self-poisonings. Acute poisonings are mainly self-poisonings. In the following, the term self-poisoning will be used.

The inclusion criteria required a primary diagnosis of self-poisoning, irrespective of intention. Patients with an additional diagnosis of self-poisoning, but with other major diagnoses, were excluded. The pattern of toxic agents, as well as clinical course and outcome, were studied in a cross-sectional multicentre study conducted in Oslo in 2003/2004 (n=947). Accidental non-self-poisonings were excluded from this sample when studying psychosocial factors and referral to follow-up services (n=908). The extent of drug abuse among this patient group was studied in a cross-sectional single-centre study from 2001 (n=405). Two papers followed a cohort of hospitalized self-poisonings, first admitted in Oslo in 1980, for 20 years. One paper includes all self-poisonings in all medical departments (n=946). The other follows a subgroup of opioid addicts treated for self-poisoning and/or voluntary detoxification during 1980/81 (n=185). Standardized mortality ratios (SMRs) were used to compare mortality in the cohort to that of the general population. Cox regression analyses were used to find predictors for death and suicide. Multinomial regression analyses were used to study differences in psychosocial factors and intended referral to further treatment.

Results: The incidence of acute poisonings in Oslo in 2003/04 was 2.0 per 100 000, of which 95.9% were self-poisonings. Benzodiazepines (18%), ethanol (17%), paracetamol (12%), opioids (7%), and gamma hydroxybutyric acid (GHB) (7%) were most frequently taken as the main toxic agent. Males drank ethanol more often and used more illicit drugs, while females tended to use more prescription drugs (benzodiazepines, paracetamol, neuroleptics, zopiclone and anti-epileptics). Females were more often evaluated as having taken the drugs in a suicidal attempt or as an act of appeal.

In analyses of urine or blood samples, drugs of abuse were found in 92% of all self-poisonings irrespective of intention. Benzodiazepines (50%) ethanol (40%), opiates (35%), cannabis (24%) and amphetamine (21%) were the most common, including both main and additional agents. The only gender difference was that cannabis was found more often among males. The agreement between clinical diagnosis and drug analysis for GHB and ethanol was

moderately good. Because kappa was lower than 0.20 for benzodiazepines and cannabis, the agreement was considered to be poor.

Of all admissions in 2003/04, 75% received treatment as well as observation, and 39% received antidotes, an increase from 21% in 1980. Complications were observed in 18% of cases, a slight reduction since 1980 (22%). Ten (1.1%) died and six (0.6%) developed permanent sequelae, of which seven and five were drug- or alcohol-related, respectively. Although in-hospital mortality was low, 40% of the patients were treated in the ICU.

According to the physicians, 37% of all self-poisonings in 2003/2004 were suicide attempts, 26% were appeals and 38% were drug-related poisonings. Overall, patients treated for self-poisonings showed a lack of social integration. Only a third of them were employed, a third were married and half were living alone. Suicide attempters and appealers had more previous suicide attempts and reported more psychiatric treatment than did those with drug-related poisoning. However, there was considerable overlap between patient groups. A third of all drug-related poisonings reported previous suicide attempts, and a third of suicide attempters reported daily substance use. Gender distribution was the only statistically significant difference between appealers and suicide attempters.

In a 20-year follow-up of self-poisonings from 1980, it was found that 37.5% of the patients had died, the SMR being 4.6 (95% C.I., 4.2–5.1). Among males, 45.3% died and 30.2% of all females died. The SMRs were 5.0 (95% C.I., 4.3–5.7) for males, and 4.2 (95% C.I., 3.6–4.9) for females. After 20 years, 7.4% of all patients had died from cardiovascular diseases, 7.1% from suicide, 4.3% from accidents, 3.3% from cancer, 1.1% had suffered another type of violent death and 14.4% had died from other diseases. Lower social group, drug abuse and a lower level of consciousness were all independent predictors of death. A suicidal motive upon admission was the only risk factor for suicide. In the cohort of opioid addicts, 70 opiate addicts died during follow-up (37.8%), with an SMR of 23.6 (95% C.I., 18.7–29.9). The risk remained high for the entire follow-up period, and the risk of death was significantly higher for all causes of death compared with the general population. There were no significant differences in SMR between self-poisonings and those admitted for voluntarily detoxification.

One out of every five patients treated for self-poisoning was discharged without any plans for follow-up. Among drug-related poisonings, 36% left hospital without plans for further treatment. Among those who were suicidal, 5% were not referred to further treatment, as also were 10% of the appealing patients. Thirty-eight percent of all suicide attempters were admitted to a psychiatric ward. Only 10% of drug-related poisonings were referred to substance abuse treatment.

Conclusions: Benzodiazepines and ethanol, which remained the most common toxic agents in self-poisonings, were found more often than suspected. Drugs of abuse were found in 9 out of 10 self-poisonings irrespective of intention. Although in-hospital mortality was low, the long-term prognosis for self-poisonings was rather poor. Although the risk of death increased for all causes, the suicide risk needs to be emphasized. A suicidal motive was an important predictor for later suicide. The risk was increased even when patients were considered to be neither suicidal nor substance abusers, indicating that focusing on intention alone did not capture all patients at increased risk. The lack of social integration, the high number of previous suicide attempts and extensive substance use may contribute to the risk of death in general and of suicide in particular. The evaluation of intention had a major impact on referral to further treatment, in spite of the increased mortality among all patients.

ABBREVIATIONS AND GLOSSARY

CK: creatine phosphokinase

GHB: gamma-hydroxy-butyrate

ICD: International classification of diseases

ICU: intensive care unit

Multinomial regression analyses: is used when the dependent variable in question is nominal (a set of categories which cannot be ordered in any meaningful way) and consists of more than two categories

NAC: N-acetyl-cysteine

Opioids: a chemical substance that has a morphine-like action in the body and binds to opioid receptors

SSRIs: selective serotonin reuptake inhibitors

Standardized Mortality Ratio (SMR): the ratio of observed to expected deaths, i.e., the ratio of the number of deaths observed in the study group to the number of deaths that would be expected if the study population had the same specific rates as the standard population

TCA: tricycle antidepressants

WHO: World Health Organization

PREFACE

I owe my interest in suicidology in general, and self-poisonings in particular, to my supervisor, Professor Øivind Ekeberg. When I was a medical student, he was my teacher in communication skills, and during our group discussions and training sessions, the complex background and the need for treatment among this patient group were emphasized. When we discussed the opportunity for me to participate in a mortality study as part of my mandatory student report, it became clear that more questions needed to be answered than could be covered by such a format. I became a student at the Medical Student Research Program from the autumn of 2003 and worked full-time as a fellowship student for one year. During this period, Professor Dag Jacobsen, who became my co-tutor, elaborated the toxicological view in this field. From March 2003, I was included in the group that organized a study of all self-poisonings in Oslo over a one-year period from 1 April 2003 to 31 March 2004. Knut Erik Hovda, and later Fridtjof Heyerdahl, were closely involved with this group while completing their doctoral fellowships. Gradually I became more involved in the collection of data, participating in the interviewing of the patients at Ullevaal University Hospital, scanning the forms collected by other participants and double-checking that the forms were complete. In parallel, the cohort study from 1980 was adjusted to produce a new project that investigated the 20-year mortality among self-poisonings. In addition, the study of drugs of abuse from 2001 was organized by combining the plotting of the forms and the analyses to enable the data analyses to be performed. Since the data collection period has concluded, the main focus of the work has been on statistical analyses and writing papers. I have worked closely with Knut Erik Hovda, Fridtjof Heyerdahl and Tor Haldorsen, both in drafting the manuscripts and in performing the statistical analyses.

During the last three years as a medical student, I did research part time, in accordance with the Medical Student Research Program. Luckily, I was allowed to be part of the milieu, both at the Department of Acute Medicine, Ullevaal University Hospital and the Department of Behavioural Sciences in Medicine, University of Oslo. I graduated from the research programme in the autumn of 2006 but continued to work part time on this project through medical school and into my internship at SIHF Lillehammer.

The Medical Student Research Program required that I complete the mandatory courses and tests according to the PhD programme and that I present the results of our research at international congresses in our field. Therefore, I presented our results at annual conferences in suicidology organized by the International Association for Suicide Prevention

(IASP) since 2004, and at the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) in 2005. Together with other students at the Medical Student Research Program in Oslo, in 2005 I participated in the founding of the first national conference for medical students' research in Norway called Frampeik. In 2007, we founded the sequel called Frampeik Alumni.

Attempted suicide has been long recognized as a strong predictor of later suicide, and this group of patients has been closely studied in the field of suicidology. The main aim of this thesis was to study the group involved in self-poisoning irrespective of intention, to expand our perspective on self-destructive behaviour. Less is known about emergency department patients who have been evaluated as being non-suicidal. To answer the research questions raised by this thesis, six papers have been included. Although this is slightly more than usual, my hope is that all of them will provide useful information about this patient group. It is hoped that more knowledge about epidemiology and substance use, as well as psychiatric treatment and socio-demographic factors, will be helpful in understanding the background of these patients to identify and organize better treatment for those at special risk. The prognosis for such patients, both in the acute setting and in the longer term, needs to be studied. Hopefully, more precise diagnosis and knowledge of this patient group will be useful in any attempt to reduce the risk of suicide, in particular, and to reduce the overall mortality rate.

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This work was carried out in the Department of Behavioural Sciences in Medicine at the University of Oslo and in the Department of Acute Medicine at Ullevaal University Hospital. The Department of Behavioural Sciences in Medicine is an interdisciplinary department with teaching and research responsibilities in medical psychology, medical sociology, psychobiology and the doctor–patient relationship. The Department of Acute Medicine, which covers a broad range of emergency medicine, consists of an observational unit, an intensive care unit and a unit for general internal medicine. Both places have an extensive knowledge of self-poisonings, but from different perspectives based on research in suicidology and the behavioural sciences, and on treatment, care and clinical research. I am grateful for being allowed to be a part of these stimulating milieus, and for all the support and practical help given to me. I would like to thank all the co-workers in both departments for this assistance.

My supervisors were Professors Øivind Ekeberg and Dag Jacobsen. I am grateful to Øivind for his guidance, support and great knowledge, but most of all, I am grateful for the goodness, enthusiasm and care shown me throughout the entire project. Dag supported me during challenges in the clinical work of a large university hospital and impressed me with his extensive knowledge of toxicology. Øivind and Dag created an inspiring oasis for clinical research in the midst of a stressful and demanding clinical practice, which I found to be an impressive achievement.

I would also like to thank my co-authors, in particular Knut Erik Hovda and Fridtjof Heyerdahl at Ullevaal University Hospital and Tor Haldorsen in the Department for Biostatistics, for all their inspiring work and contributions. I also thank Erlend Hem in the Department for Behavioural Sciences in Medicine for his friendly support.

This work was supported by the Research Council of Norway and the Medical Faculty, University of Oslo, as part of the Medical Student Research Program at the University of Oslo. I am very grateful for the structure, support and student-friendly milieu offered by this programme, for which I would like to thank Jarle Breivik, Maje Siebke and all my fellow students.

I would also like to thank my fellow interns at Sykehuset Innlandet Lillehammer, who were very supportive during my internship.

My warmest thanks go to Tormod and my family, for all their support and care.

Lillehammer, August 2008
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LIST OF PAPERS

I. Hovda KE, Bjornaas MA, Skog K, Opdahl A, Drottning P, Ekeberg O, and Jacobsen D. **Acute poisonings treated in an Oslo hospital: A one-year prospective study (I): Pattern of poisoning.** Clin Toxicol 2008; 46:35-41.

II. Bjornaas MA, Hovda KE, Mikalsen H, Andrew E, Rudberg, N, Ekeberg O, Jacobsen D. **Clinical versus laboratory identification of drugs of abuse in patients admitted for acute poisoning.** Clin Toxicol 2006; 44: 127-134

III. Heyerdahl F, Bjornas MA, Hovda KE, Skog K, Opdahl A, Wium C, Ekeberg O, and Jacobsen D. **Acute poisonings treated in an Oslo hospital: A one-year prospective study (II): Clinical outcome.** Clin Toxicol 2008; 46:42-49.

IV. Bjornaas MA, Jacobsen D, Haldorsen T, Ekeberg O. **Mortality and causes of death after hospital-treated self-poisoning in Oslo: A 20-year follow-up study**. Clin Toxicol 2009; 47:116-23

V. Bjornaas MA, Bekken AS, Ojlert A, Haldorsen T, Jacobsen D, Rostrup M, Ekeberg O. **A 20-year prospective study on mortality and causes of death among opioid addicts in Oslo.** BMC Psychiatry 2008, 8:8 (13 February 2008)

VI. Bjornaas MA, Hovda KE, Heyerdahl F, Skog K, Drottning P, Opdahl A, Jacobsen D, Ekeberg O. **Suicidal intention, psychosocial factors and referral to further treatment – a one year cross-sectional study of self-poisonings.** Submitted.

The papers will be referred to by their Roman numerals.

1. INTRODUCTION

1.1 Self-poisonings

Acute poisoning is a frequent cause of hospitalization in industrialized countries (74). Acute poisonings can be defined as exposure to a drug or another agent in assumed toxic amounts leading to hospital admission (70). About 15 to 20% of the work load of medical units, and 10% of the workload of accident and emergency departments in the United Kingdom are due to acute poisonings (73). Self-poisonings accounts for the vast majority of acute poisonings. Jacobsen et al found in a study from 1980 that 98.3% of all acute poisonings were self-poisonings (70), and this thesis will focus on this patient group. Almost all acute poisonings are self-poisonings, and this term will be used in the following.

Self-poisonings is defined as an acute poisoning where the patient has taken the toxic agent, i.e. excluding accidental poisonings. For self-poisonings, suicidal behavior and substance abuse are the main reasons behind the poisonings. Many studies focus on subgroups of self-poisonings, such as suicide attempters (125), medically serious suicide attempters (12), deliberate self-harm (66), deliberate self-poisonings (24), non-fatal drug overdoses (101) and so on. The fundamental principle behind this classification is the correct evaluation of the intention. However, the evaluation of intention among patients presenting at the Emergency Department can be difficult; the patients are often comatose, unwilling to report the use of illicit drugs and even the ambivalence and instability in the wish to die can complicate the evaluation. The validity of the patients' own given reason for the self-poisoning has been questioned (51). Both suicidal behaviour and accidental self-poisonings as a result of substance use can be seen as aspects of self-destructive behaviour, the latter as "accident proneness" (108). Self-poisonings can therefore in many respects be studied as a single risk group. Intention may be studied as one of the factors characterising the patients, and the relationship to toxic agents, treatment, substance use, psychosocial factors and prognosis can be explored. When including all self-poisonings presenting at the Emergency Department, the generalization from the sample back to a well-defined background population is made possible.

1.2. Suicidal behaviour

Suicidal behaviour is a central term in the field of suicidology. The term suicidal behaviour as used in this thesis covers three main categories: suicidal ideation, suicide attempt and suicide[1].

There are alternative definitions, however, since the terms used in suicidology still are lacking consensus (93).

Suicidal ideation is usually equivalent to suicidal thoughts, and the terms cover thoughts about committing suicide. These thoughts may be spontaneously expressed to others, or confirmed, when the person concerned is asked (108).

Suicide attempts can be defined as "an act with non-fatal outcome, in which an individual deliberately initiates a non-habitual behaviour that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognized therapeutic dosage, and which is aimed at realizing changes which the subject desired via the actual or expected physical consequences "(WHO) (102). However, this definition is wide, and includes self-harm without necessarily a wish to die. The term has also been used equivalently to the term parasuicide (102), and will be referred to as the latter in this thesis. In Norway, the definition of suicide attempts given by Retterstol has been commonly used: "A suicide attempt is a conscious and deliberate act the individual has undertaken in order to injure himself, and which the individual could not have been entirely certain of surviving, but where the outcome was not fatal. A wish to die, however weak, has been present" (108) (Translated from Norwegian by M.A.B). Here, the act might have caused death without intervention, not self-harm, and a wish to die has been present, not merely a desire for changes. This corresponds to the understanding of the term suicide attempt which is used in this thesis, and will be used in the following. The term attempted suicide has been criticised because it is used to describe a behaviour that may lack any suicidal intention. This is not the case with the definition used above, as a wish to die needs to be present.

There are several definitions of suicide. In Norway, a commonly used definition of suicide has been as follows: "Suicide is a conscious and deliberate act, which the individual undertakes to injure him- or herself, and where the injuries have led to death" (108) (Translated from Norwegian by M.A.B). In the present study, the term suicide is used according to the ICD criteria at time of death for the subject. This is consistent with the classification of suicide on death certificates provided by Statistics Norway.

Table 1. Some terms used in the field of suicidology

Term	Definitions
Suicidal behaviour	Cover three main categories: suicidal ideation, suicide attempt and suicide (Wassermann, 2001)[1]
Suicidal intention	A wish to die
Suicidal ideation	Suicidal thoughts
Parasuicide	An act with non-fatal outcome, in which an individual deliberately initiates a non-habitual behaviour that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognized therapeutic dosage, and which is aimed at realizing changes which the subject desired via the actual or expected physical consequences (WHO, 1992)[2]
Suicide attempt	A suicide attempt is a conscious and deliberate act the individual has undertaken in order to injure himself, and which the individual could not have been entirely certain of surviving, but where the outcome was not fatal. A wish to die, however weak, has been present (Retterstol et al, 2002)[3]
Suicide	Suicide is a conscious and deliberate act, which the individual undertakes to injure him- or herself, and where the injuries have led to death (Retterstol et al, 2002)[4]
Intentional self-harm	As defined by ICD-10 X60-X84. The term includes "purposely self-inflicted poisoning or injury, and suicide (attempted)"[5]

Ambivalence is an important characteristic of suicidal behaviour (108). There is an aspect of ambivalence in most suicide attempts; "should I/should I not? " An example of this can be seen when a person ingests an almost lethal dose of a toxic compound, not a certain lethal dose, letting "fate" (for example, the intervention of others) decide the outcome. The

[1] Suicide - An Unnecessary death. Danuta Wassermann 2001. Page 18-19.
[2] Parasuicide in Europe: The WHO/EURO multicentre study on parasuicide. Platt et al, Acta Psychiatr. Scand. 1992.
[3] Selvmord – et personlig og samfunnsmessig problem. Retterstol et al 2002. Page 13.
[4] Selvmord – et personlig og samfunnsmessig problem. Retterstol et al 2002. Page 12.
[5] International Classification of Diseases (ICD) 10, Chapter X.

changes in intention over time is another aspect, as some persons ingest a lethal dose, but when they can feel the effect setting in, make contact with health care services or other people and hence survive. Furthermore, a common feature of suicidal behaviour is the aspect of communication. The suicide attempt can be seen as a message to an important other. In some cases this aspect is more obvious than in others, for example when some persons ingest a merely toxic dose when the important other (spouse, friend etc.) can see it. This aspect is included in the term parasuicide, as the aim of the act is to realize "changes which the subject desired". But this act would not necessarily mean a wish to die, and is therefore not always a suicide attempt. The act would be seen as an appeal for changes, not as a wish to die. In this thesis such acts will be referred to as acts of appeal.

