Benzodiazepine and opioid dependence. Clinical and meta-analytical studies.

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Benzodiazepine and Opioid Dependence
Clinical and Meta-Analytical Studies

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Abstract

The thesis contains 4 papers, two clinical studies and two meta-analyses.

In the BZD (benzodiazepine) taper study (Paper I) 21 BZD dependent (DSM-IV) patients were included for a 10-day inpatient detoxification. The average defined daily dose (DDD) was 4.7 doses. Withdrawal symptoms were not more pronounced compared to more extended detoxification procedures reported in literature. Five patients, all with concomitant codeine dependence and a more pronounced BZD tolerance, dropped out after 2-3 days.

In the dependence rate study (Paper II) the frequency of prescribed drug dependence among 130 alcohol dependent patients in open care, 23 long-term institutionalized alcoholics, and 120 healthy controls were analysed. Alcoholics were more often dependent on total prescribed drugs, BZD and zopiclone than healthy controls 17% versus 2%, 15% versus 1%, and 5% versus 0%. Institutionalized alcoholics had higher rates than outpatient alcoholics. 1/5 of the BZD dependent and 1/3 of the opioid dependent patients reported high tolerance, DDD $\geq$ 4.0 of each drug.

Common for the third and forth paper was the meta-analytical technique. In the methadone study (Paper III) 8 RCT were included with 1,511 patients. In the naltrexone review (Paper IV) 15 RCT were included with 990 patients.

In the methadone study retention in treatment was higher (d=0.90), and opioid abuse and criminality was lower (d=0.61) and (d=0.35) respectively compared to controlled conditions. Type of study design (gradual detoxification, placebo or untreated controls) could explain some of the heterogeneity found.

In the naltrexone review naltrexone was significantly better than controlled conditions in reducing the number of opioid positive urines (d=0.44). If the retention level in the experimental group increased above a certain level naltrexone was also significantly better than the controls for difference in retention (d=0.31), craving (d=1.50), re-arrest (d=0.63), and success (d=0.43). Contingency management increased retention rate and naltrexone use resulting in a reduced number of opioid positive urines.

Key words: benzodiazepine dependence, DSM-IV, withdrawal symptoms, methadone, maintenance treatment, meta-analysis, opioid dependence, RCT, naltrexone, prescribed drugs

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Clinical and Meta-Analytical Studies

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CONTENTS

Abbreviations

ANOVA	Analysis of variance between groups
AUDADIS	Alcohol Use Disorders and Associated Disabilities Interview Schedule
BZD	Benzodiazepine
CIDI	Composite International Diagnostic Interview
CM	Contingency management
d	Standard effect size
DDD	Defined daily doses
DPX	Dextropropoxiphene
DSM	Diagnostic and Statistical Manual
ECA	Epidemiological Catchment Area
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
MADRS	Montgomery Asberg Depression Rating Scale
MHSOHS	Mental Help Supplement of the Ontario Canada Health Survey
MMT	Methadone maintenance treatment
NCS	National Comorbidity Survey
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiological Survey on Alcohol and Related Conditions
NIH	National Institute of Health
NLAES	National Longitudinal Alcohol Epidemiological Survey
NSMHWB	Australian National Survey of Mental Health and Well-Being
OR	Odds ratio
PWC	Physician Withdrawal Checklist
RCT	Randomised controlled trial
SBU	Swedish Council on Technology Assessment in Health Care
VAS	Visual Analogue Scale

Original papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Johansson BA, Berglund M, Frank A.
Effects of gradual benzodiazepine taper during a fixed 10-day schedule: A pilot study
Nordic Journal of Psychiatry 51, 281-286, 1997

II Johansson BA, Berglund M, Hanson M, Pöhlén C, Persson I.
Dependence on legal psychotropic drugs among alcoholics
Alcohol and Alcoholism 38, 613-618, 2003.

III Johansson BA, Berglund M, Lindgren A.
Efficacy of maintenance treatment with methadone for opioid dependence – A meta-analytical study
Submitted

IV Johansson BA, Berglund M, Lindgren A.
Efficacy of maintenance treatment with naltrexone for opioid dependence – A meta-analytical review
Addiction 101, 491-503, 2006

Foreword

Working with benzodiazepine (BZD) dependent patients in the mid 1990s I found that patients with concomitant dependence on prescribed opioids more often dropped out of programmes compared to those without this comorbidity. Later my interest in comorbidity increased, with particular focus on alcohol, BZD and opioids. In the late 1990s I worked for the Swedish Council on Technology Assessment in Health Care (SBU). My interest in the treatment of opioids (heroin) deepened as a result of reviewing the literature on pharmacological treatment of drug dependence. Treatment regimes with both agonists and antagonists were studied at a meta-analytical level in the studies on which this thesis is based. I used two scientific approaches: firstly, the interaction between BZD and opioids and secondly, the use of both agonists and antagonists in the treatment of opioid disorders.

Introduction

Diagnoses

Two diagnostic systems are used in psychiatry. One classification system is the Diagnostic and Statistical Manual of Mental Disorders (DSM), first published in 1952 by the American Psychiatric Association. The latest revision DSM-IV-TR was published 2000 (APA 2000). The other diagnostic system, the International Classification of Diseases (ICD) goes back to 1893, and is published by the World Health Organisation (WHO) since 1948. It covers not only psychiatric disorders but also all medical diagnoses. A tenth revision, ICD-10, came into use in 1994 (WHO 1994). The DSM system is the most commonly used in research, so this classification system has been chosen for my theses.

Dependence and withdrawal

Substance dependence

Substance dependence is a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues to use the sub-

stance despite substance-related problems. In DSM-IV-TR the diagnosis is further described as a maladaptive pattern of substance use, leading to significant impairment or distress, manifested by three or more of the following symptoms, occurring at any time in the same 12-month period: tolerance, withdrawal, substance in larger amounts or in longer periods than intended, persistent desire for the substance or unsuccessful efforts to cut down, a lot of time spent obtaining the substance, using it or recovering from its effects, social activities given up or reduced, continued use despite awareness of the problem (APA 2000, p. 192-8).

Substance withdrawal

In DSM-IV-TR substance withdrawal is described as the development of a substance-specific syndrome due to cessation or reduction in substance use that has been heavy and prolonged. The syndrome causes significant distress or impairment in important functional areas (APA 2000, p. 201-9).

Specific characteristics in benzodiazepine dependence and withdrawal

Benzodiazepine dependence

The sedative, hypnotic and anxiolytic drugs include BZD and substances similar to BZD such as zolpidem, but also barbiturates and carbamates such as meprobamate. This class contains all central nervous system (CNS) depressants and includes prescribed sleeping medications and anti-anxiety medications (Schuckit 1989a). BZD dependence can develop to significant levels, indicated by both tolerance and withdrawal (APA 2000, p. 285-6).

Benzodiazepine withdrawal

The syndrome develops after a marked decrease or cessation of a heavy intake after at least several weeks of regular use. Two or more of the following symptoms develop over hours and days: autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile or auditory hallucinations or illusions, psychomotor agitation, anxiety, and grand mal seizures (APA 2000, p. 287-9).

Specific characteristics of opioid dependence and withdrawal

Opioid dependence

Tolerance for opioids develops rapidly and physical dependence develops after a short period of use. The degree of dependence varies with the potency of the drug, the dose taken, and the length of use. Cross-tolerance is common among the opioids (Schuckit 1989b). Opioid dependence includes symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if general medical conditions exist that require opioid treatment, that are used in doses that are greatly in excess of the amount needed for pain relief (APA 2000, p. 270).

Opioid withdrawal

Opioid withdrawal develops after the cessation or reduction in heavy and/or extended opioid use. At least three of the following must be present for the diagnosis: dysphoria, nausea/vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilatation or pilo erection or sweating, diarrhea, yawning, fever, and insomnia. These symptoms cause significant distress or impairment in important functional areas (APA 2000, p. 272-3).

Evidence-based treatment

Benzodiazepines

Withdrawal treatment

In 1959 the first BZD (Librium) was introduced into the market (Benzer et al. 1995). Abrupt discontinuation of BZD is associated with more severe withdrawal symptoms than tapering the drug (Busto et al. 1986; Cantopher et al. 1990; Fontaine et al. 1984; Lundkvist 2005). The optimal speed of tapering has not been established. Harrison et al. (1984) successfully detoxified 23 high-dose BZD abusers during a 10-day inpatient programme. Programmes with durations of two and four weeks, as well as longer procedures, have been described (Schweizer et al. 1990; Tyrer et al. 1983; Tönne et al. 1995; Nieman et al. 1994). Schweizer et al. (1990) tapered successfully 63 BZD dependent patients during four weeks in open care.

For non-abusing patients with legitimate prescription and with an established dependence, the British Association for Psychopharmacology recommend a graded discontinuation of the prescribed BZD. The treatment is less clear for illicit drug users with secondary dependence also of BZD (Lingford-Hughes et al. 2004). The antagonist (partial agonist) flumazenil has been used in two studies with promising results (Saxon et al. 1997; Gerra et al. 2002).

Long-term pharmacological treatment of dependence

Agonist treatment (with the exception of other BZD) has not been studied. Due to the chronic nature of anxiety, long-term low-dose BZD treatment may be necessary for some patients (O'Brian, 2005). Antagonist treatment studies are not available.

Opioids

Withdrawal treatment

Three different methods have shown positive results: two agonists (methadone, buprenorphine [partial agonist]) and one symptomatic drug (clonidine). Withdrawal treatment usually runs over one to two weeks (non-rapid). Precipitating withdrawal by adding an opioid antagonist, usually naltrexone, can shorten withdrawal treatment (Johansson 2003a).

