Improving maintenance treatment of opiate addiction:
Clinical aspects

Kaarlo Simojoki
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Tiivistelmä

Suomessa on tällä hetkellä arvioiden mukaan n. 4 000 – 5 000 opioidien väärinkäyttäjää, joista n. 2 400 on lääkkeellisen korvaushoidon piirissä. Korvaushoito on lukuisissa tutkimuksissa todettu tehokkaimmaksi opioidiriippuvuuden hoitomuodoksi. Siitä huolimatta suhtautuminen tähän hoitoon on edelleenkin ristiriitä, mikä on myös näkynyt Suomen huumausainepoliittikassa sekä hoitojärjestelmän kehittämisessä ja kehityksessä. Erityisenä huolena on edelleen korvaushoitolääkkeiden buprenorfiinin ja metadonin väärinkäyttö tai niiden päätyminen katukauppaan. Muista Pohjoismaista poiketen buprenorfiini on Suomessa eniten suonensisäisesti väärinkäytetty opioidi. Tämä asettaa erityisiä haasteita hoidon kehittämiselle.

Tutkimus osoitti, että uuden buprenorfiini-naloksoni yhdistelmävalmisteen käyttö on yhtä turvallista kuin pelkän mono-buprenorfiinin eikä pääsääntöisesti annosmuutosia vaihdon yhteydessä tarvita. Lääkkeen murskaaminen ei vaikuttanut seerumitasoihin eivätkä tutkimushenkilöt kokeneet verrokkiryhmää enempää tai vähempää haittavaikutusta. Tämän perusteella arvioitiin, että tablettien murskaaminen ei vaikuta lääkkeen kliiniseen tehoon, ollen siten farmakologisesti yhtä tehokasta kuin kokonaisen tabletin käyttäminen. Tutkimus, jossa selvitettiin uuden merkkiainepohjaisen päihdeseulan hyötyjä ja haittoja, osoitti, että sekä potilaat että hoitohenkilökunta kokivat sen selkeästi mukavammaksi kuin perinteisen silmämääriäisen valvontaa perustuvan päihdeseulan. Tämä todennäköisesti lisää potilaisten hoitomyöntyvyyttä ja kiinnittymistä hoitoon. Lisäksi todettiin, että kyseinen uusi päihdeseula vähentää huomattavasti seulaturkimuksiin käytettyä työaikaa mikä todennäköisesti myös lisää hoidon tehokkuutta sekä tuloksellisuutta henkilökunnan pystyessä keskittymään enemmän hoitotyöhön. Seurantatutkimus osoitti, että buprenorfiini-naloksoni yhdistelmäväärinkäytyttii vähemmän ja yhdistelmävalmisteen ”katuhinta” oli koko seurantajakson ajan selvästi alempi kuin pelkän mono-buprenorfiinin, joten siten voidaan ajatella sillä olevan pienempi väärinkäyttöpotentiaali kuin pelkällä mono-buprenorfiini valmisteella.

Tutkimukset osoittivat, että on mahdollista käyttää useita keinoja, joilla voidaan vähentää buprenorfiinin väärinkäyttöpotentiaalia, lisää potilaiden hoitomyöntyvyyttä ja kiinnittymistä hoitoon, ja ne tulisikin ottaa laajamittaiseen kliiniseen käyttöön.
Abstract

The purpose of this study was to investigate whether pharmacological or clinical management methods could improve patients' adherence to treatment and reduce the resource burden, thus improving treatment effectiveness.

Finland was the first country in Europe to use buprenorphine-naloxone combination medication as part of opioid maintenance treatment (OMT), which was expected to have lower potential for diversion into the drug market. The study investigated whether the transition from mono-buprenorphine to buprenorphine-naloxone combination would cause adverse events or lower patient compliance. One way to reduce the diversion of buprenorphine medication is to crush the tablet when administering it, this has not been studied earlier, and it was investigated whether crushing mono-buprenorphine tablets would influence the kinetics and serum levels of buprenorphine, or whether patients would have adverse events following the use of crushed tablets. One main problem in OMT has been patient compliance and adherence to treatment. One main component has been visually supervised urine drug screens. Thus it was investigated whether a new unsupervised screening method would affect urine testing reliability, patient compliance, and the time/resources used by personnel in screening. The large buprenorphine abuse problem in Finland provides good possibilities for being able to study the abuse. A seven-year follow-up study evaluated the trends in street buprenorphine prices, intravenous abuse doses, and its abuse potential in Finland.

The studies showed that the use of the new buprenorphine-naloxone combination product is as safe as mono-buprenorphine alone, and that no dose adjustments are needed during medication change. Crushing of the mono-buprenorphine tablet did not affect serum levels or buprenorphine kinetics, and the study subjects did not experience more or less adverse events than the control group. It was concluded that crushing is a safe and effective management for patients with high risk of medication abuse or diversion. The study with the new marker-based urine drug screen indicated that the new method did not jeopardize the safe and reliable assessment of concomitant drug use. Both patients and medical staff thought it was more comfortable than the traditional visually controlled screen. The new method saved considerable time previously spent on controlling the screen. So it was concluded that the new screening method improves patient compliance, reduces the burden of the control time and thus may
increase the effectiveness of the treatment. The long-term follow-up study revealed that the street price of the new combination product is significantly less than of the mono-buprenorphine product and that the price difference remained the same during the follow-up period. Thus it was concluded that the abuse potential of the combination product is less than that of mono-buprenorphine.

The studies demonstrate that there are several effective methods for reducing the abuse of OMT medications, and that patient compliance and thus the outcomes of treatment can both be improved. These methods should be used broadly in the clinical management of OMT.
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>A-clinic</td>
<td>Specialized alcohol and drug rehabilitation clinic</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis Of Variance between groups</td>
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<tr>
<td>ASAM</td>
<td>American Spcoety of Addiction Medicine</td>
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<tr>
<td>APA</td>
<td>American Psychological Association</td>
</tr>
<tr>
<td>AUC 0–24</td>
<td>The Area under the Concentration-time curve over 24 hours</td>
</tr>
<tr>
<td>BZD</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum observed serum drug concentration</td>
</tr>
<tr>
<td>CYP 3A4</td>
<td>CYP3A4 cytochrome P450, superfamily of enzymes</td>
</tr>
<tr>
<td>DDI</td>
<td>Drug-drug interaction</td>
</tr>
<tr>
<td>df</td>
<td>degrees of freedom</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, fourth edition</td>
</tr>
<tr>
<td>EMCDDA</td>
<td>European Monitoring Centre for Drugs and Drug Addiction</td>
</tr>
<tr>
<td>EXCEL</td>
<td>spread sheet program by Microsoft</td>
</tr>
<tr>
<td>EUROPAD</td>
<td>European Opiate Addiction Treatment Association</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (U.S.)</td>
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<tr>
<td>GC-MS</td>
<td>Gas chromatography–mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HDL</td>
<td>Drug Rehabilitation Centre, Helsinki Deaconess Institute,</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>HUS/OPRI</td>
<td>Hospital District of Helsinki and Uusimaa, Opiate Maintenance Polyclinic, Department of Drug Psychiatry, Helsinki University Hospital</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems 10th Revision</td>
</tr>
<tr>
<td>ICH</td>
<td>The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>IHRA</td>
<td>International Harm Reduction association</td>
</tr>
<tr>
<td>i.v</td>
<td>intravenous</td>
</tr>
<tr>
<td>LCMS</td>
<td>Liquid chromatography–mass spectrometry</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>MBDB</td>
<td>N-methyl-1,3-benzodioxolylbutanamine, entactogen of the phenethylamine chemical class</td>
</tr>
<tr>
<td>MDMA</td>
<td>3,4-methylenedioxy-N-methylamphetamine, empathogenic drug of the phenethylamine and amphetamine classes of drugs</td>
</tr>
<tr>
<td>MDA</td>
<td>3,4-methylenedioxyamphetamine, entactogenic drug of the phenethylamine and amphetamine chemical classes</td>
</tr>
<tr>
<td>MDEA</td>
<td>3,4-methylenedioxy-N-ethylamphetamine, analog of MDMA</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MMT</td>
<td>Methadone maintenance treatment</td>
</tr>
<tr>
<td>MSAH</td>
<td>Ministry of Social Affairs and Health</td>
</tr>
<tr>
<td>MSTFA</td>
<td>N-methyl-N-trimethylsilyl-trifluoroacetamide</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health (U.S.)</td>
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<tr>
<td>NM</td>
<td>New marker labelling method</td>
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<tr>
<td>OMT</td>
<td>Opioid maintenance treatment</td>
</tr>
<tr>
<td>OM</td>
<td>Opioid maintenance</td>
</tr>
<tr>
<td>ORT</td>
<td>Opioid replacement treatment</td>
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<tr>
<td>OST</td>
<td>Opioid substitution treatment</td>
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<tr>
<td>RAAHE</td>
<td>Raahe Mental Health Clinic, Primary Health Care Centre</td>
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<tr>
<td>SAMSHA</td>
<td>Substance Abuse and Mental Health Services Administration, USA</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SOWS</td>
<td>Subjective Opiate Withdrawal Scale</td>
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<tr>
<td>THC</td>
<td>Tetrahydrocannabinol, cannabis</td>
</tr>
<tr>
<td>THL</td>
<td>National Institute for Health and Welfare</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>Time to maximum concentration of drug in serum</td>
</tr>
<tr>
<td>TS</td>
<td>Traditional supervised urine sampling</td>
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<tr>
<td>Tre-K-Klinikka</td>
<td>Drug Rehabilitation Polyclinic at Tampere City, K-Clinic, A-clinic Foundation</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WinNonlin Pro</td>
<td>Industry-Standard PK/PD Modelling and Analysis program</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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List of original publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I Kaarlo Simojoki, Helena Vorma; Hannu Alho. A retrospective evaluation of patients switched from buprenorphine (Subutex®) to the buprenorphine/naloxone combination (Suboxone®). Substance abuse treatment, prevention, and policy 2008; 3:16


1. Introduction

Opioid addiction is a chronic, relapsing disorder. Left untreated, high morbidity and mortality rates are seen (Cruts, Buster et al. 2008; Clausen, Waal et al. 2009; Degenhardt, Randall et al. 2009; Vicente, Giraudon et al. 2009). Psychosocially assisted pharmacological treatment of opiate dependence is used to reduce illicit opiate abuse, reduce the harms related to opiate abuse and improve quality of life. Opioid maintenance treatment (OMT) is often also referred to as Opioid substitution (OST) or opioid replacement (ORT) treatment. The most commonly used agonists are methadone, mono-buprenorphine and buprenorphine-naloxone. Of the various treatment options that have been examined, the opioid agonist treatment combined with psychosocial assistance has been found to be the most effective (McLellan, Arndt et al. 1993; Sees, Delucchi et al. 2000; Amato, Minozzi et al. 2004b; Amato, Minozzi et al. 2004c; Amato, Minozzi et al. 2008a; Amato, Minozzi et al. 2008; WHO 2009). OMT is more cost-effective compared to detoxification (Mattick, Breen et al. 2003; Mattick, Kimber et al. 2003; Mattick, Kimber et al. 2008; Minozzi, Amato et al. 2008b; Mattick, Breen et al. 2009; Polsky, Glick et al. 2010; Treatment of drug abuse: current care summary2012).

The diversion, misuse and non-medically supervised use of methadone, mono-buprenorphine and buprenorphine-naloxone combination represent a complex medical and social issue (Larance, Degenhardt et al. 2011b). Maintenance treatment for opioid dependence often involves supervised daily administration of a dose of methadone or buprenorphine, which bind significant resources to the treatment sites and also constrains the patient’s possibilities to carry out normal social activities (Sullivan, Chawarski et al. 2005), which negatively affects rehabilitation. In Finland, buprenorphine is the most widely abused opioid, causing fatal poisonings (Steentoft, Teige et al. 2006; Simonsen, Normann et al. 2011). A sublingual tablet combining buprenorphine and naloxone has been developed to deter diversion and intravenous misuse, and to be more suitable to less supervised administration. Even so there have been doubts about whether the new formulation of the drug functions as planned, while patients have been reluctant to use it following concern about the possible side effects of the naloxone compound. The profusion of national guidelines has led to many different OMT models and different approaches to clinical management in different countries and even within a country. Thus research and guidance to improve clinical management is needed.
In Finland approximately 4000–5000 persons are opioid abusers and approximately 2400 of these are in opioid maintenance treatment (OMT). It has been shown in numerous studies that pharmacologically assisted opioid maintenance therapy is the most effective method of treatment. Nevertheless, this approach to treatment is still controversial, which is partly reflected in Finland's drug policy and in the development of the clinical management of the treatment systems in Finland. A particular concern in Finland has been the abuse of maintenance medications or their diversion into the street market. This is partly due to the exceptional situation in Finland, where buprenorphine is the most intravenously abused opioid. This has overshadowed the use of maintenance treatment and created special challenges for treatment and its further development.

In Finland, OMT on a larger scale did not begin until the late 1990s, after which several decrees of the Ministry for Social Affairs and Health have guided the treatment systems and clinical management. The latest decree is from 2008, with an emphasis on shifting evaluations and treatments to primary health care as well as allowing pharmacy distribution for the buprenorphine-naloxone combination. The reforms are aimed at improving access to care, and thereby increasing the number of patients treated. Although the number of patients has risen steadily in Finland, it is still relatively lower than in other Nordic countries. The transference of maintenance treatments to primary health care and especially the use of pharmacy distribution have not developed as expected. Regarding the Current Care Guidelines, the implementation of OMT varies from one municipality to another and even from clinic to clinic. Also some of the current clinical practices demand resources that could be used for rehabilitation. Because the treatment is usually long-term, some of these procedures can decrease patient compliance and treatment outcomes.
2. Review of literature

2.1 Diagnosis and assessment of opioid dependence

2.1.1 Opioids

The term ‘opioids’ refers to a class of psychoactive substances derived from the poppy plant (including opium, morphine and codeine), as well as semi-synthetic forms (including heroin) and synthetic compounds (including methadone and buprenorphine) and endogenous compounds with similar properties. The term ‘opiate’ refers strictly to the subset of opioids that are naturally occurring or semi-synthetic, and therefore include heroin and morphine. Opioids are also classified by their potency on the opioid receptor system: for example, codeine and tramadol are considered weak, buprenorphine is considered semi-strong, and morphine, heroine, methadone and fentanyl are considered strong opioids. The three major subgroups of opioid receptors are delta, kappa and mu, and are mainly found in the brain and spinal cord, though also at other locations. The subgroups have partly overlapping, different functions and as an example the mu receptor is central in pain relief but also induces respiratory depression and euphoria, which plays an important role in opioid dependency. The delta receptor in the brain is involved in pain relief and antidepressant effects. Kappa receptors in the brain and spinal cord are linked with sedation, spinal analgesia and pupil constriction. Opioids may produce unwanted side effects such as nausea, vomiting, dizziness, and constipation, and even potentially fatal respiratory depression when overdosed. Especially in the case of opioids, the adapted tolerance following regular use can be remarkable and addicted persons can use doses that would be deadly for first-time opioid users (Salaspuro M. 2003).