Self-destructive behaviour is an important aspect of suicidal behaviour. Related to this is the "accident proneness"; persons who kill themselves over time by their ways of living (108). This is also known as to be "chronically suicidal" (108). Substance abusers can be seen as an example of this (see below).

It is estimated that worldwide between 500 000 and 1.2 million people die by suicide each year (United Nations, 1996)(65). In Norway, the suicide rate in 2006 was 16.9/100 000 for males and 6.0/100 000 for females[6]. A total of 532 persons committed suicide in 2006; 391 males and 141 females. Suicide attempts are many times more frequent, and only a small proportion of suicide attempters will eventually complete suicide (96). The lifetime prevalence of suicide attempts have been found to be 1 - 4% in some studies (75;100). However, this is probably an underestimation. For example, for the past 5 years in Norway, approximately 43 000 persons have died each year, of whom about 550 were suicides. These numbers give an approximately prevalence of suicide of 1-1.5% whereas suicide attempts occur much more frequently. Ystgaard et al found that among adolescents 15-16 years old, 6.6 % reported one or more acts of deliberate self harm over the course of the previous twelve-month period. Cutting and self-poisoning were most prevalent (135). The life time prevalence of suicide attempts is therefore probably higher than the minimum numbers given above.

The methods used for suicide and suicide attempts are somewhat different, as some methods are more lethal, such as hanging and shooting. In suicide attempts, methods are mostly "non-violent", as the persons survive. In the WHO/EU Multicentre Study of parasuicides, 64% of males and 80% of females used self-poisoning (here, the terms parasuicide and suicide attempt was used equivalently, according to the definition of parasuicide, see page 14) (84).

[6] http://www.ssb.no/emner/03/01/10/dodsarsak/tab-2008-06-27-08.html

Most suicide attempters will never commit suicide. There has been questioned whether suicide attempters and those who commit suicides are two populations or one. Beautrais found in a case-control study in 2001 that there were common risk factors for the groups such as current mood disorder, previous suicide attempts, prior outpatient psychiatric treatment, admission to psychiatric hospital within the previous year, low income, a lack of formal educational qualifications, and exposure to recent stressful interpersonal, legal and work related life events (10). Statistically significant differences were found, however, showing that suicides were more likely to be male, older, and to have a current diagnosis of non-affective psychosis. Suicides and suicide attempts can therefore be seen as two overlapping populations that share common psychiatric diagnostic and history features, but are distinguished by gender and pattern of psychiatric disorder. More males commit suicide, whereas more females attempt suicide –this is known as the gender paradox in suicide (23).

Harris et al found in a meta-analysis that virtually all mental disorders have an increased risk of suicide excepting mental retardation and dementia (54). The suicide risk was highest for functional and lowest for organic disorders with substance use disorders lying between. However, within these broad groupings the suicide risk varies widely.
Psychiatric disorders among those who make serious suicide attempts have been studied. Beautrais et al found that 90.1% had a mental disorder at the time of the attempt (12). Mood disorders, substance use disorders, and personality disorders were more common than among controls. The incidence of co-morbidity was high: 56.6% of those who made serious suicide attempts had two or more disorders. The risk of a suicide attempt increased with increasing psychiatric morbidity: subjects with two or more disorders had odds of serious suicide attempts that were 89.7 times the odds of those with no psychiatric disorder. A WHO-study of parasuicides found that subjects with physical illnesses considered psychiatric symptoms and disorders to be relevant factors in triggering suicidal behaviour, and more so than non-sufferers (34). Furthermore, Hawton et al found a considerable co-morbidity between axis I and II disorders: Co-morbidity of psychiatric and personality disorders was present in 49 patients (44%) (62). More patients with co-morbid disorders had made previous suicide attempts, and were more depressed and hopeless, reported more episodes of aggression, were more impulsive, and had lower self-esteem and poorer problem-solving skills. Co-morbidity may therefore contribute to greater suicide risk.

1.3 Substance use

Substance use disorders includes *a pattern of psychoactive substance use that is causing damage to health* (see drug dependence syndrome, International Classification of Diseases (ICD) -10, table 2 (1)). In ICD-10, chapter F10-F19 contains a wide variety of disorders that differ in severity and clinical form but that are all attributable to the use of one or more psychoactive substances, which may or may not have been medically prescribed.

According to ICD-10, identification of the psychoactive substance should be based on "as many sources of information as possible. These include self-report data, analysis of blood and other body fluids, characteristic physical and psychological symptoms, clinical signs and behaviour, and other evidence such as a drug being in the patient's possession or reports from informed third parties". Therefore, the classification of substance use disorders is based on an evaluation of all available information regarding the use of psychoactive substances, and not one form or scale in particular.

The extent of use, and hence the proportion of abuse, is hard to evaluate. The European Monitoring Centre for Drugs and Drug Addiction[7] estimated in 2002 that up to 28% of Norwegians aged 21-30 had ever tried cannabis, 8% amphetamine, 6% cocaine, 5% ecstasy, 1 % GHB and 1% heroine. This was based on a National Questionnaire Survey conducted by the Norwegian Institute for Alcohol and Drug Research (Statens instituttt for rusmiddelforskning, SIRUS). Injecting drug users is another term used in the field, but the methodology used gives only highly uncertain estimates. The number of injecting drug users were, however, estimated to be 9 000 – 12 000 in Norway in 2001, of whom the majority injected opioids and 10% amphetamine. Alcohol was not included in this survey, nor was prescribed medication such as benzodiazepines. Of the numbers mentioned above, a smaller proportion of the population will have pattern of use corresponding to the term substance abuse.

[7] http://www.emcdda.europa.eu/html.cfm/index55188EN.html

Table 2. Diagnoses in ICD-10 related to substance use: Mental and behavioural disorders due to psychoactive substance use (F10-F19)

Terms	**Definitions**
Acute intoxication	A condition that follows the administration of a psychoactive substance resulting in disturbances in level of consciousness, cognition, perception, affect or behaviour, or other psycho-physiological functions and responses. The disturbances are directly related to the acute pharmacological effects of the substance and resolve with time, with complete recovery, except where tissue damage or other complications have arisen. *Excludes:* intoxication meaning poisoning (T36-T50).
Harmful use	A pattern of psychoactive substance use that is causing damage to health. The damage may be physical (as in cases of hepatitis from the self-administration of injected psychoactive substances) or mental (e.g. episodes of depressive disorder secondary to heavy consumption of alcohol).
Dependence syndrome	A pattern of psychoactive substance use that is causing damage to health. The damage may be physical (as in cases of hepatitis from the self-administration of injected psychoactive substances) or mental (e.g. episodes of depressive disorder secondary to heavy consumption of alcohol). The dependence syndrome may be present for a specific psychoactive substance (e.g. tobacco, alcohol, or diazepam), for a class of substances (e.g. opioid drugs), or for a wider range of pharmacologically different psychoactive substances.
Withdrawal state, with or without delirium	A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a psychoactive substance after persistent use of that substance. The onset and course of the withdrawal state are time-limited and are related to the type of psychoactive substance and dose being used immediately before cessation or reduction of use. The withdrawal state may be complicated by convulsions. Delirium: as defined in F05.

Binger et al found that in a Emergency Department, 6.9% of all patient attendances were directly or indirectly related to illegal drug use, and the majority were acute injuries, overdose, and the medical complications of drug use (17). In addition, polydrug use is very common among patients treated for acute poisonings (129), and is seen frequently in fatal poisonings (49).

Substance users can be viewed as an important risk group for suicidal behaviour. The "accident proneness" which follows a long career as a substance user is considerable (108). Rossow et al found more suicide attempts among substance users who had overdosed, and the number of life-threatening overdoses and number of suicide attempts were associated (111), illustrating the risk-taking behavior and the carelessness which may be seen as a part of a self-destructive behavior.

Substance use disorders, alcohol included, is the second most frequent psychiatric precursor to suicide, only exceeded by depressive disorders (88). It is found in one fifth to one half of the cases. There is a substantial co-morbidity between drug dependence and affective disorders (89), and major depression has been seen as a late complication of alcoholism much more often than the other way around. Other substances have gained popularity in the past decades, but less is known about their relationship to psychiatric disorder. However, there is a known co-morbidity between cannabis (121), opioids (27), substance use in general (32) and a variety of mental disorders. Furthermore, substance use disorders is found to complicate nearly all of the diagnosed personality disorders identified retrospectively in suicides (112). Bakken et al found in a study of suicide attempters seeking substance use treatment, that 19% of the patients had new suicide attempts in a six-year follow-up (5). There was no difference between those who then had quit using drugs and those who were still using them.

1.4 Epidemiology of self-poisonings

Epidemiology is defined as all the elements contributing to the occurrence or nonoccurrence of a disease in a population[8]. In some contexts it is defined as the branch of medicine that investigates the causes and control of epidemics. In this thesis, however, the first definition will be used.

The evaluation of toxic agents in self-poisonings is a crucial element in the epidemiology of self-poisonings. The development of new drugs and a changing pattern in substance abuse may have changed the diagnostic panorama (67), and the impact on the

[8] http://www.yourdictionary.com/epidemiology

diagnostic evaluation and the clinical course of the patients need to be explored. The patterns of toxic agents changes over time (80;115). The diagnosis regarding toxic agents in self-poisonings is made by the physician on duty. Today, laboratory tests are secondary to clinical assessments, and normally include screening tests for ethanol, paracetamol and acetylsalicylic acid only. Knowing the patterns of toxic agents in a population supports the evaluation of which toxic agents the patient has taken. Previous studies suggest that there is a good correlation between clinical suspicion and laboratory findings (87;116). However, information about new patterns of toxic agents is scarce, and the emerging use of γ-hydroxy butyric acid (GHB) (43) and ecstasy (131) need to be assessed, as well as changes in prescriptions regarding new antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (47;119), and regulatory withdrawal and prescription recommendations for barbiturates (28;41).

Although the treatment of self-poisonings is mainly symptomatic, a correct evaluation of the toxic agents would optimize treatment and aftercare. However, the clinical impact of an imprecise diagnosis in these patients is being questioned. It is claimed that an inaccurate diagnosis is not affecting mortality (87), nor being the cause of complications (103). However, knowing the correct diagnosis could enable optimal treatment of acute poisoning by reducing the need for supervision and costly treatments and facilitating the identification of cases that require prompt drug-specific treatment (68;87;103;129). The use of antidotes has increased during the last decades, and the specificity of this use needs to be addressed. Thus, both morbidity and costs may be reduced.

Drugs of abuse are of special interest, as the use of illicit drugs may indicate substance use disorders. Emergency departments can be important venues for detecting persons in need of substance use treatment (110). Thus, correct evaluation of toxic agents is important in tailoring proper aftercare for these patients. Furthermore, underestimation of drugs of abuse can partly explain why antidotes do not reverse the effects of the suspected toxic agent in some cases.

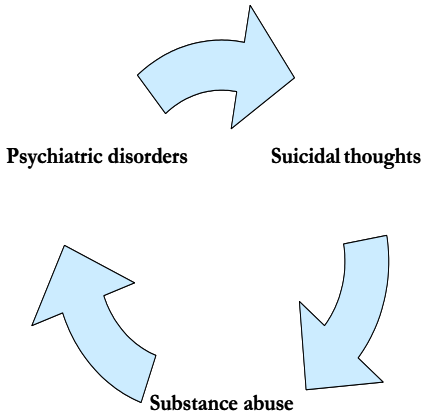
1.5 Self-poisonings and the risk of later suicide

A previous suicide attempt is the strongest known predictor of later suicide (54). Furthermore, there is a considerable co-morbidity between psychiatric disorders and substance use, and substance use is an independent risk factor for later suicide among suicide attempters (59). Both suicide attempts and suicides occur more frequently among heroine users (31) and chronic alcohol consumers (58), which emphasizes the need to address both the intention and the history

of substance abuse when a patient presents with self-poisoning (49).

The problems of substance use and suicidality are related, see figure 1. Among suicide attempters, alcohol or drug abuse has been found to be a strong risk factor for completing suicide (29). Among patients treated for drug dependence, a large proportion has attempted suicide (2). The co-morbidity between substance use disorders and mental illnesses are described both as an association between substance use and mental illnesses and between known risk factors both for substance use and suicide, such as being male, living alone and unemployment (60;63).

Figure 1. Relationship between variables



Evaluating suicide risk in a patient is a complex task. It is a paradox that many of the factors recognized as risk factors for suicidal behavior are commonly seen among the general population. Combined with the low base line of suicides, the prediction of which patients who will eventually commit suicide is inaccurate. The number of false positives is high (48). However, the risk factors are important in the evaluation of the suicidal patient, the idea being that the more risk factors, the stronger the risk for suicide. More than 60 risk factors have been identified (109).

This may be seen as the background for risk-factor research. According to Amsel and Mann (4) ”the goals of this type of research are focused on prevention in populations, its methodology is probabilistic and not deterministic, it seeks to operationalize its concepts and it is concerned with modeling the intervening paths between a risk factor and its associated

outcome." Risk factors may be used to divide the population in two groups in which the probabilities of the outcome, i.e. suicide, and therefore identifying a high risk group. "The key is to identify a subgroup of the population sufficiently enriched for the adverse outcome such that a preventive intervention can have a measureable impact" (4). In the context of suicidology, identifying a high risk group will be important for prevention, such as referral to further treatment. Both mortality in general and suicide in particular may be used as outcome variables.

Table 3. Some commonly recognized risk factors for suicide[9]

Risk factors for suicide	Increased suicide risk
Demographic factors	
Gender	Males > females
Age	M: after 70 yrs. F: highest risk 40-60yrs
Living conditions	Living alone > living in a family
Migration	Immigration
Psychiatric factors	
Psychiatric illness	Depression
	Personality disorders
	Psychosis
	Substance use disorders
Previous suicide attempts	Previous attempt or appeals
Social factors	
Parental divorce	If occurring < 15 yrs
Employment status	Unemployment
Socioeconomic class	High or low social class
Survivors	Suicides among relatives or close friends

Given several reports on the risk factors for suicidal behavior, one would expect the suicidal patients to differ from the non-suicidal patients treated for self-poisonings in these respects. The number of risk factors would be expected to be increased among the suicidal compared to the non-suicidal patients, but this has not been evaluated systematically for self-poisonings. The main focus for research has been the immediate risk of suicide, i.e. in the

[9] Selvmord – et personlig og samfunnsmessig problem. Retterstol et al. 2002. Chapter 7, 8, 11 and 13.

short term. Less is known about the importance of risk factors at admission for increased risk of suicide in the long term.

A history of a suicide attempt indicates an increased suicide risk both in the first years after the episode (57), and over the long term (123;125). Owens et al found in a meta-analyses of risk of suicides following self-harm that the strong connection between self-harm and later suicide lies somewhere between 0.5% and 2% after one year and above 5% after nine years. Suicide risk among self-harm patients is more than hundred times higher than in the general population (95). The suicide rate varies from 2% 10 years after deliberate self-poisoning (107) to 11% 10 years after a serious suicide attempt (99). A 37-year follow-up study of 100 suicide attempts by self-poisoning in Finland found a suicide rate of 13% and an elevated suicide risk over the entire adult lifetime (125). A 22-year follow-up study of suicide attempters from psychiatric services in London, reported similar trends, but in a different population – suicide attempters referred to psychiatric wards (72).

The diversity in definitions and inclusion criteria in different studies is problematic. The different inclusion criteria make the results harder to compare, but also to turn into recommendations for clinical practice. Is a medically serious suicide attempt to be seen as a more profound wish to die, and therefore at special risk for later suicide? Does the patient's choice of toxic agent always reflect the seriousness of the intent? If so, the level of complications would be seen as a marker of increased suicide risk. But studies of self-poisonings have found predictors of later suicide to be unspecific (3), and further studies of clinical predictors of patients at special risk are needed. When evaluating the suicidal intent by using a psychiatric scale, this is found to be of value for identifying those at special risk (56). However, the use of psychiatric scales and surveys in a study of patients treated in an Emergency Department is problematic, as long as the referral to psychiatric services is done by the physician on duty, mostly residents in internal medicine. Their evaluation of intent is the gatekeeper of admission to psychiatric services, and is a result of complex decision making (24), but often not with the help of psychiatric surveys. Furthermore, if focusing solely of the wish to die, other risk factors for suicide might be overlooked. Groholt et al found that among adolescent suicide attempters, the morbidity among those with no wish to die was high regarding psychosocial problems and substance abuse (51). The need for follow-up among patients with no intent to die may therefore be underestimated.

1.6 Self-poisonings and mortality

Individuals who self-poison can be seen as a risk group for increased mortality in general. Excess mortality of suicide attempters by natural and unnatural causes has been noted after five years

(11;94), eight years (57), 10 years (91), and 12 years (124). The risk was increased for death in genereal, but also for specific causes such as suicide, homicide, accidents and diseases (94). Both Ostamo et al and Nordentoft et al concluded that the risk factors found were not specific enough to predict who would eventually commit suicide, nor who had increased risk of premature death (91;94). Preventive measures must therefore be directed towards most suicide attempters.

