Abstinence-orientated replacement therapy for opioid dependence

Dissertation (Dr. philos)

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Summary

BACKGROUND

Opioid dependence is associated with substantial medical, psychological and social problems. Long-term opioid replacement therapy is the most common treatment option internationally. According to Norwegian health authority regulations, medication-assisted rehabilitation (MAR) is generally only available for persons aged 25 years or more who have treatment experience from non-medical programmes. The aim of this research project was to assess the feasibility of short-term buprenorphine replacement therapy programmes for dependent opioid users who were not eligible for the ordinary long-term programmes. I also aimed to explore individual differences in the patient group.

METHODS

The research project comprised three studies. First, a literature review was undertaken to assess post-treatment abstinence rates in former patients in methadone or buprenorphine replacement programmes. Second, 75 dependent opioid users in outpatient counselling were recruited to a 9-month buprenorphine replacement programme and followed up for two years. Third, 65 study participants' personality profiles were compared to those of an age-matched norm sample.

RESULTS

We identified 14 studies in the literature review. The pooled abstinence rate across the studies was 33%. For individuals who had left treatment voluntarily or on staff recommendations, the pooled abstinence rate was 48%, versus 22% for persons who had been discharged involuntarily or against staff recommendations.

Forty study participants (53%) completed the 9-month buprenorphine replacement programme. Three non-completers died during detoxification. At two-year follow-up, the number of deaths had increased to five. Nine participants were abstinent from all opioids (illicit and prescribed), and thirty-seven participants were still in or had returned to opioid replacement therapy.

The opioid-dependent sample was less emotionally stable, less outgoing and less conscientious than the non-clinical sample.

CONCLUSION

Abstinence-orientated buprenorphine replacement therapy did not seem to be a feasible alternative to current treatments.

Sammendrag (Summary in Norwegian)

BAKGRUNN

Opioidavhengighet er forbundet med betydelige medisinske, psykologiske og sosiale problemer. Internasjonalt er den vanligste intervensjonen langsiktig substitusjonsbehandling med opioider som metadon eller buprenorfin. Blant norske helsemyndigheters kriterier for inntak i legemiddelassistert rehabilitering (LAR) er en nedre aldersgrense på 25 år og ikke-medikamentell behandlingserfaring. Formålet med dette forskningsprosjektet var å undersøke hvor hensiktsmessig det er å tilby tidsavgrenset substitusjonsbehandling med buprenorfin til avhengige opioidbrukere som ikke fylte LAR-kriteriene. Det var også et mål å utforske individuelle forskjeller i pasientgruppa.

METODE

Forskningsprosjektet omfattet tre studier. Først gjorde vi en litteraturgjennomgang for å undersøke i hvilken grad tidligere substitusjonspasienter var avholdende fra opioider etter avvenning fra metadon eller buprenorfin. Så rekrutterte vi 75 opioidavhengige polikliniske pasienter til 9 måneders substitusjonsbehandling med buprenorfin og oppfølging i to år. Til sist sammenliknet vi personlighetsprofilen til 65 studiedeltakere med et aldersmatchet normutvalg.

RESULTATER

Vi identifiserte 14 studier i litteraturgjennomgangen. Den gjennomsnittlige andelen personer som var avholdne fra opioider etter behandling var 33 %. For personer som hadde forlatt behandlingen frivillig og etter behandlers anbefaling var andelen 48 %, mot 22 % for personer som var skrevet ut mot sin vilje eller uten anbefaling.

Førti studiedeltakere (53 %) fullførte nimånedersprogrammet med buprenorfin substitusjonsbehandling. Tre av dem som ikke fullførte døde under avvenning fra buprenorfin. Ved toårsoppfølgingen var antallet døde steget til fem. Ni deltakere var avholdende fra alle slags opioider (både illegale og foreskrevne), og trettisju deltakere var fortsatt i, eller hadde returnert til, substitusjonsbehandling.

Det opioidavhengige utvalget var mindre følelsesmessig stabile, utadvendte og pliktoppfyllende enn det ikke-kliniske utvalget.

KONKLUSJON

Det virket lite hensiktsmessig å tilby avholdsorientert substitusjonsbehandling med buprenorfin.

Contents

Acknowledgements

This research project was conducted at the Unit for Addiction Medicine, University of Oslo, in collaboration with outpatient clinics for young substance users (PUT) at Ullevål University Hospital (Oslo), Innlandet Hospital (Hamar), Asker and Bærum Hospital (Sandvika), Telemark Hospital (Skien, Porsgrunn and Kragerø) and Sørlandet Hospital (Kristiansand), and with the Norwegian Institute of Public Health's Division of Forensic Toxicology and Drug Abuse. The pharmacological expenses of the clinical study were funded by the Norwegian Ministry of Health and the running expenses were funded by Schering-Plough AS. During the research project I have been enrolled in the doctoral degree programme at the Faculty of Medicine, University of Oslo. This dissertation was completed at, and with support from, the Norwegian Knowledge Centre for the Health Services, where I currently am employed.

I am grateful to psychiatrist Torbjørn Tvedten for his persistence in helping get the research project off the ground, and for his contributions throughout. Moreover, I would like to thank my supervisor, Helge Waal, for giving me this opportunity, for the freedom he gave me and the responsibility he entrusted in me and for being so accessible. Many thanks to statistics supervisor Leiv Sandvik for his guidance, co-authorship, enthusiasm and interesting discussions.
Further, I am grateful to the laboratory staff at the Norwegian Institute of Public Health for performing urine analyses, and to the study interviewers Erik Hoel, Janet Verveda and Svein Helge Gundersen. Special thanks to clinic staff for their efforts in co-ordinating and collecting data, to general practitioners and other physicians for prescribing buprenorphine, to pharmacists and nurses for dispensing it, and, last but not least, to the participating patients. They were all essential to the research project.

I would not have been able to put this dissertation together without the assistance of a number of highly qualified people. Many thanks to co-authors of two separate papers, Robert Ali and Hilmar Nordvik, for substantial contributions. I also sincerely appreciate the comments on my writings from critical friends Jørgen Bramness, Anne Landheim, Edle Ravndal, Geir Smedslund, Inger Synnøve Moan and Liv Merete Reinar. Thank you all. And special thanks to Arild Bjørndal for the time invested in finalising the dissertation.

Finally, warm thanks to Inger and Ulf Kornør, Dag Sørum and Camilla Henning for their patience and support.

Research aims

The general objective of this research project was to assess the feasibility of abstinence-orientated buprenorphine replacement therapy. We also aimed to explore individual differences and the use of various assessment instruments. More specifically, the research aims were to:

1. Estimate to what extent opioid abstinence can be expected from former maintenance patients (paper I)
2. Examine possible relationships between patient and treatment characteristics, and abstinence rates (paper I)
3. Assess the need for research in the field of abstinence-orientated maintenance treatment in general, and time-limited buprenorphine maintenance in particular (paper I)
4. Examine changes in drug use and other relevant patient variables across three phases of treatment: stabilisation, maintenance and detoxification (paper II)
5. Assess completion, retention and compliance (paper II)
6. Identify possible predictors of programme completion (paper II)
7. Investigate how follow-up outcomes two years after study entry were related to participants' programme completion status (paper III)
8. Examine the relationships between follow-up performance and current agonist therapy status (paper III)
9. Examine whether there is a distinct personality pattern associated with opioid dependence (paper IV).

