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Buprenorphine – Features of Abuse and Methods for Improving Unobserved Dosing in Opioid Substitution Treatment

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HANNA UOSUKAINEN

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ABSTRACT

Abuse of buprenorphine has increased in Europe, North America and Asia. However, long-term studies on persons abusing buprenorphine and their clinical characteristics are lacking. Buprenorphine is used for the treatment of opioid dependence. Providing unobserved opioid substitution treatment (OST) can offer advantages in terms of client access as well as social and occupational rehabilitation but involves the risk of diversion. This thesis examined the characteristics of persons who sought treatment for buprenorphine abuse. In addition, the thesis explored possibilities for improved unobserved dosing in OST with electronic medicine dispensers (EMDs) and the provision of OST from Finnish community pharmacies.

The thesis utilized a range of data collection methods. Epidemiological analyses were conducted using data collected at the Helsinki Deaconess Institute (HDI) between January 31, 1997 and August 31, 2008 (studies I and II). Structured clinical interviews were conducted with all clients seeking treatment (n=4,817). OST clients treated with buprenorphine-naloxone (BNX) in Kuopio received their take-home BNX in EMDs over a four month period in 2010-2011 (study III). Questionnaires and drug screen data from the Kuopio University Hospital were used to investigate the impact of EMDs on diversion of BNX. A cross-sectional postal survey was conducted of all community pharmacies providing OST in Finland in August 2011 (study IV).

The proportion of clients seeking treatment for buprenorphine abuse at the HDI increased from 0% to 38% between 1997 and 2008. Most clients injected buprenorphine (81%) and used buprenorphine on a daily basis (74%). Despite more intense abuse patterns, buprenorphine clients had similar social, health and treatment-related characteristics to amphetamine clients. EMDs improved the safe storage of take-home BNX but their ability to prevent diversion was not demonstrated. About 10% of all BNX-treated clients in Finland collected their medicines from community pharmacies. Finnish community pharmacies had generally positive experiences dispensing BNX and only 26% of pharmacies had experienced problems, mainly in relation to timing or non-collection of doses.

In conclusion, this study highlighted the increasing abuse of buprenorphine in Finland. Buprenorphine clients had risky abuse patterns as evidenced by the high prevalence of injecting and daily abuse. Different methods to provide unobserved BNX dosing can produce variable outcomes and, therefore, their utility should be further examined.

National Library of Medicine Classification: QV 92, WB 330, WM 270, WM 284
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Buprenorfiini – väärinkäytön ominaispiirteet sekä opioidikorvaushoidon valvomattoman lääkkeenoton kehittäminen
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TIIVISTELMÄ

Buprenorfiinin väärinkäyttö on lisääntynyt Euroopassa, Pohjois-Amerikassa ja Aasiassa. Tästä huolimatta buprenorfiinin väärinkäyttöä ja käyttäjien kliinisiä ominaisuuksia on selvitetty puutteellisesti. Buprenorfiinia käytetään opioidiriippuvuuden hoidossa. Opioidikorvaushoitolääkkeiden valvomattomaan ottoon liittyy huomattavia etuja, kuten hoidon saatavuuden paraneminen ja potilaiden sosiaalisen sekä ammatillisen kuntoutumisen edistyminen. Riski lääkkeiden välitykseen katukauppaan on kuitenkin olemassa. Tämän väitöskirjatyön tavoitteena oli selvittää buprenorfiinin väärinkäytön takia hoitoon hakeutuneiden henkilöiden ominaisuuksia. Lisäksi tutkimuksessa selvitettiin mahdollisuuksia kehittää valvomatonta lääkkeenottoa elektronisten lääkehoidon-seurantalaitteiden avulla sekä korvaushoidon toteuttamista suomalaisissa avoapteekeissa.