The same pattern of excess mortality is seen in drug abusers, both over the short term (49) and in a 20-year follow-up study (97). Mortality rates among opioid addicts are higher than for the general population, although there are differences between countries and regions. Standardized mortality ratios (SMRs) vary from 15 times higher than expected for male drug users in Rome (7), 22 times higher for drug injectors in Glasgow (44) to 28.5 times higher for heroin addicts in Catalonia, Spain (118).

The majority of deaths among opioid addicts are from accidental poisonings (97), but death by other unnatural causes such as suicides are also increased (76;98). The AIDS epidemic has also had a major effect on this group of patients during the last decades (105). Although there has been found an increasing mortality among opioid addicts from 1980 to 1988 (33), but the emerging of AIDS can only partly explain this increase (35). A four-year prospective study of cause-specific mortality rates among opioid addicts has been done, but standardized mortality ratios were not obtained (49). Longer prospective follow-up studies show how overall mortality changes over time (46), and there would be expected that also cause-specific mortality differ between the long-term versus short-term follow-up. However, no such studies exist for this group of patients.

1.7 Referral to further treatment

The intention has traditionally a major impact on the referral of patients to secondary follow-up after treatment of the actual self-poisoning: Being referred for specialist follow-up reduces the risk for repetition (20). The well-known risk of further suicidal behaviour in patients reporting a suicidal intention has led to psychiatric follow-up of these patients. The group reporting substance abuse is less likely to receive psychiatric follow-up (21), although the co-morbidity of substance abuse and psychiatric disorders is well known (12). Differences in referrals would be expected, as different approaches probably are needed. But Suominen et al found that even suicide attempters were less likely to receive psychiatric follow-up when they reported substance abuse disorder (22). Further, it has been questioned whether or not the morbidity of the substance users treated in the Emergency Department has been underestimated (23).

In spite of the increased mortality and hence the need for intervention, Cook et al found that 67% of patients referred to The Emergency Department because of acute opioid overdose were not referred to any therapeutic programme for drug addiction (26). Throughout the last decades, studies have focused on abstinence versus continued use after different treatment programmes as an outcome measure (106), but the question remains whether or not this has an effect on mortality in the long term. Sorensen et al found in a 15-year follow-up that people who had achieved stable abstinence from injecting narcotics use were at lower risk of premature death than people with continued drug use (122). But even in the presumed abstinence group, standardized mortality ratio (SMR) was increased seven-fold. This raises the question whether or not referral to a detoxification programme has the desired effect on long term mortality in this group.

2. RESEARCH QUESTIONS

The aim of this thesis is to study self-poisonings treated at the Emergency Department as a single risk group. The pattern of toxic agents, the extent of substance use and the psychosocial risk factors among these patients need to be investigated. The long-term prognosis will be studied, as well as the follow-up treatment offered. The thesis tries to answer six main research questions:

1. What are the patterns of toxic agents, especially for drugs of abuse, according to age and gender for patients admitted to medical departments for acute poisoning during one year in Oslo? (Papers I and II)
    i. What is the annual incidence of acute poisonings in Oslo in 2003/04?
    ii. What are the patterns of toxic agents according to intention?
2. What is the concordance between the clinical assessments (including patient history) by the physicians on duty and the drug analyses in patients treated for acute poisonings? (Paper II)
3. What kind of treatment is offered to the patients in the acute setting and to what extent are the patients referred to follow-up services at discharge? (Paper III and VI)
    i. What is the clinical outcome for these patients in terms of morbidity, mortality and sequelae?
    ii. Are there changes in the clinical course of these patients compared to a similar study from 1980?
    iii. Are there differences in referral to follow-up services according to intention?
4. Are there differences in psychosocial factors, history of substance use and referral to follow-up services at discharge according to the intention of the self-poisoning? (Paper VI)
5. What are the 20-year overall and cause-specific mortality rates for all patients admitted to medical departments for self-poisoning in Oslo in 1980, and for hospital-treated opioid addicts in particular, compared to those for the general population? (Papers IV and V)
    i. Are there differences in mortality between opioid addicts voluntarily admitted for detoxification and those admitted solely for self-poisonings?
6. What factors might differentiate those who died in the follow-up period from those who survived, and what factors might predict suicide or other causes of death? (Paper IV)

3. MATERIAL AND METHODS

3.1 Materials

Five different samples, although some of them overlapping, are studied in this thesis:

Table 4. Overview of the materials included in the thesis

Paper	Inclusion	Year	N	Area	Median age	Females	Design
I , III	Acute poisonings	2003/04	947	All medical departments in Oslo	36	54%	Cross-sectional
II	Acute poisonings	2001	405	Ullevaal university hospital	31	48%	Cross-sectional
IV	Self-poisonings	1980	946	All medical departments in Oslo	31	51%	Prospective cohort
V	Opioid† addicts	1980/81	185	All medical departments in Oslo	24	47%	Prospective cohort
VI	Self-poisonings††	2003/04	908	All medical departments in Oslo	36	54%	Cross-sectional

† Only self-poisonings classified as opioid addicts in the sample from paper IV are included

†† The sample corresponds to paper I and III, but accidental non-self-poisonings are excluded

3.1.1 Inclusion criteria

The main inclusion criteria in paper I-IV and VI were exposure to a drug or another agent in assumed toxic amounts leading to hospital admission in adults (≥ 16 years). Exclusion criteria were chronic poisoning and patients with other *primary* diagnosis, such as pneumonia, even if there was an additional self-poisoning. The intention behind the self-poisoning was evaluated

in all papers except paper II, but patients were included irrespective of intention. Patients leaving the emergency room after treatment were also included.

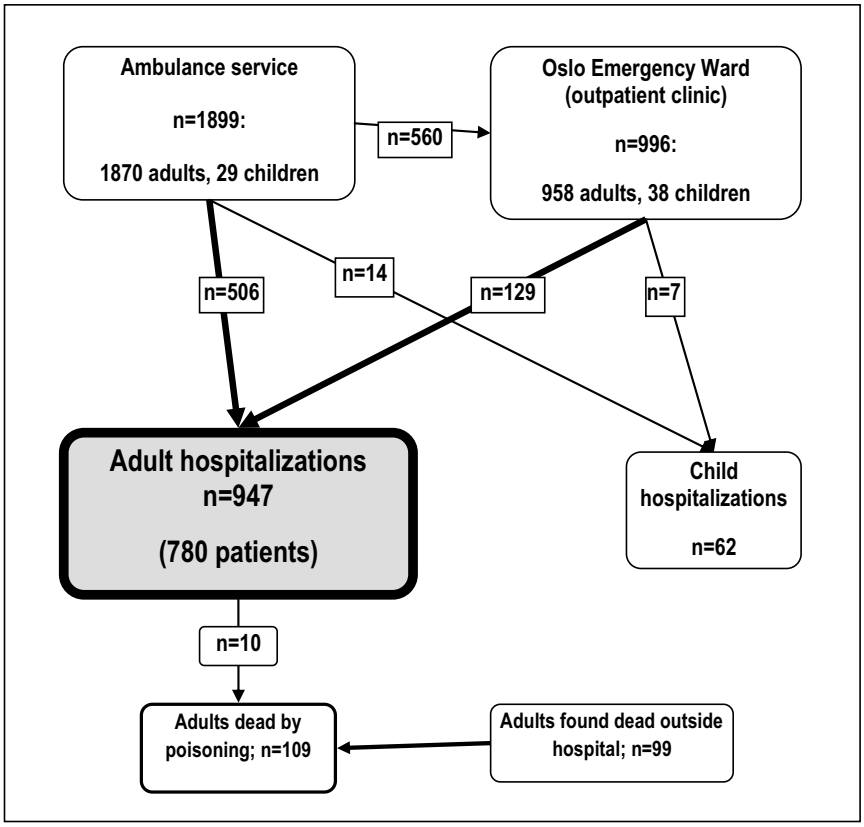
The terms *acute poisoning* and *self-poisoning* are overlapping. The difference is that *accidental non-self-poisonings* such as fire accidents (i.e. CO as the toxic agent), occupational accidents (i.e. gas exposure etc.) and taking prescribed medication in wrong doses (misspelling of the prescription, wrong dosage administered from nurse and so on) are included in acute poisonings, whereas these patients are excluded from the samples of self-poisonings.

Two patient groups are included in paper V. Firstly, from the cohort of self-poisonings in the 1980 cohort study, all patients classified as opioid addicts are included. Secondly, all opioid addicts admitted for voluntarily detoxifications in 1980 and 1981 in Oslo are included. Thus, the cohort consists of all hospital-treated opioid addicts in Oslo in 1980, and all voluntarily detoxifications from 1981 as well, in order to obtain comparable groups.

Paper I, III and VI: Acute poisonings/self-poisonings in 2003/04

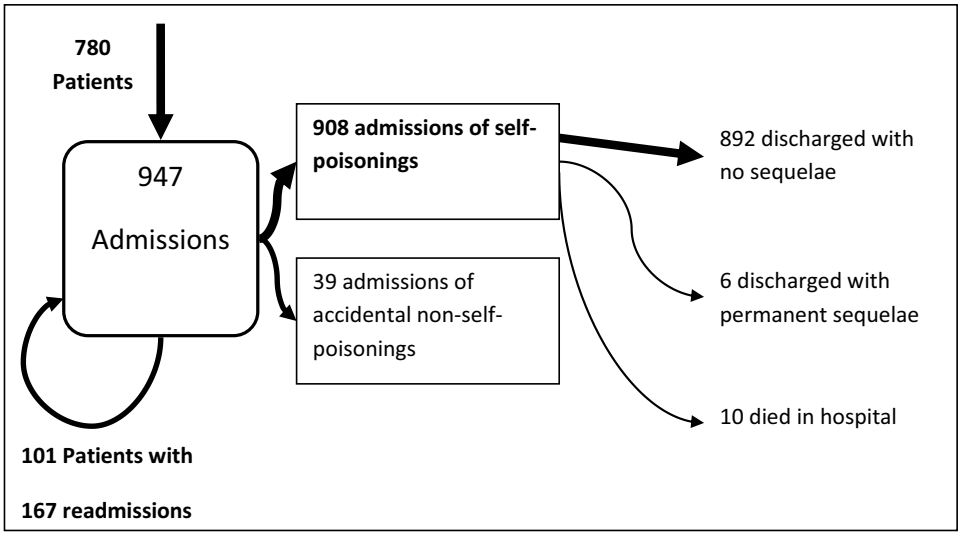
The study population in these papers was part of a larger prospective cross-sectional multi-centre study performed from April 1st 2003 until March 31st 2004, involving all four hospitals in Oslo, including the pediatric departments, and the Oslo Emergency ward (outpatient clinic), the ambulance service, and the Institute of Forensic Medicine (Figure 2). From the larger sample, the study population in these papers consists of all *hospital-treated* admissions in adults (older than 16 years) for self-poisonings during the study period. The form which was used in the study is included in the appendix.

Figure 2. Acute poisonings in Oslo in 2003/04



Physicians obtained data by completing a standardized form the morning after admission, or as soon as the patient was ready for an interview. For patients who never woke up or had cerebral damage, data were obtained from the medical file after consent from relatives. In paper VI, the intention, psychosocial factors and plans for further treatment, i.e. referral, are studied for self-poisonings only, compromising 95.9% of the acute poisonings (Figure 3). Accidental non-self-poisonings are excluded from further analyses. There were 39 such cases which were excluded because of this; including carbon monoxide poisonings caused by fire accidents (n=13), taking prescribed medication in wrong doses according to a misunderstanding (n=24), and forced intake or accidental poisoning (n=2).

Figure 3. Self-poisonings in Oslo 2003/04 treated in hospital (included in paper VI)



Paper II: Acute poisonings in 2001

This sample included all patients admitted to the Department of Acute Medicine at Ullevaal University Hospital in Oslo, Norway, because of an acute poisoning between January 1 st and December 31 st 2001. Ullevaal University Hospital covers about 140 000 inhabitants of Oslo, in addition to seriously poisoned patients from other parts of Oslo as well.

Both a completed form and a urine or blood sample were needed to do the comparison, and if either a form or a urine or blood sample was missing, the patient was excluded from further analyses. The comparison was possible in 320 cases, and 79% of the patients were included in further analyses.

The physicians were informed to write down all suspected toxic agents, not differentiating between main and additional agents. They were asked to include all suspected agents, and were not aware that drugs of abuse were the main purpose of the study. The treating physicians did not know the results of the urine or blood screening. Urine sample was obtained if possible, either in the Emergency room or later when the patient had moved to another unit. If a urine sample was not obtained, a blood sample was taken.

Paper IV and V: Self-poisonings in 1980 and voluntary detoxifications in 1981

From a cohort of acute poisonings in 1980 (70), all accidental non-self-poisonings were

excluded. The remaining patients consisted of all hospital-treated self-poisonings in Oslo in 1980, and included 98.3% of the acute poisonings. Six patients were foreigners who could not be traced and were excluded. Thus, the cohort included 946 patients, 51% of whom were females. The median age was 31 years (range 13–93 years). The first or the most serious admission (i.e., relating to the toxic agent and the amount taken) was chosen as the index episode. The mortality in the cohort has been studied after 5 and 10 years by Ekeberg et al (38;39).

All patients treated for self-poisonings who were classified as opioid addicts in 1980 were included in paper V. In addition, all opioid addicts admitted to Ullevaal University Hospital for voluntarily detoxification during 1980 and 1981 were included in the study. The present cohort consists of 185 opioid addicts either treated for self-poisoning (n=93), voluntary detoxification (n=75) or both (n=17). Those who were admitted both for self-poisonings and for detoxification were classified as voluntarily detoxifications in further analyses, as a marker of their willingness to undergo further treatment and rehabilitation.

Patients were followed to death, emigration or to the end of year 2000, whichever occurred first.

3.2 Methods

3.2.1 Design of studies

Paper I, II, III and VI are prospective cross-sectional studies, and paper I and III are studying the same sample. Paper VI studies a major subgroup from this sample. Paper IV and V are prospective cohort studies and paper V studies a subgroup of opioid addicts from paper IV in addition to opioid addicts admitted for voluntary detoxification.

3.2.2 Variables

Table 5. Variables included in the papers

	Paper I	Paper II	Paper III	Paper IV	Paper V	Paper VI
Age	x	x	x	x	x	x
Gender	x	x	x	x	x	x
Main toxic agent	x		x			
Toxic agents		x				
Evaluation of intention	x		x	x		x
Consciousness	x		x	x		
Respiratory insufficiency			x			
Hypotension			x			
Cardiac arrhythmias			x			
Hypothermia			x			
Hypoglycaemia			x			
Use of antidotes			x			
Drugs of abuse		x				
Drug dependence				x	x	
Socio-economic groups				x		
Main cause of death				x	x	
Marital status						x
Living conditions						x
Country of origin						x
Employment status						x
Education						x
Previous suicide attempts						x
Psychiatric treatment						x
Substance use						x
Follow-up services						x

Age and Gender

In paper I, II, III and VI, patients older than 16 years at time of admission were included. In paper IV and V, patients older than 15 years were included. In all papers except paper II and VI, the patient's age was used as absolute numbers in the analyses, and no age categories were made. In paper VI, the sample was divided in age groups for further analyses, in order to study differences between age groups. The categories were 16-29 years, 30-49 years and ≥50 years. Gender was recorded.

Main toxic agent

The main agent was defined as the substance supposed to be most toxic in the amounts taken: The physicians made an overall evaluation of the substance thought to cause the most severe toxicity based on information from patients, bystanders, clinical manifestations and routine laboratory analyzes. Other ingested agents were defined as additional agents.

Toxic agents

Toxic agents were defined as any substance supposed to be toxic which might contribute to the patient's condition. The physicians were informed to write down all suspected toxic agents, not differentiating between main and additional agents.

Evaluation of intention

The physician's evaluation of the reason for the poisoning was based on all information available; including the patient's own reported intention. Special attention was paid to possible written letters confirming their suicidal intent, supposed lethal doses of the toxic agent, or other active procedures to secure a lethal outcome, for example intake in remote places, or hiding themselves after intake. Information from other sources like ambulance personnel and companions were also used when available. Thus, the evaluation of intention was defined to these categories:

1. Suicide attempt (definite or possible)
2. Appeal
3. Accidental poisoning as a result of substance use / drug-related poisoning
4. Accidental non-self-poisonings

Category 4 is included in acute poisonings (paper I, II and III), but patients evaluated to be in this category are excluded from self-poisonings (paper IV, V and VI). This included fire accidents (i.e. CO as the toxic agent), occupational accidents (i.e. gas exposure etc.) and

taking prescribed medication in wrong doses (misspelling of the prescription, wrong dosage administered from nurse and so on). Manual inspection of the journals revealed these categories to fit well.

In paper VI, the patient's own evaluation of intent was recorded, and the patient was given eight different possibilities: intention to die, to escape from problems, to make impact on personal relationships, drug-related poisoning, do not remember, do not want to give information, other reasons and unknown. Only one category was chosen for each patient. Subsequently these answers were grouped into the following categories: suicide attempt (intention to die), appeal (to escape from problems and to make impact on personal relationships) and drug-related poisoning (the same category was used). Other answers were excluded from the studies of agreement.

Consciousness

In paper I and III: Consciousness was classified according to the following classification: (1) awake, (2) somnolent – can be kept awake when stimulated, (3) coma, response to painful stimuli and (4) deep coma, no response to painful stimuli. Coma and deep coma corresponded to Glasgow Coma Score <8.

In paper IV: Consciousness was classified according to the following: (1) awake; (2) soporous; (3) somnolent – can be kept awake when stimulated; (4) coma – response to painful stimuli; and (5) deep coma – no response to painful stimuli. Coma and deep coma corresponded to a Glasgow Coma Score < 8.