Long-term pharmacological treatment of dependence

Agonists

Among agonists methadone, buprenorphine, and L-alpha-acetylmethadol (LAAM) have been used with good results. LAAM is no longer used in Europe, due to cardiovascular side effects (Johansson 2003b). In the present thesis only methadone will be analysed.

Methadone Maintenance Treatment (MMT)

Methadone is a synthetic narcotic analgesic developed in Germany at the end of World War II (Lowinson et al. 1992). In 1963 Dole and Nyswander began to investigate the value of using methadone to stabilise heroin addicts, thereby allowing them access to rehabilitation (Weddington 1995). Since their primary goal was rehabilitation rather than abstinence this made possible the use of narcotic medication as a means of controlling drug use and thereby making the addict accessible to rehabilitation (Lowinson et al. 1992). MMT has several advantages over heroin. Firstly, its

onset of action is slower, thereby minimising the euphoric effect. Secondly, methadone occupies the main opioid receptors, blocking the euphoria associated with the administration of heroin (competitive antagonist). Thirdly, methadone can secondary to an improved lifestyle, eliminate the risk of infection associated with intravenous drug injection and risky sexual behaviour. Finally, MMT prevents withdrawal (cross-tolerance) and thereby allows patients to function at a level that permits attention to the psychosocial aspects of treatment (O'Connor & Fiellin 2000).

Previous reviews
Farrell et al. (1994) concluded that MMT was superior to controlled conditions for opioid abuse and criminality. The NIH Consensus Conference (1998) stated that MMT diminishes opioid use, reduces transmission of HIV and hepatitis secondary to changed lifestyle and reduces criminal activity. Ward et al. (1999) reported that methadone improved health, yielded better retention, reduced heroin abuse, improved infectious-disease transmission and reduced overdose deaths. O'Connor and Fiellin (2000) stated that MMT seems to be effective in promoting relapse prevention.

Previous meta-analyses
Marsch (1998) performed a meta-analysis on 11 studies, including three RCTs (Dole el al. 1969; Gunne & Grönbladh 1981; Yancovitz et al. 1991) comparing methadone and untreated controls. The overall result was that MMT was effective among opioid dependent individuals across a variety of contexts, cultural and ethnic groups, and study designs. MMT reduced opioid use, HIV-risk and drug-related criminal behaviour. In the Cochrane Library, Mattick et al. (2003) reported on six RCT studies. They concluded that methadone appeared to be statistically more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use, but not statistically effective in criminal activity and mortality.

Antagonists
Naltrexone acts as a competitive antagonist on the opioid receptors, thereby preventing and reversing the effects, such as euphoria, produced by opioid agonists (Comer et al. 2006). Forty years ago Abraham Wikler thought that learning was essential in the development of addiction

(Jaffe 2006), so, by blocking the opioid receptors, the addict could learn to give up opioids (Kirchmayer et al. 2002b).

Previous research

Previous research has not been able to show that naltrexone is effective in long-term treatment of opioid dependence (Kirchmayer et al. 1999, 2001-2003). Kirchmayer included 11 RCTs and concluded that the material was heterogeneous and not allowed a final evaluation. In their classical negative study Hollister et al. (1978) reported a retention rate of less than 15% for unselected heroin users after eight months or more in treatment, which was similar to placebo. In the evidence-based guidelines from the British Association for Psychopharmacology, the conclusion is that there is not enough evidence to recommend naltrexone for relapse prevention in opioid dependence (Lingford-Hughes et al. 2004). Roozen et al. (2005) included seven RCTs in their review and concluded a lack of evidence about the effectiveness of naltrexone in maintenance treatment of opioid dependence.

Psychosocial interventions

Contingency management (CM) for opioid dependent patients maintained on naltrexone has been proven successful regarding retention, opioid positive urines and naltrexone ingestion (Preston et al. 1999; Carroll et al. 2001-2002). Fals-Steward and O'Farrell (2003) showed that family concealing was superior to individual treatment among opioid dependent patients maintained on naltrexone.

Benzodiazepines and opioids – dependence, similarities and differences

Heredity

In the Vietnam Era Twin (VET) Registry 7,869 male twins, who served in the US military in Vietnam 1965-1975, were structurally interviewed by phone about their use of legitimate and illicit drugs and psychopathology. People abusing sedatives had a 20% probability of also abusing opioids. People abusing opioids had a 26% probability of also abusing sedatives. A common vulnerability factor underlying the abuse of different drugs is shown. According to Tsuang et al. (1998-1999, 2001), heroin had the largest genetic influence unique to itself (0.38).

Epidemiological studies

Large epidemiological studies of general populations have examined the prevalence of drug dependence, drug use disorders and different states of comorbidity with structured clinical diagnostic interviews, *Table 1*.

Table 1 - Epidemiological studies

Studies	N	Conducted	Assessment
North America			
ECA (Regier et al. 1990), USA	20,291	Early 1980's	DSM-III
NCS (Kessler et al. 1997), USA	8,098	1990-1992	DSM-III-R, CIDI
NLAES (Grant 1995), USA	42,826	1992	DSM-IV, AUDADIS
NESARC (Grant et al. 2004, Stinson et al. 2005), USA	43,093	2001-2002	DSM-IV, AUDADIS-IV
MHSOHS (Ross 1995), Canada	9,953	1992	DSM-III, DSM-III-R, UM-CIDI
Europé			
NEMESIS (Bijl et al. 1998, de Graaf et al. 2002), Netherlands	7,076	1996	DSM-III-R, CIDI 1.1
OSLO (Kringlen et al. 2001), Norway	2,066	1994-1997	DSM-III-R, CIDI 1.1
South America			
SAO PAULO (Andrade et al. 2002), Brazil	1,464	1991	ICD-10, CIDI 1.1
Australia			
NSMHWB (Teesson et al. 2000, Burns & Teesson 2002), Australia	10,641	1997	DSM-IV, CIDI
Total sample	145,508		

Twelve-month and lifetime prevalence

The 12-month prevalence of drug dependence and drug use disorders are 1% and 2% respectively. The lifetime prevalence for drug dependence and drug use disorders are 3% and 7% respectively, *Table* 2**.** The 12-month prevalence for prescribed drug dependence (sedative dependence, tranquilizer dependence and opioid [methadone excluded] dependence) is

less than 0.5%. The lifetime prevalence for prescribed drug dependence is 2.0%, *Table 3.* The 12-month prevalence of drug use disorders in alcohol dependence is 33% (NESARC) and 17% (NSMHWB). Lifetime prevalence of drug use disorders in alcohol dependence is 47% (ECA), 32% (NCS) and 20% (MHSOHS), *Table 2.* The NESARC figures for the 12-month prevalence for alcohol use disorders in sedative dependence, tranquilizer dependence and opioid analgesics dependence are 23%, 43%, and 74% respectively (not in figure).

Table 2 - 12-month and life-time (in brackets) prevalences in percentage

Outcomes/ Studies	Drug dependence	Drug use disorders	Alcohol dependence	Drug use disorders in alcohol dependence
ECA		(6.1)		(47.3)
NCS	1.8 (7.5)	3.6 (11.9)		(32.0)
NLAES	0.5 (2.9)	(5.9)		
NESARC	0.6	2.0 (10.0)		33.1
MHSOHS			2.9 (5.9)	(20.4)
NEMESIS	0.8 (1.8)	1.0 (3.4)	3.7 (5.5)	
OSLO	0.6 (1.9)	0.9 (3.4)	6.6 (8.8)	
SAO PAULO	0.6 (1.1)		4.5 (5.5)	
NSMHWB	2.0	2.2	4.0	17.0

Table 3 - 12-month and life-time (in brackets) prevalences in percentage of prescribed drugs

Studies/ Outcomes	NCS	NLAES	NESARC	HSMHWB
Prescribed drug dependence	0.40 (3.1)	(1.0)		
Sedative dependence	0.05 (0.7)	(0.3)	0.07	
Tranquilizer dependence	0.10 (0.9)	(0.3)	0.05	
Opioids*	0.20 (0.8)		0.11	0.2

* = methadone excluded

Clinical studies

Alcohol and prescribed drugs

Alcohol dependence and its comorbidity with prescribed drugs have been addressed in clinical studies, where the patients were generally using both prescribed and illegal drugs. In summary, 10-20% of alcoholics also have a BZD drug disorder (Krypsin-Exner 1966; Ashley et al. 1978; Busto et al. 1983). Tómasson and Vaglum (1995) reported on comorbidity rates among 351 treatment-seeking alcoholics in Iceland, and 30% had a lifetime history of abusing other substances in addition to alcohol. The lifetime comorbidity rate for other substance use disorders, sedative/ hypnotic use disorders, and opioid use disorders were 32%, 21%, and 8% respectively. Martin et al. (1996) reported on 212 problem drinkers. The most common alcohol combination was cocaine 60%, marijuana 51%, sedatives 31%, and opioids (heroin excluded) 20%. Dependence rates were not reported. Caetano and Weisner (1995) reported on 381 alcoholics. 65% had used another drug than alcohol during the past 12-month period, 12% had taken sedatives and 15% had taken opioids (heroin excluded).

Benzodiazepines and opioids

BZD are often used as a secondary drug (O'Brien 2005) in opioid abusers (Smith & Landry 1990). BZD augment the euphoria obtained from other drugs or balances the side-effects of other drugs (O'Brien 2005). Busto et al. (1996) reported on the co-dependence between BZD and prescribed opioids (narcotics excluded) in a study of 30 BZD dependent patients among whom 67% also were dependent on prescribed opioids. Seivewright and Dougal (1993) reported on 33 high-dose BZD dependent subjects among who co-abuse of opioids was common (85%). Harrison et al. (1984) reported on 23 high-dose BZD dependent patients, and found that 35% were also abusing other drugs.