Opioids are widely used in medicine for pain treatment due to their ability to relieve even severe pain related to, for example, cancer (Zeppetella and Ribeiro 2006; Wiffen and McQuay 2007). For other medical conditions they are rarely used because of their addictive nature and side-effects.
2.1.2 Drug addiction and dependence

Drug misuse is defined as the use of a substance for a purpose not consistent with legal or medical guidelines. Illicit use of opioids generally involves injecting or inhaling the fumes produced by heating the drug. Even though addiction has also long been recognized as a chronic relapsing brain disorder (Leshner 1997) the exact neurobiological processes behind it remain little understood (Buckland 2008).

The genetics behind addiction and vulnerability have been intensively research, but no clear breakthrough have been made (Duaux, Krebs et al. 2000; Kreek, Nielsen et al. 2004). From a psychiatric perspective, drug addiction displays aspects of both impulse control disorders and compulsive disorders (APA 1994), The strongest neurobiological hypothesis behind these processes are that addiction is a neurological dysfunction of brain reward (Koob, Ahmed et al. 2004; Berridge 2007; Volkow 2010; Volkow, Wang et al. 2010; Hommer, Bjork et al. 2011), motivation (Di Chiara 1998; Salamone, Correa et al. 2003), memory and the related circuitry (Koob 1998; Koob, Sanna et al. 1998; Kreek and Koob 1998; Koob and Le Moal 2001; Weiss and Koob 2001), as stated in the most recent definition of the American Society of Addiction Medicine. Even though this neurobiological aspect has been emphasised lately, there are several essential non-biological components of addiction, which include cultural and social values, situational factors, developmental variations, personality and cognitive differences. There has been and still is an on-going struggle between these two perspectives, even though clinically they cannot be separated from each other without compromising treatment outcomes. Physical dependence, tolerance and addiction are discrete and different phenomena that often make discussion challenging. The terms used in this theses will be those recommended and used by the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine (ASAM 2001):

I Addiction
Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations (ASAM 2011). It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
II Physical Dependence

Physical dependence is a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

III Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.

The way that drugs are experienced and how they bring about reinforcement differs greatly between individuals. The still unresolved question is why only a small proportion of all individuals that have used an abused drug will become addicted (Piazza and Le Moal 1996; Miller, Guttman et al. 1997; Duaux, Krebs et al. 2000; Kreek, Nielsen et al. 2004; Levran, Yuferov et al. 2012). Besides the neurobiological aspects mentioned above, two theories have addressed this issue from different angles, either social or psychiatric. The first theory proposes that if an individual because of environmental factors has a greater chance of using a drug, they will become addicted because of repeated use of it. The theory thus suggests that repeated drug use will bring about changes in the brain leading to addiction. The other theory proposes that if an individual is especially vulnerable to addiction because of their physiology this can lead to a pathological reaction to the drug, culminating in addiction. It is likely that both theories contribute to the individual variability in vulnerability to addiction, as has been shown in recent studies (Uhart and Wand 2009; Pani, Maremmani et al. 2010; Fenton, Keyes et al. 2012; Keyes, Eaton et al. 2012; Martins, Fenton et al. 2012; Read and Bentall 2012)

2.1.3 Definition of opioid dependence

Opioid dependence is recognized as a medical condition with cognitive, behavioural and physiological dimensions. Illicit use of opioids generally involves injecting, inhaling the fumes produced by heating the drug or sniffing opioid powder. Dependence does not develop without regular use, but regular use alone is not sufficient to cause dependence. It develops over time from initial experimental and recreational use to more intensive and compulsive use, usually daily. Once dependence on opioids is well established, it becomes a chronic relapsing
condition. Many opioid addicted individuals also show psychiatric comorbidity (Maremmani, Pani et al. 2010; Fenton, Keyes et al. 2012), but it is unclear whether the psychopathology was pre-existing or is a result of the opioid abuse (Pani, Maremmani et al. 2010; Maremmani, Dell'Osso et al. 2011). Opioid dependence is also related to higher mortality rates and costs to society, especially the criminal and justice system, than any other drugs (Cruts, Buster et al. 2008; Gibson, Degenhardt et al. 2008; Clausen, Waal et al. 2009; Degenhardt, Randall et al. 2009; Vicente, Giraudon et al. 2009; Hedrich, Alves et al. 2012; Nilsson I. 2012; Soyka, Trader et al. 2012).

Opioid dependence is defined according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10)(WHO 1995) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)(APA 1994). These classifications differ in some aspects and in this thesis, ICD-10 is used, as it is the officially used standard classification in Europe. DSM-IV is used mainly in the United States and much less often in Europe in the field of psychiatry, because it covers the psychiatric aspects of addiction in more detail. For this reason, it is also widely used in international research, while in many countries, addictions are treated as part of psychiatry. In many European studies the ICD-10 and DSM-IV are used side by side to make comparisons of different studies easier.

The ICD-10 diagnostic system is used in Finland and a description of the dependency syndrome states: A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state. Opioid dependence can be diagnosed if three or more of these traits are fulfilled continuously during a one-month period or if these periods are shorter repeated over a 12-month period:

1. a strong desire or sense of compulsion to take opioids
2. difficulties in controlling opioid use
3. increased tolerance over time
4. after stopping the use of opioids the patient suffers from a physiological withdrawal state
5. the patient also progressively neglects alternative pleasures or interests because of opioid use
6. misuse persists despite clear physical or psychiatric harm to the patient.
In addition using the DSM-IV criteria, used more for research purposes, one should also specify whether opioid dependence is physiological dependence (i.e. there is evidence of tolerance or withdrawal) or without physiological dependence (i.e. no evidence of tolerance or withdrawal). In DSM-IV the essential criteria are tolerance, specified as marked increase in the amount and decrease in effect, characteristic withdrawal symptoms; leading to opioids taken to relieve withdrawal. Also opioids are taken in larger amounts and for longer periods than intended. The patient also has a persistent desire or has had repeated unsuccessful attempts to quit. The patient uses much time/activity to obtain, use and recover opioids. With ongoing abuse, important social, occupational or recreational activities are surrendered or reduced by the patient and the use continues despite knowledge of adverse consequences (e.g. failure to fulfil role obligations, use when it is physically hazardous).

In both classifications, patients may also be variously classified as currently manifesting being in remission. The remission category can also be used for patients receiving agonist therapy (e.g. methadone maintenance) or for those living in a controlled drug free environment (APA 1994). Furthermore in DSM-IV those in remission can be divided into four subtypes (full, early partial, sustained and sustained partial) on the basis of whether any of the criteria for abuse or dependence have been met and over what time frame.

Since the 1970s heroin has been the most abused opioid and responsible for the largest share of drug-related diseases and deaths in the EU. Now this picture is changing and new recruitment into heroin use has fallen, which partly is because of shortage in availability, but also because other substances are taking its place, like fentanyl and buprenorphine. Especially this is the case for fentanyl in Estonia and buprenorphine in Finland (EMCDDA 2012a).

2.1.4 Opioid abuse in Finland

For long periods problematic drug abuse was dominated by amphetamines, and the use of heroin and other opiates became more widespread in Finland as late as the latter half of the 1990s. In 1997 it was estimated that there were 1 526–3 261 opioid abusers and in 1998, around 1797–2656, which was 0.06%–0.09% of the population. The majority of abusers at this
time lived in the Helsinki metropolitan area: in 1995 in the metropolitan area, the number of opioid abusers was estimated to be 487–1 393, in 1997 around 921–1 996, and in 1998 around 962–1 611 abusers, accounting for 0.17%–0.28% of the population aged 15–55 years (Partanen P. 2000). In 2005 the total estimated number of opioid abusers in Finland was 3700–4900 meaning 0.13%–0.18% of the population (Partanen A. 2007). After 2005 the use of opioids has constantly risen and according to the latest surveys, the population aged 15 to 34, 0.6% have tried opioids (Hakkarainen P. 2011a; Hakkarainen P. 2011b). The major change in the opioid abuse occurred in 2001, following which mono-buprenorphine became the most misused opioid (Alho, Sinclair et al. 2007), originating mainly from France (Tacke 2002). In recent years, the situation has remained stable and no significant changes in the Finnish opioid abuse scene have occurred (EMCDDA 2012a; Varjonen V. 2012), but the number of opioid abusers seeking treatment has still risen throughout the 2000s (Väänänen 2010)

Until now drug users in Finland were young by international comparison, but recent years have seen a change. In the past, the 20–24 years group was the largest, but now the 25–29 years and 30–34 years age groups are bigger (Vuori E. 2003; Steentoft, Teige et al. 2006; Vuori E. 2006; Vuori E. 2009; Hakkinen, Launiainen et al. 2011; Simonsen, Normann et al. 2011). What is notable, though, is that the number of drug-related deaths has been increasing in Finland and especially deaths related to buprenorphine (Boyd, Randell et al. 2003; Vuori E. 2003; Vuori E. 2006; Vuori E. 2009; Vuori E. 2012). In cases of fatal poisoning, prescribed opioids have become a major factor in Finland. Most drug-use-related poisonings are caused by buprenorphine, tramadol, methadone, fentanyl and codeine. Overdosing deaths caused by morphine, heroin or oxycodone rare. Overdosing is typically the result of multidrug use and drugs that have been injected or snorted. In 2010 fatal poisonings, opioid abuse was the main finding in 46 (out of 49 also including cases of medication use without abuse) cases of buprenorphine, in 27 tramadol (out of 47), in 16 fentanyl (out of 20) fatal poisonings, in 15 methadone (out of 15) poisonings, in 5 codeine (out of 39) and in 2 (out of 2) morphine/heroin (Vuori E. 2012). The prominent role of alcohol and benzodiazepines as an additional substance and co-occurring mental health disorders are typical of Finnish problem drug use (Hakkarainen 2009; Tourunen J. 2009; Vorma 2009; Rönkä S. 2010; Tammi T. 2011) and are central to opioid overdose deaths (Hakkinen, Launiainen et al. 2011).
Buprenorphine is a mu-opioid receptor partial agonist and kappa-opioid receptor antagonist, which means it binds to the receptors but does not produce maximum stimulation and there is an upper limit to the effect, even with increasing doses. Its physiological and intoxicating effects usually plateau at a sublingual dose of 4–8 mg. Because of this ceiling on its effect on respiratory depression and poor oral bioavailability, buprenorphine is safer in overdose than pure opioid receptor agonists. Respiratory depression from mono-buprenorphine or buprenorphine–naloxone overdose is less likely than from other opioids. However, significant respiratory depression can occur if buprenorphine is administered intravenously.

Buprenorphine is highly bound to plasma proteins. It is metabolized by the liver via the cytochrome P450 enzyme system (CYP 3A4) into norbuprenorphine and other metabolites, which are excreted in the faeces (70%) and urine (30%). The half-life of buprenorphine is highly variable: 20–72 hours, with a mean of 36 hours. With stable dosing, steady state levels are achieved over 7-10 days. Peak clinical effects occur 1–4 hours after sublingual administration, with continued effects for up to 12 hours at low doses (2 mg), but as long as 72 hours at higher doses (24–32 mg). The side effects are similar as for opioids generally. After cessation of use symptoms commence generally within 3–5 days of the last dose and can last for several weeks. The symptoms and signs of withdrawal from buprenorphine are similar to those found in withdrawal from other opioids, but withdrawal from buprenorphine is generally milder than withdrawal from methadone or heroin because of its slow dissociation from the μ receptor.

In Finland two formulations of sublingual tablets of buprenorphine are available. Mono-buprenorphine (Subutex®, Reckitt Benckiser), in three dosage strengths of 0.4 mg, 2 mg and 8 mg, and buprenorphine–naloxone (Suboxone®, Reckitt Benckiser), available in two dosage strengths of 2 mg buprenorphine with 0.5 mg naloxone, and 8 mg buprenorphine with 2 mg naloxone. The tablets take between 2 and 7 minutes to dissolve. Naloxone is a short-acting injectable opioid antagonist used in the management of opioid overdose to reverse the effects of opioids. It is poorly absorbed orally (under 10% bioavailability) and so is used for medical reasons either intramuscularly or intravenously. It has a half-life of approximately one hour but continues to have 50% receptor occupancy at 2 hours after injection due to its receptor binding.
The parenteral to sublingual potency is 15:1 compared with the 2:1 ratio of buprenorphine (Amass, Ling et al. 2004).

The addition of naloxone was designed specifically to decrease buprenorphine’s injectable abuse potential, especially by opiate abusers, and so discourage the diversion of buprenorphine from treatment. So the idea is that when taken sublingually, buprenorphine-naloxone is still an effective opioid; but when injected, the naloxone is predominant and can precipitate withdrawal (Eissenberg, Greenwald et al. 1996; Mendelson, Jones et al. 1996; Strain, Stoller et al. 2000; Stoller, Bigelow et al. 2001; Chiang and Hawks 2003; Harris, Mendelson et al. 2004; Strain, Moody et al. 2004). With persons abusing mainly buprenorphine intravenously this effect is not so clear, but still present depending on receptor occupancy (Harris, Jones et al. 2000; Comer, Sullivan et al. 2010). The difference of clinical effects of mono-buprenorphine and buprenorphine-naloxone are summarised in table 1.

The abuse potential of buprenorphine has been recognized since its inception, and Finland, France, Australia and Great Britain have reported its misuse. According to the European Monitoring Centre for Drugs and Drug Addiction 12 out of 17 member states of the European Union reported the misuse of legal buprenorphine in 2004 (EMCDDA 2005) and this situation has not changed (EMCDDA 2012a). In the latest systematic reviews of literature the misuse of

<table>
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<tr>
<th>Heroin-dependent</th>
<th>mono-buprenorphine</th>
<th>buprenorphine-naloxone</th>
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<tr>
<td>Non-dependent</td>
<td>mild agonist effect</td>
<td>attenuated agonist effect</td>
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<tr>
<td>Methadone maintained</td>
<td>antagonist effect</td>
<td>antagonist effect</td>
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<tr>
<td>Mono-buprenorphine or buprenorphine-naloxone maintained</td>
<td>agonist effect</td>
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<td>Mono-buprenorphine iv misuser</td>
<td>agonist effect</td>
<td>dose/free receptor depending on agonist or attenuated agonist effect</td>
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Table 1: mono-buprenorphine vs. buprenorphine-naloxone by injection (unpublished, Leslie Amass oral presentation 2005 and Carola Fabritius 2008 oral presentation)
buprenorphine and methadone in the European Union has spread more and is recognized as a rising problem in many countries (Yokell, Zaller et al. 2011; Casati, Sedefov et al. 2012). The current European rates of misuse of medication used treatments for opioid dependence, mainly buprenorphine and methadone, in subjects involved in the open drug scene range from 5.6% in Portugal (Vale Andrade 2007) to 73% in Finland (Alho, Sinclair et al. 2007; Partanen A. 2007) and over 50 % for slow release morphine in Austria (Beer, Rabl et al. 2010).