Osatutkimuksissa I ja II käytettiin Helsingin Diakonissalaitoksella 31.1.1997–31.8.2008 välillä kerättyä tietokantaa, joka sisältää kliinisten haastattelujen avulla kerättyä tietoa kaikista hoitoa hakeneista henkilöistä (n=4817). Osatutkimuksessa III buprenorfiini-naloksoni –yhdistelmävalmistetta käyttäneet kuopiolaiset korvaushoitopotilaat saivat korvaushoitolääkkeensä kotiannokset seurantalaitteissa 4 kuukauden ajan. Laitteiden vaikutusta yhdistelmävalmisteen välitykseen tutkittiin kyselyiden avulla sekä tarkastelemalla Kuopion yliopistollisessa sairaalassa otettuja huumeseulatuloksia. Osatutkimuksessa IV yhdistelmävalmistetta tilanneille suomalaisille avoapteekeille tehtiin kyselytutkimus elokuussa 2011.

Buprenorfiinin väärinkäytön takia hoitoon hakeutuneiden asiakkaiden osuus kasvoi 0 %:sta 38 %:iin vuosien 1997 ja 2008 välillä. Asiakkaat käyttivät buprenorfiinia pääasiassa pistämällä (81 %) ja päivittäin (74 %). Vaikka buprenorfiinin käyttäjien väärinkäyttötavat olivat intensiivisempiä amfetamiinin käyttäjiin verrattuna, sosiaalisten sekä terveyteen ja hoitoon liittyvien ominaisuuksien välillä ei ollut eroja. Seurantalaitteet paransivat yhdistelmävalmisteen kotiannostelun turvallisuutta, mutta niiden tehosta estää lääkkeen välittämistä katukauppaan ei saatu näyttöä. Noin 10 % yhdistelmävalmistetta käyttävistä suomalaisista korvaushoitopotilaista haki lääkkeensä apteekeista. Yhdistelmävalmisteen toimittaminen avoapteekeissa oli sujunut hyvin, ja vain 26 % apteekeista oli kokenut ongelmia, yleisimmin lääkkeenhaun ajoitukseen tai hakematta jääneisiin annoksiin liittyen.

Tämä tutkimus osoitti buprenorfiinin väärinkäytön yleistyneen Suomessa. Pistäminen ja päivittäinen käyttö olivat yleisiä buprenorfiinin käyttäjillä. Valvomatonta korvaushoitolääkkeiden ottoa kehittävien menetelmien vaikutukset ovat olleet vaihtelevia, joten niiden käyttöön liittyviä tekijöitä tulisi tutkia.

Luokitus: QV 92, WB 330, WM 270, WM 284
Yleinen Suomalainen asiasanasto: buprenorfiini; naloksoni; opioidit; opiaatit; päihteet; korvaushoito; väärinkäyttö; katukauppa; epidemiologia; apteekit; Suomi

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This research was conducted at the Faculty of Health Sciences, University of Eastern Finland, in collaboration between the School of Pharmacy (Pharmacology) and the School of Medicine (Clinical Medicine and Institute of Public Health and Clinical Nutrition) during the years 2009-2014. This study was finalized in 2013 while I was doing a research exchange at the School of Pharmacy and Medical Sciences, University of South Australia. I would like to thank all of the departments for providing facilities as well as all those who have participated in my research work during these years.

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Adelaide, January 2014

Hanna Uosukainen

List of the original publications

This dissertation is based on the following original publications:

I Uosukainen H, Kauhanen J, Voutilainen S, Föhr J, Paasolainen M, Tiihonen J, Laitinen K, Onyeka IN, Bell JS. Twelve-year trend in treatment seeking for buprenorphine abuse in Finland. *Drug Alcohol Depend 127: 207-214, 2013*

II Uosukainen H, Ilomäki J, Kauhanen J, Tacke U, Föhr J, Tiihonen J, Bell JS. Factors associated with buprenorphine compared to amphetamine abuse among clients seeking treatment in Finland. *J Subst Abuse Treat.* Accepted for publication.