Co-dependence involving BZD is also frequent among patients dependent on prescribed or illegal opioids. Ng and Alvear (1993) reported on 73 dextropropoxyphene (DPX) dependent patients, of whom 38% also abused BZD. Sproule et al. (1999) analysed 124 codeine dependent subjects, and 33% had problems with sedatives/hypnotics. Ross and Drake (2000) reported on 222 Australian heroin users. 26% of these subjects had a lifetime diagnosis of BZD dependence, with 22% of the current BZD users being dependent.

Tolerance differences: benzodiazepines and prescribed opioids

The use of BZD and opioids are associated with both tolerance and dependence (APA 2000, p. 270, 285-6; Gold, 1995). BZD dependence can occur without significant tolerance (O'Brien 2005). Diazepam in ordinary doses (15 mg per day for 90 days) can generate dependence (Benzer et al. 1995). Tolerance is developed more easily in opioid use (Schuckit 1989a-b).

Changes in prescription rates of benzodiazepines and opioids

Studies on prescription rates of BZD have described populations in both North America and Europe. In a Canadian study Tu et al. (2001) conclude that the annual prevalence of BZD prescriptions dispensed for elderly decreased from 1993 to 1998. Olfson et al. (2004) reported a decrease in prescribed BZD for patients with anxiety disorders in a US population. Van Hulten et al. (1998) reported of a decrease in BZD use in a Dutch population during 1983 to 1992. In Italy from 1995 to 2003 BZD consumption remained generally stable, accounting for 18,300 DDD/1000 inhabitants (Ciuna et al. 2006). Lundkvist (2005) reports about the conditions in Sweden 2003 when the BZD DDD/1000 inhabitants was 17,000. The BZD consumption did not increase in Sweden between 2003 and 2005 (The National Corporation of Sweden Pharmacies 2006). Isacson (1997) reported a stable BZD consumption during a 13-year follow-up study in a Swedish BZD using population.

Contrary to the decreasing or stable rates of BZD use the abuse of opioid analgesics (including morphine and oxycodone) is a growing health problem. In the US, opioid analgesics accounted for 9.8% of all drug abuse in 2002, while in 1997 the corresponding figure was 5.7% (Gilson et al. 2004). The legal expansion of opioid analgesics for treatment of pain, together with extended release tablets, has increased the opportunities for abuse (Woolf & Hashmi 2004). Compton and Volkow (2006) mention that 5% of US household residents over the age of 12 abused an opioid medication in 2002. The authors mention three potential reasons behind the upsurge: an increase in prescriptions of opioids, Internet access to prescription drugs including opioid analgesics, and the changes in drug formulation

and prescribing practices. In the April 6 2006 issue of NJM Friedman makes a similar conclusion citing a teenager living in San Fransisco: "I can get prescription drugs from different places and don't ever have to see a doctor. As long as prescription pills are taken right, they are much safer than street drugs." (Friedman 2006). Henricson et al. (1999) show that the utilization of codeine containing analgesics in Sweden increased during the 1990s and that high utilization of codeine was associated with high utilization of BZD.

Aims of the present study

Paper I

To investigate clinical symptoms in BZD dependent patients during a 10-day inpatient BZD taper procedure in relation to previously published studies with longer detoxification periods.

Paper II

To assess the dependence rate of prescribed drugs among alcoholics in open and institutionalized care in relation to community controls, and to calculate the rates of high- and low-dose tolerance of prescribed drugs among alcoholics.

Paper III

To analyse the effects of methadone versus control in available RCTs using a meta-analytical technique.

Paper IV

To analyse the available RCTs on naltrexone versus control using a meta-analytical technique, and to analyse psychosocial interventions during naltrexone maintenance.

Materials and methods

Benzodiazepine taper study (Paper I)

Sample

21 consecutive self-admitted BZD dependent inpatients (7 women and 14 men with a mean age of 42 years) were included in the study, which was conducted at the Department of Alcohol and Drug Diseases (DAD) in Malmö, Sweden 1993-1995. They were all diagnosed according to DSM-IV. The patients had their first contact with the department 10 years previously and had taken BZD regularly for at least 6 months and not abused heroin in the previous three months. Thirteen subjects used BZD with a half-life longer than 15 hours (LHL) and eight subjects used BZD with shorter half-life (SHL). Defined daily doses (DDD) in the LHL and SHL groups were 5.7±4.9 and 3.2±3.9 respectively. Eleven subjects (52%) had psychiatric disorders, and 14 (67%) had one or more additional substance use disorders. Seven patients (33%) were codeine dependent with a mean daily codeine dose of 484±353 mg.

Methods

The abused BZD was used for tapering. The initial dose was similar to the self-reported daily dose. Taper went on for 10 days with a daily dose reduction of 10%. BZD plasma levels and toxicological screening were performed at base line and at irregular intervals during taper. Additionally all patients received carbamazepine, 200 mg twice a day for 21 days. Concomitant codeine abuse was abruptly discontinued. Psychiatric disorders were evaluated according to DSM-IV. Withdrawal symptoms were rated on weekdays using the Physician Withdrawal Checklist (PWC) (Schweizer et al. 1990) and the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg 1979) by the same independent rater (AF). A self-rating Visual Analogue Scale (VAS) was simultaneously administered. Registration was continued throughout the entire inpatient period. Eleven subjects stayed eight days or more after taper, generally for treatment of comorbid psychiatric symptoms. The patients' medical records were studied three months after taper. If the patients did not visit the department, they were contacted by phone or a home visit.

Limitations

Small number of participants. Control data only from literature.

Dependence rate study (Paper II)

Sample

In 1997, patients at the Department of Alcohol and Drug Diseases (DAD) in Malmö, Karlsvik Rehabilitation Centre (KRC) in Höör and healthy controls at the Kirseberg Health Centre (VCK) in Malmö, were offered to consecutively fill in an anonymous self-report concerning their possible use and dependence on prescribed drugs. The number of subjects attending was 130 open-care alcoholics at DAD, 23 long-term institutionalized alcoholics at KRC (17 coerced and 6 voluntarily admitted) and 120 healthy controls at VCK. The approximate attendance rate was 75%, 70% and 95% respectively. The setting at DAD offers an extensive outpatient treatment of alcoholics, described in detail by Österling et al. (1994). The setting at KRC offers both coercive and voluntary inpatient treatment of alcohol-dependent subjects. The mean treatment period for coercive and voluntarily treated patients at KRC is 5.5 and 4 months respectively. Sallmén et al. (1997) describe the setting in detail. VCK is a primary health care centre located in a district of Malmö with 10,000 inhabitants.

Power analysis

A total of 273 subjects were included. This sample size would identify drugs with a frequency of dependence of 10% in the clinical group and 1% in the general population with a significant level of 5% and a power of 80%, according to Altman (1994).

Methods

We developed a questionnaire based on DSM-IV to assess the dependence on prescribed drugs during the previous 12-month period. The abuse of illegal drugs was also assessed. All patients were asked if they had used one or more of the listed substances during the previous 12-month period. The questionnaire covered fourteen trademarks of BZD registered in Sweden in 1998, two BZD like substances, zolpidem and zopiclone, four analgesics containing codeine, five analgesics containing dextropropoxyphene (DPX), and three muscle relaxants. The patients were asked about length of use and the daily doses of each substance. Gender, age and oc-

cupation were also reviewed. High-dose dependence for prescribed drugs was defined as DDD ≥4.0, and the definition of low-dose dependence was set to DDD <4.0.

Statistics

Chi-square with Yates correction was used for comparing differences between proportions. 95% confidence intervals (CI) for the differences in proportions (p1-p2) were calculated according to Altman (1994). The normal approximation of the binomial distribution for the differences of rates was better than for the individual scores and the CI err by being conservative, and was therefore used in the calculations.

Limitations

Self-rated questionnaire. No psychiatric evaluation. No systematic ratings.

Common aspects in the methadone and naltrexone reviews (Papers III and IV)

Meta-analytic perspectives

Meta-analysis is a quantitative method of combining results from two or more independent studies. Four factors must be defined in formulating a question that the review will answer: the patient group, the intervention, the controls, and the endpoint to be measured. Identifying relevant RCTs through key databases, extraction procedure, and a homogeneity analysis are three additional important features of the methodology (Barker & Carter 2005).

Fixed versus random models

If the sample is homogeneous, statistics of a fixed model could be used. A fixed model assumes that each study estimates the same treatment effect and that the subjects come from the same population. If the sample is heterogeneous, a random model is used. A random model assumes that the treatment effects for individual studies represent values drawn from a population of possible treatment effects. This heterogeneity originates from differences in populations, treatments or outcome measurements that are not identical between trials (Barker & Carter 2005).

Moderator analysis

When the result in a meta-analysis is heterogeneous (p<0.05) a moderator analysis can help to find out why. The crucial thing is to identify a factor that separates the groups. An ANOVA is performed to find out whether a certain effect size is significantly higher in one of the groups compared with the other; if this is so, the factor is a moderator.

The procedures

We used the standardised mean difference effect size (d) as the measurement of all outcomes. Although there is no universal agreement on the clinical interpretation, many researchers apply the convention that 0.2-0.5 is a small but important effect, 0.5-0.8 a moderate effect, >0.8 a large effect (Berglund, Thelander & Jonsson 2003). The Hedges correction was used to adjust for small sample size bias. The correction factor is 1-[3/(4n-9)], where n equals the total number of participants in the study (Hedges & Olkin, 1985). The effect sizes were calculated with the Comprehensive Meta Analysis Software Program (Borenstein & Rothstein 1998). The program could transform means, p and t-statistics but not dichotomous variables to d. For categorical data we first calculated the odds ratio

$$OR = \frac{(x_C + 0.5)/(y_C + 0.5)}{(x_E + 0.5)/(y_E + 0.5)}$$

where 0.5 has been added to each cell in order to minimise the influence of possible zeros and small groups, according to Fleiss (1981). This precautionary measure together with the Hedges correction results in a conservative handling of the calculations. The odds ratio is then transformed into d using

$$d = \frac{2r}{\sqrt{1 - r^2}}$$

where $r = \frac{\ln OR / \mathrm{SE}(\ln OR)}{\sqrt{n_C + n_E}}$,

$$\mathrm{SE}(\ln OR) = \sqrt{\frac{1}{x_C + 0.5} + \frac{1}{y_C + 0.5} + \frac{1}{x_E + 0.5} + \frac{1}{y_E + 0.5}}$$

and $\mathrm{SE}(d) = \sigma = \sqrt{\frac{n_K + n_E}{n_K \times n_E} + \frac{(\ln OR / \mathrm{SE}(\ln OR))^2}{2(n_K + n_E - 1)}}$

according to Shadish and Haddock (1994).