2.2. Treatment of opioid dependence

Treatment of drug dependence can serve a multitude of purposes. Beyond reductions in drug usage, it can help the drug user to see his or her problems from a different perspective, improve self-reliance, and empower the individual to seek and effect changes in their life; it can even confer self-esteem and give hope. At the same time, it can provide access to physical and psychiatric care and social assistance, and provide for the needs of the patient’s family as well as those of the patient.

In most cases, treatment will be required in the long-term or even throughout life. The aim of treatment services in such instances is not only to reduce or stop opioid use, but also to improve health and social functioning, and to help patients avoid some of the more serious consequences of drug use. Such long-term treatment, common for many medical conditions, should not be seen as treatment failure, but rather as a cost-effective way of prolonging life and improving quality of life, while supporting the natural and long-term process of change and recovery.

2.2.1 Definition and general criteria of opioid maintenance treatment

Treatment of opioid dependence has been defined by the World Health Organization (WHO) as a set of pharmacological and psychosocial interventions aimed at reducing or ceasing opioid use, preventing future harms associated with opioid use and improving the quality of life and well-being of the opioid-dependent patient (WHO 2009). There are two pharmacological approaches to opioid dependence treatment – those based on opioid withdrawal and those based on agonist maintenance (WHO 2009).
Detoxification is a gradual and managed medical withdrawal from the abuser’s regular level of drug use towards no drug use at all, using medications to help manage opioid withdrawal symptoms and cravings. Both methadone and buprenorphine are used in agonist assisted detoxification (Amato, Davoli et al. 2004a; Amato, Minozzi et al. 2004b; Digiusto, Lintzeris et al. 2005; Amato, Davoli et al. 2005a; Renzell and Capretto 2006, Shanahan, Doran et al. 2006). Buprenorphine detoxification can be completed in 1 or 2 weeks and methadone detoxification can take between 4 and 12 weeks. The duration depends on the starting dose, although it can vary widely. Also symptomatic medication can be used alone or beside agonist medication. The most common symptomatic medications are lofexidine (Strang, Bearn et al. 1999) and clonidine (Gossop 1988) often in combination with benzodiazepines. After detoxification, naltrexone, a long-acting, highly specific opioid antagonist, blocks opioid receptors so that the patient does not experience the usual effects of taking opioids, can be used for a small group of patients who are committed to achieving abstinence. They may benefit from naltrexone maintenance treatment (Adi, Juarez-Garcia et al. 2007; Lobmaier, Kunoe et al. 2011). Although a range of health benefits are often derived from detoxification, detoxification alone leads to lasting abstinence from drugs or significantly improved health and functioning for only a small minority of patients and many will relapse to illicit opioid use (Gandhi, Jaffe et al. 2003; Minozzi, Amato et al. 2006; Teesson, Havard et al. 2006; Minozzi, Amato et al. 2011). Maintenance pharmacotherapies can prove valuable in assisting these people to manage physical dependence, drug craving and compulsive drug use successfully (Bart 2012).

Opioid maintenance treatment (OMT), often also referred to as Opioid substitution (OST) or opioid replacement (ORT) treatment, is defined as the administration of thoroughly evaluated opioid agonists, by accredited professionals, in the framework of recognized medical practice, to people with opioid dependence, for achieving defined treatment aims. Both methadone and buprenorphine are sufficiently long-acting to be taken once daily under supervision, if necessary. When taken on a daily basis they do not produce the cycles of intoxication and withdrawal seen with shorter-acting opioids (WHO 2004; WHO 2006; WHO 2011).

Beside treatment there is also the approach of harm reduction. As the position statement from the International Harm Reduction Association states harm reduction refers to policies, programmes and practices that aim primarily to reduce the adverse health, social and economic consequences of the use of legal and illegal psychoactive drugs without necessarily reducing
drug consumption (IHRA 2010). Harm minimization philosophy involves accepting that despite all efforts to control supply and reduce demand, many people will continue to have access to licit and illicit drugs, and to use them in a way that puts them and society at risk of serious harm. Harm reduction includes services that promote safer drug use, e.g. needle and syringe exchange programs, safer injecting facilities, naloxone for overdose prevention, and information, education and communication programs for the clients also including peer outreach. Depending on local circumstances a range of drug dependence treatment options can be included, also containing opioid maintenance therapy. This means that harm reduction can be offered to drug abusers outside the treatment system but also as part of OMT for those patients who do not have the capability or will to cease drug use after entering treatment. They can be given by this approach the possibility to prepare themselves for more intensive and abstinence orientated treatment, while diminishing harms related to opioid abuse.

Considering these different perspectives of OMT implementation treatment outcomes can also be divided into two main orientations. On one hand those emphasising harm minimizing treatment goals, like reduction of drug use, viral infections (HIV, HCV), overdoses and criminality, are those which can be more easily defined and measured. Then there are the more rehabilitation orientated treatment goals, like improvement of social and health issues, quality of life and employment, which are difficult to define and measure as they are mostly individually set. Depending on the approach chosen the treatment models are differently built, which makes it challenging to define, measure and compare their effectiveness.

2.2.2 General milestones of opioid maintenance treatment

The first medically assisted treatments trials for opiate dependence started in the 1950s, when methadone was used to treat opiate withdrawal symptoms in the United States (Isbell 1948; Isbell and Eisenman 1948; Isbell, Wilker et al. 1948). Research on the issue followed and the first reports were published in the 1960s showing that relapse rates were high after leaving medically assisted treatment (Hunt and Odoroff 1962). In later studies (Wikler 1977; Dole 1988) it was discovered that an ongoing, daily enough high dose of long-acting oral methadone (Dole and Nyswander 1965; Dole and Nyswander 1967) offered a number of beneficial effects, allowing opioid addicts to function more normally (Greenstein, Resnick et al. 1984; Kreek
The findings of the first major studies were consistent and showed that methadone maintenance reduced the use of heroin, lowered death rates and criminality associated with heroin use (Joseph, Stancliff et al. 2000), and allowed patients to improve their health and social productivity (Novick, Pascarelli et al. 1988) which was also verified also by later reviews (Amato, Davoli et al. 2005b; Amato, Minozzi et al. 2008). Treatment could also diminish the transmission of infectious diseases associated with heroin injection, such as hepatitis C and HIV (Lavignasse, Lowenstein et al. 2002). Methadone Maintenance Treatment (MMT) was viewed as corrective therapy, rather than healing opioid addiction. Methadone is the most used medication in the treatment for opioid dependence, but with the expansion of use, new problems arose: diversion and overdoses. These issues have been studied especially since the late 1990s and it seems that injection of treatment medication is a problem globally and related to all treatments, affecting from under 20% to over 50% of those studied (Darke, Ross et al. 1996; Waldvogel and Uehlinger 1999; Humeniuk, Ali et al. 2003; Winstock, Lea et al. 2008; Christian Wickert C. 2009). Methadone used in treatment or diverted from treatment has also been linked to fatal overdoses (Heinemann, Iwersen-Bergmann et al. 2000; Perret, Deglon et al. 2000; Vormfelde and Poser 2001), making this an important issue to be addressed in treatment.

Buprenorphine was patented in the late 1960s for pain treatment, and being a partial agonist, it also generated interest for its possibilities to treat opioid dependence (Johnson and Fudala 1992; Walsh, Preston et al. 1994). Substantial studies were published in the 1990s (Johnson, Cone et al. 1989; Johnson, Jaffe et al. 1992; Johnson, Eissenberg et al. 1995; Eissenberg, Greenwald et al. 1996; Fischer, Gombas et al. 1999) showing that it was useable and that the outcomes were clinically relevant (Elkader and Sproule 2005; Campbell and Lovell 2012). Further, in comparison with the golden standard of methadone, buprenorphine was shown to be effective and a real alternative (Strain, Stitzer et al. 1994; Ling, Wesson et al. 1996; Raisch, Fye et al. 2002; Heilig and Kakko 2003; Mattick, Ali et al. 2003; McCance-Katz 2004; Fareed, Vayalapalli et al. 2010) and also during pregnancy (Eder, Rupp et al. 2001; Johnson, Jones et al. 2001; Johnson, Jones et al. 2003; Schindler, Eder et al. 2003; Hytinantti, Kahila et al. 2008; Kahila, Stefanovic et al. 2008; Bakstad, Sarfi et al. 2009; Jones, O'Grady et al. 2009; Jones, Kaltenbach et al. 2010; Jones, Finnegan et al. 2012; Jones, Heil et al. 2012; Welle-Strand, Skurtveit et al. 2013). It was most widely used in France in treating heroin dependence, but increasing misuse was also reported (Agar, Bourgois et al. 2001; Vidal-Trecan, Varescon et al. 2003). This same trend was then seen in other countries where buprenorphine became available.
This led to the development of a combination product containing buprenorphine and naloxone, which had a lower susceptibility to abuse (Robinson, Dukes et al. 1993) and was used less intravenously than mono-buprenorphine alone (Comer and Collins 2002; Degenhardt, Larance et al. 2009; Larance, Degenhardt et al. 2011a). Several studies have shown that the combination product is effective (Bell, Byron et al. 2004; Comer, Walker et al. 2005; Ling, Amass et al. 2005; Finch, Kamien et al. 2007; Mintzer, Eisenberg et al. 2007; Schackman, Leff et al. 2012), although buprenorphine is not as potent treatment medication as all doses of methadone (Ahmadi 2003c; Doran 2005; Connock, Juarez-Garcia et al. 2007; Mattick, Kimber et al. 2008). There are only few studies done on OMT of mainly buprenorphine addicted abusers and the treatment seems to be as effective as with heroin addicted patients regardless if they were treated with methadone or buprenorphine (Ahmadi and Ahmadi 2003a; Ahmadi, Ahmadi et al. 2003b).

Opioid dependency treatment spread in the 1960s and 1970s and programs, mainly methadone and later also buprenorphine, were built up in the USA, Australia and Great Britain. The variety of treatments provided was broad and was mainly determined by the clinic and by local practice. In several countries, the preparation of guidelines was done mainly during the 1990s (NIH 1997) and by the WHO in 2009. Even though the latest treatment guidelines are based on evidence-based medicine, the treatment programs and medications used have nevertheless differed greatly in different countries, from heroin treatment in Switzerland to strict treatment policy countries like the Nordic countries (Skretting A. 2010).

There are as many OMT models as treatment sites based on national and regional guidelines but also due to historical and cultural circumstances. This makes a comparison of the different treatment models as well as an evaluation of the outcomes of published studies somewhat challenging. An assessment of the research results often requires to some extent knowledge of clinical patient work in order to understand why an implementation in local circumstances is challenging, or to grasp the complexity of a patient’s addiction and related problems. As mentioned earlier, different perspectives on addiction itself also affect treatment models. Some are more medicine orientated and others also include psychosocial rehabilitation. When looking at Nordic countries this difference is detectable for example when comparing Denmark, which has a strongly medically, somatic harm-reduction insight, and Sweden, which is clearly geared
more to a rehabilitation orientation (Skretting A. 2010). Heroin injection treatment, which has been accepted in Denmark since 2010, would at this point be unthinkable in Finland. These two examples signify quite aptly the wide variety of approaches to carrying out OMT.

2.3 Milestones of opioid maintenance treatment in Finland

Up to 1990, Finland did not have a severe opioid abuse problem and the main focus of drug policy was on minimizing drug availability and on harm reduction. Special care services for drug users were not considered necessary until then. However, increasing problems leading into the 1990s had led the Helsinki University Central Hospital and some non-profit organizations to start developing specialized services for opioid abusers, although this mainly meant psychosocial services. In 1996, only 5 patients were officially in methadone treatment (Hakkarainen P. 2005; Selin 2010). The attitude towards pharmacological treatment was clearly visible in the statement of the national alcohol and drug cooperation group given to the 1993 opioid dependence treatment committee: “maintenance treatment for drug addicts should not be started in Finland because it does not treat the problem … but maintenance therapy in a way condemns the patient to a life-long drug addiction” (author’s translation) (Stakes 1993). With the rise of opioid-dependent persons and related harms in the later 1990s, pharmacological treatment was accepted as part of the Finnish drug policy; yet, the contradiction between non-medical and pharmacological treatment approaches still exists today.

In Finland, harm reduction has also its roots in criminal policy. Harm reduction has been especially disputed politically due to its presumed aim of liberalising the control of drug use. Opponents have feared that harm reduction practices such as needle exchange and substitution treatments would destroy the very foundations of the prohibitionist drug policy. With the changing drug abuse situation of the 1990s, the Finnish drug policy changed, leading to what has been called a dual track policy (Hakkarainen P. 2005). Studies on this change showed that rather than posing a threat to a prohibitionist drug policy, harm reduction has come to form part of prohibitionist drug policy. The implementation of harm reduction has implied an increasing involvement of the medical profession in addressing drug problems, while the criminal justice control of drug use has been intensified. Accordingly, harm reduction has not entailed a shift to a more liberal drug policy, nor has it undermined the prohibitionist penal policy. Rather, along
with the prohibitionist penal policy, it constitutes a new dual-track drug policy paradigm (Hakkarainen, Tigerstedt et al. 2007). This meant that measures such as syringe exchange services and maintenance treatment were initiated to counter drug-related public health problems, but, at the same time, the policies left intact restrictive drug policy measures built on a zero tolerance to drugs (Perälä 2012).

Public attention focused on preventing diseases transmitted by injecting drug users in 1998, when the HIV epidemic began among Finnish drug users. Since 1997, health counselling centres have been established throughout the country and in the past years, their number has increased further. However, there is some variation in service provision depending on the facilities. The health counselling centres that exchanged needles and syringes to prevent infectious diseases are located mainly in cities with over 100 000 inhabitants and are available in more than 30 locations across Finland. According to available data, in 2011 the number of clients at health counselling was 1 134 with 84 586 visits and the number of syringes changed was 3.5 million (Tanhua H., Virtanen A. et al. 2011; EMCDDA 2012b).

Current harm reduction services in Finland include outreach work and health counselling centres. The outreach work mainly involves street patrols, with the aim of mediating between drug users and the official care system. Peer work is emerging in several locations and focuses towards reaching the most excluded and most concealed groups of drug users. Health counselling centres are low threshold facilities catering for problem drug users, offering referral to treatment, case management, information on drug-related diseases and risks such as overdoses, needle exchange, as well as testing of infectious diseases and vaccinations against viral hepatitis A and B is offered and small scale health care (A-clinic Foundation 2000).