III Uosukainen H, Pentikäinen H, Tacke U. The effect of an electronic medicine dispenser on diversion of buprenorphine-naloxone-experience from a medium-sized Finnish City. *J Subst Abuse Treat 45: 143-147, 2013*

IV Uosukainen H, Bell JS, Laitinen K, Tacke U, Ilomäki J, Turunen JHO. First insights into community pharmacy based buprenorphine-naloxone dispensing in Finland. *Int J Drug Policy 24: 492-497, 2013*

Contents

Abbreviations

ADF	Abuse-deterrent formulation
BUP	Single-ingredient buprenorphine
BNX	Buprenorphine-naloxone combination product
BZD	Benzodiazepine
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMD	Electronic medicine dispenser
GP	General practitioner
HDI	Helsinki Deaconess Institute
ICD	International Classification of Diseases
IDU	Injecting drug user
IM	Intramuscular
IV	Intravenous
NEP	Needle exchange program
OR	Odds ratio
OST	Opioid substitution treatment
PO	Prescription opioid
SD	Standard deviation
SII	Social Insurance Institute of Finland
SPSS	Statistical Package for the Social Sciences
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
χ^2	Chi-squared

1 Introduction

Opioid abuse is a major public health problem worldwide (Degenhardt & Hall 2012). Abuse refers to harmful psychoactive substance use causing damage to health (World Health Organization 2012). The abuse of prescription opioids (PO) has been increasing in Europe, North America and Asia (Degenhardt et al. 2008, Holmes 2012, Fischer et al. 2013b). Buprenorphine is a semi-synthetic partial agonist at mu (μ) opioid receptors and it produces opioid agonist-like effects (Martin et al. 1976, Cowan et al. 1977, Walsh et al. 1994). Early studies indicated that buprenorphine had low abuse potential (Martin et al. 1976, Cowan et al. 1977, Jasinski et al. 1978, Lewis 1985). However, buprenorphine abuse has been reported since the 1980s (O'Connor et al. 1988), and more recently in Europe (Casati et al. 2012), the United States of America (USA) (Johanson et al. 2012), Australia (Aitken et al. 2008), and South Asia (Larance et al. 2011a). National reports have indicated that buprenorphine abuse is especially common in Finland (Forsell et al. 2010, Varjonen et al. 2012). A combination product containing buprenorphine and the opioid antagonist naloxone was developed in order to deter the intravenous (IV) abuse of buprenorphine (Mendelson & Jones 2003). However, the addition of naloxone has not been sufficient to prevent buprenorphine abuse e.g., (Bruce et al. 2009, Duke et al. 2010). Most studies examining the characteristics of buprenorphine users have been cross-sectional, had small sample sizes or had short follow-up periods. In addition, the clinical characteristics of buprenorphine users are not well-established. Characteristics such as older age, mental health disorders, using opioids only by swallowing or sublingually, and no prior opioid dependence treatment contacts may be associated with successful treatment outcomes (Dreifuss et al. 2013).

Buprenorphine is marketed internationally as an opioid analgesic and for the treatment of opioid dependence. Several studies have shown that buprenorphine is effective and safe when used in opioid substitution treatment (OST) e.g., (Johnson et al. 1995b, Fudala et al. 2003, Mattick et al. 2008). Buprenorphine has enabled the provision of OST in primary health care and office-based settings (Fiellin et al. 2008, Gunderson & Fiellin 2008). This can increase the flexibility of OST in terms of client access and autonomy, especially if unobserved dosing is allowed. Unobserved dosing refers to the daily administration of OST medicines without direct supervision of treatment staff (Bell 2010). It can offer substantial benefits, such as increased accessibility to OST, positive effect on social and occupational rehabilitation and less stigma to OST patients (Bell et al. 2004, Anstice et al. 2009, Gunderson et al. 2010). Community pharmacies can provide convenient and flexible dosing sites for OST patients (Chaar et al. 2011). In many countries community pharmacies have a major role in OST provision (Berbatis et al. 2005). According to Finnish legislation, buprenorphine-naloxone combination product (BNX) may be dispensed by community pharmacies since February 2008 (Ministry of Social Affairs and Health 2008). However, no studies have examined the provision of OST in Finnish pharmacies. OST, especially unobserved dosing, involves the risk of diversion (Bell 2010). Diversion refers to the supply of pharmaceuticals to the illicit drug market or to persons whom they were not intended (Larance et al. 2011c). About 30% of OST patients reported having diverted their medicines within the previous 6 months (Larance et al. 2011b). Various methods have been used and suggested as ways to prevent or reduce diversion, such as training for health care professionals, abuse-deterrent formulations, urine drug screens and regulatory controls

(Fudala & Johnson 2006). The possibilities offered by technical devices have not been examined thoroughly.