The different meta-analytical calculations were also tested for homogeneity with the Comprehensive Meta Analysis Software Program (Borenstein & Rothstein 1998). A random effect model was used in all calculations. If heterogeneity was present (p<0.05), the different study designs (Paper III) and retention (Paper IV) were studied as moderators with a variance analysis (ANOVA) from the same statistical package.

Small study biases

In order to check the influence of small study biases we re-analysed the data according to Moyer et al. (2002) using only studies with sufficient power. A medium effect-size of 0.50 needs at least 23 subjects in each group to achieve a power of 0.80 at a level of significance of 0.05. Applying this to the methadone review (Paper III), the studies by Dole et al. (1969) and Gunne and Grönbladh (1981) would be excluded due to low power. Applying this to the naltrexone review (Paper IV) would exclude the studies of Lerner et al. (1992), Shufman et al. (1994), and Curran and Savage (1976). The analysis of the remaining studies gave similar results to our main analysis in both reviews and would not change the main findings.

Search strategy

A systematic search was made in Medline (1966 – June 2004 (Paper III) – October 2003 (Paper IV)), Embase, PsychINFO, PsychLITT, the Coch-

rane Central Register of Controlled Trials and in the Cochrane Database of Systematic Reviews. The following search terms were used: methadone, maintenance treatment, substance use disorders, and randomized controlled trials (Paper III) and opioid use disorders, randomized controlled trials, and naltrexone (Paper IV). The references in published articles, reviews and meta-analyses were checked. There were no language restrictions. No systematic search was made for unpublished studies.

Inclusion criteria

All studies included opioid dependent patients according to the DSM or ICD classification systems. Only studies with duration of at least 6 weeks and with a minimum of 20 patients were included (Paper III) and outpatient studies with duration of at least four weeks and a minimum of 20 subjects (Paper IV). The studies had to be randomized controlled trials comparing methadone versus controlled conditions (Paper III), and naltrexone versus control, naltrexone versus other treatments or psychosocial or psychopharmacological treatment during naltrexone maintenance (Paper IV).

Extraction procedure

All studies were systematically and independently reviewed by two authors (BAJ, MB). Differences in scorings were discussed and resolved by agreement. A professional statistician (AL) transformed categorical data to d-statistics in collaboration with the two other researchers.

Quality assessment

The Swedish Council on Technology Assessment in Health Care (SBU) checklist (Berglund, Thelander & Jonsson 2003) was used. The checklist included eleven items. The maximum score possible was 33 for individual studies and 36 for multicentre studies. In the naltrexone review (Paper IV) we also used the Jadad checklist, including three items (Jadad et al. 1996). The maximum score possible was 5 for each study. The last checklist was not applicable for studies with randomization for psychosocial treatment.

Outcome measures

All reported outcome variables were registered, categorised, and, if possible transferred into the standard mean difference (d) and used in the meta-analyses.

RESULTS

Effects of gradual benzodiazepine taper during a fixed 10-day schedule: A pilot study (Paper I)

Clinical characteristics in the different outcome groups

There were no age or sex differences between the three outcome groups: successful outcome (SO), non-successful outcome (NSO), and dropouts (D). The SO were treated longer than the NSO: 29.5±15.4 days versus 18.1±7.5 days, (p<0.01). The D-patients stayed in treatment for 5.0±2.3 days, *Table 4*.

Table 4 - Clinical characteristics for the outcome groups

	Duration of treatment (days)	DDD	BZD with short half-life	Additional substance dependence	Codeine dependence	Psychiatric disorders
Completers n = 16						
Successful n = 8	29.5±15.4 p<0.01	3.9±1.2	50%	50%	0%	75%
Non-successful n = 8	18.1±7.5	3.6±1.1	37.5%	62.5%	25%	50%
Drop-outs n = 5	5.0±2.3	7.9±3.2 p=0.001	20%	100%	100%	20%

Successful (SO) = BZD-free 3 months post taper

Non-successful (NSO) = relapse within 3 months

Benzodiazepines

The SO and the NSO did not differ with regard to DDD. The D however took significantly higher DDD (p=0.001) compared to the other groups. Among the SO 50% used BZD with SHL. Corresponding rates in the NSO and D were 37.5% and 20% respectively, *Table 4*.

Comorbidity

14/21 (67%) of the BZD dependent patients also had another substance use disorder. Of these, 12 subjects (86%) were alcohol dependent and 7 (50%) codeine dependent. 43% were dependent of more than one psychoactive drug including alcohol. 7/21 (33%) of the BZD-dependent patients were also dependent on prescribed opioids (codeine containing analgesics). Codeine dependence was only present in the NSO (25%) and the D (100%) groups. The psychiatric comorbidity rates were 75%, 50%, and 20% in SO, NSO, and D respectively, *Table 4*.

Benzodiazepine withdrawal symptoms

The five most frequent symptoms during taper according to PWC were fatigue (87%), restlessness (69%), concentration difficulties (69%), anxiety (62%) and lethargy (62%). Severe symptoms such as convulsion, confusion, delusion and hallucination did not occur. No differences were

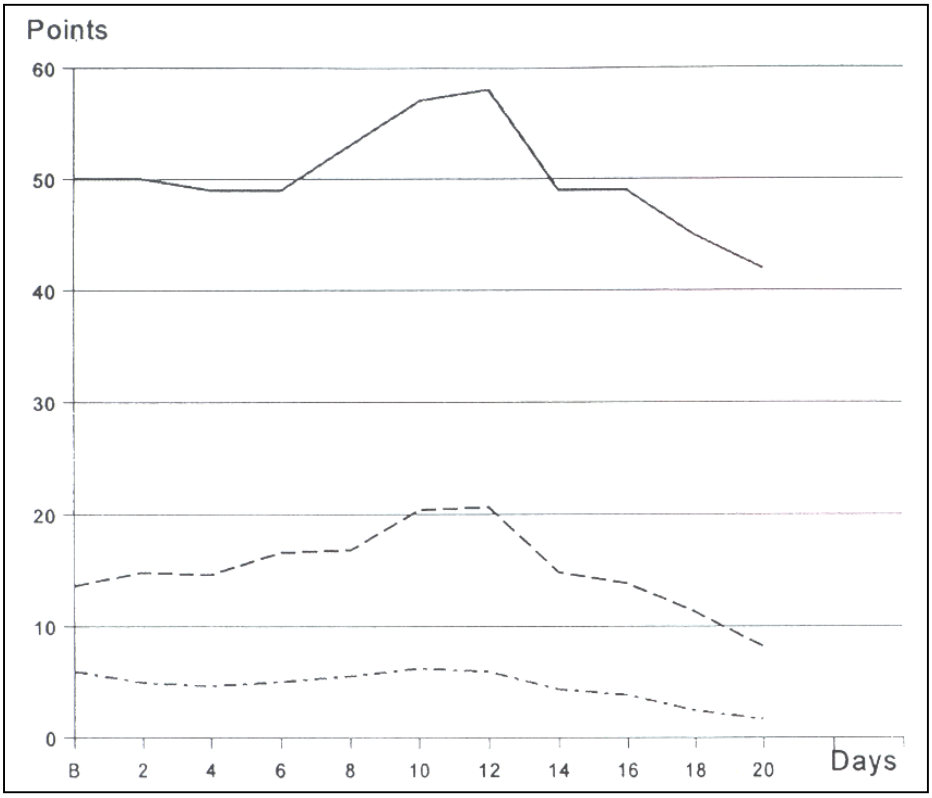

Figure 1 - Withdrawal development in 16 completers. Calculations based on arbitrary scores every 2nd day.(——) Visual analogue Scale; (-----) Physician Withdrawal Checklist; and (-.-.-.) Montgomery Åsberg Depression Rating Scale.

observed between SO and NSO. The withdrawal symptoms were modest, with peak scores between days 10 and 12. PWC increased by 52% from baseline to peak, MADRS by 5%, and VAS by 16%. One week after taper the withdrawal scores decreased below baseline, *Figure 1*.

Conclusion

It was possible to use short-term tapering in BZD dependence without additional symptoms compared to previous reports of more extended tapering procedures. Undiagnosed concomitant codeine dependence strongly influenced outcome.

Dependence on legal psychotropic drugs among alcoholics (Paper II)

Demographic characteristics

Demographic features differed noticeably between alcoholics and controls. The employment rate among the patients at Department of Alcohol and Drug Diseases (DAD), Karlsvik Rehabilitation Centre (KRC), and at Kirseberg Health Centre (VCK) were 55%, 41% and 92% respectively. The alcoholics were older and unemployed more often than the healthy controls ($p<0.001$). The alcoholics were more often male than the healthy controls ($p<0.001$).

Dependence rate on prescribed drugs among alcoholics

The total rate of prescribed drug dependent alcoholics was higher in the institutional group than in the open care setting (35% and 14% respectively). The alcoholics were more often dependent on total prescribed drugs, BZD and zopiclone than the healthy controls (17% versus 2%, 15% versus 1%, and 5% versus 0%), *Table 5*.