List of papers

The following papers, which will be referred to by their Roman numerals in the text, will form the basis of the dissertation:

I. Kornør H, Waal H.

From maintenance to abstinence: a literature review.

Drug and Alcohol Review 2005; 24: 267-274

II. Kornør H, Waal H, Ali R.

Abstinence-orientated buprenorphine replacement therapy for young adults in outpatient counselling.

Drug and Alcohol Review 2006; 25: 123-130

III. Kornør H, Waal H, Sandvik L.

Time-limited buprenorphine replacement therapy: 2-year follow-up outcomes in relation to program completion and current agonist therapy status.

Drug and Alcohol Review 2006; in press

IV. Kornør H, Nordvik H.

Five-factor model personality traits in young opioid-dependent adults.

Submitted for publication

Introduction

OPIOID DEPENDENCE

The opioids comprise *opiates* (e.g. opium, morphine, codeine) derived from the poppy plant, as well as semi-synthetic compounds (e.g. heroin) and synthetic compounds (e.g. methadone, buprenorphine). In addition to their analgesic properties, opioids elicit an exaggerated sense of well-being or happiness, and this makes them likely to attract abuse.

People who use opioids regularly are at risk of developing a dependence syndrome. Opioids stimulate central opioid receptors in the brain, where the μ-receptor probably is the most important with regard to dependence (1). For individuals with opioid dependence, the use of opioids, most often heroin, has become a central aspect of their lives. They usually spend most of their days acquiring and administering the drug, and show little interest in other activities they used to appreciate. With time, people become tolerant to opioids so larger doses are needed to achieve the desired effect. Many people who are dependent on opioids wish to stop using them, but find it too difficult and tend to relapse. As the opioid effect withdraws, individuals typically experience intense physical and psychological discomforts. Among these are nausea, tremors, chills or profuse sweating, muscle and stomach cramps, diarrhoea, loss of appetite, insomnia, anxiety and irritability.

Opioid dependence syndrome is a diagnosis in the WHO diagnostic system ICD-10 (code F11.2) (2), requiring three of the following criteria to be met in the last 12 months:

- Strong desire or sense of compulsion to take opioids
- Difficulties in controlling opioid-taking behaviour
- Withdrawal state on cessation or reduction of opioid use
- Tolerance to opioids (increased dose needed to obtain desired effect)
- Progressive neglect of alternative pleasures or interests
- Persistent use despite harmful consequences.

It has been estimated that the prevalence of opioid dependence is one percent in adults over 15 years globally (3). The condition imposes substantial burdens of ill-health and social problems at both individual and societal levels. Due to the respiratory depressant effect of opioids, overdoses may be fatal. An estimate from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) suggests a mortality rate among opioid users that is 20 times higher than in corresponding age groups without opioid use (4). Findings from the National Treatment Outcome Research Study (NTORS), a large prospective cohort study conducted in the UK, showed that overdose was the most common cause of death among drug users (5). One third of the deaths were caused by other events, such as self-inflicted injury, accidents, violence or medical conditions. Other prevalent health problems among dependent opioid users include infectious diseases due to intravenous use (e.g. hepatitis C, HIV/AIDS) and psychiatric disorders. Opioid dependence is also associated with social problems, such as unemployment, homelessness and acquisitive crime. In sum, the burden of illness and social problems can be heavy. As a result, users need complex services.

The aetiology of opioid dependence is not entirely established. A number of aspects are believed to be involved, including biological, psychological and socioeconomic factors (6;7). For instance, Robinson and Berridge's incentive-sensitisation model of substance dependence offers an explanation for the persistent craving for substances, even when tolerance is developed and the euphoric effect decreased, or after long periods of abstinence (8;9). In their view, neurobiological processes that occur in conjunction with separate episodes of substance use can lead to increased feelings of needing drugs over time. According to the self-medication hypothesis (10-12), emotionally unstable individuals may experience that their psychological distress is alleviated when they use opioids. In that respect, using opioids can be seen as a response in a negative reinforcement process (13;14) – it removes an aversive stimulus (psychological distress), reinforcing the response (increased tendency to use opioids). Opioid use has also been associated with sensation seeking and engagement in risk behaviours (15-17). Zuckerman views sensation seeking as a personality trait with biological foundations, making some people more inclined to engage in risk behaviours than others (18). Paper IV considers the role of personality in opioid dependence, comparing personality traits in a group of stabilised dependent opioid users with traits in a non-clinical age-matched sample.

OPIOID REPLACEMENT THERAPIES

In the 1960s, US psychiatrists Vincent P. Dole and Marie Nyswander conducted the first trials where opioid-dependent patients were treated with the synthetic opioid methadone (19). The purpose of this treatment was to replace the use of illicit opioids with a long-acting agent that prevented both withdrawal symptoms and craving for opioids.

Methadone was first synthesised in Germany in 1937. During World War II, there was a shortage of morphine in Germany, and methadone became an important analgesic for surgical use. Like other opioid agonists, methadone binds to and activates the μ opioid receptor (20). Methadone has a long half life (15 to 55 hours), allowing single daily doses.

Side effects of methadone include respiratory depression, sleep disturbances, weight gain, sexual dysfunction and constipation. The research literature regarding methadone-related cognitive impairment is too inconsistent to draw conclusions (21). Although used as an analgesic in some cases of cancer in some countries, its most common clinical use today is opioid replacement therapy for opioid dependence.

Internationally, methadone maintenance treatment (MMT) is the most widely used opioid replacement therapy alternative. MMT typically involves daily supervised dosing of oral methadone dissolved in syrup, accompanied by some kind of psychosocial intervention. Numerous studies with various designs have consistently shown that methadone maintenance therapy is associated with increased retention in treatment, and reductions in illicit opioid use, criminal activities, infectious diseases and mortality (22-26).

In addition to methadone, the opioid replacement therapy umbrella embraces other compounds, such as slow-release morphine, levo-alpha-acetylmethadol (LAAM), heroin and buprenorphine. Buprenorphine has become the most common alternative to methadone in opioid replacement therapy, except in France, where ten time more patients are treated with buprenorphine than with methadone (27).

Furthermore, replacement therapies can be used with different treatment objectives. While maintenance treatment has a long-term or indefinite perspective, there are also time-limited treatment options, aiming at abstinence from all opioids. Maintenance treatment with buprenorphine (BMT) or methadone (MMT) appear to have similar outcomes, although retention in BMT is lower than in MMT (6;28). When it comes to abstinence-orientated opioid replacement therapies, however, many addiction medicine clinicians and researchers suggest that buprenorphine is more suitable than methadone.

THE NORWEGIAN SETTING

The prevalence of dependent opioid users in Norway is difficult to determine. A 2002 survey estimated the number of injecting opiate users to between 11,000 and 15,000 (29). We assume that the majority of injecting opiate users are dependent and that intravenous injection is the most common route type of administration among people with opioid dependence, so we will use the 11,000 – 15,000 estimate in the rest of this thesis. A different 2002 survey showed that primary heroin users were the second largest patient group after primary alcohol users in Norwegian treatment and care facilities for substance use disorders (30). The treatment system has traditionally relied heavily on three non-medical modalities: inpatient detoxification, outpatient counselling and residential programmes. In 1998, however, medication-assisted rehabilitation (MAR) based on methadone maintenance therapy was introduced.