Clinical variables

Respiratory insufficiency was defined as either arterial blood-gas analysis showing respiratory acidosis by standard criteria (pH<7.3, pCO_2>7.0 kPa) or hypoxia (pO_2<8.0 kPa), or clinical need for ventilation support. Hypotension was defined as systolic blood pressure below 85 mmHg in at least two subsequent measurements. Cardiac arrhythmias were registered from the cardiac monitoring screens or EKG. Conduction disturbances were classified as arrhythmia, but sinus tachycardia was not. Cardiac arrest was classified as such, not as arrhythmia. Hypothermia was defined as body temperature below 35ºC and hypoglycaemia as serum-glucose level below 3.5mmol/L. Further criteria were according to general clinical terminology. The use of antidotes and treatment were recorded.

Drugs of abuse

The term "drugs of abuse" include prescribed medication (benzodiazepines, opiates), illicit drugs (cannabis, cocaine, ecstasy, GHB, amphetamine, opiates) and ethanol. The patients might have taken other drugs as well, but this was not investigated.

Drug dependence

Classification of abuse was based upon patient interviews and records. The basic criteria included information on daily or regular use of the respective compound or its substitute (i.e., barbiturates for heroine), including withdrawal symptoms if the compounds were not administered. This was therefore based upon all information available, in accordance with the ICD criteria, see page 19.

Socio-economic groups

Education level and income were used to define four socio-economic groups based on education and yearly income, where socio-economic group 1 was considered the highest and 4 the lowest. For those under 30 years of age the same parameters in the parents in part also determined the social class. Of the couples included, the person with the highest social score determined the social class for both subjects.

Main cause of death

The underlying cause of death was chosen as the main cause of death, according to the criteria given both by International Classification of Diseases (ICD) and Statistics Norway. This corresponded to the classification of causes of death in the reference population provided by Statistics Norway (table 7). Death certificates were based on forensic autopsy records in all cases that were not due to natural causes of death. ICD-8 was used for deaths occurring before 1987, ICD-9 for deaths from 1987 until 1996, and ICD-10 for deaths from 1996 to 2000.

Table 6. Classification according to the ICD system

	ICD-8 (1969-85)	ICD-9 (1986-95)	ICD-10 (1996-)
All causes	001-989	001-E989	A00-Y89
All diseases	001-796	001-799	A00-R99
Cancer	140-209	140-208	C00-C97
Cardiovascular diseases	390-441.1 444.3-458 782.4	390-459	I00-I99
Accidents	E800-E929 E940-E942	E800-E929	V01-X59 Y85-Y86
Suicides	E950-E959	E950-E959	X60-X84 Y87.0
Other violent deaths	E930-939 E960-989	E930-958 E960-989	Y88-89

Psychosocial factors

Socio-demographic variables recorded were marital status, living conditions, country of origin according to place of birth or parental place of birth, occupational status and education (highest degree completed according to the Norwegian education system).

Previous suicide attempts and psychiatric treatment (both current and former) were recorded, as reported by the patients. For former psychiatric treatment, the highest level of treatment was used in further analyses, i.e. psychiatric ward admission was rated higher than psychiatric outpatient treatment. The patients were asked to report the frequency of their substance use, and what kind of substances they were using.

Follow-up services

The categories for referral were: General Practitioner (GP), suicide prevention team, substance abuse treatment, psychiatric outpatient clinic, psychiatric ward (voluntarily or involuntarily), other arrangements, left hospital against medical advice and discharge without any plans for aftercare. More than one category could be offered each patient.

3.2.3 Chemical analyses (Paper II)

Blood or urine samples were obtained from each patient, and frozen (-20 ° C) for later analyses. Analyses were performed at the Department of Clinical Chemistry, Ullevaal University Hospital.

Urine samples were analyzed for amphetamine, benzodiazepines, cannabis, cocaine and opiates using an immunologic assay. The samples were analyzed for ethanol using an enzymatic assay. Analysis of ecstasy in urine was based upon fluorescence polarization immunoassay (FPIA) and if above cut-off (250ng/mL), by gas chromatography with mass spectrometer (GC-MS) GHB was measured by a gas-chromatographic method with flame ionization detection (GC-FID) and a head-space-injector

If the sample was positive for amphetamine, the cut-off value for ecstasy was set to 250ng/mL and the sample was analysed using GC-MS. This method would specify the presence of amphetamine, methamphetamine, MDMA and/or MDA in the sample. With the exception of amphetamines, the initial screening was not confirmed by a second test.

Serum analyses of benzodiazepines, cannabis, opiates and cocaine were performed as for urine, except for the reagents. Ethanol, GHB, amphetamine and ecstasy in serum was measured almost the same way as for urine; see paper II for further details. The immunologic methods gave semi-quantitative answers only. Although the chromatographic methods for amphetamine and ecstasy gave quantitative answers too, we only used qualitative results in the statistical analyses. The relative importance of each substance was therefore not evaluated.

3.2.4 Statistical analyses

The standardized registration forms were optically scanned and processed using TeleForm Desktop version 9.1 (TeleForm, Verity Inc., Sunnyvale, California) in paper I, III and VI. In paper II, IV and V the variables were plotted manually in SPSS (SPSS Inc., Chicago, IL, USA). In paper IV and V, data were analysed using programs for survival analysis and for Cox regression analysis in Stata (StataCorp 2003, Stata Statistical Software Release 8.0, Stata Corporation, College Station, TX, USA). For all other data analyses, SPSS version 12.01 – 16.0 was used. The level of statistical significance was set at $p<0.05$.

Paper I, II and III

Groups were compared using Pearson's chi-square tests. In paper II, Cohen's Kappa was used to measure agreement between clinical assessments and laboratory analyses. Kappa > 0.21 was considered fair, > 0.41 was considered moderate and >0.61 was considered good (77).

Kappa = 1 indicates complete agreement. Logistic regression analyses were used to adjust for independent variables in paper III. All comparisons with the former study from 1980 (70;71) were corrected for this difference by excluding accidental non-self-poisonings in the calculations.

Paper IV and V

The mortality in the cohort was compared to the mortality in the general population, with reference rates according to age and gender. Person-time under observation, categorized by five-year calendar periods and five-year age groups (15–19, 20–24, etc.), was obtained for each gender. Mortality rates in the general population for the same cross-classification served as reference rates. Expected death was computed by multiplying the observed person-time in the cohort by the reference rate. Standardized mortality ratios (SMRs) were computed by taking the ratio of observed to expected deaths. The mortality ratios were adjusted for age changing in the cohort over time.

For SMRs, the 95% confidence intervals (95% CI) were computed, based on the assumption that observed deaths follow the Poisson distribution. In the analysis of total mortality, attained age was chosen as the time variable. In the analysis of suicide, time since discharge was used as the time variable. Univariate analysis was performed first, followed by multivariate analysis, which included all variables with $P < 0.15$ in the univariate analysis.

In Paper IV, predictors for death and for suicide were found using Cox regression analyses.

Paper VI

To compare agreement between the doctor's and the patient's evaluation of intention, Cohen's Kappa was used (see paper II). Multinomial regression analyses were used to compare the groups according to psychosocial factors, with the physician's evaluation of intention as the dependent variable. Suicide attempt was used as the reference category. Multinomial analyses included all variables with $p \leq 0.02$ in the crude analyses.

4. SUMMARY OF RESULTS

4.1 Paper I

Hovda KE, Bjornaas MA, Skog K, Opdahl A, Drottning P, Ekeberg O, Jacobsen D.
Acute poisonings treated in hospitals in Oslo: A one-year prospective study (I): Pattern of poisoning.
Clin Toxicol. 2008; 46:35-41.

This paper presents the results from a prospective cross-sectional multi-centre study of all adult patients (16 years or older) hospitalized in Oslo with a main diagnosis of acute poisoning, irrespective of intention, over a one-year period (n=947, 54% females, median age 36 years).

The aims of this paper were to study:

- The incidence of hospital treated acute poisonings during one year
- The patterns of toxic agents according to age and gender
- The intention behind the poisoning according to gender and toxic agents

There were 947 (31 %) hospitalizations; annual incidence 1.9 (per 1,000) in males and 2.1 in females. Benzodiazepines (18%), ethanol (17%), paracetamol (12%), opioids (7%), and gamma hydroxybutyric acid (GHB) (7%) were most frequently taken. Males drank more often ethanol ($p=0.008$) and used more illicit drugs (opioids: $p<0.001$, GHB: $p<0.001$, amphetamine: $p=0.046$, and cocaine: $p=0.013$), while females tended to use more prescription (and over-the counter, i.e., paracetamol) drugs (benzodiazepines: $p=0.012$, paracetamol: $p<0.001$, neuroleptics: $p=0.024$, zopiclone: $p=0.012$, and anti-epileptics: $p=0.02$). Overall, physicians defined 10% as a definite and 25% as a possible suicidal attempt (total 35%). Females were statistically significantly more often evaluated to have taken the drugs in a definite or possible suicidal attempt, or it was considered done as an appeal for help. Males were more often classified to have done it for intoxication purposes. The different intentions were also reflected by the differences in main agents taken, where suicide attempters more often used prescribed medications.

4.2 Paper II

Bjornaas MA, Hovda KE, Mikalsen H, Andrew E, Rudberg, N, Ekeberg O, Jacobsen D. **Clinical versus laboratory identification of drugs of abuse in patients admitted for acute poisoning.**
Clin Toxicol 2006;44: 127-134

This paper presents the results from a prospective cross-sectional study of all acute poisonings treated at the Department of Acute Medicine, Ullevaal University Hospital, during one year in 2001 (n= 405, 52% males, median age 31 years). The focus of the study was drugs of abuse, which was defined as ethanol, benzodiazepines, opiates, cannabis, amphetamine, GHB, cocaine and ecstasy. Both an evaluation form and a blood or urine sample were needed to compare the results, and therefore 320 (79%) of the cases were included in the analyses.

The aims of the study were:

- To assess the pattern of drugs of abuse according to age and gender
- To evaluate the concordance between the clinical assessments (including patient history) by the physicians on duty and the drug analyses in these patients

A total of 478 drugs of abuse were suspected and 621 were found. The most frequent toxic agents found were benzodiazepines (50%), ethanol (40%), opioids (35%), cannabis (24%) and amphetamine (21%). Ninety-two percent of all patients treated for acute poisonings had used drugs of abuse, irrespective of suicidal intention.

The agreement between the clinical assessments and the laboratory findings was best for GHB and ethanol (kappa=0.43) and for opiates (k=0.38). For benzodiazepines and cannabis, the concordance was poor (k=0.18 and 0.10, respectively). However, the correct clinical evaluation for these substances was 59% and 79%, respectively.

Paper III

Heyerdahl F, Bjornaas MA, Hovda KE, Skog K, Opdahl A, Drottning P, Ekeberg O, Jacobsen D.

Acute poisonings treated in hospital in Oslo: A one-year prospective study (II): Clinical outcome.

Clin Toxicol 2008;46: 42-49.

This paper presents the results from a prospective cross-sectional multi-centre study of all adult patients (16 years or older) hospitalized in Oslo with a main diagnosis of acute poisoning, irrespective of intention, over a one-year period (n=947, 54% females, median age 36 years).

The aims of this study were:

- To register the level of consciousness, use of antidotes and other treatments, complications, and outcomes related to toxic agents, gender, age, and the intentions of the poisonings.
- To study the impact on clinical outcome and treatment from the apparent changes in the toxicological panorama since 1980

Of 947 admissions, 222 (23%) were comatose. Seventy-five percent received treatment besides observation; 39% received antidotes, increased from 21% in 1980, most frequently flumazenil (23%) and naloxone (14%). Complications were observed in 173 (18%), slightly reduced from 1980 (22%). Complication rates were highest for methanol (67%), cardiovascular drugs (55%), amphetamine (44%), and opioid (42%) poisonings. Ten (1.1%) died and six (0.6%) got permanent sequelae, of which seven and five were drug- or alcohol-related, respectively. Although the overall mortality was low, and the median duration of the hospital stay was only one day, 40% of the patients were treated in the ICU. Drug- and alcohol-abuse related poisonings were most severe.

4.4 Paper IV

Bjornaas MA, Jacobsen D, Haldorsen T, Ekeberg O.

Mortality and causes of death after hospital-treated self-poisoning in Oslo: A 20-year follow-up.

Clin Toxicol 2009;47: 116-23

This paper presents the results from a prospective cohort study of all patients discharged after self-poisonings from all medical departments in Oslo in 1980, with a follow-up period of 20 years (n=946, 51 % females, median age 31 years).

The aims of this study were to determine:

- The 20-year overall mortality rate for all patients admitted to medical departments for self-poisoning in Oslo in 1980
- The mortality in the cohort compared with the general population of Norway
- The causes of death
- Factors that might differentiate those who died in the follow-up period from those who survived
- Factors that might predict suicide or other causes of death.

During follow-up 355 (37.5%) of the patients died. Among males, 45.3% died, and 30.2% of all females died. The SMRs were 4.6 (95% C.I., 4.2–5.1) in total, 5.0 (95% C.I., 4.3-5.7) for males, and 4.2 (95% C.I., 3.6–4.9) for females. After 15 years, the SMR was still 3.3 (95% C.I., 2.5–4.2). Sixty-seven patients committed suicide; SMR 26.7 (95% C.I., 20.8–33.9). After 20 years, 7.4% of all patients had died from cardiovascular diseases, 7.1% by suicide, 4.3% by accidents, 3.3% from cancer, 1.1% from other violent death, and 14.4% from other diseases. The risk of death from all causes was significantly higher during the entire follow-up period. The risk factors for death were not specific enough to identify those at special risk, and were male sex, a lower level of consciousness upon admission, substance abuse, and lower socio-economic class. A suicidal motive upon admission was the only risk factor for suicide.

4.5 Paper V

Bjornaas MA, Bekken AS, Ojlert A, Haldorsen T, Jacobsen D, Rostrup M, Ekeberg O.

A 20-year prospective study of mortality and causes of death among hospitalized opioid addicts in Oslo.

BMC Psychiatry 2008, 8:8 (13 February 2008).

This paper presents the results from a prospective cohort study of 185 hospitalized opioid addicts either treated for self-poisonings in 1980 (n=93), voluntary detoxifications in 1980/81 (n=75), or both (n=17). Median age at inclusion was 24 years, range 16-41, 53% males. These included admissions to all medical departments in Oslo. The cohort was followed for 20 years.

The aims of this study were:

- To study mortality rate and causes of death among opioid addicts treated for self-poisonings or voluntary detoxifications during a 20 year follow-up
- To compare the mortality of the cohort with the general population
- To investigate whether or not participation in a detoxification program can be protective

During the follow-up period, 70 opiate addicts died (37.8 %), with a SMR equal to 23.6 (18.7-29.9). The SMR remained high during the whole period, ranging from 32.4 in the first five-year period, to 13.4 in the last five-year period. Among females, 23 (31.4%) died, whereas 47 (48.5%) of all males died during follow-up. The registered causes of death were accidents (11.4%), suicide (7.1%), cancer (4.3%), cardiovascular disease (2.9%), other violent deaths (2.9%), other diseases (71.4%). Among the 50 deaths classified as other diseases, the category "drug dependence" was listed in the vast majority of cases (37 deaths, 52.9% of the total). The risk of death was significantly higher for all causes of death compared to the general population. There were no significant differences in SMR between self-poisonings and those admitted for voluntarily detoxification.

4.5 Paper VI

Bjornaas MA, Hovda KE, Heyerdahl F, Ekeberg O, Skog K, Drottning P, Opdahl A, Jacobsen D.

Suicidal intention, psychosocial factors and referral to further treatment – a one year cross-sectional study of self-poisonings.

Submitted.

This paper presents the results of a cross-sectional multi-centre study of 908 self-poisonings treated in medical departments in Oslo during one year. Accidental non-self-poisonings were excluded. There were 54% females, median age was 36 years. Multinomial regression analyses were used; suicide attempts were used as reference category.

The aims of this study were:
To study the socio-demographic and psychiatric characteristics of patients presenting with self-poisonings in the Emergency Departments in Oslo during one year:

- How do the patients and the physicians evaluate the intention in each case?
- How do these characteristics vary according to the evaluated intention?
- What are the plans for follow-up of these patients at discharge?

Overall, there were a good correlation between the patients and the physician's evaluation of intention. According to the physicians, 37% were suicide attempts, 26% appeals and 38% were drug-related poisonings. Overall, patients showed a lack of social integration. In addition, more than half of the patients reported previous suicide attempts and 58% reported previous or current psychiatric treatment. Daily substance use was reported by a one third of all patients. Those who were males, younger than 30 years old, reporting substance use of any frequency or were living with their parents were more likely to be evaluated as drug-related poisonings than suicide attempters. Being from Asia, being temporarily on sick-leave or reporting previous suicide attempts and/or psychiatric treatment made it less likely to be evaluated as a drug-related poisoning. Females were more likely to be evaluated as appeals, but in all other aspects there was no difference between appeals and suicide attempters. Almost one out of five patients was discharged without plans for follow-up, including 36% of drug-related poisonings. Among suicide attempters, 5% were discharged without such plans, as were 10% of appeals.

5. DISCUSSION

This thesis includes a broad spectre of data for all patients treated for self-poisonings in Oslo, the capital of Norway. The papers presented give an overview of the epidemiology, substance use, psychosocial characteristics and prognosis of self-poisonings in Oslo. Six papers are included in the thesis in order to study the complexity of this patient group. Our main findings were that even today, ethanol and benzodiazepines remained the most common agents, and the substance use was substantial among all patients. The patient group showed a lack of social integration irrespective of intention. More than half of all patients reported previous suicide attempts and psychiatric treatment, although more among suicide attempters than drug-related poisonings. The short term prognosis in terms of mortality was good for hospitalized patients. However, the long-term prognosis showed a markedly increased mortality and risk of suicide for all subgroups. In this context, one out of five patients was discharged without plans for follow-up.

A strength of the studies presented is that the whole city is included (except for paper II), and the inclusion period is one year. The inclusion of all patients presenting as self-poisonings at the acute departments is quite uncommon in the field of suicidology, where different terms and inclusion criteria have been used to select subgroups of patients within the group of self-poisonings such as self-harm, medically serious suicide attempters, deliberate self-poisonings etc. (11;95;130). However, the inclusion of all self-poisonings, irrespective of intent, is in consistence with the treatment of the patients at the acute departments, as seen in paper III. This inclusion is also common in the field of toxicology. The patient group is therefore complex, and six papers are included in order to describe different aspects: epidemiology, substance use, psychosocial factors and prognosis for self-poisonings.