Illegal drugs

Illegal drugs were used more frequently among the institutionalized alcoholics than among the alcoholics in open care, 35% and 8% respectively. The alcoholics had a higher rate of illegal drug abuse than the healthy controls, 12% versus 0%.

Table 5 - Dependence on prescribed drugs among alcoholics in open and institutionalized care, respectively, and among healthy controls during the past 12-month period

Prescribed drugs	Alcoholics in open care (%) n=130	Alcoholics in institutionalized care (%) n=23	$p_1 - p_2$ (95% CI)	Alcoholics total group (%) n=153	Healthy controls (%) n=120	$p_1 - p_2$ (95% CI)
Benzodiazepines	12	30	18 (-2; 38)	15	1	14 (8; 20)
Zolpidem	3	4	1 (-8; 10)	3	0	3 (0; 6)
Zopiclone	4	9	5 (-7; 17)	5	0	5 (1; 9)
Codeine	3	13	10 (-4; 24)	5	1	4 (0; 8)
Dextropropoxyphene	2	9	7 (-5; 19)	3	1	2 (-1; 5)
Prescribed drugs	14	35	21 (1; 41)	17	2	15 (9; 21)

High- and low-dose dependence versus length of dependence

Benzodiazepines and related drugs

Only four out of a total of 23 BZD dependent alcoholics (2/16 in open care and 2/7 in institutionalized care) had developed a high-dose BZD dependence. None of the five zolpidem- or the seven zopiclone dependent alcoholics had developed a high-dose dependency. In open care, mean DDD for low-dose BZD dependence was 1.1±0.6 and for high-dose BZD dependence 11.5±9.2. Among the institutionalized alcoholics, the mean DDD for low-dose BZD dependence was 1.7±1.0 and for high-dose BZD dependence 5.5±0.7. The mean DDD for zolpidem- and zopiclone-dependent patients in open care were 1.4±0.7 and 1.1±0.5 respectively. In institutionalized care, the figures were 1.0 and 1.5±0.7, respectively. There was no positive correlation between DDD and length of use, *Figure 2*.

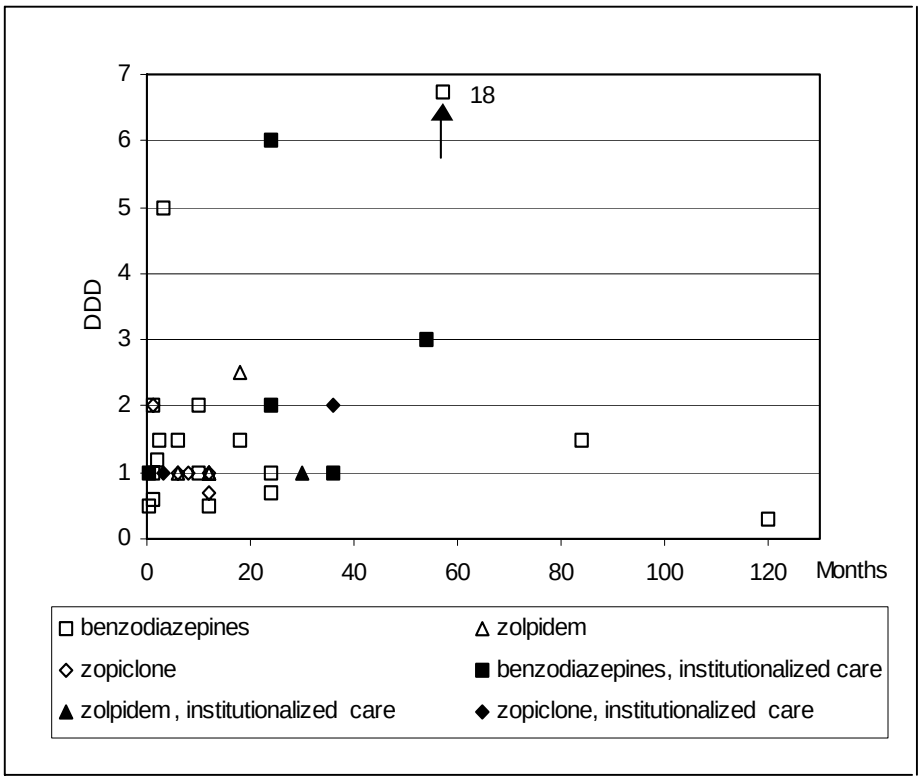

Figure 2 - Dependence on benzodiazepines and related drugs among alcoholics in open and institutionalized care, respectively, related to reported length of dependence. Only the highest DDD for each patient was selected.

Legal opioids

Two codeine dependent alcoholics out of a total of 7 had developed high-dose codeine dependence. Both patients were treated in open care. None of the five DPX dependent alcoholics had developed high-dose DPX dependence.

Conclusion

Alcoholism is associated with prescribed drug dependence and illegal drug misuse. High-dose BZD dependence is infrequent among BZD dependent alcoholics.

Efficacy of maintenance treatment with methadone for opioid dependence – A meta-analytical study (Paper III)

Characteristics of individual RCT

Table 6 shows an outline of the eight RCT on methadone maintenance included in the study compared with controlled conditions. A total of 1,511 subjects were included in the different studies. Four were published in the US, one in Sweden, one in Thailand, one in China and one in Australia. One study was published per decade in the 1960s, 1970s and 1980s. Three studies were published in the 1990s and two studies were published between 2000 and 2003.

Table 6 – Included studies, methadone versus control

Studies		Number	Weeks	Design
Dole et al.	1969	28	50	Untreated
Newman & Whitehill	1979	100	156	Placebo
Gunne & Gröhnblad	1981	34	104	Untreated
Yancovitz et al.	1991	301	64	Untreated
Vanichseni et al.	1991	240	6	Gradual detoxification
Strain et al.	1993 1994	95 (247)	26	Placebo
Sees et al.	2000	179	26	Gradual detoxification
Dolan et al.	2003	382	17	Waiting list

Types of outcome

Our technique made it possible to include most of the available studies (7/8) in three separate meta-analyses. Opioid abuse was used as an outcome in all studies. 6/7 studies evaluated retention and 5/7 criminality. A total of 18 results – 14 dichotomous and 4 continuous variables – were included in the meta-analysis. The outcome measures were sub-classified according to type of control group: gradual detoxification, placebo and untreated controls respectively. Outcome measures for retention, opioid abuse and criminality were presented in meta-analyses.

Other outcomes not analysed in the meta-analyses were: mortality (3), employment or school (1), psychosocial functioning (1), rehabilitation (1), Addiction Severity Index (ASI) (2) (Bergman et al. 1996), depressive symptoms (1), withdrawal symptoms (1), dose adequacy (1), shared syringes (1), HIV prevalence (1), HCV incidence (1), HIV risk behaviour (1), methadone (non-prescribed) abuse (1), amphetamine/ cocaine abuse (4), barbiturate abuse (1), benzodiazepine abuse (1), and alcohol abuse (2).

Meta-analyses

The results of the meta-analyses for retention, opioid abuse and criminality are presented. The combined analyses, expressed in standard mean differences (d), were all significant: d=0.90, d=0.61 and d=0.35 respectively. Test for heterogeneity was significant for all three analyses, but in the subgroups (3/7) were homogeneous. Type of study design was a significant moderator in 5/9 comparisons. All three comparisons were significant for retention, concerning abuse (gradual detoxification versus untreated controls), and criminality (gradual detoxification versus untreated controls). The meta-analysis for abuse is presented in *Figure 3*.

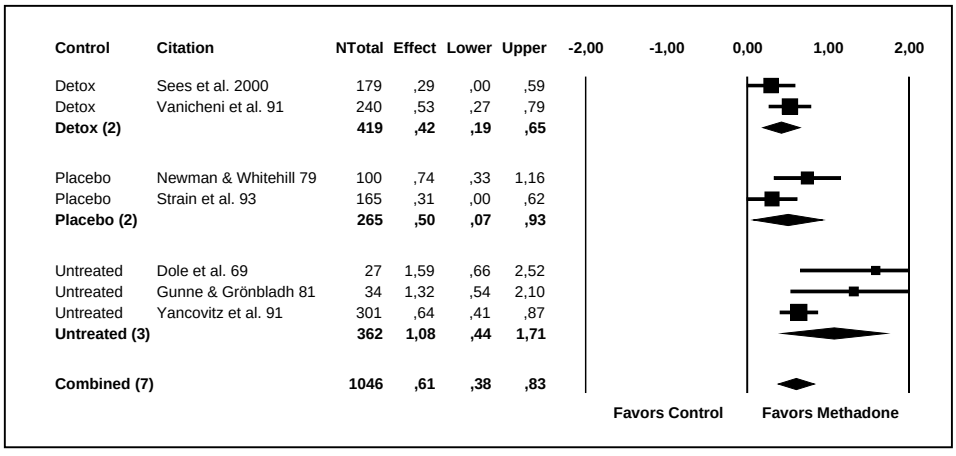

Figure 3 - Standardized mean differences. Methadone versus non-active control related to different study design. Outcome measure: abuse. Detoxification group d = 0.42 (0.19, 0.65). Placebo group d = 0.50 (0.07, 0.93). Untreated group d = 1.08 (0.44, 1.71). Combined analysis d = 0.61 (0.38, 0.83).

Conclusion

Methadone maintenance treatment in opioid dependence shows positive effects on retention, opioid abuse and criminality compared with controlled conditions. Type of study design could explain some of the heterogeneity found. A different meta-analytical approach made it possible to confirm effects of methadone on retention and opioid abuse from previous studies and document effect on criminality.

Efficacy of maintenance treatment with naltrexone for opioid dependence – A meta-analytical review (Paper IV)

Included studies

Fifteen studies fulfilled the inclusion criteria and were included in the analysis. Of the 15 studies, eight were published in the US, six in Europe and one in China. Three studies were published in the late 1970s, eight in the 1990s and four studies between 2001 and 2003.