2.3.1 Stipulations and statutes regulating OMT in Finland

In Finland in the period 1995–1997, treatment was conducted based on the recommendations of the Ministry of Social Affairs and Health. In 1997, the Ministry issued a Decree that would more broadly govern treatment practices, with a maximum treatment period set at 3 months, although this was already extended to one year in 1998. In the Decree from 2002, treatment for one month or less was considered to be detoxification. Treatment which lasted longer than one
month was named either substitution if it aimed at a life free of drug use, or maintenance if it aimed at minimizing the harms and improving the life conditions of the person unable to stop abusing drugs. The evaluation for treatment had to be done in general hospitals, mainly psychiatric, or at the Järvenpää addiction hospital. The criteria for receiving treatment were tight and patients had to go through several detoxification treatments to establish they were unable to stop opioid abuse without OST. After the induction of treatment, they could be transferred to A-clinics if the patient’s condition was stable enough. This led to long waiting lists especially in the larger cities, despite the existence of a guaranteed statutory time frame to receive treatment within 6 months being established in 2005. The Decree was further revised so as to respond to the waiting lists.

The main purpose of the latest amendment of the Decree (MSAH 33/2008; http://www.finlex.fi/fi/laki/alkup/2008/20080033 ) was to increase the supply of OST to better match need, while at the same time maintaining treatment-related controls so as to limit leakage of medicines into the black market. The 2008 Decree emphasized that treatment staging is based on disease severity in accordance with specialist care and primary health care services, that treatment evaluations and initiation are shifted from institutional care to outpatient units, and also that pharmacies are able to distribute the buprenorphine–naloxone combination. In 2009 only 31 patients received reimbursements for their buprenorphine–naloxone medicine expenses. The number of patients receiving reimbursement increased threefold in 2010, involving 95 individuals at an expense of EUR 245 373. Since then, the rate of increase has slowed and in 2011 the possibility for pharmacy dispensing remains small scale in Finland, with only 123 patients receiving their medication from the pharmacy and 175 in 2012. This is below 10% of patients treated with the combination medication, even though it is now the most used preparation. There are no time limits on treatment whatsoever, and the 2008 Decree does not specify in detail the content of treatment. Treatment is rather perceived as a kind of framework, building on the best available knowledge. Methadone or buprenorphine can be used either in detoxification in order to get a person drug free or in substitution treatment. Substitution should aim at rehabilitation or reducing harms or improving the quality of life. Harm reduction is thus accepted as a goal, on a par with rehabilitation or detoxification. The decree memorandum emphasizes that treatment should follow the needs of each individual patient, and that pharmacological treatment alone is not enough. The decree claims that treatment has to be psychosocially assisted and every patient has to have an individual treatment plan.
At the same time as treatment regulations were loosening, a buprenorphine-naloxone combination drug became available in Finland in late 2004, introduced to lower the risk of misuse and was quickly adopted by the treatment units. Together with the introduction of the buprenorphine-naloxone product mono-buprenorphine was shifted under the special permission procedure. In this case it meant that the medication was only to be used for pregnant patients and for patients with a specific justification for it evaluated by the physician responsible for the treatment. The special permission has to be renewed annually. Buprenorphine-naloxone is now the most used preparation in Finland for patients treated with buprenorphine.

2.3.2 Current status of opioid maintenance treatment in Finland

The number of patients in treatment has been rising alongside the changes made in legislation (Figure 1), but is still low compared to other Nordic countries (Skretting A. 2010). Finland had been lacking an official register of patients in treatment, but it was established in spring 2012. Using several sources, including about 90 treatment units in Finland, it was calculated that in summer 2012 2 436 patients were in treatment, of which 230 were treated with mono-buprenorphine, 1 334 with buprenorphine-naloxone and 875 with methadone (THL 2012).

Figure 1: Patients in OMT 1997–2012
The majority of patients are polydrug abusers (Onyeka, Uosukainen et al. 2012) and in 2010 55% of patients seeking treatment at outpatient units abused opioids, of which were 32% buprenorphine compared to 2% abusing heroin (Väänänen 2011). Currently OMT is at a turning point in Finland due to increasing demand for treatment and reduced economic resources in the municipalities. As a result, many treatment units have tried to find new ways of producing treatments more effectively. At the same time, with municipalities aiming at better cost-effectiveness, they have sought competitive bidding for service provision as well as restricting access to treatment. For patients in treatment, the trend in municipalities seems to be towards transferring clients into harm-reduction treatment and narrowing it to just the supply of medicine, a trend that has significant risk factors associated with it (Vormfelde and Poser 2001; Jenkinson, Clark et al. 2005; Larance, Degenhardt et al. 2011a; Larance, Degenhardt et al. 2011c; Johanson, Arfken et al. 2012).
3. Related research and aims of the study

3.1 Research related to the current study

The main research on buprenorphine has been on its efficacy, especially when compared to methadone (Fischer, Gombas et al. 1999; Ahmadi 2003c; Doran, Shanahan et al. 2003; Doran 2005; Connock, Juarez-Garcia et al. 2007; Curcio, Franco et al. 2011). Only during the last few years has the spectrum of research broadened to involve the more clinical aspects of conducting treatment in different settings. Therefore only a limited number of the studies published have been relevant therefore to the research done in this study.

Finland was the first country in the world, in late 2003, to see patients switched en masse from mono-buprenorphine to the combination formulation buprenorphine–naloxone. At that point the research available consisted of small scale studies concerning safety and effects (Fudala, Yu et al. 1998; Strain, Stoller et al. 2000; Stoller, Bigelow et al. 2001; Chiang and Hawks 2003; Mintzer, Correia et al. 2004), but no publications had yet emerged on switching from mono-buprenorphine to buprenorphine–naloxone. The publication from Study I was the first, although later studies reported similar outcomes (Montesano, Zaccone et al. 2010; Stimolo, Favero et al. 2010).

Before and during the switch from mono-buprenorphine to buprenorphine–naloxone, many clinics and prisons in Finland had begun crushing mono-buprenorphine medication before administering it to patients in order to minimize the risk of medication diversion. Clinical observations had suggested that crushed mono-buprenorphine tablets may yield the same or even better response than whole tablets (Muhleisen, Spence et al. 2003). At that point the only published data on bioavailability and pharmacokinetics of mono-buprenorphine concerned the liquid form of mono-buprenorphine (Strain, Moody et al. 2004; Compton, Ling et al. 2006; Compton, Ling et al. 2007). There were no published data concerning the pharmacokinetic or pharmacodynamic properties of crushed mono-buprenorphine tablets. Studies related to this issue of crushing medication since have been published, but they have been conducted with the buprenorphine–naloxone combination product and were more clinically orientated (Muhleisen P 2010).
Urine drug testing performed regularly or randomly plays an important role in substance abuse treatments. Drug testing can be used to measure compliance or treatment outcome, especially with opioid use discontinuation it is an essential treatment indicator, and can also ensure the safe administration of medication because concomitant drug abuse can resolve in OMT medication denial. That means that often patients have a high intention to manipulate their urine sample. Legally it is also crucial to ensure that the urine being analysed can undoubtedly be connected to the correct person. To ensure this, urine sampling is often strictly controlled, which can be a humiliating situation and ties up human resources. This strict control may negatively affect mutual trust, lower patient compliance and be a reason for professionals not use them as part of treatment (Dupouy, Bismuth et al. 2012).

A new marker method that makes supervision unnecessary was introduced by labelling the urine with modified polyethylene glycols, which are taken orally, quickly excreted through the kidneys, and do not occur in natural urine. They are detected only in the first urine after marker consumption. The different molecular weight marker solutions can be identified by LCM and linked to the person to whom it was given. In this procedure, only the consumption of the marker solution must be supervised. Drug testing is performed using normal, standard methods. Urine labelling has mainly been used in Germany as part of treatment and no international studies have been published on how this could enhance opioid maintenance treatment. The studies available considered the method (Gauchel, Huppertz et al. 2003; Huppertz, Gauchel et al. 2004) or reliability compared to conventional methods (Schneider, Ruhl et al. 2008). The publication of Study III was the first concerning patient compliance and financial considerations.

Before the introduction of the buprenorphine–naloxone combination product, earlier studies on buprenorphine were mainly on efficacy, safety and tolerability of the product. Later, the main focus has been on the abuse liability of the formulation (Mammen and Bell 2009). Several studies on buprenorphine abuse have been published, most of them are short-term follow-ups (Robinson, Dukes et al. 1993; Comer, Sullivan et al. 2010; Kemp 2012; Wish, Artigiani et al. 2012), while long-term follow-up studies are rare (Smirnov and Kemp 2012). However there are few studies from countries or regions where buprenorphine is the most abused opioid, such as it is in Finland.
3.2 Aims of the study

The principal aim of this study was to explore what factors could improve patient compliance and adherence to treatment, and thus may improve the OMT outcomes.

The specific aims of this study were:

1) to study the trends of drug and opioid abuse in Finland (metropolitan area), i.e. the trends in street price and means of administration of abused maintenance medications especially monobuprenorphine and buprenorphine-naloxone (IV).

2) to study if the use of the buprenorphine–naloxone combination medication, which was designed to reduce diversion and intravenous misuse, would have an effect on medication dose and abuse, treatment outcomes and drug abuse (I, IV).

3) to investigate if the different medication administration procedures (i.e. crushing the buprenorphine tablets) will affect to the pharmacokinetic and bioavailability of buprenorphine (II).

4) to study if the new drug screening method (i.e. no visual control of the urine screen) could have an effect on patient compliance without compromising the reliability of the drug testing as part of treatment (III).
4. Methods

4.1 Study participants

Study I included the patient records from a total of 64 patients out of 87 patients treated with mono-buprenorphine in five treatment sites who fulfilled the criteria and were switched from mono-buprenorphine to buprenorphine-naloxone (Table 2). All patients who were switched were included in this study. The main reasons for exclusion were significant multidrug abuse and/or the decision of the responsible physician not to change the medication, no specific arguments were collected. Out of these 64 patients, 60 (93.8%) continued OMT with buprenorphine-naloxone into the follow-up period. Of these, 52 (81.2%) were male, 12 (18.7%) were female, and the average age was 29.9 years (SD ± 7 years). The mean mono-buprenorphine treatment (days) was 63.3 (SD ± 363 days) and before medication change, a mean daily mono-buprenorphine treatment dose of 22.9 mg (SD ± 5.4 mg). At this point it was estimated there were around 400 patients were treated with mono-buprenorphine.

<table>
<thead>
<tr>
<th>Total Subjects (n)</th>
<th>Total</th>
<th>RAAHE</th>
<th>HDL-01</th>
<th>Tre-K-Klinikka</th>
<th>HUS</th>
<th>Espoon A-Klinikka</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
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<td>1</td>
<td>2</td>
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<td>7</td>
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<tr>
<td>Age (yrs)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>29.9</td>
<td>28.0</td>
<td>33.6</td>
<td>27.8</td>
<td>30.8</td>
<td>29.9</td>
</tr>
<tr>
<td>SD</td>
<td>7.0</td>
<td>4.4</td>
<td>5.1</td>
<td>3.1</td>
<td>11.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Median</td>
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<td>27.5</td>
<td>34</td>
<td>27</td>
<td>28</td>
<td>31</td>
</tr>
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<td>22 - 34</td>
<td>29 - 45</td>
<td>22 - 33</td>
<td>22 - 71</td>
<td>23 - 38</td>
</tr>
</tbody>
</table>

Table 2: Participating Clinics and Patient demographics per Clinic for Study I. (Drug Rehabilitation Centre, Helsinki Deaconess Institute (HDL-01), Raahé Mental Health Clinic, Primary Health Care Centre (Raahe), Opiate Maintenance Polyclinic, Department of Drug Psychiatry, Helsinki University, Hospital, (HUS), Drug Rehabilitation Polyclinic at Tampere City, K-Clinic, A-clinic Foundation, (Tre-K-klinikka), Espoo A-clinic, A-clinic Foundation (Espoon A-klinikka)
Study II was conducted with 16 opioid-dependent persons out of whom 13 were in OMT either at the Espoo Treatment and Rehabilitation Centre, the Helsinki K-Clinic, or the Järvenpää Addiction Hospital. Three subjects were not in OMT, but fulfilled the other inclusion criteria (i.e. having a stable dose, 20–24 mg/day, for at least 4 weeks and no cannabis use 10 days prior to the study). The study persons had an average opioid dependence of 8 (SD ± 3.74) years for males and 7 (SD ± 4.45) years for females. One study subject discontinued treatment after the first day; the data for that subject were excluded from the analysis. Of the subjects, 10 were male (62.5%) and 6 were female (37.5%) and the mean age was 30 (SD ± 8.02) years and 25 (SD ± 4.23) years for men and women respectively. For males the mean weight was 83 (SD ± 7.86) kg and for females it was 59 (SD ± 16.31) kg.

Study III included healthy volunteer patients undergoing treatment for their substance abuse problem at the Espoo Treatment and Rehabilitation Centre, A-clinic Foundation. Subjects were recruited into the study from the opioid dependence maintenance treatment unit (n = 29), the detoxification department (n = 26), and the outpatient department (n = 2). In the New labelling method (NM) group there were 20 patients in OMT, 11 in detoxification, and 1 as outpatient. The same numbers for the Traditional supervised urine sampling (TS) group were respectively 9, 15, and 1.

The subject population comprised 37 males (65%) and 20 females (35%). There were no gender differences between the two study groups. The mean age was 36 years (SD ± 8.76) in the New marker group (NM) test group and 40 years (SD ± 10.16) in the traditional supervision (TS) test group. The average time in treatment was 32.4 months (SD ± 35.69) in the NM group and 16.5 months (SD ± 30.43) in the TS group. In the NM group, one study subject discontinued the study after three samples, and another discontinued the study after three samples but returned to the study 2 days later. Both completed the study questionnaire.

Study IV participants were volunteer persons using harm reduction services in the Helsinki metropolitan area over 2-week periods in the years 2005–2010 (excluding 2009). In total 1507 individuals completed the questionnaires. The mean response rate was 50.8% (calculated as the return rate % of the individuals who visited the service units during the study period) and ranged from 45.4 (2008) to 58.2% (2005). Of the respondents, 1023 were male (68%) and 478
(32%) were female. The average age in 2005 was 27.8 (SD ± 6.9) years; by 2010 it had risen to 31.9 (SD ± 8.6) years (t=-4.234 df=488, P<0.001, see table 3 for detailed information.