The purpose of this thesis was to examine both the abuse and therapeutic use of buprenorphine. This thesis examined the characteristics of persons who sought treatment for buprenorphine abuse. In addition, the thesis explored possibilities for improved unobserved OST dosing with electronic medicine dispensers (EMDs) and the provision of OST from Finnish community pharmacies.

2 Review of Literature

The focus of this literature review was buprenorphine abuse and diversion. The literature searches were performed using PubMed, MEDLINE and Google Scholar. The searches were performed using a combination of Medical Subject Headings (MeSH) and key words. These included 'buprenorphine', 'buprenorphine-naloxone', 'abuse', 'misuse', 'substance-related disorders', 'opioid', 'dependence', 'addiction', 'diversion', 'prescription opioid', 'treatment', 'opioid substitution treatment', 'efficacy', 'supervision', and 'community pharmacy'. Reference lists of included articles were searched for articles not identified in the database search. Publications in languages other than English or Finnish were excluded. The review focused on human studies. Preclinical studies were excluded with the exception of early animal studies examining the basic pharmacology of buprenorphine. The relevant publications were included in the respective chapters concerning buprenorphine in general (see 2.1) and the use of buprenorphine in OST (see 2.3.2; 2.3.3). Studies concentrating solely on the cost-effectiveness of OST were excluded. Studies examining the epidemiology of buprenorphine abuse in Chapter 2.2.3.1 have been presented in chronological order.

2.1 BUPRENORPHINE

2.1.1 Pharmacology

Buprenorphine was developed in 1966 at the research laboratory of Reckitt & Coleman in England (Campbell & Lovell 2012). Buprenorphine is a semi-synthetic opiate derivative made from thebaine which is a natural alkaloid in opium (Davids & Gastpar 2004). Buprenorphine is a partial mu (μ) opioid receptor agonist with lower intrinsic activity compared to full agonists (Martin et al. 1976, Cowan et al. 1977, Lewis 1985). Therefore, it does not activate receptors as completely as a full agonist (Martin et al. 1976). Buprenorphine produces an action with rapid onset and long duration (Cowan et al. 1977, Walsh et al. 1994). Depending on the route of administration, the onset of buprenorphine effects occurred in 6-90 minutes and effects persisted up to 72 hours (Umbricht et al. 2004). Buprenorphine shows high affinity for and slow dissociation from receptors which explain the long duration of action and difficulty to displace it from receptors (Lewis 1985, Walsh & Eissenberg 2003). Buprenorphine has a bell-shaped dose response curve which means that as the dose increases the effect increases to a maximum and then starts to decrease, despite the dose still increasing (Johnson et al. 2003).

Buprenorphine's desired effects are thought to be mediated mainly by its mu receptor agonism (Takemori et al. 1986, Tzschentke 2002, Walsh & Eissenberg 2003, Johnson et al. 2003). It has a high affinity for kappa (κ) opioid receptors with antagonist effects (Su 1985, Leander 1987, Leander 1988). At delta (δ) opioid receptors, buprenorphine acts as an antagonist with high affinity and low efficacy (Negus et al. 2002) and it may block epsilon (ε) opioid receptors at small doses (Mizoguchi et al. 2003). Buprenorphine also activates opioid receptor-like (ORL-1) receptors which are considered as the fourth group of opioid receptor family (Lutfy & Cowan 2004). It has been speculated that the bell-shaped dose response curve may stem from buprenorphine's differing effects at mu and kappa receptors (Johnson et al. 2003). Cowan and colleagues (1977) suggested that mu effects are predominant at low doses whereas kappa effects offset them at higher doses.