Self-poisonings can be investigated by studying hospital figures and statistics, but due to the retrospective design these studies are inaccurate and tend to underestimate morbidity (18;53). The studies presented here were designed to ensure that patients were included consecutively, and the cohort studies were prospective. It is however possible that some cases were missed due to several collaborators in four different hospitals, both in 1980 and 2003/04. Extensive follow-up of all participating hospitals were done to ensure that the number of possible missed cases was low.

The exclusion of accidental non-self-poisonings in papers IV and VI were done to get a more homogenised material. These patients were not included in the main groups defined as suicide attempters, appeals and drug-related poisonings, and therefore not meaningful to study in the context of self-destructive behaviour. The slightly different inclusion criteria in the

studies included may therefore be seen as a weakness of the thesis. However, paper IV and VI included 98.3% and 95.9% of all acute poisonings respectively.

The inclusion of all patients treated as self-poisonings in the acute departments in a whole city made it possible to generalize from the study population back to a well-defined background population. The epidemiological and clinical data presented in papers I and III may therefore be seen as representative for the city of Oslo at the time. The comparison between our study from 2003/04 and the study by Jacobsen et al in 1980 was possible due to similar methodology (70;71). For paper II, only patients treated at Ullevaal University Hospital were included. The hospital covers an area including all social classes, and it represents a fairly good cross-section of the population of Oslo, but being a tertiary care centre means that severe poisonings are somewhat overrepresented. For paper IV and V, the SMRs were calculated based on mortality rates from Norway in general, not Oslo in particular. However, around 1980 the clustering of substance users was more extensive in Norway than today, and people moved from rural areas to Oslo where the drug market was more evolved. Thus, for opioid addicts, those treated at medical departments in Oslo could be seen as representing other parts of the country as well. As for self-poisonings in general, the comparison of these patients with mortality rates from the rest of the country could lead to a possible bias, slightly overestimating the increased mortality in the cohort.

In the following, the main findings of the thesis will be discussed in comparison with other studies.

5.1 Incidence

The annual incidence of hospitalization due to acute poisonings in 2003/04 in Oslo was 2.0 per 1000; 1.9 in males and 2.1 in females (paper I). Eighty-seven percent of the patients were admitted once, whereas the rest had more than one admission. This included 947 admissions among 780 patients, compared to 1212 admissions among 1047 patients in 1980 (70). The annual incidence in 1980 was 2.7 per 1000. The reduction from 1980 was statistically significant ($p<0.001$), and the incidence decreased more for males (3.0-1.9 per 1000, $p<0.001$) than for females (2.5 – 2.1 per 1000, $p=0.01$).

The studies, although separated by 23 years, used the same inclusion criteria and methodology, and both studies covered the whole city of Oslo. Therefore, a comparison is valid. The reduction observed is probably partly due to the present treatment of most of the opioid overdoses on site (20), which has increased with the use of naloxone as an antidote. The exclusion of patients with other primary diagnoses, such as pneumonia, could have

excluded important acute poisonings from the present study. However, most of these patients would have their clinical course affected by the primary, non-poisoning diagnoses. Again, this was similar for the 1980 study.

The female dominance persisted, in accordance with other studies reporting 51-56% females (9;22). Compared to the 1980 study, the patients were somewhat older (median age 36 years versus 31 years), probably partly because of the already mentioned pre-hospital treatment of the young opioid addicts (median age in paper V was 25 years). The age distribution observed fits another Norwegian study from Trondheim during 1978 to 2000 (117), where the median age was 34.4 years. A Spanish study found a median age of 33 years (22), whereas patients were younger in Sri Lanka (median age 25 years), probably due to young people taking pesticides and a generally younger population (37).

5.2 Pattern of toxic agents

Benzodiazepines and ethanol were the main toxic agents in 2003/04, suspected in 18% and 17% of the cases, respectively (paper I). Not differing between main and additional agents, benzodiazepines and ethanol were the drugs of abuse most frequently found by laboratory analyses in paper II as well; in 50% and 40% of all cases, respectively. They were also the most frequently suspected agents in paper II, but the agreement between suspected and found agents for each case was inaccurate, with kappa 0.18 for benzodiazepines and kappa 0.43 for ethanol.

The clinical evaluation of toxic agents is difficult, and although routine drug analyses were available for the physicians in paper I, these only included ethanol, benzodiazepines, salicylate and paracetamol. Clinical assessments alone are known to be inaccurate (103). However, Rygnestad et al found a concordance of 86 to 96% when combining results from routine screening and clinical evaluation of the patients (116). The findings are therefore considered valid. The treatment of self-poisonings is mainly symptomatic (paper III), with the exception of the use of antidotes, and it may be argued that an accurate diagnosis regarding toxic agents is not necessary in the acute setting. However, the use of antidotes were extensive in the 2003/04 study (paper III), where 39% of all patients received such agents. The corresponding figures in 1980 were 21%, despite the fact that opioid addicts now are mainly treated on site. Flumazenil may cause seizures (81), and allergic reactions are reported in patients treated with NAC intravenously (30). Therefore, an accurate application of antidote is preferable, which in turn relies upon a precise diagnosis regarding toxic agents.

The higher number of found than suspected cases in paper II may be caused in part by the physicians focusing mainly on the main agents, while the laboratory analyses detected most agents. The results from routine laboratory analyses were not available to them as they were in the 2003/04 study, which may have contributed to higher discrepancies. The relative importance of each agent was not evaluated, as only qualitative answers were used for further analyses. Some of the agents had long half-lives such as cannabis (42), whereas other had short half-lives, for example GHB and ethanol, and may not be detected up to 24 hours. The eventual therapeutic use of some substances (benzodiazepines, opiates) was not taken into account. However, even therapeutic use needs to be taken into account when evaluating patients treated for self-poisonings. Therefore, the evaluation of agreement in paper II was considered representative.

Benzodiazepines and ethanol were followed by paracetamol (12%), opioids (7%) and GHB (7%) as the most frequently suspected main agents in paper I. In paper II, which focused on drugs of abuse, opiates were identified in 35% of the cases and GHB in 12%. Amphetamine was found in 21% of all cases in paper II, but was only suspected in 5% in paper I, including both main and additional agents. The difference was seen in spite of the fact that both papers included all acute poisonings, although paper II focused solely on drugs of abuse in further analyses. In paper VI, 4% of all patients reported a daily use of amphetamine. Compared to 1980, benzodiazepines and ethanol were the main agents in 18% and 20% of the cases, respectively, corresponding to our findings in 2003/04. In 1980, these agents were followed by opioids (15%), neuroleptics (11%) and antidepressants (10%). Paracetamol becoming more frequent and opioids becoming less frequent corresponds to other reports (9;130). As mentioned before, the pre-hospital treatment of opioid addicts contributes to the reduction of opioid poisonings (20). The frequency of suspected GHB poisoning (7% in paper I) was twice the number found in a Spanish study (85), but lower than the figures in paper II (GHB found in 12% of the cases). However, the relative importance of GHB in each case found in paper II is not known. Nevertheless, the relatively high percentage seen in paper I could be an underestimate rather than an overestimate, when consulting the findings of paper II. Since 1980, SSRI's have become extensively used (119), and this can probably explain why TCA's were only seen in 2% of the cases in 2003/04.

There were gender differences in the pattern of toxic agents used, as males tended to use more illegal substances and alcohol, while females used more prescription drugs (paper I). This was in accordance with findings in the 1980 study, as well as other studies regarding paracetamol and opioids for example (9;130). Paracetamol mainly dominated among the

younger patients, whereas antidepressants and tranquilizers were more commonly seen among the elderly, in correspondence with other studies (9;130).

5.3 Substance use

In Paper II, 92% of all patients had used one or more drugs of abuse prior to admission to hospital, irrespective of intention. Physicians tended to underestimate the use of these substances, as there were 30% more agents found in the laboratory analyses than suspected clinically. In paper VI, 37% of all patients reported daily substance use. Not surprisingly, those treated for drug-related poisonings reported more (48%). However, the daily substance use was quite substantial even among suicide attempters and appeals, with 35% and 25% respectively. Ethanol and prescribed drugs (such as benzodiazepines) were most commonly used (by 52% and 51% of the daily users, respectively).

Clinical assessments alone did not uncover all substances administrated in paper II. The physicians may, however, have focused mainly on the main toxic agents, whereas drugs of abuse were frequently additional agents. As only the presence of each substance was evaluated, not the relative importance, this may have contributed to the underestimation. However, the physicians were aware of the ongoing study and may have recorded more substances than they normally would have suspected, reflecting a possible information bias. They were, however, not aware that drugs of abuse were the main purpose of the study. In paper I, ethanol and benzodiazepines were the most frequently suspected *main* agents, closely followed by opioids and GHB. This emphasises the importance of drugs of abuse in these patients. The results are therefore considered representative.

The validity of self-reported substance use has been questioned. A study of adolescents treated for substance use disorders found that both underestimation and overestimation of substance use was quite common (133). This is probably also true for patients treated for self-poisonings reporting their substance use. In addition, patients may be reluctant to report the use of illicit drugs (such as heroin, cocaine, amphetamine, ecstasy, GHB). In the study from 2003/04, the patient's self-reported substance use was not confirmed by laboratory analyses, and the validity of the reports was therefore not evaluated. Due to the high figures of drugs of abuse found in paper II, and the recognition of substance use as a risk factor for suicide attempt (55) and vice versa (63), the self-reported substance use in paper VI seems relevant.

Amphetamine was surprisingly common (paper II), and were found in one fifth of all cases. Amphetamine was detected about twice as often as GHB in all age groups. Even 8% of

patients older than 50 years old had positive tests for amphetamine. The use of amphetamine seems to have increased since the 1980s, where Taylor et al found the drug in only 2% of patients (129), corresponding to 1.8% found in the 1980 study by Jacobsen et al. In paper I, amphetamine was suspected in 5% of the cases, but this was not confirmed by laboratory analyses. However, this was an increase compared to the 1980 study. The presence of ephedrine from cold remedies cannot be distinguished from drug abuse and may have contributed to some cases, but the difference between suspected and found cases of amphetamine cannot be fully explained by this. The self-report of substance use in paper VI suggests that 4% of all patients use amphetamine on a daily basis. Among drug-related poisonings, 12% used amphetamine, 5% daily. Among suicide attempters, 4% reported a daily use of amphetamine. There is a marked difference between the prevalence of amphetamine in paper I and II, indicating that this "old" drug of abuse is more commonly used than suspected clinically.

One out of three patients had positive findings for opioids in paper II, and 43% of patients older than 50 years had traces of opioids in blood or urine. Opioids were considered the main agent in 7% of the cases in paper I. When including additional agents, opioids were suspected in 17% of all cases. Although opioids can be misused as drugs of abuse, they are not illicit per se. The high number of cases is therefore not necessarily an indication of abuse. It was not possible to make a distinction between therapeutic use and drug abuse in the laboratory analyses. Popular painkillers containing codeine is the most likely explanation. Skelton et al found that codeine accounted for 63% of all opiate-positive samples (120). However, even therapeutic use needs to be taken into account in the treatment of self-poisonings. There can even be a fine balance between use and misuse for prescribed opioids. The percentage of opioids as the main toxic agents in the 1980 study was 15%, a reduction probably caused by the current onsite treatment of overdoses (20), and not a reduction in the use of opioids as drugs for substance use.

GHB was considered the main toxic agent in 7% of all self-poisonings in paper I. This is a quite new drug, and was therefore not used in 1980. The concordance between suspected and found agents was rather good for GHB, kappa 0.43, possibly due to recognition of the "toxidrome" of this drug: a combination of bradycardia, hypotension and a state of consciousness varying between coma and agitation in the same patient (78). GHB were more frequently seen among the young, but were seen in 8% of those aged 50 or older as well. The emerging use of this drug may be seen as an indicator of its availability; the patients using whatever drugs are at hand.

The polydrug use in 60% of all hospitalized patients in paper II and the recognition of nine out of ten patients testing positive for drugs of abuse, indicates a substantial substance use in the patient population. Addressing the substance use in these patients is important both in the acute treatment, as a basis for the use of antidotes (paper III), but also for detecting patients in need of substance use treatment in (paper VI). Emergency departments can be important venues for detecting the need of such treatment (110).

5.4 Psychosocial characteristics of self-poisonings

Paper VI demonstrated a lack of social integration and a high proportion of previous suicide attempts and substance use among self-poisonings in all subgroups based on intention. Only one third of the patients were employed, one third was married and more than half of all patients were living alone. More than half of the patients reported previous suicide attempts and 37% daily substance use.

The patients were grouped according to intention as assessed by the physician. No forms or scales were used, and thus the inter-rater variability was not evaluated. The same method was used in paper IV. This method resembles how patients are evaluated at the emergency departments in everyday practice, and was therefore considered clinically relevant. The same argument may be used for the self-reported data on psychosocial characteristics: the validity of the answers remains unknown, but the situation is similar to the clinical setting.

The lack of social integration is known from studies of suicide attempters as an important risk factor for suicidal behaviour (16;36;90;92). It is therefore interesting that socio-demographic factors did not vary more between the intentional groups: education and marital status had no impact. Those being on sick leave were more likely to be evaluated as suicide attempters, whereas those living with parents were more likely to be evaluated as a drug-related poisonings. Social isolation as a risk factor for suicidal behaviour may be associated to the increased risk of suicide for self-poisonings in general (paper IV). The risk was increased not only for suicide attempters and substance abusers including opioid addicts (paper V), but for patients neither suicidal nor substance abusers as well. The lack of social integration has also been found to be a risk factor for increased mortality in a sample of healthy employees (14). The increased mortality for self-poisonings may therefore be related to this factor as well.

A previous suicide attempt is the strongest known predictor for suicide (54) and further suicidal behaviour. The higher proportion reporting previous suicide attempts among the present suicide attempters corresponds to this (paper VI), as well as the increased suicide

risk among suicide attempters during 20 years (paper IV). Substance abuse is the second most frequent precursor to suicide (88), and 37% of all patients reported daily substance use. The importance of this risk factor must be recognized when treating self-poisonings, since so many patients report substance use. Moreover, the figures are probably an underestimate, since 30% more drugs of abuse were found than suspected in paper II.

Appeals and suicide attempters did only differ in the gender distribution, as females were more likely to be evaluated as appeals than suicide attempters. For all other psychosocial characteristics, the groups were similar. The difference in evaluated intention probably means that the suicide attempters were in a deeper crisis at time of admission. Medically serious suicide attempts are at higher risk and use different substances (11;130). However, the proportion of risk factors for suicidal behaviour among appeals might explain some of the increased long-term mortality and risk of suicide among non-suicidal patients in paper IV, and the follow-up of patients classified as appeals must take this into account.

One third of all drug-related poisonings had previous suicide attempts and one third of suicide attempters reported daily substance use. The subgroups were therefore overlapping. This corresponds to a study of repetitions among the same cohort of self-poisonings from 2003/04, which found that for 24% of the repeaters of self-poisonings, the evaluated intention changed during one year (69).

5.5 Short-term prognosis

The short-term prognosis was good for hospitalized patients, the in-hospital mortality being 1.1% in the 2003/04 study (paper III). There were 0.8% of patients who were discharged with permanent sequelae.

The mortality in the 1980 study was 0.5%, but the increase was not statistically significant. Our samples were not large enough to detect even a substantial change in mortality, given the low numbers of in-hospital mortality, and hence the number of cases needed for the power of the study.

The mortality observed resembles a Finnish study from 1992, where the in-hospital mortality was 0.7%. A study from Zimbabwe found a mortality of 4.4%, reflecting the high number of pesticide poisonings in developing countries (128). In our study, three deaths resulted from opioids, two from ethanol and in two cases benzodiazepines were the main agents. Methanol, paracetamol and cocaine poisoning resulted in one death each. It is worth emphasizing that even such common agents as ethanol and benzodiazepines can result in fatal poisonings. Recent studies from Belgium found that three out of ten fatal poisonings were due

to benzodiazepines (19). Few studies supports similar high numbers, but the cause of death may often be diagnosed as the respiratory complications, such as aspiration pneumonia, rather than the actual poisoning. The number of lethal cases may therefore be underestimated.

Although the in-hospital mortality was low, 99 persons died of fatal poisoning outside hospital as well (paper I), i.e. 91% of all deaths in the study period. These patients were not included in the figures presented here, but must be taken into account when discussing the short-term mortality of self-poisonings. A study of the Norwegian Patient Register and the Norwegian Causes of Death Register from 1999 to 2004 by Lilleeng et al, found that 80% of deaths by acute poisoning occurred outside hospital (79). The mortality of self-poisonings is therefore higher than the in-hospital mortality. However, based on these registers, Lilleeng et al estimated the mortality rate in hospital to 0.8%, slightly less than in our study. It is possible that the figures for Oslo are somewhat higher than for the country in general, due to clustering of substance use in urban areas as a consequence of availability.

For those who survived with permanent sequelae, anoxic brain damage was most common (paper III). This was observed in 0.6% of the cases, the corresponding figures in 1980 was 0.1%. The increase may be attributed to more extensive intensive care treatment during the last decades, i.e. more severe poisonings survive, but the figures are too small to be statistically significant.

5.6 Long-term prognosis

The long-term prognosis for this patient group was rather poor. During 20 years 37.5% of the patients treated for self-poisonings in Oslo in 1980 died (paper IV). The mortality was 4.6 times higher than expected, compared to the general population. For opioid addicts, 37.8% were dead during 20 years of follow-up, the mortality being 23.6 times higher than expected according to age distribution.