Norwegian inpatient detoxification services treated 8,573 persons with substance use disorders in 2002 (30). These treatment episodes constituted 48% of all inpatient treatment episodes for the patient group that year. Inpatient detoxification involves the provision of psychosocial and/or medical care with the aim of alleviating withdrawal symptoms. Detoxification programmes are usually not regarded as treatment per se, but

rather as a gateway to long-term, abstinence-orientated treatment (31;32). In Australia, the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) compared entry rates into post-detoxification treatment for five different detoxification methods (33). Entry rates were: 65% for buprenorphine outpatient detoxification, 63% for detoxification under sedation, 42% for detoxification under anaesthesia, 27% for outpatient detoxification with symptomatic medications, and 12% for inpatient detoxification with symptomatic medications. So, the detoxification method used in Norway had the lowest entry rate. Other studies have reported poor completion rates in inpatient detoxification (32;34-39). For detoxification completers, however, abstinence rates at 6-18 months' follow-up have been reported in a range from 15% to 79%.

There were 14,323 individuals with substance use disorders in Norwegian outpatient clinics in 2002, attending an average of 8.3 sessions each (30). Outpatient counselling typically consists of regular individual and/or group sessions with eclectic therapeutic approaches. It is delivered at a relatively small cost and can be adjusted to patients in different situations with different needs. Findings from the US Drug Abuse Treatment Outcome Study (DATOS) showed that outpatients were younger, more likely to be employed and to be criminally active, and less likely to be dependent on heroin than patients in other treatment modalities (40). Furthermore, the research team concluded that outpatient counselling was less effective for heroin dependence than for other substance use disorders. The DATOS results regarding outpatient treatment for opioid dependence have been supported by Norwegian findings (30;41).

In 2004, approximately every second treatment programme in Norway was a residential rehabilitation unit (30). These programmes are for the most part based on theoretical, ideological or religious approaches, such as therapeutic communities, the Minnesota model and evangelical centres. The main treatment goal is usually abstinence from psychoactive substances. Programme duration varies from 3 months to 1-2 years. According to Norwegian and UK studies, a majority of residential patients are opioid dependent (30;42), while cocaine dependence appears to be the most prevalent substance use disorder among US patients (40). Residential programmes are often challenged by high drop out rates and relapse to daily substance use (43-49). The National Treatment Outcome Study (NTORS) reported a general opioid abstinence rate of just over 50% one year after discharge from UK residential treatment programmes (50).

Medication-assisted rehabilitation (MAR) has become a nationwide treatment option since its introduction in Oslo in 1998. Methadone is the preferred replacement agent, but buprenorphine was introduced as an alternative in 2001. MAR has a long-term perspective, where integrated psychosocial services play a central role. In 2003 the number of MAR patients across the country approached 3000 (51), or somewhere between 20% and 27% of the estimated opioid dependent population. The mean age of patients was 38 years, and 69% were male.

Admission criteria have been characterised as rather restrictive compared to other countries:

- Age ≥ 25 years
- Long-term drug misuse dominated by opiates
- Reasonable extent of admissions to non-medical, abstinence-orientated treatments

Although exceptions from these criteria can be granted in cases of serious disease or when indicated by comprehensive considerations, MAR is ruled out as a treatment option for young opioid-dependent adults and/or those with little treatment experience. Norwegian practitioners and health authorities have therefore shown some interest in short-term, abstinence-orientated replacement therapy as an alternative for those under the MAR age limit.

ABSTINENCE-ORIENTATED BUPRENORPHINE REPLACEMENT THERAPY

Buprenorphine was first marketed as an analgesic in the USA in the 1980s. In 2001, high-dose buprenorphine treatment for opioid dependence was approved in both the USA and in Norway.

Like methadone, buprenorphine is a synthetic opioid with similar opioid effects. The two compounds do differ somewhat in their pharmacological profiles, however (52). Most importantly, methadone is a full agonist, while buprenorphine is a partial agonist. Its ceiling effect is a product of the partial agonism. While agonists have a linear dose-response curve, that of buprenorphine is sigmoid. This means that at a certain dose level, higher buprenorphine doses will extend the duration of its effects rather than intensify them. In a clinical perspective, this gives a potential for alternate-day dosing (52). Perhaps more importantly, the ceiling effect is associated with a reduced overdose risk.

Another special characteristic of buprenorphine is its high affinity to the μ receptor. If the majority of μ receptors are already occupied by an opioid agonist when buprenorphine is taken, the agonist effect will be replaced by the antagonist effect of buprenorphine, causing withdrawal reactions (53). It is therefore essential that patients are advised to leave sufficient time between the last use of an opioid agonist and the first administration of buprenorphine. Moreover, when the μ receptors are occupied by buprenorphine, there will be an agonist blockade, mitigating the effects of other, "competing" opioids (54;55).

Buprenorphine's poor oral bioavailability is also an important distinction from methadone (53). As it is destructed in the gastrointestal tractus, buprenorphine tablets are administered sublingually. It will take five to ten minutes to absorb tablets in this manner, implying that supervised administration is more time-consuming than for methadone, which is quickly swallowed.

The opioid withdrawal syndrome on cessation of buprenorphine treatment has been described as milder than that associated with withdrawal from methadone or other full opioid agonists (56-58). While detoxification from methadone is associated with considerable discomfort of long duration and strong cravings for opioids (59-61), peak withdrawal from buprenorphine is usually experienced within the first two to five days after dosing cessation, with mild symptoms persisting for weeks.

Theoretically, short-term buprenorphine replacement therapy may be profitable for young and treatment-naïve individuals for several reasons:

- The ethics of keeping people in treatment longer than necessary is always questionable.
- Time-limited treatment as opposed to indefinite maintenance would increase patient turnover and the total number of patients treated per year.
- A subgroup of treatment-seeking persons might find an indefinite treatment perspective unattractive for different reasons. Some might want to get rid of opioid dependence as such, some might dislike enduring monitoring, and some might experience conflict between self-fulfilment or ambitions and ongoing therapy.
- It has been demonstrated that selected individuals are able to detoxify from methadone and achieve long-term abstinence (23;24).
- The pharmacological profile of buprenorphine suggests that it is a better choice than methadone in time-limited programmes.

Bickel et al (62) have compared the efficacy of buprenorphine and methadone in a 90-day outpatient detoxification programme. Outcomes were heroin use and retention, and results were equally poor for both agents. In another study, participants received either behavioural therapy or standard psychosocial treatment in addition to a 160-day buprenorphine programme (63). The programme completion rate was higher in the behavioural therapy group. A 16-week buprenorphine-reduction study resulted in a completion rate of 31%. Previous participation in Alcoholics Anonymous (AA) was a predictor of completion (64). Fewer psychiatric symptoms at intake were predictive of treatment completion in a buprenorphine treatment programme lasting three to four months (65). Only one of 29 patients completed a discontinuation trial consisting of 4 to 12 weeks' maintenance followed by a five-week double-blind dose-reduction phase (66). Paper II provides completion outcomes from a prospective study of a 9-month buprenorphine programme.

None of the study examples mentioned above reported follow-up outcomes after cessation of buprenorphine replacement therapy. The research literature on abstinence-orientated buprenorphine treatment at the time this research project was initiated is thus not exhaustive. In Paper I, the research literature was systematically searched to identify possible studies containing post-treatment outcomes. Furthermore, post-treatment outcomes of the 9-month buprenorphine programme are reported in Paper III.