There is a ceiling on buprenorphine's effects at high doses (Martin et al. 1976, Walsh et al. 1994). Walsh and colleagues (1994) examined the effects of sublingual buprenorphine in non-dependent opioid users (n=4). For all measures (physiologic, subjective and behavioural), there was a ceiling dose and larger doses did not produce greater effects. For most euphoria-sensitive measures, the ceiling dose was between 8 and 16 mg and the 32 mg dose produced lower scores usually. However, the presence of ceiling effect depends on the intensity of stimulus and the endpoint chosen, e.g., it applies to respiratory depression but not to analgesia (Pergolizzi et al. 2010). Pergolizzi and colleagues speculated that use of the term 'partial agonist' is only appropriate when describing buprenorphine's functions which are dependent upon the conditions under which the drug is used, and it is not buprenorphine's characteristic per se. Mechanisms behind the ceiling effect are not totally clear. Harris and colleagues reported that less than dose-proportional increase in concentrations may contribute to the ceiling effect, indicating pharmacokinetic mechanisms behind it (Harris et al. 2004). However, another study claimed that pharmacokinetic adaptations do not explain the ceiling – at least at the dose range 2-16 mg intravenously (IV) – and suggested that pharmacodynamic adaptations are more likely to explain this phenomenon (Huestis et al. 2013). It has been speculated that buprenorphine's effects on ORL-1 receptors may contribute to buprenorphine's ceiling effect as well as its bell-shaped dose response curve (Lutfy & Cowan 2004).

The bioavailability of oral buprenorphine is very low due to extensive first-pass metabolism in the gastrointestinal tract and liver (Chiang & Hawks 2003, Elkader & Sproule 2005). The bioavailability of sublingual buprenorphine has been estimated to be between 28-51% (Kuhlman et al. 1996, Mendelson et al. 1997b, Harris et al. 2000). In non-dependent opioid users, a decrease in bioavailability was seen with increasing sublingual buprenorphine doses (Harris et al. 2004). Elkader and Sproule (2005) reviewed clinical pharmacokinetics studies examining buprenorphine and summarized that maximum plasma concentration was reached in approximately one hour after sublingual administration (range 0.7-3.5 h). The rapid sublingual absorption is followed by an accumulation in various organs and a delayed systemic absorption. Buprenorphine is highly lipophilic with a large volume of distribution and an ability to cross the blood-brain barrier. Buprenorphine is extensively metabolized by *N*-dealkylation to norbuprenorphine, which is the primary metabolite, and conjugated with glucuronic acid (Cone et al. 1984). CYP3A4 is the major cytochrome P450 enzyme mediating this reaction (Iribarne et al. 1997, Kobayashi et al. 1998). Norbuprenorphine is an active metabolite although its effects are weaker than those of buprenorphine (Cone et al. 1984, Elkader & Sproule 2005). Buprenorphine undergoes enterohepatic circulation which may prolong its effects (Cone et al. 1984). Buprenorphine has a long elimination half-life, but significant variation in values exists (Elkader & Sproule 2005). In the studies reviewed by Elkader and Sproule, the mean elimination half-life ranged between 2 and 44 hours. Differences may be related to assay sensitivities as well as different routes of administration (IV, intramuscular IM, sublingual). Kuhlman and colleagues (1996) reported that elimination half-life is longer for the sublingual route compared to IV administration. Buprenorphine is mainly eliminated in faeces while the excretion in urine plays only minor role (Cone et al. 1984).

2.1.2 Effects in humans

Buprenorphine produces opioid agonist-like effects in humans (Jasinski et al. 1978, Mendelson & Mello 1992, Pickworth et al. 1993). It causes decreased respiratory rate, miosis, increased heart rate, varying changes in systolic and diastolic blood pressure, analgesia, sedation, and nausea in some individuals. Some studies have reported that study participants experienced euphoria after IV administration (Pickworth et al. 1993), while

others have reported only ‘general feeling of contentment’ and not getting ‘high’ after subcutaneous administration (Mendelson & Mello 1992). Buprenorphine may cause constipation, a common side-effect of opioid use (Lange et al. 1990). Constipation has been reported by 1-5% of patients receiving buprenorphine for the treatment of pain (Kress 2009) and by 33-47% of buprenorphine-treated OST patients (Ray et al. 2004, Magnelli et al. 2010). Tolerance develops to the sedative and analgesic effects of buprenorphine (Martin et al. 1976, Cowan et al. 1977). Tolerance means “a decrease in response to a drug dose that occurs with continued use” (World Health Organization 2012). Both physiological as well as psychosocial factors may contribute to the development of tolerance. Cessation of regular buprenorphine consumption leads to a mild-to-moderate opioid-type withdrawal syndrome which usually starts slowly and peaks at about 5 days after the last buprenorphine dose (Fudala et al. 1990, San et al. 1992).