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
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<th>2007</th>
<th>2008</th>
<th>2010</th>
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<td>176</td>
<td>260</td>
<td>411</td>
<td>384</td>
<td>276</td>
</tr>
<tr>
<td>male</td>
<td>131</td>
<td>170</td>
<td>278</td>
<td>258</td>
<td>186</td>
</tr>
<tr>
<td>female</td>
<td>45</td>
<td>90</td>
<td>133</td>
<td>124</td>
<td>87</td>
</tr>
<tr>
<td>mean age</td>
<td>27.8 (SD ± 6.9)</td>
<td>29.7 (SD ± 8)</td>
<td>30 (SD ± 7.80)</td>
<td>31 (SD ± 8)</td>
<td>31.9 (SD ± 8.6)</td>
</tr>
<tr>
<td>Years of opioid iv misuse</td>
<td>7.3 (SD ± 4.9)</td>
<td>7.6 (SD ± 4.53)</td>
<td>8.6 (SD ± 6.47)</td>
<td>8.8 (SD ± 6)</td>
<td>9.8 (SD ± 6.66)</td>
</tr>
<tr>
<td>Years of mono-buprenorphine iv misuse</td>
<td>4.17 (SD ± 2)</td>
<td>4.8 (SD ± 2.50)</td>
<td>5.4 (SD ± 3.13)</td>
<td>5.5 (SD ± 3)</td>
<td>7.2 (SD ± 4.03)</td>
</tr>
<tr>
<td>Years of buprenorphine-naloxone iv misuse</td>
<td>N.A.</td>
<td>1.7 (SD± 1.7)</td>
<td>1.8 (SD ± 0.9)</td>
<td>2.4 (SD ± 2.2)</td>
<td>4.0 (SD ± 3.4)</td>
</tr>
</tbody>
</table>

Table 3: Demographics for Study IV (unpublished from study IV)

### 4.2. Ethical considerations and funding

The studies were approved variously by the independent Hospital District of Helsinki and Uusimaa Ethical Committee, the Finnish National Agency of Medicines, the THL Ethics Committee and the Ethical Committee of the A-Clinic Foundation. Data protection was ensured throughout in accordance with the regulations governing the National Institute for Health and Welfare (and previously the National Public Health Institute). All the studies were conducted according to the ICH Guidelines for Good Clinical Practice and the 1964 Declaration of Helsinki.

**Study I permissions**
Independent Hospital District of Helsinki and Uusimaa Ethical Committee notification (given 24.8.2004)

**Study II permissions**
Independent Hospital District of Helsinki and Uusimaa Ethical Committee (502/E3/2003)
The Finnish National Agency of Medicine (KL# 22/2004)
Study III permissions
Independent Hospital District of Helsinki and Uusimaa Ethical Committee (347/13/03/00/08)

Study IV permissions

All the studies were coordinated and funded by the Department of Mental Health and Alcohol Research of the National Public Health Institute in Finland (or from 2009, the National Institute for Health and Welfare).

Kaarlo Simojoki has received lecture fees from Schering-Plough, MSD, Boehringer-Ingelheim, Helsinki city, GlaxoSmithKline, Ruma Gmbh, Orion, RBP, Lundbeck, Professio, HUS, has received paid congress trips from Schering-Plough, Reckitt Benckiser Pharmaceuticals Finland, Azanta, Lundbeck and has been an OMT-HCV advisory board member at Schering-Plough until 2010.

4.3 Study designs and methods

Study I was retrospective, involving data collection from opioid-dependent patient’s records who had undergone a switch from mono-buprenorphine to buprenorphine/naloxone and having a mono-buprenorphine dose of at least 12 mg/day prior to change. Data were collected using structured data collection forms and possible missing data was collected afterwards from every site. Five treatment centres were randomly chosen from 20 treatment centres that were using mono-buprenorphine. Two of the centres are located in Helsinki (HDL, HUS), one in the district of Southern Uusimaa (Espoon A-klinikka), one in central Finland (Tampere), and one in northern Finland (Raahe). At the time the centres were selected both Raahe and HDL announced that they had more than 10 patients being treated with buprenorphine, but at the time of data collection they had less than 10 patients who fulfilled the inclusion criteria for the study.

Data were collected for three days during the week of the medication switch and at 1, 2, 3 and 4 weeks following the transfer to the new formulation. The earliest date of switch from mono-
buprenorphine to buprenorphine-naloxone was 5 November 2003 and the latest date of switch was 4 December 2004. Information gathered was mono-buprenorphine dose on the day the transfer was recorded, and the buprenorphine-naloxone doses used during the four weeks following the switch once per week. Drug misuse measures as well as length of non-opioid drug use were also recorded. The frequency of clinic visits, and therefore prescription size of take-home medication for continued use, was based on the usual clinic practice at least once weekly. All clinics conducted urine tests at least once a week. Adverse events considered as being associated with the switch from mono-buprenorphine to buprenorphine-naloxone on the day of the switch, days 2 and 3, and weeks 1 to 4 following the switch were recorded. The same adverse events four months after the study period were also collected. The Medical Dictionary for Regulatory Activities (MedDRA) coding was followed. Overall patient complacence (patient satisfaction with the switch to buprenorphine-naloxone) and compliance (related to regular visit attendance, appropriate medication intake, and history or signs of misuse), with reasons for non-compliance, were recorded on each of the weekly visits to the clinic before and after the switch. The data gathered from patient records prior to the switch (mono-buprenorphine dose, drug misuse and frequency of clinic visits) is considered as baseline data. The data collection was repeated four months post-transfer (follow-up period) with 6 specified questions a) current treatment status: still in treatment/not in treatment b) current treatment medication: Suboxone®, Subutex®, methadone, other (specify) c) misuse activity of opioids: any signs of misuse, yes/no d) patient satisfaction: yes/no e) adverse events: any since the primary data collection f) abuse of Suboxone®: if yes specify patient’s experience. All answers had to be specified and findings described.

Primary outcomes of this study were a) dose of buprenorphine before and after switching to Suboxone®, b) weaning (dose adjustments) and noticed adverse reactions during the 4-week study period and the follow-up period and c) physical signs and patient reports of intravenous misuse of buprenorphine. Secondary outcomes were a) knowledge of opiate (heroin)/opioid abuse evident from urine tests, b) patient satisfaction/dissatisfaction with buprenorphine-naloxone during the 4-week study period and at the end of the follow-up period and c) frequency of patient’s visits to the treatment clinic before and after the switch to buprenorphine-naloxone d) current treatment status and medication at the end of the follow-up period. The outcomes were summarised for all patients, by study site and by treatment phase.
Study II had a double-blind, double-dummy, randomized crossover design that compared crushed and whole mono-buprenorphine tablets on a range of pharmacokinetic variables. All participants were stabilized on a dosage of 24 mg mono-buprenorphine per day for at least 7 days prior to blood sampling. Subjects were then randomized into 2 groups. They received either crushed or whole active or placebo tablets according to the study plan. The blind was maintained by using placebo and active 8 mg mono-buprenorphine tablets, with neither the study doctor nor the patient being aware of whether the crushed or whole tablet was the active drug. Crushing of the tablets was always performed with a commercially available tablet crusher and the tablet dissolution time, which was defined as the number of minutes that elapsed between placing the tablets in the patient’s mouth and the point at which the tablet was no longer visible to the study personnel, was measured. Blood samples were taken prior to the administration of the study medication (baseline) and at 30, 60, 90, 120, 180, 240 and 360 min after dosing. The next morning, a 24-hour blood sample was taken. All Gas chromatography-mass spectrometry (GC-MS) analyses were done at the accredited laboratory of the National Institute for Health and Welfare. Drugs were extracted from basic solutions (pH approx. 9) by liquid-liquid extraction using toluene containing deuterated buprenorphine as an internal standard. After evaporation of the solvent, the extracted compounds were silylated by MSTFA (N-methyl-N-trimethylsilyl-trifluoro-acetamide). The samples were analysed with the Agilent Network GC-MS 6890/5973 instrument. Separation was carried out on a DB-35MS (30 m/0.32 i.d./0.25-μm film) fused silica capillary column, using helium as a carrier gas. The oven temperature program was increased from 180°C (1 min) to 340°C (4 min). Selected ion monitoring was used in the electron impact mode and ions 450 and 482 for buprenorphine; 468, 500, 510 and 542 for norbuprenorphine; and 454 for deuterated buprenorphine were followed. The method was found to be sensitive, and the limit of quantization was 0.5 ng/ml for both buprenorphine and norbuprenorphine. The accuracy and precision of the method at the concentration level of 0.5 ng/ml were as follows: 9.4% (buprenorphine) / 4.6% (norbuprenorphine) for accuracy; 5.3 (buprenorphine) / 13.0 (norbuprenorphine) intraday assay, and 7.9 (buprenorphine) / 27.7 (norbuprenorphine) interday assay. The linearity range for both analyses was 0.5–15 ng/ml. This GC-MS method has been accredited by the Finnish Accreditation Service.

The extent of opioid craving (Rosenberg 2009) was measured with a visual analogue scale (VAS), a psychometric response scale, which is a measurement instrument for subjective
characteristics or attitudes that cannot be directly measured (Hasson and Arnetz 2005). When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end points. In this study participants rated the current intensity of their desire to use opioids from 0% (none at all) to 100% (more than ever). Opioid withdrawal symptoms were measured with the Subjective Opioid Withdrawal Scale (SOWS) (Handelsman, Cochrane et al. 1987; Gossop 1990). It is a self-administered scale for grading opioid withdrawal symptoms and contains 16 symptoms whose intensity the patient rates on a scale of 0 (not at all) to 4 (extremely). The total scores range from 0 to 64 and mild withdrawal is considered to be a score of 1 – 10, moderate withdrawal is considered to be a score of 11 – 20 and severe over 21 scores.

Primary outcomes of this study were buprenorphine and norbuprenorphine pharmacokinetic parameters (C max, T max, AUC 0–4, AUC 0–24) of whole and crushed buprenorphine tablets. Secondary outcomes were pharmacokinetic parameters, including a) opioid withdrawal, as measured by the SOWS, b) opioid craving, as measured by the VAS, c) patient reports of possible adverse events and d) dissolution time of the whole versus crushed tablet,

In Study III the subjects were randomized into two groups, the new marker method (NM) group and the traditional supervised (TS) sampling group. The study was conducted from 11.11.2008 to 15.01.2009.

In the NM group three different molecular weight markers were used and were given to the patients in a random fashion. The patients did not know the molecular weight of the solution they received. The marker vials, which contained 30 ml of the marker solution, were individually labelled. The marker was then mixed with approximately 100 ml of a sweet soft drink. Patients were asked to drink this solution 30-45 minutes prior to the delivery of urine. They were then allowed to urinate without supervision in the clinic or to take the urine test tube home and return it to the clinic within 1 week. After patients submitted the urine sample (20–50 ml), the test tube was directly identified with a bar code label according to the routine procedure of the Central Laboratory Cologne. An accompanying order sheet was labelled with the patient’s name, the type of drug analyses requested, and the type of marker substance that was used. Samples were then sent to the Central Laboratory Cologne via shuttle service twice a week. Prior to shipping, the samples were stored in a refrigerator in a closed room. At the
Central Laboratory, order sheets were read by an automatic chart reader. Urine samples were centrifuged and directly transported to the analytical site for determination of marker substances and drug analyses by gas chromatograph detector (Hewlett Packard, 5790 Series II, connected with a mass selective detector 5972; Hewlett Packard, Palo Alto, USA).

In the TS test group, direct inspection of patients while urinating was conducted by trained clinical staff. The patients were asked to provide the sample using a test toilet, which had mirrors on the walls to ease supervision. Patients were asked to undress sufficiently, which was determined by the person supervising. After depositing the sample in the test tube, the patient closed the test tube and gave it to the supervisor. The urine was then quick screen tested in a separate closed room immediately or later during the same day; in the latter case, the sample was stored in a refrigerator. The screening test used is manufactured by SYNTRON Bioresearch, Inc., an FDA-registered medical device manufacturer, and was supplied by Labema. Only if it was needed the quick screen result was confirmed by LCMS.

Following urine testing, subjects in both groups completed a questionnaire. The information gathered included when the urine test was requested, where it was performed, and whether the situation was pleasant or unpleasant, which was asked and recorded by the personnel soon after each urine test. Each subject was asked to deliver a urine sample once or several times, depending on the treatment phases and visits. In the NM test group, information was also gathered on the given marker, whether the patient took the urine test at home, and, if so, whether the sample was delivered. A questionnaire was created that included background information, two questions measuring satisfaction on a likert-type 1-6 scale (Jamieson 2004; Pell 2005; Carifio and Perla 2008; Norman 2010), and the patient’s preferred testing system. The questionnaire was given to the subjects at the end of the study period, or earlier if the patient was unlikely to return to treatment during that period, for example, if the patient was in detox treatment.

All personnel members who were involved in taking urine samples for the study (n = 10), out of whom 7 worked in OMT, 2 in detoxification, and 1 at outpatient clinic, completed a questionnaire. It included 4 background information questions, three likert-type 1-6 scale questions, four multiple-choice questions and two open-ended questions. All employees were experienced in the addiction field and were, on average, 40 years old. All of them had had a
long experience in collecting TS urine tests and 60% (n = 6) had performed over 20 NM tests, 10% had performed between 10 and 20 tests, 20% had performed between 5 and 10 tests, and 10% had performed less than 5 tests.

The primary outcomes of this study were a) return rate of the urine samples, b) detected manipulation of urine samples and c) patient satisfaction with the used method. The secondary outcomes were a) employee satisfaction, b) estimated time used for the sampling and controlling procedure, and c) economic trade-off. It was also intended to see if it would be possible to allow patients to give their urine sample outside the clinic, opening new opportunities for flexible testing.

Study IV was conducted by a questionnaire consisting of multiple-choice and fill-in-the-blank questions at harm reduction services in the Helsinki metropolitan area over 2-week periods in the years 2005–2010 (excluding 2009). Survey completion was voluntary and anonymous; the return or non-return of the survey had no influence on the services provided by the centre. The centre visitors were instructed to fill out the questionnaire only once. Personnel at the harm reduction unit did not receive the completed surveys but directed participants to place the surveys in a box accessible only to the investigators. No identifying information was obtained.

The questionnaire consisted of two parts, of which the first part was for all drug abusers; the second was to be answered only by buprenorphine abusers. The number of answers obtained were reported individually in the result section. Twelve questions were asked on all study surveys since 2005, and for that included into the study. New questions were added (five in 2007, and two more in 2010) in subsequent years and have also been used in the analyses, because they gave important new information. Some survey questions required two part responses; for example, “At what age did you start using drugs, and when was the first time you injected?” If only one part was completed, neither part was included in the analysis.

The questionnaire included background (gender and age), first intravenously abused drug and opioid. Two questions focused on the patterns of drug: 1) What is currently the drug you most frequently use; 2) Which drugs do you use in addition to the previously mentioned drug. Responses were categorized into 7 subgroups: a) all buprenorphine products, b) all amphetamine/methamphetamine drugs, c) heroin or morphine, d) MDMA, MDA, MDEA,
MBDB or ecstasy, e) cocaine, f) oxycontin, and g) other drug (if not fitting into classes a-f). For both for mono- buprenorphine and buprenorphine-naloxone was asked the duration of intravenous abuse, frequency and dose of abuse, route of abuse, street price paid for an 8mg tablet, and from where the buprenorphine was obtained. HCV infection prevalence and demand for entering opioid maintenance treatment were asked. For further analyses of buprenorphine as first abused intravenous opioid the respondents were divided into 6 subgroups, defined by the researcher, according to the length of their intravenous opioid abuse: less than one year, 1–3 years, 3–5 years, 5–7 years, 7–9 years and over 10 years. The ranges for the subgroups were chosen upon clinical experience and to ensure big enough samples from the data for analysis.

Primary outcomes of this study were a) first intravenously abused opioid b) duration of mono-buprenorphine and buprenorphine-naloxone abuse c) changes in abused buprenorphine prevalence d) changes in buprenorphine street prices.