The physician on duty, i.e. at the acute departments, classified the patients according to suicidal motive and substance abuse. The classification was based on clinical evaluation, including patient records, information from companions and from the patients themselves. No scales or forms were used. The criteria for being classified as a suicide attempt was rather strict and tried to rule out cases considered to be solely an appeal, i.e. where there was no serious wish to die. For substance abusers, the classification was based upon all information available, with reference to the ICD criteria. However, this was a subjective measure, and the inter-rater reliability was unknown. The lack of standardization may be seen as a weakness of the studies. However, the approach reflects how the assessments are done in the clinical

setting, and is relevant as the physicians are important gatekeepers for referral to further psychiatric evaluation. As discussed in paragraph 5.4, the method allowed us to generalize our findings back to clinical practise. The method turned out to be clinically relevant, as those considered to be suicidal at admission had an increased risk of suicide, corresponding to other studies (11;125). Also, in paper VI, the agreement between the evaluation made by patients and physicians was found to be good (kappa 0.68).

The causes of death were obtained from Statistics Norway. Although the validity of these data regarding suicides was satisfactory in 1985 (40), the autopsy rate in Norway has declined since then (13). Therefore, the accuracy of death certificates is probably less valid, and our numbers regarding suicides must be considered a minimum.

The high mortality of patients treated for self-poisonings was observed in a rather young cohort; median age in 1980 was 31 years. The SMR remained increased for the whole period, indicating that admission for self-poisoning is a serious predictor for increased risk of death not only through an immediate crisis or illness, but is a marker of increased risk at least for 20 years. Suominen et al found an increased risk of suicide even after 37 years in a cohort of suicide attempters (125). A suicidal motive upon admission was not associated with increased mortality during the period, as SMR for the suicide attempters was 3.4. Increased mortality for suicide attempters has been found in other studies (94), but in a group of patients with self-poisonings, a suicidal motive had no additional effect on mortality in general. For those classified as substance abusers, the SMR was 7.3 (paper IV). However, for opioid addicts, the SMR was 23.6 (paper V). The mortality in the 1980 cohort versus the cohort of opioid addicts was rather similar (37.5% versus 37.8%), but the median age was only 24 years among opioid addicts and thus, the estimated number of death was lower. The high SMR found among this subgroup of self-poisonings corresponds to other European studies (6).

Even for patients considered to be neither suicidal nor substance abusers the risk of death was increased, with a SMR of 2.6 (paper IV). The risk was increased for all causes of death. This indicates that identifying subgroups of self-poisonings at risk of death and completing suicide, does not capture all individuals at risk. It might be more meaningful to consider all patients with self-poisonings to be at risk.

In paper V, mortality did not change from referral to voluntary detoxification. Unfortunately, information about compliance for each patient was not known, and we don't know who achieved abstinence or not. Those who were admitted to voluntary detoxification may also have been in a poor medical and physical state, as this was one of the criteria for

admittance. These patients were generally not motivated for the treatment required to achieve abstinence. Other studies indicate that achieving abstinence reduces mortality, although the mortality rate is still increased compared to the general population (122).

The risk of death was significantly increased for all causes, both for self-poisonings in general and opioid addicts in particular. The increased risk of death, even from natural causes, is consistent with the increased mortality associated with mental disorders (55). Drug dependence was the underlying cause of death in 53% of all deaths among opioid addicts (paper V), and in 13% of all deaths among substance abusers in general (paper IV). Although the death of unintentional overdoses was of major concern in these patients, there is no category literally equivalent to this term in the ICD system. Therefore, drug dependence as the underlying cause of death was included in the group called other diseases when computing the SMRs. This was done to obtain the same categories as used by Statistics Norway. The SMR for this single cause of death was not calculated. These figures would have provided minimal additional information. If drug dependence is a chronic disease, a symptom of which is opioid addiction, one would expect that only those suffering from the disease would die from it; that is, there would be a low number of death in the general population. Even when all other diseases were included in the general population, death from drug dependence outnumbered the total number of deaths from all other diseases.

5.7 The risk of suicide

The suicide rate, like the mortality rate, remained high for the entire follow-up period in paper IV. The SMR for suicide was 26.7 for all self-poisonings. The suicide risk was highest the first two years after the index episode, but after five years there was no further decline. Even in the last five year period, the suicide risk was increased 23.4 times. The continuing risk of suicide is consistent with the life time risk after suicide attempts reported by Suominen et al in Finland (125).

The risk of suicide was increased for opioid addicts as well (paper V). The SMR was 10.7 for opioid addicts, whereas the SMR for substance abusers in general (paper IV) was 21.5. The difference here may be due to the smaller cohort in paper V, meaning that the figures have broader confidence interval, i.e. they are less accurate. However, this could also be attributed to the increased overall mortality in this subgroup (23.4 times vs. 7.3), where more opioid addicts would die of other causes such as drug dependence. Those who take the highest risks will probably die early. It has been shown that the number of active drug addicts declines mainly from death, rather than from long-term abstinence (52).

For suicide attempters, the risk of suicide was increased 64.1 times. A former suicide attempt is the strongest known risk factor for completing suicide (54), and our finding is consistent with this. But the SMR for suicide was increased even for patients considered neither suicidal nor substance abusers (SMR 22.9, paper IV). Since both suicide attempters and substance users are known risk groups for suicidal behaviour, it would be indicated to focus on these subgroups in a population of self-poisonings when planning further referral to follow-up services. However, our finding indicates that focusing on these subgroups does not capture all patients at increased risk. This could be because their ideation was either missed or inadequately investigated, or because the burden of mental illnesses including personality disorders was higher among these patients than for the general population. However, this also reflects the variability in the wish to die for suicidal patients, complicating the evaluation of intention. Even acts of appeal (i.e. not evaluated as having a wish to die in the initial episode) have increased risk of suicide. Clinicians may underestimate the seriousness of such acts. Our findings suggest that a substantial number of such patients will in time complete suicide, and their suicidal behaviour calls for more systematic follow-up of these patients.

5.8 Predictors of death and suicide

Male gender, lower socio-economic class, substance abuse and a lower level of consciousness at admission were all independent predictors of death among self-poisonings (paper IV). Suicidal intent was the only independent predictor of suicide during the 20-year follow-up period.

The clinical variables were obtained in a cross sectional study from 1980 (70;71), and the classification of suicidal intent, socioeconomic class and substance abuse was done by the physician on duty. However, the inter-rater variability was not evaluated. The lack of standardization may be questioned, but the method reflects the way evaluations are made in clinical setting. The assessments turned out to be clinically relevant.

Mortality rates for males are generally higher for males than for females[10], and our findings correspond to this. Accordingly, the difference in SMRs between genders was not statistically significant. The lack of gender differences were also seen in studies of homeless people with drug addiction (25). Other studies of drug addicts have found higher SMRs for either males (49;97) or females (7;55). The diversity of findings may be due to different inclusion criteria. Our sample of hospitalized opioid addicts may have been more prone to

[10] http://www.ssb.no/emner/02/nos_befolkning/nos_c607/tab/t-501.html

accidental poisoning, and such incidents are perhaps less correlated to gender than behavioural traits, such as the pattern of drug use.

Cause-specific mortality is known to be related to socio-economic class; for cardiovascular diseases (83), cancer (134) and suicide (61), mortality rates are higher for lower socio-economic classes. This is generally reflected in overall mortality rates. Our findings correspond to this. Drug abuse as a predictor of increased mortality was confirmed in paper V, as the risk of death among opioid addicts was higher than for self-poisonings in general. In paper III, drug-related poisonings led to coma more frequently than other poisonings. Lower level of consciousness at admission may be a marker of a more serious poisoning, i.e. a more serious suicide attempt or a more serious overdose.

Interestingly, suicidal intent was not a predictor for death among self-poisonings. Suicide attempters are known to have increased mortality even from natural causes (104). But being suicidal gave no additional effect on mortality figures for self-poisonings in general. However, suicidal intent was an independent predictor of suicide, in concordance with other studies (54). Male gender, substance abuse and lower socio-economic class are well-known risk factors for suicide (109), but were not independent risk factors for suicide among self-poisonings.

5.9 Referral to follow-up

Almost one out of five patients treated for self-poisonings in 2003/04 were discharged without *any* plans for follow-up, even when excluding those who left hospital against medical advice (paper VI). Those evaluated as suicide attempters had plans for follow-up in 93% of the cases, whereas drug-related poisonings had no plans in 36% of the cases.

Unfortunately, there was no information in this study about whether or not the patients did actually receive the treatment planned, nor if they chose not to accept the treatment offered. However, the information, although scarce, was useful, since one can hardly hope that patients receive more treatment than what is planned at discharge. A study of suicide attempters found that compliance was better when plans for follow-up were made before discharge (50). Furthermore, the inclusion of all self-poisonings made comparison between subgroups possible. Traditionally, studies have focused on the follow-up of subgroups such as suicide attempters (127) or acute opioid overdoses (26). Different approaches are probably needed for different subgroups, but the number of patients discharged without any follow-up seems too large in the context of the high mortality found in paper IV and V.

Among suicide attempters 38% were admitted to a psychiatric ward, 20% involuntarily. In a Swedish study from 1994, 57% of suicide attempters were admitted to psychiatric in-patient care (114), but since then the use of outpatient care has increased in psychiatry as well as in other parts of the health care services. However, 5% of suicide attempters in paper VI were discharged without any plans for aftercare. Suominen et al concluded in a study from 1998 that few suicide attempters with major depression receive adequate treatment prior to the attempt, but surprisingly, the treatment situation was not necessarily any better after the attempt (126). The 64-fold increased risk of suicide among suicide attempters found in paper IV indicates that the follow-up of these patients is of major importance.

Only 10% of drug-related poisonings were referred to substance use treatment (institution or outpatient care). The low proportion of drug-related poisonings who were referred to follow-up corresponds to a study of patients treated for an acute opioid overdose, finding that 67% of the patients were not referred to substance use treatment (26). Although our study includes a broader spectre of substance users, and therefore the treatment need may vary, paper IV found that substance abuse was an independent risk factor for increased mortality. Furthermore, the 24-fold increased mortality of opioid addicts in paper V was higher than for suicide attempters, where the risk of death was increased 3.4 times. However, there was no difference in mortality between those admitted for voluntary detoxifications and those treated for self-poisonings among opioid addicts in paper V. Unfortunately we do not know whether or not they completed the treatment. Sorensen et al found in a 15-year follow up that abstinence gave lower mortality rates than continuing drug addiction, although mortality was still increased compared to the general population (122). Thus, the referral to further treatment seems justified. The motivation for further treatment among many drug abusers may be moderate or low, but the serious prognosis calls for motivational work by professionals who may have contact with them, e.g. general practitioners or social workers.

Patients with appeals were referred to psychiatric outpatient treatment in 47% of the cases, and admitted to a psychiatric ward in 15% of the cases. Ten percent were discharged without plans for follow-up. On group level the patients were treated at lower level in the health care services compared to suicide attempters, probably related to the lower perceived risk of suicide in the short term. However, the appeals and the suicide attempters differed only in gender distribution when comparing psychosocial factors. Surprisingly, the appeals reported previous suicide attempts and psychiatric treatment to the same extent as suicide attempters. This corresponds to the increased risk of suicide even among patients considered

to be neither suicidal nor substance abusers found in paper IV. If intention is given too much weight, physicians may be tempted to underestimate the increased mortality risk for these patients. The treatment offered may not be sufficient.

Overall, the studies regarding the follow-up of self-poisonings are few and generally too small, even for subgroups. Little is known about the effectiveness of different types of physical and psychosocial treatment of self-harm (64). However, this must not be an excuse for not trying to establish proper aftercare for these patients in the clinical setting, as long as their risk for suicide and increased mortality is well established.

5.10 Self-poisonings as a high risk group

According to Amsel and Mann (4), the importance of identifying a risk group is the opportunity for a more targeted prevention strategy. The hypothesis that patients treated for self-poisonings are a high risk group for suicidal behaviour and increased mortality in the long term was investigated in paper IV and V. Not only suicide risk, but death by all causes was increased for patients treated for self-poisonings. All subgroups were at increased risk compared to the general population.

Traditionally, the patients included in this thesis are viewed as risk groups according to intention. To determine the correct intention can be problematic in patients presenting with self-poisonings, as a substantial number of patients are comatose on admission (paper III), and tend to under-report the use of drugs of abuse (paper II). Acts of appeals are in many cases not related to a wish to die (i.e., not a suicide attempt), but the communicative aspect of the act is substantial (108). Nor is hospitalization because of substance use to be seen as a suicide attempt, but like appeals, it can be seen as a mark of self-destructive behaviour (45). However, the fact that the patients classified as neither suicidal nor substance abusers still had increased risk for both death in general and suicide in particular, is an argument for considering all self-poisonings as a high risk group. Not revealing the patients' true intention or substance use behaviour may be argued as a reason for misclassification. However, paper VI shows that risk factors used in the evaluation of suicidality are overlapping for different intentional groups.

All self-poisonings must be considered a high risk group in terms of increased mortality and suicide risk over time. The term self-poisoning is useful in the emergency departments, where the patient group is easy to identify. This is clinically relevant for referral to further treatment. Paper VI shows that a substantial number of patients are discharged without plans for further aftercare. This may not be sufficient, as long as their prognosis on

group level in the long term is rather poor. In the Emergency Departments, focus will usually be on treatment of the actual poisoning episode, focusing on short-term mortality, whereas mortality in the long-term is of secondary importance. Furthermore, this patient group may not be regarded as highly as for example those treated for acute myocardial infarction, a disease which tends to affect patients in more prominent positions in the society. The follow-up of patients treated for self-poisonings often seems casual, not structured and well-funded in clinical trials such as the follow-up of those treated for myocardial infarctions or cancer, patient groups which also have an increased mortality in the long term. Patients treated for self-poisonings may not be motivated for further treatment. They may not accept the treatment offered, which makes it hard to establish proper aftercare. But do we focus enough on increasing the patient's motivation, or identifying his or her perceived needs? This is a major challenge in the treatment of self-poisonings.

In order truly to help someone else, I must understand more than he–but certainly first and foremost understand what he understands.
Søren Kierkegaard

6. CLINICAL IMPLICATIONS

Knowing the pattern of toxic agents used among patients treated for self-poisonings is useful in the clinical setting, as acute treatment is based upon clinical evaluation rather than laboratory analyses because of the delay before these results become available. Suspecting the correct toxic agents means a more precise use of antidotes and better supportive treatment. This thesis demonstrated that the most common substances taken are also the most common toxic agents used for self-poisoning (Papers I and VI). Ethanol and benzodiazepines, which were found among half of all patients (Paper II), must always be taken into account. Four out of 10 patients who died had taken ethanol and benzodiazepines, which emphasizes that these common agents are also potentially lethal (Paper III). Although opioid overdoses are now mainly treated on site, a third of all hospitalized patients had traces of opiates in blood or urine samples (Paper I). Paracetamol was suspected as being used by 12% of all patients. The recognition of paracetamol, benzodiazepines and opioids is important for the use of antidotes. The emerging use of GHB is interesting, as this drug was found in 12% of the patients (Paper II). The "toxidrome" of this drug seems to be recognized by physicians, as the agreement between suspected and found agents was good. The extensive use of amphetamine, which was found in 21% of the patients in Paper II, was only suspected in 5% of the patients in Paper I. This "old" drug of abuse seems to be much more commonly used than suspected clinically. Overall, physicians seem to underestimate the use of drugs of abuse, as we found 30% more agents than were suspected clinically.

Physicians found that a third of self-poisonings were suicide attempts, a third were acts of appeal and a third were drug-related poisonings (Paper VI). Risk factors for suicidal behaviour were found among all intention groups, such as a lack of social integration, substance abuse, previous suicide attempts and previous or current psychiatric treatment as a marker of psychiatric disease. Although there were differences between those who attempted suicide and drug-related poisonings, there was an extensive overlap between the groups. A third of all suicide attempters indicated daily substance abuse, whereas a third of those suffering drug-related poisonings had attempted suicide previously. Gender distribution was the only risk factor that differentiated between those with appeals and those who had attempted suicide, thus emphasizing the importance of not underestimating the seriousness of such acts when plans are made for follow-up at discharge.

Although the short-term prognosis was good for hospitalized self-poisonings, the long-term prognosis was rather poor. All self-poisonings had an increased risk of death compared with the general population, and this risk was increased for both natural and unnatural causes

of death (Paper IV). Opioid addicts were at special risk and drug dependence was the major cause of death (Paper V). Although suicide attempters were at special risk for completing the suicide, the risk was also increased for those who were neither suicidal nor substance abusers. Therefore, being hospitalized for self-poisoning was an important marker of increased risk for both suicide and increased mortality for up to 20 years after the initial admission. Therefore, patient follow-up must be directed towards all patients including those who had attempted suicide, appealers and those with drug-related poisoning. However, more than a third of all those with drug-related poisoning were discharged without *any* plans having been made for their aftercare. Even among suicide attempters, 5% were discharged without such plans. In the context of their increased risk of death in general and suicide in particular, this hardly seems sufficient. Because in 2003/04 the median age of these patients was 36 years, reducing the mortality rates among this patient group is of major importance. Although different approaches are probably needed, the follow-up of patients treated for self-poisonings should include all patients. Plans need to be made prior to discharge, in accordance with the patient's needs as evaluated by both the patient and the physician.

7. FUTURE RESEARCH

Any comparison between studies of poisoned patients requires some uniformity of classifications. Today, the borders between the groups are vague and are adopted differently in different studies (64;102;115). Consensus regarding definitions and inclusion criteria may not be the main goal, but explicit criteria are crucial to apply the results in clinical practice. Furthermore, differently defined samples might be useful in different clinical settings, a topic that should be explored. For example, self-poisonings might be a useful term in the emergency department, while self-harm might be more useful in psychiatric services, because of the way health care services are organized. However, these classifications may be influenced by regional differences and differences between countries (15). This aspect must be included in future studies.

Finding a suitable classification of consciousness in the poisoned patient is another challenge. As in other fields of emergency and intensive-care medicine, evidence-based treatment for this group may be difficult to obtain through prospective, randomized and double-blind trials.