Buprenorphine’s effects depend on the person to whom it is administered and his/her recent history of opioid use and the level of tolerance and possible dependence (Walsh & Eissenberg 2003). Zacny and colleagues examined subjective, psychomotor and physiological effects of IV buprenorphine in healthy volunteers (n=16) (Zacny et al. 1997). Buprenorphine induced miosis, decreased respiratory rate, impaired psychomotor performance and increased the ratings of ‘nodding’, ‘skin itchiness’, ‘turning of the stomach’, ‘dizziness’, ‘nauseousness’ and ‘sleepiness’. Buprenorphine did not increase ‘drug liking’ ratings. Morphine produced less severe subjective and psychomotor-impairing effects than buprenorphine. Saarialho-Kere and colleagues reported similarly that buprenorphine (sublingual administration) depressed respiration, impaired different measures of performance and produced drowsiness and mentally slow/muzzy feelings in healthy volunteering study participants (n=12) (Saarialho-Kere et al. 1987). In opioid experienced study participants not dependent on opioids, buprenorphine produced similar physiological effects (pupil constriction, depressed respiration, changes in blood pressure) but also typical opioid agonist effects, such as positive mood and increased ‘drug liking’ ratings, however, these effects were not dose-related (Jasinski et al. 1978, Weinhold et al. 1992, Pickworth et al. 1993, Walsh et al. 1994, Walsh et al. 1995b, Umbricht et al. 2004). Umbricht and colleagues (2004) compared the effects of sublingual and IV buprenorphine and found out that effects were generally similar but after IV administration the onset and peak effects occurred earlier and the duration of effects was shorter. Drug users may prefer IV administration, due to rapid onset of effects. On the other hand, adverse effects, such as nausea and vomiting, may decrease the abuse potential by injecting.

Buprenorphine effects in opioid-dependent persons depend on the level of dependence, opioid used, dose and time since last opioid dose (Walsh & Eissenberg 2003). In untreated heroin-dependent opioid users (n=8), IV buprenorphine produced non-significant physiological effects and increased opioid agonist measures (e.g., ‘drug liking’) (Mendelson et al. 1996). Strain and colleagues reported similar results with regard to physiological effects (Strain et al. 1992). They examined the effects of IM buprenorphine on opioid-dependent methadone maintained study participants (n=6). Buprenorphine produced minimal physiological effects and neither agonist nor antagonist-like effects. Strain and colleagues conducted a further study with a similar study design but shorter time period between methadone and buprenorphine doses (2 hours vs. 20 hours) (Strain et al. 1995). They reported that buprenorphine produced non-dose-related antagonist-like effects. Walsh and colleagues demonstrated that sublingual buprenorphine precipitated opioid withdrawal symptoms 40 hours after methadone dosing (30mg or 60 mg/day) in methadone-maintained opioid-dependent study participants (especially in those maintained on higher dose) (Walsh et al. 1995a). Therefore, it has been hypothesized that buprenorphine-precipitated withdrawal follows a U-shaped time-action curve (Walsh &

Eissenberg 2003). However, in addition the opioid used before buprenorphine administration and its dose seem to affect the withdrawal symptoms caused by buprenorphine. Schuh and colleagues demonstrated that IM buprenorphine produced opioid agonist-like effects in morphine-maintained (15 and 30 mg/day) opioid-dependent study participants (n=6) but these effects were diminished as morphine-doses were increased up to 120 mg per day (Schuh et al. 1996). Authors speculated that this was probably due to the development of cross-tolerance to acute opioid effects. However, withdrawal syndrome was not precipitated by buprenorphine which may have been explained by a relatively low level of dependence of the study participants. Fudala and colleagues reported contrasting results from their study in which opioid-dependent morphine-maintained (15 mg/day) study participants (n=10) were given IV buprenorphine without any statistically significant effects (Fudala et al. 1998).