PROJECT HISTORY

In 1997 Skien-based psychiatrist Torbjørn Tvedten developed an abstinence-orientated buprenorphine replacement therapy programme in response to the poor availability of effective interventions for young and untreated heroin users. The programme, consisting of a combination of time-limited (12 months) buprenorphine replacement and cognitive behaviour group therapy at Tvedten's private practice, was tried out in cooperation with the local social services. Thirty-eight patients were included in the programme; 20 patients (53%) were discharged due to programme rule violations and 18 (47%) completed dose reductions as planned. Among the discharged patients, one was enrolled in a thera-

peutic community at seven-month follow-up, four had buprenorphine prescribed by Danish physicians, two were serving prison sentences, eight had relapsed to regular heroin use and four were dead. Outcomes were more favourable for the programme completers; five had relapsed, one was deceased, but the remaining patients were characterised as well-functioning (all outcomes refer to personal communication with Torbjørn Tvedten).

The programme was not approved by the health authorities because it was not an approved research project, and buprenorphine was not a registered agent for the management of opioid dependence. In 1999, the programme was forced to an abrupt and premature end, shortening the planned treatment duration for many patients. Tvedten perceived the preliminary outcomes as promising, and took the initiative to design a university based study.

Methods

LITERATURE REVIEW (PAPER I)

We searched the literature in two batch operations. The first batch was studies of time-limited or abstinence-orientated opioid replacement therapies, and the second batch was studies on termination of opioid maintenance treatment with long-term perspectives.

We searched MEDLINE, Pre-MEDLINE and PsychInfo for studies published between 1966 and July 2003. For the first batch, every possible combination of *buprenorphine* or *methadone*, and *short-term*, *intermediate*, *time-limited* or *abstinence-orientated* were used as search terms. In addition *buprenorphine reduction* and *methadone reduction* were used separately. Search terms in the second batch were *buprenorphine maintenance* or *methadone maintenance* combined with *detoxification*, *withdrawal* and *abstinence*. The database searches were supplemented with hand searches in reference lists of central publications, such as overview articles and textbooks.

Studies on detoxification, defined as programmes of less than 30 days' duration, were excluded. Patients had to be aged at least 18 years and studies were required to report post-treatment abstinence rates and length of follow-up interval. There were no inclusion criteria regarding study design or other methodological issues. Article titles, abstracts and full text papers were screened by the two authors independently.

Key findings were summarised in meta-analyses. For continuous variables, pooled means were calculated by multiplying sample means with the respective sample sizes and dividing the sum of these products by the sum of sample sizes. The corresponding calculations for categorical variables were to divide the sum of each study's prevalence by the sum of sample sizes.

CLINICAL STUDY (PAPERS II AND III)

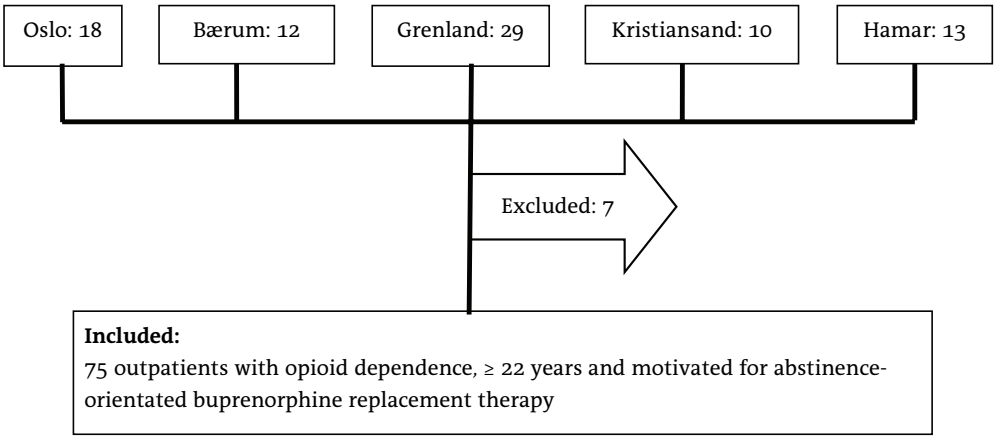
The study was designed as a time series with one pre-treatment assessment and eight follow-up assessments. It was conducted during 2002 – 2005 at the Unit for Addiction

Medicine, University of Oslo, and at five outpatient clinics (PUT) in Oslo (Ullevål), Bærum, Hamar, the Grenland area and Kristiansand. Each participant entered the study for two years.

Participants

Seventy-five heroin users in, or presenting for, counselling were recruited from the five participating clinics, where opioid replacement therapies were not ordinarily offered. The number of participants at each clinic varied from 10 to 28 (Fig 1).

Figure 1. Participant recruitment



Inclusion criteria were:

- Opioid dependence according to ICD-10 criteria (2)
- Age ≥ 22 years
- Motivation for abstinence-orientated buprenorphine therapy.

The age limit was set at 22 years due to Norwegian treatment restrictions, excluding patients younger than 25 years of age from substitution therapy. The 22-year-olds would reach the age of 24 at completion of the study, and would be close to the official age limit if they wished to transfer to ordinary maintenance treatment programmes. The motivation criterion was chosen in an attempt to exclude participants with a long-term maintenance goal. Eligibility criteria assessments were undertaken by clinicians based on their professional judgement, often after consulting other clinicians or the Unit for Addiction Medicine.

Exclusion criteria were:

- Severe psychiatric or somatic diagnosis
- Forthcoming imprisonment.

These criteria were set in order to avoid any harmful effects of the treatment, and to ensure that patients were able to attend both counselling sessions and assessments. Seven patients were excluded; 3 declined participation, 2 had forthcoming prison sentences, 1 refused to be interviewed, and 1 had a medical condition contraindicating buprenorphine therapy.

Interventions

Outpatient counselling
Clinicians were instructed to conduct treatment as usual, which generally implied multidisciplinary, eclectic therapeutic approaches and individual sessions of diverse intensity. Six professions were represented: 15 psychologists, 3 nurses, 9 social workers, 3 physicians/psychiatrists, 1 social scientist and 1 teacher. Behavioural therapy group sessions were also available for some patients. Counselling was delivered independently of the buprenorphine therapy, that is, the termination of one should not automatically imply the termination of the other.

Buprenorphine replacement therapy
The buprenorphine replacement therapy programme had an upper time limit of 9 months, including induction and detoxification. We used the sublingual tablet formulation of buprenorphine (Subutex®). Daily, supervised dispensing took place in pharmacies for most patients. Local public health services paid daily home visits to patients living in remote areas. Whenever it was impossible to dispense supervised doses (such as Sundays and holidays), doses were doubled the day ahead. Trials of alternate-day dosing of buprenorphine suggest that this is well tolerated by most patients (56;67-69). No doses were administered without supervision.

Patients were instructed to abstain from opioids a minimum of 8 hours prior to their first dose of buprenorphine. To prevent early dropout due to insufficient dosages, a flexible dosing scheme was used: 2 – 4 mg on Day 1, 6 – 8 mg on Day 2, then 8 – 10 mg the following 5 days, after which buprenorphine was individually dosed up to a maximum of 16 mg daily.

Systematic 2 mg weekly dose reductions were initiated after week 25, which left sufficient time to pause the dose reductions at some stage if necessary, or to make several attempts to detoxify from buprenorphine within the nine-month time limit. Requests for continued buprenorphine treatment and transfer to ordinary maintenance programmes were individually appraised.