Ten studies with a total of 595 subjects compared naltrexone versus control, *Table 7*.

Table 7 - Included studies, naltrexone versus control

Studies		Number	Weeks	Design	Follow-up (months)
Curran & Savage	1976	38	36	Placebo	-
Hollister et al.	1978	124 (192)	32	Placebo	6
Rawson et al.	1979	58	38	Psycho-social	12
Ladewig	1990	20	On-going	Psycho-social	-
San et al.	1991	50	26	Placebo	6
Lerner et al.	1992	31	8	Placebo	12
Shufman et al.	1994	32	12	Placebo	12
Gerra et al.	1995	142	11	Placebo	3
Cornish et al.	1997	51	26	Psycho-social	-
Guo et al.	2001	49	26	Placebo	-

Five studies (n=364) compared different psychosocial interventions during naltrexone maintenance, *Table 8*. One study (Rawson et al. 1979) was included in both the first and second analysis.

Table 8 - Included studies, naltrexone maintenance (all) with psychosocial interventions

Studies		Number	Weeks	Design	Follow-up (months)
Rawson et al.	1979	43	38	Behaviour therapy	12
Preston et al.	1999	58	12	Contingency Management	-
Carroll et al.	2001	127	12	Contingency Management	-
Carroll et al.	2002	55	12	Contingency Management	6
Fals-Stewart & O'Farrell	2003	124	24	Family versus individual	12

Naltrexone versus control

Outcome variables

Six outcomes variables were found during the study period, and three outcomes in the follow-up period, *Table 9*. The nine outcomes were used in the calculations.

Table 9 - Outcome variables, naltrexone versus control

6 outcome variables during study period	
Differences in retention	10 studies
Opioid positive urines	10 studies
Success	3 studies
Psychiatric symptoms	2 studies
Craving	2 studies
Re-arrests	1 study
3 outcome variables during follow-up period	
Opioid abuse	6 studies
Psychiatric symptoms	2 studies
Re-arrests	1 study

Differences in retention levels in the experimental group

In *Figure 4* the included studies are plotted with retention in the experimental group as a function of duration. Ladewig (1990) was excluded from analysis because the study was ongoing. The classical negative study by Hollister et al. (1978) was used as a reference. The retention figures of the studies are compared with the same time figure in Hollister's retention curvature. The increase in retention rate (%) compared to Hollister et al. (1978) was measured manually. Due to differences in methodology in reports of retention, the studies could only be grouped as high retention and low retention studies, and no regression analysis could be performed.

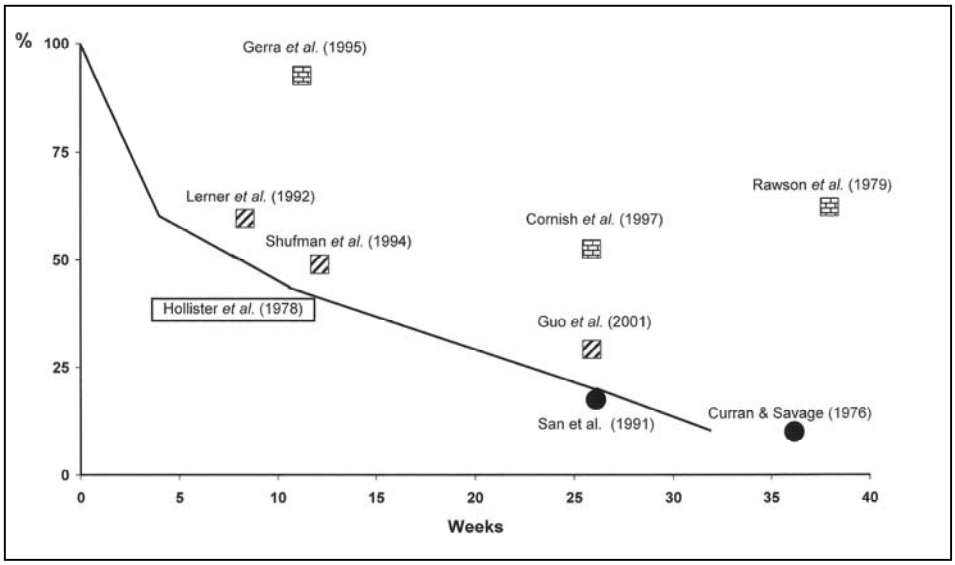

Figure 4 - Naltrexone versus control. Study period. Included studies plotted with retention in the experimental group as a function of duration. Hollister et al. (1978) is used as a reference.
Increase in retention rate compared to Hollister:

30-50% *10%* *The same retention as Hollister*

Three studies (Gerra et al. 1995; Rawson et al. 1979; Cornish et al. 1997) report higher retention rates (49%, 51%, and 31% respectively) than Hollister et al. (1978). Gerra et al. (1995) and Rawson et al. (1979) had included subjects who were already on naltrexone, and Cornish et al. (1997) included subjects on probation. This probably explains the high retention levels. Three studies (Lerner et al. 1992; Shufman et al. 1994; Guo et al.

2001) show an increase in retention compared to Hollister and co-workers of about 10%. Two studies (San et al. 1991; Curran & Savage, 1976) report the same retention rate as Hollister. The two groups with three studies respectively with higher retention rates than those of Hollister were homogeneous with no outcome differences and were clustered together. They are called high-retention studies in the forthcoming analysis.

Moderator analysis

In the total group, all outcomes with the exception of differences in retention and psychiatric symptoms (follow-up) were heterogeneous. Retention in the experimental group was found to be a moderator, explaining most of the heterogeneity found. An ANOVA analysis between the high and low retention groups showed a significant difference between the groups for all outcome variables except psychiatric symptoms (follow-up), i.e. naltrexone was significantly more effective in the high retention group than in the low retention group in relation to controlled conditions. In the high retention group, differences in retention and opioid abuse (follow-up) were homogeneous, while in the low retention group all variables were homogeneous.

Efficacy analysis

Opioid positive urines (*Figure 5*), craving and psychiatric symptoms (follow-up) were significantly better in the total naltrexone versus control group. In the high retention group, naltrexone was significantly better than controlled

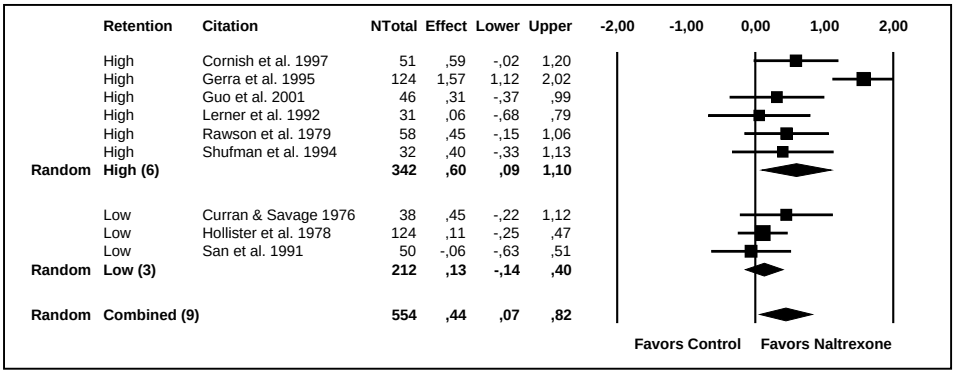

Figure 5 - Meta-analysis. Naltrexone versus control. Outcome measure: opioid positive urines. High retention group d = 0.60 (0.09, 1.10) Low retention group d = 0.13 (-0.14, 0.40). Combined analysis d = 0.44 (0.07, 0.82).

conditions for the following outcomes: differences in retention *(Figure 6)*, opioid positive urines, success (1 study), craving (1 study) and re-arrests (1 study). For opioid abuse (follow-up) the level of significance was not reached. In the low retention group, naltrexone showed better results for craving (1 study) and psychiatric symptoms (follow-up) (1 study).

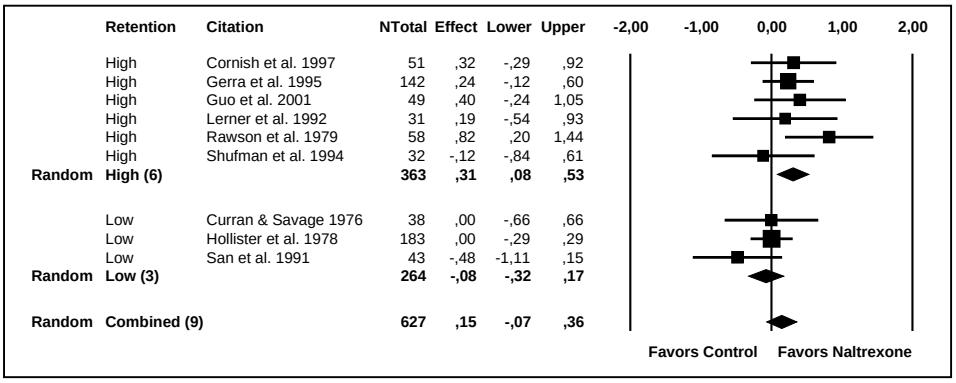

Figure 6 - Meta-analysis. Naltrexone versus control. Outcome measure: differences in retention. High retention group d = 0.31 (0.08, 0.53) Low retention group d = -0.08 (-0.32, 0.17). Combined analysis d = 0.15 (-0.07, 0.36).

Naltrexone treatment with/without psychosocial or psychopharmacological interventions

Outcome variables

Five outcomes were found for the psychosocial studies, three during the study period and two during follow-up, *Table 10*.