4.4 Statistical analyses

In all the studies the main results were reported either as percentages or total number of respondents and with means ± SD if not otherwise specified. Because the studies differ from each other, the analysis is clarified below.

In Study I descriptive statistics were used to summarise the data. The protocol stated that a Chi squared test would be conducted to determine the statistical significance of trends in changes of test variables. It was later determined by the principal investigator that this test was not necessary with the data collected. Demographics and baseline parameters were summarised by study site and by treatment phase, for all patients. Efficacy analyses included doses of buprenorphine (in the form of mono-buprenorphine or buprenorphine-naloxone before and after attempted switch to buprenorphine-naloxone).

In Study II, the subject, treatment, time and plasma concentration data were manually entered into an Excel 97-2003 spreadsheet. These data were imported into WinNonlin Pro version 5.0.1 (Pharsight Corp., Mountain View, Calif., USA). Standard non-compartmental pharmacokinetic methods were used to estimate Maximum observed serum drug concentration (C_max), time to
maximum concentration of drug in serum (T_{max}) and The Area under the Concentration - time curve over 24 hours (AUC 0–24). The AUC 0–24 and C_{max} were analysed on a log scale using an ANOVA model to assess bioequivalence between Form I (the test) and Form V (the reference). The analysis of variance for a 2-way crossover design included the following fixed factors: sequence, period and form, and subject (sequence) as a random effect. The two 1-sided t-test hypotheses were tested at the 0.05 level of significance by constructing 90% confidence intervals (CI) for the ratio of test-to-reference means. The two test treatments were considered bioequivalent if the 90% CI of the relative mean C_{max} and AUC 0–24 of the test to reference were within 80%–125%.

For Study III, subject and staff background information and questionnaire responses were manually entered into a Microsoft Excel 97-2003 spreadsheet and then analysed using Excel functionality calculating mean values and SD. Survo versio 3.35 was used to calculate Student's t, chi2, df and p-value (one-sided test).

In Study IV, the number of respondents differs from question to question as participants were free to complete any or all portions of the survey. The number of answers obtained was reported individually in the result section. The results, Student's t, chi2, df and p-value (one-sided test), were calculated by using the Survo version 3.35 program and were also partly entered manually into a Microsoft Excel 97-2003 spreadsheet and then analysed using Excel calculating mean values and SD.
5. Results

5.1 Trends of opioid abuse in Finland

The results are based on Study IV investigating the trends of opioid abuse in Finland. The results were compared to published results (original data was not available) of the RISKI study, which was conducted from 2000–2002 on injecting drug users visiting harm reduction services, describing their background and drug use on the basis of baseline interviews (Partanen A. 2004a). According to the RISKI results, six month prior to the study, 17% misused monobuprenorphine sublingually, 17% intranasally and 67% intravenously. The administration route for heroin was 14% by smoking, 8% by inhalation and 50% by intravenous injection (n = 494).

In the 2005 (n = 153) questionnaire, the average intravenous opioid misuse had lasted 7.3 years (SD ± 4.9); which steadily increased over the next years to an average of 9.8 years (SD ± 6.7) in 2010 (n = 226) (t=-4.005 df=377 P<0.001).

The onset age was not asked in the 2005 survey, but the mean onset time of opioid abuse was 18.3 years (SD ± 4.8) in 2007 (n = 382), 18.07 years (SD ± 4.5) in 2008 (n = 326) and 18.6 years (SD ± 5.1) in 2010 (n = 245) (t=-1.365 df=569 P=0.0863 ) (Table 4).

<table>
<thead>
<tr>
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<th>first time drugs iv abuse (n = 244)</th>
</tr>
</thead>
<tbody>
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<td>&lt; 10</td>
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</tr>
<tr>
<td>11-15</td>
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<td>23.4%</td>
</tr>
<tr>
<td>16-17</td>
<td>20.0 %</td>
<td>21.7 %</td>
</tr>
<tr>
<td>18-20</td>
<td>15.4 %</td>
<td>30.3 %</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>6.2 %</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Table 4: First abuse and intravenous abuse of drugs (not opioids) in 2010 (unpublished from study IV)
The first intravenously abused drug was inquired of since 2007, when 60.2% (n = 344) stated that heroin or morphine was their first intravenously abused opioid, and 30.5% abused buprenorphine. In 2010 (n = 234) the percentage starting intravenous drug use with heroin or morphine had fallen to 51.3%. Buprenorphine as the first intravenously abused drug increased by 13.9% (44.4% in 2010)(Chi2=14.81 df=3 P<0.0020). In 2007 9.3 % of respondents answered having started with another drug (non-opioids); this percentage decreased to 4.3% in 2010 (Chi 2=0.736671 df=1 P=0.3907) (Figure 2).

Figure 2: First intravenously abused opioid (published in Study IV)

In 2005 and 2006 heroin/morphine was the third most misused intravenous substance, but since 2007 it has been passed by the category “other drug”, which includes among other mainly benzodiazepines and so-called designer drugs, with annual frequencies varying between 21.3% and 44.9%. Heroin/ morphine were abused in 2005 by 2.3%; this increased to 11.7% in 2007 and has since declined to 8.3% in 2010 (Chi2=49.6211 df=20 P<0.001) (Figure 3).
Figure 3: Two most abused intravenous drug groups and the use heroin/morphine (unpublished from Study IV)

Data not included in Study IV, but presented in this thesis from the 2007 (n = 314), 2008 (n = 275) and 2010 (n = 210) surveys gives a more detailed picture concerning intravenously misused opioids. As assumed, based on earlier studies (Alho, Sinclair et al. 2007), heroin is the first abused intravenous opioid for the clear majority (50–70%) in the population having abused opioids over 7 years and in the under 1 year group for less than 0.9%–3.4%. When looking at the data for buprenorphine it is the most largest (23%–34%) first intravenously abused opioid for the abuser group with a 3–5 year history of intravenous abuse. In the group with less than 1 year intravenous abuse buprenorphine is the first intravenous abused opioid for 15% in 2007 and in 2010 for 10.3% of the respondents (Chi2=11.9823 df=5 P<0.0350). Based on the data it seems that the number of new opioid abusers having buprenorphine as their first intravenously used opioid has started to decrease since 2007 after being at its highest before 2004, but due to
the small responder number no reliable conclusion can be made (Chi²=1.16339 df=2 P=0.5589) (Figures 4–5).

Figure 4: First abuse intravenous opioid: heroin (unpublished data based on data from Study IV)

Figure 5: First abuse intravenous opioid: buprenorphine (unpublished data based on data from study IV)
5.1.1 Abuse of mono-buprenorphine and buprenorphine- naloxone

The duration of intravenous abuse of mono-buprenorphine in 2005 (n = 173) was 4.2 years (SD ± 2); in 2010 (n = 201) it was 7.2 years (SD ± 4) (t=-8.954 df=372 P<0.001). The duration for buprenorphine-naloxone was 1.7 years (SD ± 1.7) in 2006 and 4 years (SD ± 3.4) in 2010 (t=-4.928 df=153 P<0.001).

The majority reported daily intravenous use: 81.7% in 2005 (n = 148) and 74.3% in 2010 (n = 187). There was no significant change in frequency of daily mono-buprenorphine injection from 2005 to 2010. Most injected 2-4 times daily, reported by 67.7% in 2005 and 74.1% in 2010 (Chi2=23.7943 df=16 P=0.0940).

In 2005 (n = 145), the 12-month prevalence for buprenorphine-naloxone abuse was 67.3% and had been tried once by 23.4%, more than twice by 35.8% and for at least two weeks regularly and frequently by 8.1%. In 2010 (n = 174) the amounts were correspondingly 8%, 56.7% and 14.4%. (Chi2=27.2508 df=3 P<0.001). The prevalence for the responders’ lifetime buprenorphine-naloxone abuse in 2005 was 68%, and in 2010 80.5% (Chi2=6.24875 df=1 P<0.001).

The abuse route of buprenorphine-naloxone was changed during the study years. In 2005 (n = 111) 60.4% misused intravenously, 4.5% nasally and 13.5% sublingually while 21.6% reported mixed ways (asked only in 2006). This was changed by 2010 (n = 140) when 69.3% misused intravenously, 24.3% nasally and only 6.4% sublingually (Chi2=40.8666 df=12 P<0.001).

One means for measuring a drug’s monetary value to subjects is to determine the street price of the drug and this was asked in all surveys. In 2005 (n = 176) the mean street price for mono-buprenorphine was 28 Euros; it had increased by 53.2 % to 42.9 Euros in 2010 (t=-15.12 df=329 P<0.001). The corresponding average price of buprenorphine-naloxone was 12.3 Euros in 2005 and increased by 103.2% to 25 Euros in 2010 (t=-11.49 df=223 P<0.001). The price of buprenorphine-naloxone was 56% lower than mono-buprenorphine but in 2010 the price difference had declined to 41.7%. During the same time the daily mean dose of mono-buprenorphine dropped by 22.9% from 7.0 mg to 5.5 mg (t=-3.234 df=361 P=0.0007). The
daily average dose for buprenorphine-naloxone (asked since 2006, n= 182) decreased by 36.6% from 8.2 mg to 5.2 mg in 2010 (n= 105) (t=-3.194 df=165 P=0.0008 Figure 6).

Figure 6: Street price of mono-buprenorphine and buprenorphine–naloxone (published in Study IV)

Correlations between price and use mono-buprenorphine -0.6232 and buprenorphine–naloxone -0.8171

Respondents were asked for the first time in 2010 where they obtained their buprenorphine. For mono-buprenorphine (n = 161), the majority (91.3%) reported buying it from a street dealer, 22.4% from a person attending official substitution treatment, and 8.7% imported it themselves from abroad. For buprenorphine-naloxone (n = 125), the corresponding numbers were 68.8% bought from a dealer, 49.2% from a person in substitution treatment, and only 2.4% brought it abroad (Chi2=24.3302 df=2 P<0.001).
The number of respondents being in OMT was also looked at and in 2006 the questions were answered by 141 clients (80.1%) and in 2010 by 192 (69.6%). Out of these, 8 (5.7%) were in treatment in Finland in 2006 and 29 (18.8%) in 2010 (Chi2=18.1778 df=3 P=0.0004). In 2006 24 (14.9%) were in treatment abroad, but in 2010 only 2 (1.3%) abroad (Chi2=44.7355 df=3 P<0.001) The number of respondents who wished to enter OMT programs was 43% in 2006 (n = 112) and 64.1% in 2010 (n = 123) (Chi2=9.84766 df=3 P=0.0199). In 2010, of the remaining 84 respondents, 45.2% had fulfilled the criteria for OMT and lined up treatment, 26.2% had not been accepted for treatment, and 28.6% had repeatedly attempted to enter treatment but had not fulfilled the criteria. There was no clear correlation between the time in years of opioid intravenous use and wish of entering OMT, being -0.0413 (t=-0.541 df=171 P=0.2947).

5.2 The use of buprenorphine-naloxone combination in OMT

5.2.2 Transfer from mono-buprenorphine to buprenorphine-naloxone combination

In Study I, 58 patients (90.6%) switched from mono-buprenorphine to combination at the same dose of mono-buprenorphine that they had been receiving as mono-buprenorphine alone. One patient was transferred with a higher buprenorphine-naloxone dose (2 mg), two with lower doses (2–4 mg) and three patients were "titrated" with daily increases of buprenorphine-naloxone (patient anxiety over the transfer) up to the previous mono-buprenorphine dose. Out of the 60 patients finishing the four-week study period 53 patients (82.8%) were treated throughout the study period with only buprenorphine-naloxone (Table 5), and 46 of these (71.9%) were maintained at the same dose of buprenorphine-naloxone. During the four-week period, four patients (6.3%) had dose reductions and one patient (1.6%) had a dose increase with buprenorphine-naloxone. Two patients (3.1%) had temporary dose changes during the four-week study period and seven patients had titrated dosing (2–3 day interval in increase). At the four-month follow-up out of the 26 patients continuing treatment with buprenorphine-naloxone, 10 patients (38.5%) were treated with the same dose of buprenorphine-naloxone, 15 patients (57.7%) had dose reductions (2 mg–16 mg), and one patient (3.8%) had a dose increase (2 mg).
Table 5: Reasons for discontinuation of buprenorphine-naloxone (unpublished from Study 1)

At baseline, nine patients (14.1%) showed physical evidence, i.e. needle marks of intravenous drug misuse and seven of them reported abused mono-buprenorphine and two abused heroin. Forty-seven patients (73.4%) indicated that they were not abusing mono-buprenorphine or heroin and showed no signs of intravenous misuse or positive urine opioid tests. Information on intravenous misuse of mono-buprenorphine was not recorded for eight patients (12.5%) prior to switch, for 3 at week one (4.7%), one at week two (1.6%) and three (1.6%), 2 at week four (3.1%) and eleven during follow-up (18%). At weeks one, two and three, signs of intravenous abuse of mono-buprenorphine or buprenorphine-naloxone were seen in 11% (n = 7), 4.7% (n = 3), and 9.4% (n = 6), respectively. Three patients who had records of intravenous misuse at baseline did not continue misusing during the four-week follow-up period, and three new patients with intravenous misuse were observed during this period. Over the four-week study period, there was no evidence of misuse of other opioids. During the follow-up period, 16.4% (n = 10) showed signs of intravenous buprenorphine abuse, one patient (1.6%) informed the investigator having used heroin.
(Table 6). Of the buprenorphine intravenous abuse, buprenorphine-naloxone was misused by 8.2% (n = 5), once each by four patients and twice by one patient.

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>TOTAL</th>
<th>RAAME</th>
<th>MDL</th>
<th>Tre-K-Klinikka</th>
<th>MUS</th>
<th>Espoon A-Klinikka</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>8</td>
<td>9</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Signs of Intravenous Misuse Before Switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs of IV Misuse During Week 1</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Signs of IV Misuse During Week 2</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Signs of IV Misuse During Week 3</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Signs of IV Misuse During Week 4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Signs of IV Misuse During follow-up</td>
<td>7</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

a: Patient told the investigator having used heroin.

Table 6: Signs of Intravenous Misuse by Treatment Centre (unpublished from Study I)

Whether treating patients with buprenorphine-naloxone affects the frequency of patient misuse of buprenorphine could not be determined from this study. During the 4-week study period other drugs were misused including 10 patients cannabis (15.6%), 2 patients benzodiazepines (3.1%) and 1 patient amphetamines (1.6%). During the follow-up period other drugs were misused including 4 patients amphetamines (6.6%) and 1 patient each benzodiazepines (1.6%) and zolpidem 1.6%.