Outcomes and assessments

Substance use and associated problems were assessed with the Norwegian version of the European Addiction Severity Index (EuropASI) (70;71). The EuropASI is a structured interview with focus on seven different problem areas related to substance use:

- Medical health
- Employment status and financial support
- Alcohol use
- Other substance use

- Criminal activity
- Family and social relations
- Mental health.

EuropASI interviewers were certified after attending a three-day training course. The intake interview was conducted prior to the first buprenorphine dose, with follow-up versions administered at 3, 6, 9, 12, 18 and 24 months thereafter.

Substance use was also assessed by urine screening at intake and at 3, 6, 9, 12, 18 and 24 months' follow-up. Unsupervised urine samples were collected by clinicians or interviewers, and participants were reassured that results were confidential and for research use only. The urine specimens were analysed for heroin (by detecting the metabolite 6-monoacetylmorphine), methadone, buprenorphine, benzodiazepines, amphetamines, cocaine, cannabis and ethanol at the Norwegian Institute of Public Health. Screening was performed using immunoassay (EMIT), followed by gas-chromatography/mass-spectrometry (GC/MS) or liquid-chromatography/mass-spectrometry (LC/MS) for confirmation of positive results.

Current symptoms of psychological distress were assessed by the Revised Symptom Checklist 90 (SCL-90-R), a 90-item multidimensional self-report questionnaire designed to screen for a broad range of psychological problems (72). For each problem item subjects are asked to indicate the degree of discomfort they have experienced the last 7 days. Scores range from 0 (no discomfort at all) to 4 (very high degree of discomfort). The mean cross-item score, Global Symptom Index (GSI), in a Norwegian normal population has been estimated to 0.32 (73). The SCL-90-R was completed by the patients at the clinics after a short instruction. The assessment schedule was identical to that of EuropASI and urine sample collection.

To examine psychiatric diagnoses, the Munich Composite International Diagnostic Interview (M-CIDI; 74) was administered. The M-CIDI is a comprehensive, standardised interview for assessment of mental disorders, including substance use disorders, according to the definitions and criteria of both ICD-10 (2) and DSM-IV (75). Interviews took place a minimum of 5 weeks after buprenorphine induction, when we assumed that patients were stabilised. We used a computerised version of the M-CIDI, where the patients' answers were entered directly and diagnoses automatically produced. Interviewers had attended a three-day training course and were certified administrators.

Special forms were used for the continuous registration of counselling session attendance, dose changes and dosing attendance.

Statistical analyses

The statistical package SPSS for Windows, version 11.0 (76), was used in all analyses. Due to the quality and quantity of the collected data, analyses were based on a before-and-after study design rather than a times series, where repeated measures analyses would have been more appropriate. Descriptive statistics were calculated as means with standard deviations (SD) or as percentages. Bivariate analyses of continuous variables were performed by t-tests or Mann Whitney tests, and comparisons of categorical variables by

chi-square or Fisher Exact tests. Odds ratios with 95% confidence intervals were obtained from logistic regression models, controlling for possible confounding variables.

PERSONALITY TRAIT STUDY (PAPER IV)

The study was designed as a case-control study, with 65 cases from the clinical study. The mean age of the opioid-dependent sample was 26.8 years (SD 3.4; range 22-39). Twenty-two subjects (34%) were women.

Non-clinical controls (n = 676) aged 22-39 years were selected from a national database at the Norwegian University of Technology and Science, containing scores of 1153 individuals representing a wide range of the general Norwegian population. The mean age of the control group was 26.8 (SD 3.7), and females and males represented 45% and 55%, respectively.

The Norwegian version of the Revised NEO personality Inventory (NEO-PI-R) (77;78) was used for five-factor model (FFM) personality trait assessments (79). The NEO-PI-R is a 240-item inventory measuring five personality traits, each containing six sub-traits or facets:

- Neuroticism
  - Degree of emotional stability and proneness to experience negative affects
  - Facets: *Anxiety, Angry Hostility, Depression, Self-Consciousness, Impulsiveness, Vulnerability*
- Extraversion
  - Degree of preference for company of other people and dominance in social settings
  - Facets: *Warmth, Gregariousness, Assertiveness, Activity, Excitement-Seeking, Positive Emotions*
- Openness to experience
  - Degree of conventionality and adherence to traditions
  - Facets: *Fantasy, Aesthetics, Feelings, Actions, Ideas, Values*
- Agreeableness
  - Degree of egocentricity and competitiveness
  - Facets: *Trust, Straightforwardness, Altruism, Compliance, Modesty, Tender-Mindedness*
- Conscientiousness
  - Degree of purposefulness, strong will and determination
  - Facets: *Competence, Order, Dutifulness, Achievement Striving, Self-Discipline, Deliberation*.

The NEO-PI-R items are statements of personality tendencies accompanied by five-point rating scales, ranging from “strongly disagree” to “strongly agree”. Analyses of Norwegian NEO-PI-R data have indicated satisfactory reliability coefficients and very similar factor structure with other countries (80).

A minimum of 5 weeks after buprenorphine induction, when we assumed they had achieved a stable state, patients were requested to complete the NEO-PI-R at the clinics. Instructions were given both verbally and in writing, and clinic staff members were available for answering any questions regarding the inventory.

Analyses were conducted using the statistical package SPSS for Windows, version 11.0 (76). Each individual's T-scores (mean=50, SD=10) were calculated on the basis of a national norm database.

Cohen's *d* effect sizes (81) were calculated for the differences in T-scores between opioid dependent subjects and controls. Statistical power calculations showed that a medium effect size difference ($d \geq 0.50$) at the 0.01-level with power = 0.91 could be detected with 65 participants in the opioid-dependent sample and 676 in the control group.

ETHICS

Approvals were granted from the Regional Committee for Medical Research Ethics, Norwegian Medicines Agency and the Data Inspectorate. All participants were informed both orally and in writing about the study, and signed informed consent forms.

Results

LITERATURE REVIEW (PAPER I)

Aim 1: To estimate to what extent opioid abstinence can be expected from former maintenance patients

Fourteen studies met the inclusion criteria and were included in the review. The studies were mostly prospective cohort studies of former methadone maintenance patients, authored by US researchers in the 1970s. A total of 1902 participants were included in the studies. These were selected for detoxification and post-treatment studies from a population of 9718 methadone maintenance patients. The mean time interval between detoxification from methadone and follow-up assessment was 28 months.

There were substantial variations in how abstinence was defined in the included studies. The term abstinence could involve both opioid and non-opioid substances, and time frames from one month up to several years. Further, abstinence did not necessarily imply complete abstention from opioids. It could imply not returning to replacement therapy, not relapsing to intravenous use, or no intense use.

Termination of methadone maintenance therapy could be categorised as either "therapeutic" or "non-therapeutic". Therapeutic detoxification was characterised as special programmes for patients who wished to leave treatment, and were considered by clinicians to have reached the treatment goals. On the other hand, non-therapeutic detoxification was the result of a process where patients left treatment against clinical advice, or were involuntarily discharged because of programme rule violations or programme closure. Disregarding the circumstances for termination of methadone maintenance treatment, follow-up abstinence was achieved by 611 of 1902 participants (33%; range 22% to 86%). When "therapeutic detoxification" was compared to "non-therapeutic detoxification" the pooled abstinence rates were 48% and 22%, respectively.

Aim 2: To examine possible relationships between patient and treatment characteristics, and abstinence rates

The cross-study mean age was 30 years. Seventy nine percent were men. The participants had been in methadone maintenance treatment for an average of 22 months, and had used illicit opioids regularly for an average of 7 years.