Table 10 - Outcome variables, naltrexone maintenance (all) with psychosocial interventions

3 outcome variables during study period	
Differences in retention	5 studies
Opioid positive urines	5 studies
Naltrexone ingestion	5 studies
2 outcome variables during follow-up period	
Abstinence/opioid abuse	3 studies
Re-incarceration	1 study

Efficacy analysis

The three studies with contingency management (CM) were analysed together. All variables were homogeneous. CM improved retention, opioid positive urines (*Figure 7*) and naltrexone ingestion compared to controlled conditions.

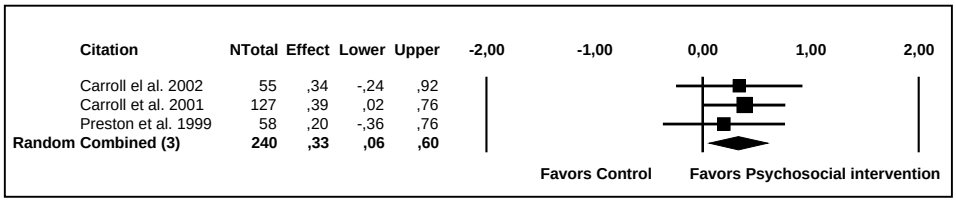

Figure 7 - Meta-analysis. Naltrexone treatment with/without psychosocial interventions. Outcome measure: opioid positive urines d = 0.33 (0.06, 0.60).

Conclusion

Studies with a certain level of retention in the experimental group demonstrated better outcomes than controlled conditions in meta-analyses. Contingency management could increase the retention rate in naltrexone maintenance.

General discussion

Benzodiazepines and prescribed opioids

The basic knowledge about BZD and opioids including prescribed codeine or dextropropoxyphene (DPX) is well known. Both substances are associated with tolerance, dependence, withdrawal (DSM-IV-TR) and comorbid alcohol dependence (Tómasson & Vaglum 1995; Caetano & Weisner 1995; Martin et al. 1996). Tolerance develops rapidly to most opioids, BZD seems to be associated with a less strong tolerance (Schuckit 1989a-b). BZD and opioid withdrawal can be treated with agonists – other BZD and methadone respectively. Two promising studies on flumazenil in BZD withdrawal treatment have been published (Saxon et al. 1997; Gerra et al. 2002). Treatment with agonists and antagonists for long-term treatment of BZD dependence has not been established. For opioid dependence, treatment with agonists has been proven effective (Mattick et al. 2003). Until our study on naltrexone (Paper IV), treatment with antagonists had shown inconclusive results (Kirchmayer et al. 1999, 2001-2003; Roozen et al. 2005; Minozzi et al. 2006). Co-dependence between BZD and opioids (both illegal and prescribed) is common (Harrison et al. 1984; Ng & Alvear 1993; Busto et al. 1996; Sproule et al. 1999; Ross & Darke 2000), but the interaction between the two substances is not well known.

Benzodiazepine withdrawal – issues on tapering speed and opioid influence

In the BZD taper study (Paper I) it was shown that it is possible to perform a ten-day indoor BZD detoxification procedure without additional withdrawal symptoms compared to more traditional, extended procedures described by Schweizer et al. (1990). There is still insufficient knowledge about optimal tapering speed. The design in our pilot study had limitations – for example, the small number of participants and controls only from literature. Another finding was that undiagnosed codeine dependence was present in all dropouts. It is reasonable to assume that untreated opioid withdrawal symptoms contributed to patient dropout.

Dependence on alcohol and prescribed drugs

Our outpatient alcoholics had a similar rate of BZD comorbidity to that reported in the literature. Busto et al. (1983) and Ross (1993) reported that 10-20% of alcoholics developed a concomitant BZD misuse or dependence. One finding in the dependence rate study was that institutionalized alcoholics were more often dependent on prescribed drugs (35%) than alcoholics in open care (14%). Alcoholics in general (17%) were more dependent than healthy controls (2%).

Different severity for different severity of alcoholism

The institutionalized alcoholics probably had a more severe form of alcoholism including a more pronounced tolerance. They were more often dependent on prescribed drugs. Thus, severity of alcohol dependence seems to be related to rate of prescribed drug dependence.

Dependence on both benzodiazepines and codeine

In the BZD taper study (Paper I), 33% of the subjects were also codeine dependent. Among the 23 BZD dependent patients in the dependent rate study (Paper II), 26% were co-dependent on prescribed opioids. These results differ from those of Busto et al. (1996) who reported a co-dependency rate of 67%. The difference in prevalence might be explained by differences in tolerance. Busto and colleges included patients with an average diazepam DDD of 14.0. In our taper study the patients had an average diazepam DDD of 4.7. In the dependence rate study only 17% of the BZD dependent alcoholics had a DDD ≥4. These findings support the suggestion that codeine dependence is related to a higher level of BZD tolerance.

Eight of eleven (73%) codeine or DPX dependent alcoholics in the dependence rate study (Paper II) were also BZD dependent. These results differ from both Sproule et al. (1999) and Ng and Alvear (1993) who reported co-dependence rates of 33% and 38% respectively among their patients who also abused alcohol, 15% and 8% respectively. Our small sample prevents the possibility of drawing any certain conclusions concerning the cause of the differences.

High versus low tolerance

In order to understand the findings above it is important to discuss high and low tolerance. In Paper II we evaluated high- and low-dose BZD- and codeine dependence among alcoholics, and this had not previously been done in a systematically sampled, clinical population. The categorisation in high-dose versus low-dose BZD dependence divided the 23 BZD dependent alcoholics into one large group with no increase in tolerance and one small group (4 subjects) with a considerable increase in tolerance. In the latter group all four subjects had used cannabis, three had used amphetamines and two opioids. This observation has according to our knowledge not previously been reported in a systematic way.

A valuable concept is the classification in poly-drug versus multi-drug abusers, introduced by Kaufman (1976) and further developed by Schuckit (1989c). Polydrug involvement indicates the use of more than one psychoactive substance, not including opioids, whereas multidrug use involves two psychoactive substances other than alcohol, nicotine, caffeine, or prescribed medications. The opioid dependent subjects (7/21) in Paper I all had a high level of both codeine and BZD tolerance, >4 DDD respectively. Four had additional substance use disorders. In the dependence rate study (Paper II) the small group of high-dose BZD dependent alcoholics (4/23) consisted of men under 40 years of age. Two were dependent of more than one legal prescribed drug. All four had used cannabis; three had used amphetamine and two opioids during the past 12 months. The mechanisms behind these findings are not very well known. Personality traits and personality disorders may influence (Schuckit 1989c; Fridell 2006). Thus, subjects with multidrug abuse often have a more pronounced tolerance of BZD than polydrug abusers.

Issues of meta-analyses

The technique used in the meta-analyses is based on transformation of all outcome variables into d-statistics and analysis of homogeneity. If the results were heterogeneous a search was made for moderators to explain the heterogeneity. The technique is similar to that used by Moyer et al. (2002). Moyer's study was acknowledged as an important contribution to the field and was published in Addiction, the top ranked journal on addiction medicine. Some authors have criticized components used in this technique (Poikolainen 2002); firstly, for transforming dichotomous vari-

ables into continuous variables, and secondly for using heterogeneous studies in the same analysis using randomized techniques (Poikolainen 1999, Kirchmayer et al. 1999, 2001-2003). We acknowledge these objections but do not consider that they make our main findings invalid. Study design (Paper III) and retention in treatment (Paper IV) turned out to be moderators explaining most of the heterogeneity found.

Methadone review

Mattick et al. (2003) reported on six studies and concluded that methadone was more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use, but not statistically effective in criminal activity and mortality. Fourteen dichotomous results were included. Continuous variables were excluded. The material is described in five meta-analyses: retention in treatment (n=3), morphine positive urines (n=2), self-reported heroin use (n=3), criminality (n=3), and mortality (n=3). The test of heterogeneity was non-significant in all the analyses except retention, indicating that treatment effects were homogeneous. One explanation to this might be the small number of included studies and outcomes in each separate analysis.

In the present meta-analysis, continuous outcomes were reported in two studies (Strain et al. 1993-1994; Sees et al. 2000) with four separate results. Their d-values are at the same magnitude as the d-values from the dichotomous variables. One difference between the present study and that of Mattick et al. (2003) was that we included two extra studies: Sees et al. (2000) and Dolan et al. (2003). We transformed both dichotomous and continuous variables into a common effect measurement (d), while Mattick and co-workers included dichotomous variables only. With our approach we could include two more results compared to Mattick and collaborators, criminality from Strain et al. (1993-1994) and from Sees et al. (2000). We also made a moderator analysis using the type of study design as moderator, which explained some of the heterogeneity. Contrary to Mattic and collaborators we did not perform a meta-analysis on mortality because mortality rates in the control groups differed more than fivefold between the different studies.

The main results of the present paper are that methadone increases retention in treatment and reduces opioid abuse and criminality compared to controlled conditions in outpatients, and reduces opioid abuse in prisoners. The type of design influenced the effect sizes. The results are generally comparable with those of Mattic and co-workers even if the techniques were different.

Naltrexone review

Kirchmayer et al. (1999, 2001-2003) included 11 studies. A recent update of these reports shows similar results (Minozzi et al. 2006). Kirchmayer and colleagues sub-grouped the studies in five categories of different study designs and analysed only one category at a time for outcome. There were three meta-analyses with 4, 2, and 2 studies respectively.

We found nine outcome variables (during the study period) that could be transformed into effect sizes including difference in retention (10 studies), opioid positive urines (10 studies), success (3 studies), psychiatric symptoms (2 studies), craving (2 studies), re-arrests (1 study), and for the follow-up period opioid abuse (6 studies), psychiatric symptoms (2 studies), and re-arrests (1 study). Seven outcome variables were analysed in separate meta-analyses.