Patient treatment compliance information was collected for the four-week study period. Compliance was related to regular visit attendance, appropriate medication intake, and history or signs of misuse. Overall, 60.0% of patients were compliant with buprenorphine-naloxone treatment throughout the four-week study period. Overall compliance decreased slightly during the first week, but stayed at the same level for the rest of the four-week study period. The highest rate of compliance occurred at Centre Raahe where all patients were compliant with buprenorphine-naloxone treatment throughout the four-week study period. Centre HDL had a relatively high rate of compliance for the first three days after the switch, but by the end of the first week, only two of the nine patients (22.2%) were compliant with the buprenorphine-naloxone treatment and it stayed at this level through the rest of the four-week study period.
During the four-week study period, two patients from HDL discontinued due to a lack of compliance and during the four-month follow-up period, six patients discontinued due to a lack of compliance, 3 at HDL, 2 at Tre K-klinikka and 1 at HUS.

Twenty-four patients (37.5%) were satisfied with the switch from mono-buprenorphine to buprenorphine-naloxone every time the question was asked during the four-week study period and 26 patients (40.6%) were dissatisfied every time they were asked. The 14 other patients (21.9%) were satisfied at some point during the four-week study period and nine of these patients were satisfied at the end of the four-week study period. Twenty-six of the 27 patients (96.3%) who were still being treated with buprenorphine-naloxone at the end of follow-up were satisfied (Figure 8). During the four-month follow-up period, four patients discontinued buprenorphine-naloxone treatment, 2 from HDL and Espoon A-klinikka, because of dissatisfaction with it.

From some of the comments recorded at clinical visits, dissatisfaction and non-compliance was a reaction to being forced to switch from mono-buprenorphine to buprenorphine-naloxone.
During the four-week observation period, 32 of the 64 patients (50.0%) reported adverse events. The adverse events were mostly mild withdrawal symptoms associated with the switch from mono-buprenorphine to buprenorphine-naloxone. During the follow-up period, 19 of the 61 patients (31.1%) treated reported adverse events. Overall, 35 patients (54.7%) treated with buprenorphine-naloxone alone or in combination with mono-buprenorphine reported adverse events through the whole study period. There were three patients who experienced adverse events that were considered to be severe by the investigator during the four-week study period. During the follow-up period, only one adverse event was considered to be severe. One patient discontinued treatment with buprenorphine-naloxone during the four-week study period due to adverse events at Espoon A-klinikka and six patients discontinued due to adverse events during the follow-up period, 1 at Tampere K-klinikka and Espoon A-klinikka, and 4 at HUS/Opri. There were no deaths or serious adverse events in this group of patients.

5.2.3 Bioavailability of mono-buprenorphine, crushing mono-buprenorphine tablets

The aim of Study II was to investigate whether crushing the buprenorphine tablets before administering it to patients in order to minimize the risk of medication diversion would affect the efficacy of medication. Measuring mono-buprenorphine serum levels, the peak
buprenorphine T\textsubscript{max} serum level was observed approximately 1 hour after administration of the crushed tablets, and the mean was 1.44 h ± 0.6 (SD); the mean for whole tablets was 1.68 h ± 1.4 (SD). The C\textsubscript{max} (ng/ml) was 9.727 ng/ml ± 3.4 (mean ± SD) for crushed tablets and 9.591 ± 3.8 for whole tablets. These differences were not significant (Figure 9). The differences were even smaller with norbuprenorphine with serum levels almost identical in both study groups on both study days (Figure 10).

Figure 9: Mean buprenorphine serum concentrations, grouped by crushing, all subjects (published in Study II)

Figure 10: Mean norbuprenorphine serum concentrations, grouped by crushing, all subjects (unpublished from Study II)
The study subjects were interviewed before they received study medication and at 5h and 24h after administration to estimate the opioid withdrawal by using SOWS and craving by using VAS. There was no significant difference between the withdrawal average scores when the study subjects received whole or crushed mono-buprenorphine tablets, although the scores varied from 0 to 42 points. There was also no difference in the opioid craving scores, as measured by VAS, between the groups, visits or mode of drug administration (crushed and whole tablets). There were no significant differences between average tablet dissolution time of whole and crushed tablets (Table 7).

<table>
<thead>
<tr>
<th></th>
<th>Crushed</th>
<th>Whole</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate withdrawal (SOWS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (baseline)</td>
<td>9.0±7.0</td>
<td>12±1</td>
<td>0.20</td>
</tr>
<tr>
<td>5h</td>
<td>7.0±7.0</td>
<td>6.0±6.0</td>
<td>0.32</td>
</tr>
<tr>
<td>24h</td>
<td>9.0±9.0</td>
<td>10.0±10.0</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Opioid craving (VAS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (baseline)</td>
<td>3.9±3.7</td>
<td>5.0±42.0</td>
<td>0.1</td>
</tr>
<tr>
<td>5h</td>
<td>3.3±3.4</td>
<td>1.2±2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>24 h</td>
<td>3.4±4.0</td>
<td>4.3±4.2</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Time to dissolution</strong></td>
<td>16.53±6.0</td>
<td>16.63±5.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 7: Withdrawal and VAS scores, and dissolution time for whole and crushed tablets
(published in Study II)

In total, nine different study subjects reported adverse events during the study. In the whole tablet group, four patients reported adverse events (fatigue and dysphoria). In the crushed tablet group, eight participants reported six events (pollacisuria, fatigue, headache, strange feeling, craving and pain). Three subjects reported adverse events on occasions, one subject only when administered the whole tablet and five subjects only when administered the crushed tablet. There were more adverse events reported in the crushed tablet group. No severe adverse events were reported.
5.3 The effect of a new drug screening method on treatment adherence, patient compliance and time spent on screening

In Study III, 168 samples were collected; 69% for the new method (NM) test group (n = 116), and 31% in the traditional sampling (TS) test group (n = 52). In the NM group, the total return rate was 98.3% (n = 114). When the samples were taken home, which was done in 87% (n = 101) of the NM cases, the return rate was 97% (n = 98) (Figure 11). For the NM, drug analyses were done at the laboratory and all positive results were confirmed by the HPLC method. Benzodiazepines was the most and opioids were the rarest drugs found; buprenorphine was not included in the drug analyses, because it was the OMT medication many patients (Figure 12).

Figure 11: The return rate (n) of urine samples in the new marker group. P=0.9474 (published in Study III).
Of the 57 patients participating in the study, 53 returned the questionnaire (93%). Subjects were also asked what they had experienced with the method to which they had been assigned during randomization. In the NM group, 94% (n = 31) answered the question of whether “taking the marker was an unpleasant experience”, and 83.9% (n = 26) stated that it was not unpleasant (Chi2=1.44935 df=1 P=0.2286). On a 1–6 point scale the question “How unpleasant is the waiting time after taking the marker before giving the urine sample?” was answered by 96.7% (n = 32) of the NM group. The mean score of their answers was 1.9. In the TS group, 84% answered the question “How unpleasant is it to provide a urine sample under supervision?”, which was rated on a 1–6 point scale and the mean score was 2.9.

When asked which method the subjects would prefer, 96.7% (n = 32) of the NM test group answered the question; in this group, 71.9% (n = 23) preferred marker testing, 18.7% (n = 6) supervised testing, and 9.4% (n = 3) had no preference. In the TS test group, 80% (n = 20) answered the question; 60% (n = 12) preferred the marker system and 40% (n = 8) preferred supervised testing (Chi2=3.63805 df=2 P=0.1621).
On a 1–6 point scale the personnel rated the unpleasantness of preparing and giving the NM test as 1.2 (mean). The unpleasantness of supervising patients (TS group) was rated at 3.4 (Chi2=2.99761 df=1 P=0.0833). All employees preferred to administer the NM test. While answering the questionnaire, some staff members commented verbally (unpublished) that urine sample collection was unpleasant only with the traditional, supervised method due to the low level of patient cooperation or the long urination time.

The employees were also asked to estimate the total average working time (in minutes) that they needed for one urine sample and also to estimate how much working time the NM test saves (Figure 13). For TS urine samples, 40% took 5-10 minutes, 50% took 10-20 minutes, and 10% required over 20 minutes. When using the NM test, 30% needed less than 5 minutes and 70% took between 5 and 10 minutes. One staff member was unable to estimate the time saved due to limited experience with the method.

Figure 13: Employee estimation of how much working time was saved by using the new marker method (published in Study III)
Eight employees also commented on the effects of urine testing on the staff–patient relationship. Most stated that TS testing has a negative impact on openness in therapeutic treatment, especially if the supervisor is also the patient’s therapist. Many employees expressed the opinion that supervising may lead to manipulation attempts, due to the mistrust felt by patients. Interestingly, there were several comments that using the NM test also includes a therapeutic element, as the patient is given responsibility for his/her own treatment. A majority of comments referred to the working time saved and ease of applying the NM test.
6. Discussion

6.1 Main findings

The combination buprenorphine-naloxone was introduced to help eliminate diversion and intravenous use of buprenorphine. The combination is supposed to have a lower potential for intravenous abuse than mono-buprenorphine alone. In Study IV the prevalence of responders for lifetime buprenorphine-naloxone abuse did rise from 68%, to 80.5%, and the number of respondents abusing buprenorphine-naloxone more frequently did increase clearly, indicating that the abuse potential was perhaps not so low as expected when the product was taken into use. One reason for this could be the fact that mono-buprenorphine was already the most abused opioid in Finland (Uosukainen, Kauhanen et al. 2013), which is different from many other countries, lowering the threshold to try abuse buprenorphine-naloxone and the naloxone effect due to the pre-existing mono-buprenorphine receptor binding. One other reason could be that buprenorphine-naloxone is the mainly used medication formulation in OMT in Finland and it is known that the more an intoxicating medication is used in treatment the higher is the overall misuse. Even in this kind of environment, daily use of buprenorphine-naloxone (14.7%) was still clearly lower than with mono-buprenorphine (74.3%). One reason could be the finding that 80% reported that they had a “bad” experience with the combination product, while less than 20% reported it “similar” to experiences with intravenous mono-buprenorphine, which was published from the same data in another article (Alho, Sinclair et al. 2007) and also in other studies (Hakansson, Medvedeo et al. 2007; Bazazi, Yokell et al. 2011). Also only a fifth had never tried it in 2010 compared to one third in 2005, when the buprenorphine-naloxone street price was over 50% lower than that of mono-buprenorphine. During the period studied, the street price of both mono-buprenorphine and buprenorphine-naloxone rose, but the price difference remained and in 2010 buprenorphine-naloxone was still over 40% cheaper than mono-buprenorphine. However due to the street value, which parallels the abuse potency, and the fact that under 15% of respondents used buprenorphine-naloxone frequently, it could be concluded that the lower potential of regular abuse did not significantly decrease even after being available on the street market for years and being abused more frequently. This is also seen in opioid abusers seeking treatment of whom 92% abused mono-buprenorphine and 8% buprenorphine-naloxone in 2010 (Väänänen 2011). In 2011 the amount of buprenorphine-naloxone abuser seeking treatment had fallen to 5% (Väänänen 2012).
Buprenorphine has been the most abused opioid in Finland since the beginning of this century (Alho, Sinclair et al. 2007; Uosukainen, Kauhanen et al. 2013). This study gave new information about the misuse pattern of opioid abusers. On average, abusers had abused with other opioids for 2.5–3 years before switching to buprenorphine. According to the data, these were mainly prescription opioids. Data produced by KELA, the Social Insurance Institution of Finland, on the “number of recipients and prescription data” shows that the number of patients receiving opioids has more than doubled between 2008 and 2011, from 166 271 to 409 185, the biggest group being the 312 955 patients receiving codeine (KELA 2012). Considering this in combination with the data from this study it seems likely that there is a connection between these trends, because prescription opioids are much easier to obtain and cheaper than buprenorphine, and thus likely the main abused opioids in the first years of misuse. Taking into account that in 2008 only 1.6% and in 2010 1.4% reported using oxycodone intravenously, which are low percentages compared to international data, which found for example that 4.8% abused oxycodone intravenously (SAMSHA 2011) in the USA in 2010 and this appears to be a rising problem (Aquina, Marques-Baptista et al. 2009; Fischer B. 2010; Butler, Black et al. 2011; Roxburgh 2011; Fischer B. 2012; SAMHSA 2012). It is surprising that there has been no research on this issue in Finland especially when considering that at least occasionally of patients’ entering treatment 4% abused tramadol, 4% oxycodone, 3 % codeine preparations and 1 %fentanyl (Väänänen 2012). This is a clear deficiency, and a discussion regarding the clinical practices of opioid prescription should certainly be initiated quickly. A change was also seen in the way of abusing buprenorphine- naloxone especially in the rise of intranasal abuse, which is in line with EU trends where a decline in intravenous abuse and a rise in other ways of abuse is seen (EMCDDA 2012a), which also has pharmacodynamic and pharmacokinetic backgrounds (Middleton, Nuzzo et al. 2011).

According to the results of the study, OMT was discontinued more often after the switch to buprenorphine-naloxone than in other international studies (Montesano, Zaccone et al. 2010) or OMT dropouts observed in other Finnish studies (Pirkola, Heikman et al. 2007; Vorma 2009): treatment was terminated by 11.7 % and to methadone were transferred 21.7%. The latter is very high considering the rather low rate of concomitant drug abuse, which is the main reason for this transfer, recorded by the study sites. There is also quiet a big difference between the study sites as to patient satisfaction. The greatest patient satisfaction and fewest numbers of
adverse events was recorded at Treatment Centre RAAHE. Even though each patient at this centre only visited once a week, patients lived at the treatment centre and were provided with lots of counselling before and during the switch from mono-buprenorphine to buprenorphine-naloxone. The counselling provided the patients with information about buprenorphine-naloxone treatment and gave them the possibility to discuss their concerns. The positive results from this centre are most likely a result of the counselling and information provided by the centre personnel. Comments from the treatment centre physicians indicate that patients who have been switched more recently have had fewer adverse events and the switch has been more successful. The physicians believe that this newer group of patients was better informed about buprenorphine-naloxone treatment. Insufficient medication effect was reported by 2 patients contrary to a remarkable proportion (57.7%) of patients who wanted to lower their dose. The study indicates that forcing patients into treatment regimens, i.e. medication switch, did negatively affect compliance. It was seen with the switch from mono-buprenorphine to buprenorphine–naloxone, when treatment discontinuation increased considerably. This emphasizes the importance of cooperation with the patients when making decisions regarding treatment management (Mikkonen A. 2008).