Mean methadone doses prior to detoxification ranged from 20 mg to 87 mg. The detoxification process lasted from 7 weeks to 7 months. Three of the studies reported detailed protocols for trials of different detoxification regimes. Patients were advised to take post-detoxification counselling in four studies.

Relationships between patient or treatment characteristics and post-treatment abstinence were examined in 11 studies. Only six of these described a statistical method for analysing data.

Patient characteristics examined for possible abstinence relationships were age, duration of severity of dependence, time in treatment, detoxification difficulties or duration, pre-treatment social problems or polydrug use, ethnicity, criminal behaviour/prison sentences, employment/educational level, in-treatment substance use, and gender.

Treatment characteristics were methadone dose, therapeutic detoxification and psychosocial support during detoxification.

Overall, the single characteristic most frequently associated with abstinence was voluntary participation in detoxification programmes with eligibility criteria ("therapeutic detoxification").

Aim 3: To assess the need for research in the field of abstinence-orientated maintenance treatment in general, and time-limited buprenorphine maintenance in particular

Two of the 14 included studies were designed as randomised controlled trials, comparing different regimes for methadone detoxification. The remaining studies were naturalistic prospective studies without controls or comparisons.

Only one study reported abstinence rates after time-limited opioid replacement therapy. The agent used in that study was methadone. Buprenorphine was only used in one of the studies, and then as a transition between methadone and abstinence. At the time this review was conducted, no studies could be identified that reported post-treatment outcomes of abstinence-orientated buprenorphine replacement therapy.

Aim 4: To examine changes in drug use and other relevant patient variables across three phases of treatment: stabilisation, maintenance and detoxification

All 75 participants were interviewed with the EuropASI at study entry. The number of participants interviewed after 3, 6 and 9 months was 64 (85%), 55 (73%) and 41 (55%), respectively.

At study entry, the mean number of days during the last 30 days with substance use was 24 for illicit opioids, 13 for sedatives, 3 for amphetamines, 10 for cannabis, 14 for poly-drug use, 1 for heavy drinking, and 19 for intravenous use. At 3 months, when patients were stabilised on buprenorphine, there were statistically significant ($p<0.05$) reductions in all substance use categories. Exceptions were amphetamines and heavy drinking, where the frequency of use remained low. Significant reductions were also seen in the mean number of days spent experiencing drug problems and engaging in illegal activities.

Compared to the 3-month assessments, there was a reversed tendency at 6- and 9-month follow-up for all the above variables, although the measures were still significantly reduced when held against pre-treatment levels.

With regard to psychological distress, the mean number of days out of the last 30 experiencing psychiatric problems was 11 at baseline and remained stable until the detoxification phase at 9 months, when it increased to 18 days ($p<0.01$). Mean Global Symptom Index (GSI) scores decreased from 1.3 at intake to 0.9 and 1.0 at 3- and 6-month follow-up, respectively. At the 9-month assessment, however, the mean GSI score had returned to the intake level.

Three participants died during the detoxification phase. Causes of death were heroin/benzodiazepine overdose, suicide and road traffic accident.

Aim 5: To assess completion, retention and compliance

Forty patients (53%) completed the buprenorphine programme. Among the non-completers, 22 (29%) had buprenorphine replacement therapy continued and 10 (13%) had dropped out. The last three non-completers were the deceased participants.

At 9 months, patients had attended averagely 19 counselling sessions each, which constituted 74% of scheduled sessions. The 9-month retention rate for counselling was 67 patients (87%). With regard to medical compliance, 91% of scheduled buprenorphine doses had been taken. The mean buprenorphine dose at 3 months was 13.6 mg.

Aim 6: To identify possible predictors of programme completion

The number of lifetime previous treatment episodes for substance use disorders was the only variable that achieved a significant odds ratio (OR 0.82; 95% CI 0.70-0.97) in a logistic regression model adjusting for clinic allocation and buprenorphine dose at 3 months.

Completers had fewer previous treatment episodes than non-completers. Other patient characteristics (demographic, psychosocial and psychiatric variables) or treatment factors (compliance) did not influence completion.

Aim 7: To investigate how follow-up outcomes 2 years after study entry were related to participants' programme completion status

Sixty eight participants (91%) were interviewed after two years. At this point, five participants were dead, and the remaining two could not be contacted. The follow-up rate based on the number of living participants was 97%. Among the 68 interviewed participants, 38 were completers and 30 were non-completers.

Nine completers reported abstinence from all opioids. Completers had been employed for 9 of the last 30 days at follow-up, while non-completers had been employed for 2 days ($p=0.012$). Otherwise, there were no differences between completers and non-completers in follow-up performance.

Relative to measures at study entry, both completers and non-completers had reduced the number of days during the last 30 days with street opioid use, sedative use, poly-substance use and intravenous use.

Aim 8: To examine the relationships between follow-up performance and current agonist therapy status

Among the 38 completers, 17 (45%) had returned to some kind of opioid agonist replacement therapy at follow-up. The number of non-completers in agonist therapy was 20. So, there were 37 participants in agonist therapy and 31 participants in the no agonist therapy group two years after study entry.

There were statistically significant differences ($p<0.05$) between the agonist therapy group and the no agonist therapy group with regard to performance during the 30 days prior to follow-up assessments. Participants currently in agonist therapy had spent less time using street opioids (2 vs. 13 days), using two or more substances (3 vs. 10 days), injecting drugs (2 vs. 10 days) and engaging in illegal activities (0 vs. 6 days). In addition the agonist therapy group had been employed for 8 of the last 30 days, as opposed to 3 days in the no agonist therapy group.

PERSONALITY TRAIT STUDY (PAPER IV)

Aim 9: To examine whether there is a distinct personality pattern associated with opioid dependence

The five-factor model personality profile for the opioid-dependent sample differed considerably from that of the non-clinical controls: NEO-PI-R scores were higher on *Neuroticism*, lower on *Extraversion* and lower on *Conscientiousness* (d = 1.7, -1.2 and -1.6, respectively). The two groups were similar with regard to *Openness to experience* and Agreeableness, but did differ on *Agreeableness* facets *Trust*, *Straightforwardness* and *Modesty* (d

= -1.1; -0.5; and 0.6, respectively). Unexpectedly, there were only modest differences between the samples in *Neuroticism* facet *Impulsiveness* and *Extraversion* facet *Excitement seeking*.

Discussion

SUMMARY OF FINDINGS

As judged by our literature review (paper I), there were few studies in the research literature on abstinence after termination of opioid replacement therapies. Study designs and heterogeneity made it difficult to determine a reliable abstinence rate, but the pooled estimate of post-treatment abstinence was 33%. Only one of the 14 included studies examined the outcomes of a time-limited, abstinence-orientated programme, while the remaining 13 studies assessed outcomes after termination of long-term maintenance therapy. Methadone was the replacement agent in all studies except for one, where buprenorphine was used in the last phase of detoxification from methadone.

In paper II, we found that 53% of the patients completed the 9-month buprenorphine replacement therapy. Compliance and retention were good, and there were reductions in substance use during buprenorphine replacement therapy. Psychiatric problems escalated in the detoxification phase.