The five categories in Kirchmayers paper (2002b) were naltrexone versus placebo, naltrexone versus placebo plus behaviour therapy for both groups, naltrexone versus placebo after pre-treatment with naltrexone for both groups, naltrexone plus behaviour therapy versus behaviour therapy alone, and naltrexone versus behaviour therapy. This technique possibly means that the studies become more homogeneous in terms of design. However, most of the features defining the categories were inclusion or non-inclusion of behaviour therapy. It is not obvious that these differences a priori make it obligatory to divide the material into categories before analysis. On the contrary, general psychotherapy research report on a common outcome phenomenon for all types of psychotherapy, possibly because of the strong influence of common effects (Lambert, Garfield & Bergin 2004). In our analyses behaviour therapy was not a moderator. Even if there are advantages in defining groups that have similar design, the small number of studies obviously decreases the power of the analysis. Our large comparisons were also surprisingly homogeneous,

supporting the solid nature of our approach. We found that the differences in retention rates were a moderator, explaining most of the heterogeneity found.

Roozen et al. (2005) included seven RCTs and we used six of them in our analysis. Roozen and co-workers mention that the material showed wide heterogeneity in population, intervention and outcome assessment, and concluded that statistical pooling was not justifiable.

In our review of the influence of naltrexone on opioid dependence, we concluded that naltrexone above a certain retention level was effective, which not has been shown in previous reviews (Kirchmayer et al. 1999, 2001-2003; Roozen et al. 2005; Minozzi et al. 2006). The effect on differences in retention was 0.31 and on opioid positive urines 0.60.

Influence of psychosocial treatment on retention

RCTs have shown that psychosocial interventions can increase retention in treatment of opioid-dependent patients maintained on naltrexone. Contingency management (CM) is more effective than non-CM for opioid dependent patients maintained on naltrexone (Preston et al. 1999; Carroll et al. 2001, 2002). Behavioural family counselling has been proven more effective than individual-based treatment (Fals-Stewart & O'Farrell 2003).

Differences in effect sizes – issues of retention

An important aspect of the technique used is that differences in effect sizes could be understood in a more integrated way. In his paper *A Better Widget*, Berglund (2005) suggests that different types of treatment, for example agonists and antagonists, have different level of effectiveness. The effect size for methadone was 0.90 and the corresponding figure for naltrexone was 0.30 in his paper. The variation could be explained by differences in design but could probably also illustrate actual differences. The agonists are more effective but might also produce more side effects as a dependence development.

Suggested research in the future

A more profound understanding of the relationship between tolerance and dependence of BZD and opioids are called for. Why is abuse of opioids associated with high dose BZD dependence? Future research will probably include molecular genetic approaches and neuro imaging techniques.

A new field is also the development of drugs for treatment of BZD withdrawal, flumazenil, a BZD receptor antagonist with a small agonist activity (Saxon et al. 1997; Gerra et al. 2002).

The field of naltrexone depot development has done important progress during late years (Foster et al. 2003; O'Neil 2005). The first randomized controlled trial has recently been published (Comer et al. 2006) and show a better effect with sustained release naltrexone compared with placebo.

General conclusions

- BZD taper with a daily 10% reduction shows similar efficacy as more extended tapering procedures described in literature. Concomitant codeine dependence is associated with worse prognosis (Paper I).

- Alcohol dependent subjects have a rate of dependence on prescribed drugs of 17%, including BZD dependence 15% and dependence of prescribed opioids 8%. The total rate of prescribed drug dependence was higher among institutionalized alcoholics (35%) compared with alcoholics treated in open care (14%). Only a small group of BZD dependent alcoholics developed a high-dose BZD dependence (Paper II).

- Methadone maintenance treatment in opioid dependence shows robust effects for retention, opioid abuse and criminality compared with controlled conditions. Type of study design could explain some of the heterogeneity found (Paper III).

- Naltrexone for opioid dependence is effective if the retention rate is increased above a certain level. Retention is the key variable for understanding the mechanisms of the effect of naltrexone in opioid dependence. The retention rate can be increased by the different psychosocial interventions (Paper IV).

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Populärvetenskaplig sammanfattning (summary in swedish)

Livstidsprevalensen för läkemedelsberoende hos alkoholberoende patienter varierar mellan 20% och 45%. I normalbefolkningen är livstidsprevalensen av läkemedelsberoende cirka 2%; livstidsprevalensen för beroende av benzodiazepiner (BZD) respektive legala opioider (metadon exkluderat) är 0.3-0.9% respektive 0.8%. Förskrivningen av BZD har de senaste åren legat konstant eller visat en svagt neråtgående trend både i Nordamerika och Europa, medan förskrivningen av legala opioider ökat.

Avhandlingen består av fyra delarbeten, två kliniska studier med patienter från Beroendecentrum i Malmö, samt två meta-analytiska arbeten. I de två sista studierna undersöktes behandlingseffekten av metadon respektive naltrexon genom att systematiskt gå igenom litteraturen och analysera samtliga studier som använt en randomiserad, kontrollerad metodik.

I det första arbetet inkluderades 21 BZD beroende (DSM-IV) patienter som avgiftades inneliggande under 10 dagar. Deras genomsnittliga definierade dygnsdos (DDD) var 4.7 doser. 52% hade även en annan psykiatrisk diagnos och 67% hade också ett annat, samtidigt missbruk. Behandlingen utgick från det preparat och den dos patienten missbrukat. Under behandlingen minskades dosen med 10% per dag. Förloppet studerades med bl a Physician Withdrawal Checklist. Abstinenssymptomen var inte mer uttalade än vid längre avgiftningar som rapporterats i litteraturen. 16 patienter, varav två med ett samtidigt kodeinberoende, fullföljde behandlingen, medan fem patienter, alla med ett samtidigt kodeinberoende och en mer uttalad BZD tolerans avbröt avgiftningen redan efter två-tre dagar.

I den andra studien redovisas frekvensen av läkemedelsberoende hos 130 alkoholberoende öppenvårdspatienter. Denna grupp jämfördes med 23 alkoholberoende patienter inskrivna på institution (LVM-hemmet Karlsvik) samt med 120 hälsokontroller. Konsekutiva patienter och hälsokontroller fick anonymt fylla i ett frågeformulär med frågor om tablettbero-

ende och missbruk av illegala droger den gångna 12-månadersperioden. Alkoholberoende patienter var i större utsträckning än hälsokontroller beroende av läkemedel, 17% mot 2%. Bland samtliga alkoholberoende patienter var 15% beroende av BZD och 8% av läkemedel innehållande opioider. Av de alkoholberoende patienterna i öppen vård var 12% beroende av BZD och 5% av analgetika innehållande opioider. Patienterna som vårdades på institution rapporterade högre frekvenser, 30% respektive 22%. En femtedel av de BZD beroende och en tredjedel av de opioidberoende patienterna rapporterade en hög tolerans (DDD ≥ 4.0) av respektive drog. Missbruk av illegala droger var vanligare bland institutionsvådade alkoholister än bland patienter i öppen vård, 35% respektive 8%.

Gemensamt för det tredje och fjärde arbetet var den meta-analytiska tekniken. Samtliga inkluderade studier granskades systematisk och oberoende av två bedömare. Samtliga utfallsmått identifierades. Både dikotoma och kontinuerliga variabler omvandlades till standardiserade scores (d). Effektstorleken 0.2-0.5 bedömdes vara en liten men betydelsefull effekt, 0.5-0.8 en moderat effekt och > 0.8 en hög effekt. För de statistiska beräkningarna användes en random model. Om materialet var heterogent gjordes en moderator analys för att undersöka vilken faktor som delade grupperna åt. En ANOVA analys gjordes för att undersöka om en viss effektstorlek var högre i någon av grupperna. Om signifikanta skillnader hittades innebar detta att faktorn var en moderator.

I metadonarbetet inkluderades åtta RCT studier med totalt 1,511 patienter. Effektmåtten kvarstannande, missbruk och kriminalitet analyserades med meta-analytisk teknik.

I naltrexonstudien inkluderades 15 RCT studier. Tio RCT studier med totalt 595 patienter jämförde naltrexon mot kontroller. Sex effektmått (skillnader i kvarstannande, opioidpositiva urinanalyser, framgångsrik behandling (drogfrihet under hela behandlingstiden), psykiatriska symptom, merbegär (”craving”) samt ny fängelsedom) analyserades under studieperioden. Tre effektvariabler (opioidmissbruk, psykiatriska symptom samt ny fängelsedom) analyserades under uppföljningsperioden. Vidare inkluderades fem RCT studier med 394 naltrexonbehandlade patienter som randomiserades till olika psykosociala behandlingsmetoder, bl a kontingensförstärkning under samtidig naltrexonbehandling. Här analyserade totalt fem effektmått.

I metadonarbetet bekräftades att metadon var effektivt vid opioidberoende; kvarstannandet i behandlingen var högre (d=0.90) och missbruk samt kriminalitet var lägre (d=0.61) respektive (d=0.35) jämfört med kontrollerna. I analysen framkom att effektstorleken var beroende av vilken typ av vetenskaplig design (kontrollgrupp) som använts.

I naltrexonstudien framkom att kvarstannandet i behandling var en avgörande faktor för behandlingseffekten. Graden av kvarstannande var en moderator som förklarade det mesta av den heterogenitet som framkom i analyserna. Naltrexon var signifikant bättre än kontrolltillstånden på att minska antalet opioidpositiva urinanalyser (d=0.44). Om retentionen i experimentgruppen översteg en viss nivå var naltrexon även signifikant bättre än kontrollerna avseende skillnad i retention (d=0.31), merbegär (d=1.50), ny fängelsedom (d=0.63) samt framgångsrik behandling (d=0.43). Med hjälp av kontingensförstärkning kunde kvarstannandet i behandlingen öka, vilket medförde att opioidmissbruket minskade.

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