Although guidelines on treatments such as gastric lavage and activated charcoal are available, there is criticism of the evidence upon which they are based (21). Differences in reports and recommendations regarding antidotes such as flumazenil (8;81;132) and naloxone (20;82;86) reveal that comprehensive trials regarding their most common effects in the treatment of acute poisoning are still needed.

In the future, predictors of a correct evaluation of toxic agents might be sought. Are patient and companion histories truthful, in particular, when it comes to drugs of abuse? The relative importance of these substances in the intoxicated patient may also need to be examined further.

The persistent high suicide ratio found in Paper IV might be investigated further in empirical studies to evaluate further developments of the suicidal process in these patients (108), and factors that might influence this process.

Studies of mortality and suicide rely on official statistics regarding causes of death. In Norway, the reliability of these statistics and death certificates should be investigated further, as the autopsy rate has decreased (13).

The long-term prognosis after an episode of self-poisoning calls for improved aftercare for these patients. Although they can be considered to be a single risk group, different approaches for aftercare are probably needed for these patients. The lack of intervention studies should be the main focus for future studies in the field. Evaluations of the

effectiveness of treatments for deliberate self-harm (64), have concluded that there is still considerable uncertainty about which forms of psychosocial and physical treatments for self-harm patients are the most effective, the inclusion of insufficient numbers of patients in trials being the main limiting factor. For patients presenting with self-poisonings, an evaluation of the types of aftercare currently offered to these patients, resource availability, patient satisfaction and their effectiveness on symptoms and quality of life would be useful. Some studies suggest that the need for intervention is greater than that which is currently offered (113;126).

Treatment for substance abuse has showed a beneficial effect on mortality (122), although we were not able to reveal such an effect in our analyses. It is worth emphasizing that not all drug addicts die early. More research is needed to determine what makes patients who survive different from those who die. Such information would be helpful both in choosing therapy and in identifying those at special risk.

8. CONCLUSIONS

In this study, the annual incidence of acute poisonings in Oslo was 1.9 (per 1000) in males and 2.1 in females. Ethanol and benzodiazepines were the main toxic agents, although new agents such as GHB were surprisingly common. Substance use was considerable irrespective of intention, as even a third of all suicide attempters reported daily substance use. Laboratory analyses discovered drugs of abuse in 92% of all patients, and the usage of drugs of abuse was generally underestimated by physicians. Overall, there was a lack of social integration among those who self-poisoned, as a third of them were permanently disabled, a third had only the lowest level of education, and half of the patients were living alone. Half of all the patients had previous suicide attempts. The short-term prognosis for self-poisonings was good for hospitalized patients, as 99% survived the initial episode. However, after 20 years, almost half of all males and a third of all females had died, the mortality being 4.6 times higher than expected. The mortality rates increased for all causes of death, but clinical predictors were too broad to identify individuals at special risk. For opioid addicts, mortality increased 23.6 times compared with the general population. The risk of suicide increased for all self-poisonings irrespective of intention, but a suicidal motive upon admission was the only independent predictor of suicide. Among drug-related poisonings, 36% were discharged without plans for further follow-up. However, all cases of self-poisoning must be considered a high risk group in terms of their increased mortality and suicide risk over time. Therefore, the follow-up services that these patients are offered must be investigated further.

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ERRATA

1. Paper IV: During the proof reading stages of Paper IV, I asked the editors to correct one paragraph in the results section. Unfortunately, they were not able to do this before the initial print of the paper, but they declared that they would implement the changes in the electronic version. This has not been done yet, and I therefore provide the corrected paragraph below. The corrected figures are used in the discussion of the results in the thesis.

Paper IV: Mortality and causes of death after hospital-treated self-poisonings in Oslo: A 20-year follow-up

Page 4, in the section called "Risk of suicide", line 15:

Twenty-four patients considered to be suicidal at admission died by suicide (SMR, 64.1; 95% CI, 43.0–95.7). This equates to 15.6% of those considered suicidal on admission died by suicide during the follow-up. Forty-three patients considered to be non-suicidal at the time of admission died by suicide during the follow-up period (SMR, 19.3; 95% CI, 14.2–26.3), of whom 28 were classified as substance abusers. Among those classified as substance abusers, the SMR was 21.5 (95% C.I., 14.6-31.5). In patients considered to be neither suicidal nor substance abusers at admission, 15 (4.2%) died by suicide during follow-up (SMR, 22.9; CI, 14.9–35.1).

2. List of papers, page 13 and Summary of results, p. 44: "accepted for publication" changed to "Clin Toxicol 2009;47:116-23".

3. The numbering of tables: "table 4" is changed to "table 3", "table 5" to "table 4", "table 6" to "table 5" and "table 7" to "table 6".

Appendix

Løpenummer: | | | | | – |

Intoxstudie Oslo 2003

Navn/f.nr (barkode):

Dato innlagt: | | | | | | | ddmmåå

Somatiske aspekter:

Tid innlagt:

☐ < 1 døgn
☐ 1-2 døgn
☐ >= 3 døgn__ant døgn

Innlagt:
☐ Aker
☐ Diakonhjemmet
☐ Lovisenberg
☐ Ullevål
☐ Barnesenteret
☐ Bærum

Avdeling:
☐ Poliklinisk
☐ Vanlig post
☐ OVP < 1 døgn
☐ OVP 1-2 døgn
☐ OVP >= 3 døgn

Årsak til mistanke om intox/hovedagens
(Du kan krysse av flere)
☐ Pasientens eget utsagn
☐ Komparenter
☐ Klinikk/Symptomer
☐ Andre forhold_____

Agens:
Merk kun ett hovedagens (H)
Eventelt flere Tilleggsagens (T)

	(H)	(T)
1. Amfetamin	☐	☐
2. Benzodiazepiner	☐	☐
3. Cannabis	☐	☐
4. Dekstropropoksyfen	☐	☐
5. Ecstasy	☐	☐
6. Etanol	☐	☐
7. Etylenglykol	☐	☐
8. Flunitrazepam	☐	☐
9. GHB	☐	☐
10. Hjerte-karmed. Hva?_____	☐	☐
11. Opiater	☐	☐
12. Paracetamol	☐	☐
13. Metanol	☐	☐
14. Nevroleptika	☐	☐
15. Kokain	☐	☐
16. TCA	☐	☐
17. Annet_____	☐	☐

Tid eksponering-innleggelse:
☐ < 1t
☐ 1-2 t
☐ 3-6 t
☐ >6 t
☐ Ukjent

Inntaksmåte av agens *(Du kan krysse av flere)*:
☐ po_____
☐ inhal_____
☐ injek_____
☐ perkutan_____
☐ ukjent_____

Bevissthet ved innkomst
☐ Våken
☐ Somnolent - lar seg vekke
☐ Komatøs - reagerer på smerte
☐ Komatøs - reagerer ikke på smerte

Komplikasjoner *(Du kan krysse av flere)*:
☐ Ingen
☐ Insuff resp
☐ Hypotensjon
☐ Sirk. Stans
☐ Rytmeforstyrrelser
☐ Pneumoni
☐ Andre_____

Forløp:
☐ Overlever
☐ Overlever m/sequele. Hvilke:_____
☐ Mors Meldt politiet? ☐ Ja ☐ Nei

Tiltak *(Du kan krysse av flere)*:
☐ Ingen/Observasjon
☐ Generelle (Væske, oppvarming etc.)
☐ Kull
☐ Ventrikkelskylling
☐ Intubert
☐ Respirator
☐ Rescusitasjon
☐ Dialyse
☐ Andre_____

Antidot *(Du kan krysse av flere)*:
☐ Ingen
☐ Anexate
☐ Mycomust
☐ Naloxon
☐ Andre_____

R 4290407534

I spenummer: | | | | | | – |

Demografiske aspekter:

Kjønn:
- ☐ Mann
- ☐ Kvinne

Alder i år: | | |

Sivilstand:
- ☐ Aldri vært gift
- ☐ Gift/Samboende
- ☐ Enke(mann)
- ☐ Skilt/Separert
- ☐ Ukjent

Bor sammen med:
- ☐ Bor alene
- ☐ Bor med foreldre
- ☐ Bor med andre
- ☐ Bor på institusjon
- ☐ Annet_____
- ☐ Ukjent

isk opprinnelse:
- ☐ Norsk
- ☐ Annet nordisk land
- ☐ Annet europeisk land
- ☐ Nord-Amerika
- ☐ Sør-Amerika
- ☐ Afrika
- ☐ Asia
- ☐ Australia, Oseania
- ☐ Ukjent

Bostedsfylke
- ☐ Oslo
- ☐ Akershus
- ☐ Annet_____
- ☐ Ukjent

Bydel:
- ☐ Bydel i Oslo: | |
- ☐ Asker
- ☐ Bærum
- ☐ Ukjent
- ☐ Annet_____

Arbeidssituasjon:
- ☐ Yrkesaktiv, i arbeid
- ☐ Yrkesaktiv, midl. syk
- ☐ Arbeidsledig
- ☐ Pensjonist
- ☐ Uføretrygdet
- ☐ Student (heltid)
- ☐ Husmor/far
- ☐ Militærtjeneste
- ☐ Annet; spesifiser:_____
- ☐ Ukjent

Utdanning:
Velg kun høyeste utdaning
- ☐ Grunnskole
- ☐ Videregående skole (Yrkesfag/-skole)
- ☐ Videregående skole (Alm.fag/gymnas)
- ☐ Høyskole/Universitet (< 4 år)
- ☐ Høyskole/Universitet (>= 4 år)
- ☐ Annet:_____
- ☐ Ukjent

Psykiatriske aspekter:

Pasientens angivelse av hensikt:
- ☐ For å dø
- ☐ Flukt fra problemer
- ☐ Påvirke mellommenneskelige forhold
- ☐ Uhell/beruselse
- ☐ Husker/Vet ikke
- ☐ Vil ikke gi opplysninger
- ☐ Annet_____
- ☐ Ukjent

Klinisk vurdering av hensikt:
- ☐ Sikkert selmordsforsøk
- ☐ Mulig selvmordsforsøk
- ☐ Apell
- ☐ Uhell/rus

Tidligere selvmordsforsøk
- ☐ Ingen
- ☐ Ja, siste 12 mnd
- ☐ Ja, lenger enn 12 mnd
- ☐ Ja, husker ikke når
- ☐ Ukjent

Bruk av rusmidler:
- ☐ Aldri
- ☐ Enkelttilfelle
- ☐ Sjeldnere enn hvert halvår
- ☐ Oftere enn hvert halvår, sjeldnere enn hver måned
- ☐ Månedlig
- ☐ Oftere enn hver måned, sjeldnere enn ukentlig
- ☐ Ukentlig
- ☐ Daglig
- ☐ Ukjent

(Du kan krysse av flere):
- ☐ Alkohol
- ☐ Tabl: (A el. B-prep)_____
- ☐ Opiater
- ☐ Ecstasy
- ☐ GHB
- ☐ Amfetamin
- ☐ Kokain
- ☐ Cannabinoider (Hasj/Marihuana)
- ☐ Andre:_____

Nåværende psykiatrisk behandling *(Du kan krysse av flere)*:
- ☐ Poliklinisk
- ☐ Innlagt psyk. avd

Hvis ikke innlagt:
- ☐ Tidligere poliklinisk behandling
- ☐ Tidligere innlagt på psyk. avd.
- ☐ Ukjent tidligere psyk. behandling
- ☐ Ingen
- ☐ Ukjent

Oppfølging etter utskrivning (Du kan krysse av flere):
- ☐ Ingen oppfølging
- ☐ Primærhelsetjeneste i bydel
- ☐ Selvmordsforebyggende team
- ☐ Alkoholistomsorgen
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A 20-year prospective study of mortality and causes of death among hospitalized opioid addicts in Oslo

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Abstract

Background: To study mortality rate and causes of death among all hospitalized opioid addicts treated for self-poisoning or admitted for voluntary detoxification in Oslo between 1980 and 1981, and to compare their mortality to that of the general population.

Methods: A prospective cohort study was conducted on 185 opioid addicts from all medical departments in Oslo who were treated for either self-poisoning (*n* = 93, 1980), voluntary detoxification (*n* = 75, 1980/1981) or both (*n* = 17). Their median age was 24 years; with a range from 16 to 41, and 53% were males. All deaths that had occurred by the end of 2000 were identified from the Central Population Register. Causes of death were obtained from Statistics Norway. Standardized mortality ratios (SMRs) were computed for mortality, in general, and in particular, for different causes of death.

Results: During a period of 20 years, 70 opioid addicts died (37.8%), with a standardized mortality ratio (SMR) equal to 23.6 (95% CI, 18.7–29.9). The SMR remained high during the whole period, ranging from 32.4 in the first five-year period, to 13.4 in the last five-year period. There were no significant differences in SMR between self-poisonings and those admitted for voluntarily detoxification. The registered causes of death were accidents (11.4%), suicide (7.1%), cancer (4.3%), cardiovascular disease (2.9%), other violent deaths (2.9%), other diseases (71.4%). Among the 50 deaths classified as other diseases, the category "drug dependence" was listed in the vast majority of cases (37 deaths, 52.9% of the total). SMRs increased significantly for all causes of death, with the other diseases group having the highest SMR; 65.8 (95% CI, 49.9–86.9). The SMR was 5.4 (95% CI, 1.3–21.5) for cardiovascular diseases, and 4.3 (95% CI, 1.4–13.5) for cancer. The SMR was 13.2 (95% CI, 6.6–26.4) for accidents, 10.7 (95% CI, 4.5–25.8) for suicides, and 28.6 (95% CI, 7.1–114.4) for other violent deaths.

Conclusion: The risk of death among opioid addicts was significantly higher for all causes of death compared with the general population, implying a poor prognosis over a 20-year period for this young patient group.

Background

Mortality rates among opioid addicts are higher than for the general population, although there are differences between countries and regions [1]. Standardized mortality ratios (SMRs) vary between 15 and 28 in different studies [2-4]. In spite of the increased mortality, and hence the need for intervention, Cook et al. found that 67% of patients who attended an emergency department because of acute opioid overdose were not referred to any therapeutic programme for drug addiction [5]. During the last few decades, studies have focused on abstinence versus continued drug use following participation in various treatment programmes, as an outcome measure [6], even though there is still some doubt about whether such programmes have a long-term effect on mortality. In a 15-year follow-up study, Sorensen et al. found that people who had achieved stable abstinence from injectable narcotics use were at lower risk of premature death when compared with those who continued using drugs [7]. However, even in the presumed abstinence group, there was a sevenfold increase in SMR. This raises the question whether referral to a detoxification programme has a satisfactory effect on long-term mortality.

Although the majority of deaths among opioid addicts are from accidental poisonings [8], deaths from other unnatural causes, such as suicide, have also increased [9,10]. The co-morbidity between drug dependence and suicide has been described both as an association between drug dependence and mental illness [11], and between known risk factors for both drug dependence and suicide, such as gender, living alone and unemployment [12]. In an empirical review, Wilcox et al. estimated the SMR for suicide associated with opioid dependence, but did not estimate SMRs for other diseases [10]. In another empirical review, Harris and Barraclough calculated SMRs for both natural and unnatural causes of death associated with opioid dependence [13].

Review studies, which have proven useful in pointing out the increased mortality in this patient group, have used expected number of deaths based on WHO data, rather than patient data. The analyses in Harris and Barraclough's review were based on 10 papers with a follow-up period ranging from 1 to 28 years, and the SMRs for natural causes of death were based on only one study. Longer prospective follow-up studies of opioid addicts show how the overall mortality rate changes over time [14], it being expected that cause-specific mortality would also differ between long-term and short-term follow-up studies. Although cause-specific mortality rates were measured in one four-year prospective cohort study, no SMRs were obtained [15]. Prospective cohort studies in the field are relatively uncommon [15], and even rarer is the opportunity to compare the cohort with a well-defined background population that includes a whole city. However, long-term prospective studies of excess mortality among opioid addicts, in particular, would be useful for obtaining more specific information about opioid addictions as a subgroup of substance use disorders.

During recent decades, the AIDS epidemic has had a major effect on this group of patients [16]. Although mortality among opioid addicts increased from 1980 to 1988 [17], this increase can only be partly explained by the emergence of AIDS [18]. Cause-specific SMRs during recent decades would be helpful in studying mortality in this group of patients.

The aims of this study were to study the mortality rate and causes of death among opioid addicts who had been treated for self-poisoning or admitted to voluntary detoxification in 1980 and 1981 during a 20-year follow-up investigation. The study compared this cohort with the general population. The study's design allowed an investigation of whether participation in a detoxification programme can be protective.

Methods

Participants

The study included all opioid addicts hospitalized due to self-poisoning in Oslo in 1980, as well as all opioid addicts admitted for voluntary detoxification in 1980 and 1981 (Table 1). All patients who were discharged following treatment for self-poisoning and classified as opioid abusers in 1980 in Oslo (454,000 inhabitants) medical departments, were included. This subgroup was obtained from a larger prospective cohort study that included all patients treated for self-poisoning in Oslo medical departments in 1980 [19,20]. Patients leaving directly from the emergency room after treatment were also included in the study. The first, or the most serious, admission (i.e.,

Table 1: Opioid addicts treated at medical departments in Oslo in 1980/1981

	Self-poisonings *n* = 93	Voluntary detoxification *n* = 92	Total *n* = 185
Females	32	54	86 (46.5%)
Males	61	38	99 (53.5%)
Median age	24	23	24
Average number of admittances	1.4	1.4	1.4

according to the toxic agent used and the amount taken) was chosen as the index episode.

All opioid addicts admitted to Ullevaal University Hospital for voluntary detoxification during 1980 and 1981 were included in the study. During the late 1970s, the number of opioid addicts increased rapidly in Oslo, particularly among young people. The treatment facilities were rather poor. Therefore, from 1980, the Department of Acute Medicine (previously Medical Department 7) accepted the responsibility for treating up to three opioid addicts simultaneously. These people were in need of detoxification, either before further treatment in drug addiction units, or due to their poor overall health, Ullevaal University Hospital serving this function for the whole city [21]. Before admittance, volunteer patients were interviewed to obtain their agreement regarding the ward's rules, and they were informed that no opioids or benzodiazepines would be prescribed. They were offered neuroleptics and medication, such as alimemazin, which served as hypnotics. Their health contact person was usually present on admission. They had daily meetings with a social worker or a psychiatrist for support and planning further treatment. The staff at the units received regular supervision. About 75% of those patients who were detoxified were transferred for further planned treatment programmes. About 50% of those in a bad physical condition, left the unit before they were advised to do so. The average length of stay for the total group was 3.5 days. Although patients who had experienced an opioid drug overdose were offered interviews with a social worker or a psychiatrist, most of them were not interested in further treatment and left the hospital when they were able to do so.