Two years after entry into the clinical study, nine participants were abstinent from all opioids (prescribed and illicit), 37 were in some kind of opioid replacement therapy and 22 were not (paper III). The number of deaths had reached five, and two participants could not be contacted for follow-up assessments. Current agonist replacement therapy status had a larger impact on participants' performance at 2-year follow-up than their programme completion status.
The personality trait study (paper IV) showed that individuals with opioid dependence appear to have a distinct personality profile compared with non-clinical controls.

METHODOLOGICAL LIMITATIONS

This research project had an observational approach rather than an effect focus. We obtained an overview of the relevant research literature, we observed outcomes during and after buprenorphine replacement therapy, and we described the patient group's distinct personality profile. The observational approach widened the probability of detecting

relevant outcomes, but also the probability of findings being spurious. More rigorous research designs would have lowered the risk of bias. They would also have made it possible to determine more decisively the direction of causality.

Literature review (paper I)

In the literature review several actions could have been made to increase the specificity and sensitivity of the search strategy. First, additional databases, such as the Cochrane Library, EMBASE, ISI and CINAHL, could have been searched. Second, search terms could have been more elaborate to include as many variations as possible. Third, limiting included study designs to randomised controlled trials (RCTs) would have allowed a discussion of abstinence as a treatment effect rather than as an associated outcome. Finally, critical appraisals of the included studies would have indicated to what degree the review findings were trustworthy.

A major reason for conducting a less rigorously designed literature review was our intention to obtain a broad overview of the existing literature on post-replacement therapy outcomes. Previous scoping searches in the research databases had resulted in very few identified studies, and none whatsoever on buprenorphine. We wanted to perform a more systematic search to verify our preliminary findings.

Clinical study (papers II and III)

The most important weakness of the clinical trial was the lack of a control or a comparison group. The randomised controlled trial (RCT) is widely recognised as the most reliable research design for evaluating the effectiveness of interventions (82;83). Non-randomised controlled trials and observational studies are not only more prone to bias, they tend to overestimate treatment effects (25;84). Nevertheless, there are objections to the suitability of RCTs in substance dependence treatment research. Gossop proposes some technical and theoretical problems regarding the RCT design for evaluations of interventions for substance use disorders (85):

- The problem complexity and heterogeneity of people with substance use disorders may influence outcome despite random allocation to intervention and control groups
- Patients within one group may respond differently to treatment
- Selection criteria may exclude a number of representative persons, imposing external validity problems
- There may be important differences between people who accept participation in RCTs and those who do not
- Ethical problems arise concerning control groups being offered no or inferior treatment
- Treatment contents and durations are usually fixed in RCTs, while they are not in the real world
- RCTs do not provide information about what works within a complex intervention package

In my view, most of these problems are not exclusive to RCTs in the field of substance dependence, and the arguments for conducting RCTs still stand.

With a randomised controlled design we would have been equipped to detect proper effects of time-limited buprenorphine replacement therapy compared with placebo outcomes. However, the available research evidence at the time suggested that buprenorphine replacement therapy was more effective than placebo with regard to in-treatment use of illicit opioids and retention (86-89). It therefore seemed unethical to run a study where half the participants were offered inferior treatment (counselling only). Furthermore, dependent opioid users can easily determine whether they are given the active agent or not, eliminating the advantages of blinding (90). Another alternative was to design an RCT comparing time-limited buprenorphine replacement therapy with indefinite treatment. However, our patient group consisted of individuals who were ineligible for or not motivated for indefinite treatment within the current prescription regulations, making this route impossible. Finally, we considered inviting additional outpatient clinics to participate with patients as non-randomised controls, but abandoned the idea because of the ethical issues. We also felt we were unlikely to obtain many representative controls, because they would have to take part in a full assessment scheme lasting two years but without the benefits of extra treatment.

To include a sufficient number of participants, we chose to carry out a multi-centre study. Clinicians were given the responsibility for appraising study eligibility, administering questionnaires, collecting urine samples and submitting them for analysis, as well as managing both counselling and buprenorphine therapy. Most of these tasks were new to a majority of clinicians, and were added to an already substantial workload. We learned that there were many disadvantages associated with involving clinicians in data collection.

First, we cannot be certain of how each clinician understood and applied the inclusion criteria. While it was possible to exclude patients who had been unduly included, there is a risk that eligible individuals were not included. To obtain better insight into participant recruitment, we could have registered sex, age and diagnosis for all the participating clinics' patients.

Second, despite monthly reminders and two-month data collection margins, it proved difficult to obtain follow-up data as planned. SCL-90-R questionnaires and urine samples were missing for more than 50% of the patients at nine months. At this stage we transferred the data collection responsibility to the study interviewers, which did improve the situation somewhat, but the missing data rate remained high for the urine samples. Furthermore, many of the samples that were collected could not be used to validate self-reports because the two measures were taken with too great time intervals. As a consequence, no objective verification of abstinence versus non-abstinence was available. Research on the validity of self-reports is inconsistent, with one review concluding that "self-reports of drug users are sufficiently reliable and valid to provide descriptions of drug use" (91), and another that "the magnitude of drug use underreporting documented in this review could seriously bias prevalence estimates and treatment outcome studies"

(92). It seems reasonable to assume that underreporting of substance use will not occur deliberately as long as participants are assured that answers are confidential.

Third, the routine for collecting and submitting buprenorphine dosing data failed for some patients. For instance, we lack information on doses prescribed and number of doses taken during months 7 to 9 for 11 patients (15%). It also became evident that clinicians were not always adhering to the protocol regarding buprenorphine management, prescribing too high a dose in one case, and allowing take home doses in a few cases.

All these problems constitute a substantial threat to the study's internal validity. They could probably have been limited in a more ideal setting, such as a research clinic, permitting closer cooperation between researchers and practitioners and more standardised procedures.

The problem of missing data led to a change in analysis strategy. With a time series design and complete data sets, as planned, we would have been able to carry out analyses of variance for repeated measures. However, with unequal numbers of patients and different individuals assessed at each follow up, the time series approach was replaced by a before-and-after design. This is particularly evident in Paper II, where each follow-up outcome is compared to study entry measures.

Personality trait study (paper IV)

The case-control design does not determine the direction of causality. On one hand, the clinical sample's distinct personality profile could be understood as part of the aetiology of opioid dependence. Several investigations have documented that personality traits are remarkably stable (93), that they have a significant hereditary component (94), and that they have behavioural implications, i.e., they influence behavior in any situation and they contribute to decisions on which situations individuals are motivated to enter and participate in (95). On the other hand, the opioid-dependent sample's personality profile could be explained by a shared, distinctive lifestyle associated with long-term substance use. There is evidence suggesting that personality traits are less stable, and thus more susceptible to external influences, in younger adults than older adults (96).

The NEO-PI-R was not administered until the sixth week of buprenorphine replacement therapy, when patients were assumed to have achieved stability with regard to substance use. We do not know, however, to what extent participants were under the influence of drugs when completing the personality inventory. The first in-treatment assessments of drug use were 3 months after the first buprenorphine dose. At that time, as shown in paper II, substance use was modest and significantly reduced since inclusion assessments.

STRENGTHS OF THE RESEARCH PROJECT

Major strengths of this research project were the broad and systematic review of relevant literature, a 97% follow-up rate at 2 years in the clinical study and statistically solid observations in the personality trait study.

With the wide inclusion criteria chosen in the literature review (paper I), we obtained a good overview of the various research designs that had been used in this field, as well as patient characteristics. And, perhaps most importantly, we ascertained that with our search strategy, no previous studies examining outcomes after abstinence-orientated buprenorphine replacement therapy could be identified. We can therefore be quite confident that our clinical study is the very first of its kind.