Lowering the supervision of medication does result in increasing adherence without compromising treatment outcomes, for example, in the form of opioid abuse and overdoses (Bell, Shanahan et al. 2007). However, at the same time it has been shown that less supervision could increase diversion (Monte, Mandell et al. 2009). On the other hand supervision binds resources, which may lead to limited access, which could itself increase mortality rates (Nilsson I. 2012). In this respect the transfer to buprenorphine-naloxone may also serve as part of an overall strategy to curb misuse of buprenorphine. This is an important observation because the abuse of mono-buprenorphine is a rising problem in many countries (Hakansson, Medvedeo et al. 2007; Wish, Artigiani et al. 2012). Based on the fact that participants were only asked in 2010 where they had bought their buprenorphine-naloxone (without specifying the origin), no solid conclusions about buprenorphine-naloxone diversion from treatment units could be made, but it seems clear that mono-buprenorphine is still the first preferred opioid of abuse of these two formulations. This underlines the conclusion that the use of the buprenorphine-naloxone combination formulation could be a possibility for reducing controlled dispensing without greatly increasing the risk of diversion (Stimmel 2007; Johanson, Arfken et al. 2012). This has led to the consideration in many countries, such as France, Spain and
Portugal, of a wider use of buprenorphine–naloxone (Courty 2012; Patricio 2012; Teran 2012; Touzeau 2012). However, recent publications suggest that abuse of the buprenorphine–naloxone combination would be a growing problem (Bazazi, Yokell et al. 2011; Johanson, Arfken et al. 2012). It has been shown that patients in combination medication treatment can inject without any adverse symptoms (Bruce, Govindasamy et al. 2009; Mammen and Bell 2009). Whether treating patients with buprenorphine-naloxone affects the frequency of patient misuse of buprenorphine could not be determined from this study, though the results could still lead to the conclusion that the full potential of the buprenorphine-naloxone formulation is probably achieved in environments where mostly opioids other than mono-buprenorphine are abused. Pharmacological research indicates (Strain, Walsh et al. 2002; Correia, Walsh et al. 2006) that the naloxone compound diminishes the abuse viability, which can lead to the assumption that a clinical setting in which the medication is used could have a more important impact regarding diversion and misuse (Mammen and Bell 2009). This was also indicated in this study when looking at patient compliance, satisfaction, treatment termination at different study site after switching medication to buprenorphine-naloxone. There is very little clinical research on this specific issue, however, offering treatment that is more than just medication alone should be emphasized (Amato, Minozzi et al. 2004b; Amato, Minozzi et al. 2004c; Fiellin, Pantalon et al. 2006; Amato, Minozzi et al. 2008b). In all treatment settings the patients should have the possibility to modify their addictive behaviour, which includes intravenous misuse (Vidal-Trecan, Varescon et al. 2003; AIHW 2010).

Due to the chronic nature of opioid dependence, treatment is long-term, even lifelong, and if the resources of the OMT are not increased, the treatment capacity will gradually fill up and less and less new patients can be included. This issue has become even more important because financial resources remain at the same level which hinders access to treatment (Tanhua H., Virtanen A. et al. 2011). The aim of this thesis was to explore what factors could improve patient compliance and adherence to the treatment, and thus OMT outcomes, without leading to an intolerable increase of unwanted harm related to treatment like medication diversion. One way of achieving this is the crushing of buprenorphine tablets, which according to the data has no effect on blood concentration, withdrawal symptoms or craving, and makes it possible to use the medication in patient groups with a high risk of diversion. This is clinically relevant for patients at high risk for diversion or attempted buprenorphine smuggling from supervised medication suspension. Crushing the medication is an good alternative to treatment termination.
or to being switched onto methadone, which in many countries, including Finland, is often conducted for high risk patients. Methadone is dispensed in a liquid form that makes controlling and observation easier, faster and the smuggling of medication from the clinic harder (Winstock, Lea et al. 2008). Crushed mono-buprenorphine has been in wider clinical use in Ireland (NSHHB 2006) were clinicians where advised to review their patient to determine that mono-buprenorphine is being swallowed rather than dissolved, or if it is being diverted. This guidance was given in 2006 regardless of the fact that at that point no studies had been carried out on the effect on the bioavailability of mono-buprenorphine after crushing the tablets. It was hypothesized that crushing increases the surface area of the drug which would in turn increase the dissolution and absorption of the drug. It was also suspected also that crushing would increase saliva production, which in turn would enhance the possibility of swallowing unabsorbed drug. As shown in this study, the absorption was not altered by crushing but the possibility of increased swallowing decreasing the medications effect could not be verified nor rebutted. It seems that the rationale behind this guidance was patient control rather than enhancing treatment availability. What should be considered is that this patient group are often at high risk of concomitant drug consumption in which case the safety profile of buprenorphine may be an advantage.

Patient compliance is also often affected by supervised urine testing, because it is regarded unpleasant both by patients and staff. For the treatment unit personnel, supervision also sets challenges: personnel shortage due to same gender controls, organizational delays and extra work due to significant expenditure of time, lack of daily routine planning reliability, and last but not least, the fact that control of manipulation is not the job of trained medical staff. Their competence should be used for treatment, e.g. counselling, which is in the end more important for patient rehabilitation and treatment outcomes, than urine drug screening. The use of a new method for drug screening was well accepted by patients, significantly saved on working time and did not compromise treatment safety in terms of undetected concomitant drug abuse. This was in line with the small amount of published studies dealing with this method (Schneider, Ruhl et al. 2008). By using the new method the trained staff could focus on consultation rather than supervision, enhancing patient treatment and increasing the number of treated patients. There are new studies from Finland with other technical innovations, such as electronic compliance monitoring (Tacke, Uosukainen et al. 2009), showing that significant time and cost savings can be achieved with those techniques. This is important, because the number of opioid
abusers seeking treatment has, according to this study, almost doubled from 2006 to 2010 and the mean opioid abuse time has also risen implicating that there still is an unmet need for treatment at least in the metropolitan area.

6.2 Methodological considerations and limitations

Study I was a retrospective evaluation and, given the nature of the study, there was no control group. The appropriate clinical patient data were used to assess any safety, adverse events and compliance changes associated with a switch from mono-buprenorphine to the buprenorphine–naloxone combination product. Data were received from the treatment centres on case report forms and descriptive statistics were used for summarising. However, the data collected was inspected by the research group, while the variables in this study have been used in other studies on opioid dependence, and should therefore be appropriate. Study I is limited by its retrospective nature and the differences in clinical practice between the study sites. The treatment procedures did differ in the centres especially in respect of the policy on take-home medication, urine testing and also determination of treatment due to drug abuse. Also counselling provided to the patients with information about buprenorphine-naloxone treatment did differ at the study sites. Probably there was also a difference how physicians did record, e.g. drug abuse, adverse effects and carry out needle mark inspections. What also has to be considered is the attitude of the physicians themselves towards the buprenorphine-naloxone product. If the physician had any doubt concerning the safety or efficacy of the product it would be exceptional if this would have had no effect on the patients. This could explain the high (15%) switch back to mono-buprenorphine. However, the main aim was to determine the doses of buprenorphine-naloxone associated with acceptable adverse events during the switch of medication from mono-buprenorphine, and this should not compromise the value of the data.

In Study II, the SOWS and VAS indicators were used to estimate opioid withdrawal symptoms and craving. Although they are both validated in Finland and clinically widely in use, they are subjective measurements and they cannot be used to compare results with the other study subjects. In order to avoid this problem a crossover design was used. Data collection for Study II was started in May 2004, which was half a year after the majority of maintenance patients
were switched to buprenorphine-naloxone. The study size was calculated to be sufficient for reliable data analyses. The main limitation is related to the study design, where patients were stabilized on 24 mg of mono-buprenorphine and then had whole or crushed medication in seven–day intervals. The stabilization time (two weeks) for these patients was, according to prior pharmacokinetic studies, sufficient to prevent interference with the gathered data. When plasma levels are measured in a steady state dosing situation, buprenorphine in the plasma comes partly from the dosing period being examined and partly from previous doses. This is shown by the plasma level measured at time zero or pre-dose; the buprenorphine in the plasma at this time is clearly from the previous dose(s). At steady state, which the study could claim after seven days of regular, fixed dosing, the area under the plasma curve (AUC) between zero and 24 hours (the interdose period) is equal to the AUC from zero to infinity following a single dose and gives an acceptable means of comparison of the two treatments. Therefore, when whole tablets have been taken for seven days and then as the whole tablet test dose, the plasma levels between zero and 24 hours are fully representative of whole tablets at steady state. However, when whole tablets have been taken for seven days but the test dose is crushed tablets, then the plasma levels between zero and 24 hours are represented by a mixture of the contribution of the whole tablets and the crushed tablet test dose. So the study cannot claim that the plasma levels are representative of crushed tablets at steady state. Although the study does not meet generic bioequivalence standards according to the FDA, this study still provides valuable information for clinical practice.

Study III included a questionnaire that was created for this study only and has not been validated. The questionnaire included background information, two questions measuring patient satisfaction on a six-point Likert scale, and the patient’s preferred testing system. The use of a unique questionnaire makes comparison to other studies difficult, but on the other hand a 1–6 scale is widely used for assessment research. Study III had several limitations. First the study sample was collected from three different patient groups (maintenance treatment, detoxification and outpatient unit), and may thus have some selection bias. Also the number of reported attempts at manipulation could be biased, as patients in different phases or treatments have a different motivation to manipulate their urine depending on the advantages they might obtain when providing a negative drug result. The focus of this study, however, was on analysing the risk of manipulation when using the new marker method and patient compliance and staff satisfaction.
Study IV was based on a questionnaire. One of the major challenges in the data analysis was grouping the declared data on the drug of abuse into the correct categories, given that a lot of street names for the drugs were used. For each uncertain drug name, the participating study site was asked to provide as precise an estimate as to which group it should be categorised into. The categories were kept the same over the full period of the study so as to maintain comparability. Study IV has two main limitations: firstly the response rate varied greatly between the study years and it was not possible to calculate for every year the exact return rate due to the anonymity of the service. Secondly the questionnaires used differed slightly annually and the questions were partly phrased differently, which may lead to some bias. However, the content of the questions of the main variables were similar. On the other hand, it seems that grouping between opioid and non-opioid users was successfully conducted over the years, because the response rates were similar to the portion of opioid abusers of overall intravenous users in Finland, and regardless of the different phrasings, the meaning of the questions were the same from one year to another.

All studies, except IV, have too small sample sizes to infer strong conclusions.
7. Conclusions and future implications

Reports and studies from countries with a long history of OMT have shown that when treatment access is expanded, the harms related to treatment tend to increase (Ritter and Di Natale 2005; Monte, Mandell et al. 2009; AIHW 2010). Several different approaches can be taken to diminish the misuse of treatment medication, diversion and overdoses in particular. At the same time the balance between higher costs of supervision and its impact on access to treatment needs to be considered. Increased supervision binds resources, with less treatment available overall, resulting in higher mortality, infection and crime rates. On the other hand a lack of adequate supervision leads to more medication misuse and diversion. However, management of the OMT is not so one-sided, as the use of safer preparations with lower abuse potential have opened new possibilities to carry out medication dosing in a more flexible way (Amass, Kamien et al. 2000; Perez de los Cobos, Martin et al. 2000; Petry, Bickel et al. 2000; Amass, Kamien et al. 2001; Bell, Shanahan et al. 2007; Amass, Pukeleviciene et al. 2012). This allows for a less supervised administration of the medication (Bell, Shanahan et al. 2007), without negatively effecting two of the primary outcomes; opioid abuse and retention. It is also important to make OMT more and more available in primary care, where it is easily accessible for patients (Amass, Ling et al. 2004; Wittchen, Apelt et al. 2008; Lee, Grossman et al. 2009), is more cost-effective (Jones, Moore et al. 2009; Schackman, Leff et al. 2012), and also allows new patients to enter into treatment (Sullivan, Chawarski et al. 2005) with good outcomes (Fudala, Bridge et al. 2003; Fiellin, Moore et al. 2008). Good treatment availability is also an important factor in declining the number of new drug, especially opioid, abusers, which has been detected at EU level after rises in treatment access possibilities (EMCDDA 2012a). This should also be more emphasized in Finland because there is still a burden for treatment access, and many opioid abusers are not able to get OMT even if they wanted to. More research is needed to clarify the reasons why patients are unable to enter OMT.

Repeated research has demonstrated that it is important to invest in the education of treatment personnel (Lofwall, Wunsch et al. 2011). Untrained personnel lack medical knowledge and knowledge of prescription practices (Leonardi, Hanna et al. 2008; Barry, Irwin et al. 2009; Larance, Degenhardt et al. 2011c; Larance, Ambekar et al. 2011d, Johanson, Arfken et al. 2012) or are using insufficient medication regimens (Roux, Villes et al. 2008a; Roux, Villes et
al. 2008b; Lofwall, Wunsch et al. 2011), which all may negatively effect treatment outcomes and also higher the risk of medication diversion.

An important role in enhancing treatment efficacy is the possibility to use pharmacist dispensing, which has been possible in Finland for the buprenorphine–naloxone combination only since 2009 for patients treated with buprenorphine-naloxone. Considering international practices, clearly the proportion of patients receiving treatment in this way could clearly be higher. In the main, pharmacists are willing deal with supervised medication suspension (Raisch, Fudala et al. 2005; Lofwall, Wunsch et al. 2010) but caution has to be taken to ensure adequate education aimed at preventing diversion (Winstock, Lea et al. 2008), as well as considering financial issues, given that pharmacies are private enterprises (Winstock, Lea et al. 2007).

The combining of naloxone with buprenorphine has had positive outcomes on restricting diversion and misuse in Finland to some extent compared to mono-buprenorphine. In other opioid abuse surroundings the effect is probably more evident, also providing new possibilities for flexible medication dispensing. Patients’ attitudes towards combining with naloxone for safety reasons have become more accepting (Daulouede, Caer et al. 2010; Shearer, Mammen et al. 2010). Moreover, attempts to develop a methadone–naloxone combination product (Nutt and Jasinski 1974; Bell, Shearer et al. 2009) would also be a big step towards safer treatment.

Treatment has clearly been shown to be cost-effective for mono-buprenorphine, buprenorphine–naloxone and methadone (Doran, Shanahan et al. 2003; Doran 2005; Martinez-Raga, Gonzalez Saiz et al. 2010; Schackman, Leff et al. 2012) when compared to detoxification or no treatment, especially when using flexible medication dispensing (Baser, Chalk et al. 2011; Weiss, Potter et al. 2011). Even though the costs of OMT have lately been the key issue in Finnish discussions, leading to suggestions for treatment models that involve only treatment with medication, one needs to keep in mind that this trend involves great risks in terms of treatment outcomes. Addiction is a complicated disease and needs to be treated in a multi-professional way, addressing flexibly the challenging psychological and social problems of patients. Counselling is needed in its various forms and its use on an individual basis is associated with better treatment outcomes (McLellan, Arndt et al. 1993; Galanter, Dermatis et al. 2004; Fiellin, Pantalon et al. 2006; Gorelick 2006).
Investing in individual treatment possibilities by, i.e. introducing new technical methods into clinical settings, goes hand in hand with the realisation that medication is not at the centre of treatment, but rather rehabilitation, which when successfully conducted increases confidence that the medication abuse is low. OMT has (Kirn 1988) and will remain controversial until better quality evidence on clinical management emerges. Improving treatment, safety concerns and health economics are complex questions, and there are no simple answers. Nevertheless, a lot can be achieved with good clinical management with no decrease in treatment quality. Regarding the severity of opioid addiction, treatment needs to be flexible and sufficiently long lasting. In most cases (cost-)effective treatment means tailored treatment schemes for individual patients. Most importantly, the background of OMT should be medical and ethical, not purely economic, otherwise, rising costs and diminishing treatment safety could lead to severe consequences – with a high price, paid for by patients and society alike.
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