The present cohort contained 185 opioid addicts treated for either self-poisoning (n = 93), voluntary detoxification (n = 75), or both (n = 17). Those who were admitted initially for self-poisoning and later for detoxification were classified in further analyses as voluntarily detoxifications, to indicate their willingness to undergo further treatment and rehabilitation. Some patients were hospitalized several times (Table 2). Since information about the status of the patients at discharge was only available for groups and not individuals, the statistical significance of this variable was not investigated. There were 99 (53.5%) males and 86 (46.5%) females. Their median age was 24 years (range 16–41), 72% of patients being in the 20–29 year age group (n = 133).

Table 2: Number of self-poisonings and voluntary detoxifications among the cohort of opioid addicts during 1980/1981

Group	*n*	%
1 self-poisoning	71	38.4
> 1 self-poisoning	22	11.9
self-poisoning *and* voluntary detoxification	17	9.2
1 voluntary detoxification	58	31.4
> 1 voluntary detoxification	17	9.2
Total	185	100.1

Design

Classification of abuse was based on patient interviews and records. The basic criteria were information about daily, or regular, use of the respective compounds, including withdrawal symptoms if the compounds were not administered.

The causes of death were classified according to the death certificates provided by Statistics Norway and grouped according to the appropriate standards. Thus, the same classification was used for both the study population and the general population. Death certificates were based on forensic autopsy records for all cases that did not involve natural causes [22]. Appropriate categories from the International Classification of Diseases (ICD) were used for deaths occurring before 1987 (ICD-8), for deaths from 1987 to 1996 (ICD-9), and for deaths from 1996 to 2000 (ICD-10). All deaths were categorized according to their major cause: cardiovascular disease, cancer, other diseases, suicide, accidents, and other violent deaths. The category, other diseases, consisted of all diseases except for cardiovascular diseases and cancer. Other violent deaths consisted of all external causes of injury, except for suicides and accidents. There was no specific cause of death for four patients, three deaths being recorded as 799 unknown (ICD-9), and one being recorded as R999 unknown (ICD-10). These cases were all classified as other diseases.

Mortality in the cohort was compared with that of the general population of Norway. Reference rates were computed in terms of five-year calendar periods and five-year age groups (15–19, 20–24, etc.) for each gender. Patients were followed to emigration, death or the end of 2000, whichever occurred first. Dates of emigration and death were obtained from the Central Population Registry. Person-time under observation, categorized by five-year calendar periods and five-year age groups (15–19, 20–24, etc.), was obtained for each gender. Mortality rates in the general population for the same cross-classification served as reference rates. The expected number of deaths was computed by multiplying the observed person-time in the cohort by the reference rates for each cell in the cross-classification, and appropriately adding the results. SMRs were computed by taking the ratio of observed to expected deaths (i.e., the ratio of the number of deaths observed in the study group to the number of deaths that would be

Table 3: Deaths and standardized mortality ratios (SMRs) for opioid addicts for each five-year period

	Self-poisonings		Voluntary detoxification		Total	
	Deaths	**SMR (95% CI)**	**Deaths**	**SMR (95% CI)**	**Deaths**	**SMR (95% CI)**
Period 1	12	28.8 (16.3–50.7)	10	38.0 (20.5–70.7)	22	32.4 (21.3–49.1)
Period 2	11	28.2 (15.6–51.0)	9	31.1 (16.2–59.7)	20	29.5 (19.0–45.7)
Period 3	11	27.5 (15.5–49.7)	5	16.0 (6.7–38.4)	16	22.5 (13.8–36.7)
Period 4	6	12.1 (5.4–26.9)	6	15.1 (7.0–33.7)	12	13.4 (7.6–23.7)
Total	40	23.5 (17.2–32.0)	30	23.8 (16.6–40.0)	70	23.6 (18.7–29.9)

expected if the study population had the same specific rates as the standard population).

Data analyses

The 95% confidence interval (95% CI) was computed for each SMR, based on the assumption that observed deaths follow a Poisson distribution. Stata release 8.0 programmes were used for survival analysis (Stata Corporation). For other data analyses, SPSS version 14.0 was used (SPSS Inc.). Comparisons between groups were performed using chi-squared tests, $P < 0.05$ being considered statistically significant.

Ethics

Permission for both the original cohort study and the follow-up study was obtained from the National Data Inspectorate and the Regional Ethics Committee, both of which agreeing that informed consent was not necessary. Asking the patients' permission in advance to check whether they had committed suicide or had died from other causes during a 20-year follow-up period was considered unethical. All data were stored anonymously by substituting a number code for each patient's name, and placing the data in the locked office of the head physician.

Results

Mortality rates

During the 20-year follow-up period, 70 of the patients died (37.8%), including 23 females (31.4%) and 47 males (48.5%). Five patients (2.7%) had emigrated, and 110 patients (59.5%) were still alive. The overall SMR was 23.6 (95% CI, 18.7–29.6). The SMR was 23.4 (95% CI, 17.6–31.1) for males, and 24.2 (95% CI, 16.1–36.4) for females, this difference between males and females being non-significant. SMR was increased in each successive five-year period following the initial self-poisoning (Table 3), the highest SMR occurring in the first five years, 32.4 (95% CI, 21.3–49.1). The median age at death was 34 years, with a range from 20 to 58.

Differences between patients treated for self-poisoning and those treated voluntarily for detoxification

Forty patients (43.0%) died among those solely discharged after self-poisonings, and 30 patients (48.4%) died among those treated voluntarily for detoxification (Table 3). The SMR was 23.5 (95% CI, 17.2–32.0) for those discharged after an episode of self-poisoning, whereas the SMR was 23.8 (95% CI, 16.6–34.0) for those who were admitted voluntarily for detoxification. The difference in SMR between groups was not statistically significant, nor were there any significant gender differences. For both groups, mortality was highest during the first five years after admittance, and remained high during the whole period thereafter.

Causes of death

The main causes of death were categorized as accidents (n = 8, 11.4%), suicide (n = 5, 7.1%), cancer (n = 3, 4.3%), other violent deaths (n = 2, 2.9%), cardiovascular disease (n = 2, 2.9%), and other diseases (n = 50, 71.4%). The other diseases category compromised the vast majority of deaths. In 37 cases (52.9% of the total), the cause of death was classified in ICD-8 and ICD-9 as category 304, Drug dependence (Table 4), and listed according to ICD-9 as a natural cause of death.

SMRs were significantly increased for all causes of death (Table 5). The other diseases category had the highest SMR, 65.8 (95% CI, 49.9–86.9). Accidental poisonings, that is overdoses, were included in the accidents category, with an SMR equal to 13.2 (95% CI, 6.6–26.4). There were five suicides among the deaths, the SMR for suicide being 10.7 (95% CI, 4.5–25.8).

HIV/AIDS caused one death among the patients in this study (Table 4), and three deaths that occurred in 1990, 1992 and 1994 were classified as immune system disorders. Additional causes of death were bronchopneumonia, Hodgkin's disease and unspecified infectious or parasitic disease.

Table 4: Deaths during follow-up that were classified as other diseases. The deaths are further specified according to the ICD systems.

Code	Title	*n*	%
304	Drug dependence	37	74.0
305	Non-dependent abuse of drugs	2	4.0
279	Disorders involving the immune mechanism	3	6.0
B20.1	HIV	1	2.0
F11.0	Psychiatric diseases and behavioural diseases caused by opiate dependence	1	2.0
F12.0	Mental and behavioural disorders due to use of cannabinoids	1	2.0
F19.0	Psychiatric diseases and behavioural diseases caused by multiple drug dependence	1	2.0
799	Unknown	3	6.0
R999	Unknown	1	2.0
Total		**50**	**100**

For the 37 deaths classified as drug dependence, an additional cause of death was mainly category 965, poisoning by analgesics, antipyretics and antirheumatics (ICD-9) accounting for 28 of the cases. For the rest of the group, acute or subacute endocarditis, unspecified bronchopneumonia, accidental poisoning by alcohol, accidental poisoning by barbiturates, and poisoning by other unspecified drugs or medicinal substances were listed.

In ICD-10, the drug dependence category per se does not exist. However, one death was classified as F11.0, psychiatric diseases and behavioural diseases caused by opiate dependence, and Hepatitis C and HIV were stated as additional causes of death. One death was classified as F19.0, psychiatric diseases and behavioural diseases caused by multiple drug dependence, with no additional cause of death listed. One death was classified as F12.0, mental and behavioural disorders due to use of cannabinoids, whereas chronic viral hepatitis B was an additional cause of death.

The numbers of deaths in each five-year period were too small to obtain cause-specific SMRs. However, causes of death were distributed evenly throughout the study period.

Discussion

This prospective study followed all hospital-treated opioid addicts from the same large city, up to as long as 20 years. All patients were traced during this period, thus minimizing selection bias. Causes of death were obtained for all patients, enabling cause-specific mortality ratios to be determined so that they could be compared with those of the general population.

This study's main finding was the high mortality rate of 37.8%. One-third of females and almost half of males died. This high mortality rate was observed in a young patient group, for which the median age during 1980 and 1981 was 24 years. When corrected for the expected number versus the observed number of deaths, SMRs showed no statistically significant gender differences. Although in absolute numbers males had a higher mortality ratio than females, the expected number of deaths among males was higher as well. Therefore, the SMRs for males and females were almost identical, there being a 23-fold increase in mortality. In this study, the effect of opioid addiction seemed to overrule the effects of age and gender on mortality.

The SMR of 23.6, found for this cohort, is similar to SMRs obtained in other long-term European studies [1], although there were differences in the inclusion criteria for these studies. SMRs were 15 times higher for male drug

Table 5: Causes of death during a 20-year follow-up of opioid addicts

Cause of death	Females	SMR (95% CI)	Males	SMR (95% CI)	Total	SMR (95% CI)
Cardiovascular disease	0	-	2	7.1 (1.8–28.4)	2	5.4 (1.3–21.5)
Cancer	2	5.1 (1.3–20.5)	1	3.3 (0.5–23.6)	3	4.3 (1.4–13.5)
Other diseases	15	63.8 (38.5–105.9)	35	66.7 (47.9–92.9)	50	65.8 (49.9–86.9)
Accidents	2	20.8 (5.2–83.2)	6	11.8 (5.3–26.2)	8	13.2 (6.6–26.4)
Suicide	3	25.9(8.3–80.2)	2	5.7 (1.4–22.9)	5	10.7 (4.5–25.8)
Other violent deaths	1	43.2 (6.1–306.7)	1	21.4 (3.0–151.8)	2	28.6(7.16–114.4)
Total	**23**	**24.2 (16.1–36.4)**	**47**	**23.4 (17.6–31.1)**	**70**	**23.6 (18.7–29.9)**

users in Rome compared with the general population [2], 22 times higher for drug injectors in Glasgow [3], and 28.5 times higher for heroin addicts in Catalonia, Spain [4].

The lack of gender differences has also been observed in other studies, such as those conducted with homeless people who had a drug addiction [23]. However, other studies have found higher SMRs for either males [8,15] or females [2,13]. This diversity of findings may be due to different inclusion criteria. Gender differences have been observed when notified addicts or drug users, who were recruited from drug treatment centres, were included whereas the present study included hospital-treated opioid addicts. Therefore, this subject sample may have been more prone to accidental poisoning, such incidents being less correlated to gender perhaps than to behavioural traits, such as the pattern of drug use. Irrespective of toxic compound, the SMR for hospital-treated opioid addicts was much higher than that for hospital-treated self-poisonings. In a 20-year follow-up study of all self-poisonings treated in Oslo hospitals in 1980, the SMR was 4.6 (95% CI, 4.1–5.1), compared with 23.6 in the present cohort [24]. Opioid addicts are therefore at special risk. There were a higher number of deaths in the first five-year period of the study, and a decrease in SMR from 32.4 in the first five-year period to 13.4 in the last five-year period. It is suggested that those who take the highest risks will probably die early, leading to a decrease in mortality for the cohort as a whole. It has been shown that the number of active drug addicts declines mainly from death, rather than from long-term abstinence [25]. The decrease in SMR may also be due partly to increased mortality in the general population over time, leading to a relative reduction in the ratio.

There was an increased mortality for all causes of death among opioid addicts when compared with the general population, including both natural and unnatural causes of death. This was consistent with what is known about substance abusers in general [13]. The causes of death were mainly drug-related, as has been observed in other studies [3,15]. Five suicides occurred in the cohort. The increased risk of suicide among opioid addicts accords with other studies [9,10]. There has been controversy about the possible existence of a substantial number of hidden suicides among accidental poisonings. So far, the results support the hypothesis that most deliberate poisonings are accidental [26,27]. In the present study, the causes of death were obtained from Statistics Norway, and our group reported on the validity of these data in 1985 [28]. Since then, autopsy rates have been declining in Norway, and the reliability of death certificates has been questioned [29]. Therefore, the suicide numbers may well be too low. Mortality in the study population was compared with mortality rates from the whole country. Although the expected lifespan is lower in Oslo than the average for the country as a whole, it is less than one year below the average. Although SMR values found in the current study may be somewhat high, this will not change the study's major findings.

Only five deaths were registered as specific natural causes of death, three being cancer and two being cardiovascular diseases. The SMRs increased significantly, possibly due to confounding factors such as lower socio-economic status or tobacco use. Nevertheless, opioid addicts represent a group that is at high risk for excess mortality, not only from drug-related deaths, but also because of their increased risk of death from cancer and cardiovascular diseases. The increased risk of death, even from natural causes, is consistent with the increased mortality associated with other mental disorders [13].

Only one death could be classified as being caused by AIDS, although three deaths were stated as "disorders involving the immune mechanism". In other studies, AIDS has accounted for a majority of the deaths among opioid addicts [4]. A study of HIV-positive opioid addicts in Oslo found that drug overdose was a major cause of death, thus overriding the effect of AIDS on mortality [30].

The major cause of death was drug dependence, as registered in the other diseases category. In order to compare this cohort with the general population, we used the same categories as Statistics Norway. Although the SMR for this single cause of death was not calculated, this value would have provided minimal additional information. If drug dependence is a chronic disease, a symptom of which is opioid addiction, one would expect that only those suffering from the disease would die from it; that is, there would be a low number of deaths in the background population. Even when all other diseases were considered in the general population, death from drug dependence outnumbers the total number of deaths from all other diseases. As the classification of drug-related deaths is problematic in the ICD system, the term "drug-related deaths", used in mortality statistics, is currently being developed by the European Monitoring Centre for Drugs and Drug Addiction.

The category, drug dependence, is not equivalent literally to any category in ICD-10. Chapter X4 can be used for accidental poisonings, whereas F10 to F19 cover psychiatric and behavioural disorders caused by drug dependence. The incongruence of these classification systems makes it difficult to know if the categories cover the same spectrum of patients.

In this study, mortality did not change from referral to voluntarily detoxification. Our hypothesis was that those treated solely for self-poisonings would have a poorer prognosis, since such people were not sent to drug addiction units on a regular basis. Sorensen et al. found a significant decrease in mortality for those who achieved abstinence [7], but in the present study, it was not known whether patients completed or discontinued the detoxification programme. Those who joined the programme voluntarily may have also been in a poorer physical condition, since this was one of the criteria for admittance. Some of the patients admitted for detoxification were transferred to other units specialising in the treatment of addicts, whereas others were admitted for a few days of detoxification in the medical department because of their extremely poor medical and physical state. Generally, these patients were not motivated to partake in treatment required to achieve abstinence, and were among those with the most serious drug addiction problems. In addition, we did not have information about the completion rate for those transferred for further treatment.

Unfortunately, in retrospect, we were unable to trace the status of each patient at discharge, but could only do so for the group as a whole. However, the high level of mortality in both subgroups supports the hypothesis that referral to a detoxification programme alone is not sufficiently effective to prevent the excess mortality for this group. Patients probably need a longer and more closely supervised follow-up, both to improve their physical health and to achieve abstinence.

Since the relatively small numbers of deaths in each category did not make it meaningful to obtain cause-specific SMRs for each time period, it was not possible to investigate how cause-specific mortality ratios change over time. Subgroups might have been used in the statistical analyses to evaluate the effect of repeated treatments on mortality. However, the resulting groups would be too small to reveal any statistically significant differences. It might be worthwhile investigating in larger studies whether there could still be a difference between patients seeking repeated treatments and other patients.

The fact that mortality in this group was quite high when compared with the general population is a great challenge to our society. It is worth emphasizing that not all drug addicts die early. More research is needed to discover what makes those patients who survive different from those who die. This information would be helpful both for choosing therapy and for identifying those at special risk.

Conclusion

The mortality rate was much higher among opioid addicts than in the general population, and most deaths were related to drug dependence. The risk of death was highest in the first five-year period, but the risk of death remained high throughout the whole 20-year follow-up period. There were no differences between those admitted for voluntary detoxification and those admitted solely for self-poisonings. Opioid addiction also seemed to override the effects of age and gender on mortality.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MAB helped obtain information on each patient's status and their cause of death, participated in the design of the study, and drafted the manuscript. ASB helped obtain information on each patient's status and their cause of death, and helped draft the manuscript. AO helped obtain information on each patient's status and their cause of death, and helped draft the manuscript. TH performed the statistical analyses. DJ obtained the cohort of hospitalized opioid addicts admitted for self-poisoning and participated in the design of the study. MR obtained the cohort of patients admitted for voluntarily detoxification. OE conceived of the study, participated in its design and coordination, and helped draft the manuscript. All authors read and approved the final version of the manuscript.

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