In the clinical study, a 2-year follow-up with 73 of 75 patients (97%) accounted for, gave us valuable insight in changes that had occurred in association with treatment (paper III). At this time, the study sample could be divided in two, either by completion status or by current agonist therapy status, allowing group comparisons. Although group allocation was in no way randomised, it made sense to study outcome differences between the groups. The findings made it quite clear that whether people completed the time-limited treatment programme or not was not a key issue. Of far greater importance for positive changes in substance use and employment status was the being in agonist replacement therapy at follow-up.

The high follow-up rate also allowed assessments of two crucial long-term outcomes for the sample as a whole: abstinence and mortality rate. Even though it is not possible to show that abstinence or death were treatment effects, we cannot exclude the possibility that they were. If they are effects, one might conclude that one person will die for every second treatment success in abstinence-orientated buprenorphine replacement therapy.

Despite a modest number of cases in the personality trait study, differences of medium and large effect sizes were found. In addition, a statistical power of 0.91 strongly suggests that the personality traits of people with opioid dependence are in fact different from those of non-clinical peers.

RESULTS IN THE LIGHT OF PREVIOUS RESEARCH

The pooled abstinence rate in our literature review (paper I) was lower than that in Milby's review from 1988 (33% vs. 41%) (97). Possible explanations for an inferior pooled abstinence rate in our review are different definitions of abstinence, different number of studies included and different time frames for study selection. Our definition of abstinence (abstaining from both prescribed and illicit opioids) was probably more conservative than Milby's ("staying off methadone"), limiting the number of individuals fitting into the category. Also, our pooled abstinence rate was calculated on the basis of twice as many single studies, and for a much larger time frame than in the Milby review (1965-2003 vs 1970-1975).

However, regarding the pooled abstinence rate for "therapeutic detoxification", the two reviews were in agreement. An improved prognosis after therapeutic detoxification was also found in Magura's review of negative consequences of leaving methadone replacement therapy (98).

Our clinical trial appeared to be the first to report post-treatment outcomes of buprenorphine replacement therapy (papers II and III). But, there are a few examples in the literature of studies reporting in-treatment outcomes and completion rates of time-limited buprenorphine programmes, as we do in paper II. The post-treatment outcomes can be seen in the light of previous research on termination of methadone replacement therapy.

Compared to other studies, our clinical study had some favourable outcomes, but also a rather discouraging one. First, our participants attended 74% of their scheduled counselling sessions throughout the first 39 study weeks, which almost doubles the 90-day attendance rate in a study (n=396) where a special psychosocial intervention was given to improve compliance (99). Second, the buprenorphine dosing attendance rate in our study (91%) confirmed that buprenorphine is well liked by patients, as seen in other studies (55;100). Third, our 53%-programme completion rate exceeded what has been seen in previous research (3%-44%) (62;64-66;101). Fourth, in-treatment illicit opioid use rates have been reported in a meta-analysis of methadone studies to range from 47% to 76% (102). This contrasts with our observation at 3 months, at which point the mean number of days with illicit opioid use during the last 30 days was 2. Finally, our study's in-treatment mortality rate seemed unprecedented. In the Australian research programme National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD), for instance, there were no deaths during 312 person-years of treatment (103), while the mortality rate in our study was 3 out of 75 over a 9-month in-treatment observation period.

In a review published in 2001, Magura and Rosenblum posed the question "What are the observed consequences of leaving methadone maintenance?" (98). Their main findings were that people who left methadone maintenance treatment tended to relapse to illicit opioid use and that their risk of dying increased considerably. The 2-year follow-up outcomes in our clinical study (paper III) support Magura and Rosenblum's findings. Two more participants had died after discontinuation of buprenorphine replacement therapy, in addition to the three participants who died during detoxification. Also, the number of days during the last 30 days with illicit opioid use had increased from 2.3 at 6-month assessment, to 13 days at 2-year follow-up. It seems that our assumption that buprenorphine would be more appropriate than methadone in an abstinence-orientated perspective was flawed. Furthermore, our assumption that young adults with opioid dependence would profit from short-term replacement therapy was also flawed.

Our findings in the personality trait study (paper IV) that persons with opioid dependence scored high on *Neuroticism* and low on *Conscientiousness* were in accordance with previous US results (104-106), indicating that traits and disorder are related across cultures. Furthermore, the high *Neuroticism* scores are supportive of the self-medication hypothesis: people may use opioids to reduce psychological distress. However, as we do

not know the direction of causality, or whether there is a causal relationship at all, *Neuroticism* may, in fact, be a result rather than a cause of long-term opioid use.

An important difference between Norwegian and US observations, however, was that the Norwegian opioid-dependent sample had low *Extraversion* scores compared to the controls, while there was no distinction between groups on this trait in the US studies. Our cases were rather few, and it is not unlikely that low *Extraversion* was specific for this particular group of people and not for Norwegians with opioid dependence in general. The difference between American and Norwegian samples could also be an expression of cultural differences.

IMPLICATIONS FOR FURTHER RESEARCH

There seems to be sufficient research on in-treatment outcomes of opioid replacement therapies to suggest that they do reduce illicit opioid use and retain patients in treatment over time (6). Also, although existing studies are few, outdated and methodologically weak, they do indicate that there may be serious risks associated with terminating treatment prematurely (97;98; paper I). An open question still is, "How long is long enough?" Some people may need to be maintained on methadone or buprenorphine indefinitely, while some people will be able to detoxify after a limited time in treatment. Ethically and methodologically sound studies should be designed to investigate when to terminate treatment for whom.

The five-factor model of personality has obtained a central position in contemporary personality trait theory. The impact of group personality profiles have been examined in several fields, including occupational psychology and mental health. Merely describing the personality characteristics of individuals with opioid dependence is not enough. We need to know more about how personality traits influence prognosis. It could also be useful to model treatment programmes using knowledge of the group's typical personality profile, and evaluating the effectiveness of such programmes compared to standard treatment.

IMPLICATIONS FOR PRACTICE AND POLICY MAKING

The overall objective of this research project was to evaluate the feasibility of abstinence-orientated buprenorphine replacement therapy. Based on the findings from the literature review (paper I) and the clinical study (papers II and III) there is every reason to warn policymakers and practitioners that discharging patients from treatment prematurely involves a certain risk of serious deterioration, such as relapse and death.

Opioid replacement therapies are still a controversial issue in Norway. National guidelines are being developed as I write, and one of the questions that has been addressed in the media with regard to these guidelines is the suggestion of moving the age limit from 25 to 18 years. Many of the participants in our clinical study were under the age of 25 and seemed to profit from replacement therapy while in treatment. More importantly,

the existing international research evidence on the effectiveness of opioid replacement therapy is based on studies where the inclusion criterion regarding age is usually 18 years. I cannot see any evidence-based reason for the health authorities to keep withholding an effective treatment option from adults over the age of 17.

With regard to personality assessments, they may, along with other standardised assessments, prove useful to the clinician in tailoring an individual course of treatment. Knowing that a patient or a patient group is emotionally unstable, introvert and unstructured could guide the choice of therapeutic method and therapists' outcome expectations.

CONCLUSION

Abstinence-orientated buprenorphine therapy did not prove to be a feasible treatment for opioid dependence because of low completion and post-treatment abstinence rates, but also because of a considerable number of deaths.

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