2.1.3 Use as an opioid analgesic

Initially, buprenorphine was developed as an analgesic (Campbell & Lovell 2012). Its analgesic properties were demonstrated in the first studies examining its effects (Cowan et al. 1977, Jasinski et al. 1978). Animal studies indicated that it is 25-40 times more potent as an analgesic than morphine (Cowan et al. 1977). Buprenorphine's analgesic effects come from its agonist effects at mu opioid receptors (Johnson et al. 2005). Buprenorphine shows a relatively slow onset and offset of the antinociceptive action which are more likely to be caused by biophase distribution than slow receptor association-dissociation kinetics (Yassen et al. 2006). Nevertheless, buprenorphine has been used successfully in the management of acute pain (Johnson et al. 2005). According to the World Health Organization (WHO) three-step ladder for the treatment of cancer pain in adults, buprenorphine is included in to step III opioids which are regarded as strong opioids (Wolff et al. 2012, World Health Organization 2013). Buprenorphine is used for the treatment of moderate to severe pain (Johnson et al. 2005). An International Expert Panel has recommended that buprenorphine should be the first-line opioid analgesic in elderly people, if they have impaired hepatic and renal function because these impairments have no effect on buprenorphine's half-life (Pergolizzi et al. 2008). There are different buprenorphine formulations including products administered by parenteral, transdermal and sublingual routes (Johnson et al. 2005). Typical sublingual dose ranges between 0.2-0.4 mg and parental dose between 0.3-0.6 mg every six hours. The 72-hour buprenorphine patch, which is the most commonly used transdermal buprenorphine formulation, releases buprenorphine 35, 52.2 or 70 µg/hour.

Several studies have proven buprenorphine's efficacy in the treatment of acute pain (Downing et al. 1977, Harcus et al. 1980, Tigerstedt & Tammisto 1980, Gundersen et al. 1986, Carl et al. 1987). A more recent study compared the analgesic effects of sublingual buprenorphine (0.4 mg) and IV morphine (5 mg) for acute pain management in a randomized controlled trial (Jalili et al. 2012). Pain scores and the frequency of adverse effects were similar in both groups. Sublingual buprenorphine was easier and quicker to administer compared to morphine. The slow onset of analgesia (approximately one hour after a sublingual administration) should be taken into account when using buprenorphine for acute pain (Hoskin & Hanks 1991). However, Carl and colleagues (1987) reported that the sublingual absorption of buprenorphine was rapid and there were no differences in pain intensity between patients receiving IM or sublingual buprenorphine.

The long duration of action and the possibility to use non-parental routes of administration make buprenorphine a good treatment option for chronic pain (Hoskin & Hanks 1991). In one of the first studies examining buprenorphine's effects in the treatment of chronic pain, sublingual buprenorphine was given to 141 patients with moderate cancer

pain (Robbie 1979). Of these patients, 94 discontinued treatment after less than 1 week. The most commonly reported reason was side-effects such as drowsiness. The remaining 47 patients used buprenorphine on average for 12 weeks with good analgesic results. Zenz and colleagues administered epidural buprenorphine or morphine to 139 patients with severe cancer pain and reported that 87% of patients had remarkable pain relief (Zenz et al. 1985). Sublingual buprenorphine was administered to 51 elderly patients with chronic moderate pain and statistically significant improvements in pain scores were achieved within 48 hours (Nasar et al. 1986). No unwanted side-effects were reported by 71% of patients. At least in the early studies examining buprenorphine's effectiveness in pain treatment, constipation has been a rare side-effect (0-2% of patients) (Robbie 1979, Nasar et al. 1986). However, doses have been lower compared to studies, which examined buprenorphine's effects in opioid-experienced persons e.g., (Mello et al. 1982, Lange et al. 1990, Umbricht et al. 2004).

More recently, research has concentrated on transdermal buprenorphine. A randomized, double-blind, controlled multicentre study of patients with severe chronic pain found that 35 and 52.2 µg/hour products of transdermal buprenorphine were more efficient in pain management than placebo (response rates 37% and 48% vs. 16%, $p<0.05$) (Sittl et al. 2003). Another study reported that 70 µg/hour transdermal buprenorphine was more efficient than placebo in the treatment of severe chronic cancer pain in a randomized double-blind trial (n=289) ($p=0.0003$) (Poulain et al. 2008). Wolff and colleagues conducted a systematic literature review comparing transdermal buprenorphine to transdermal fentanyl and oral morphine (Wolff et al. 2012). Compared to fentanyl, there were no differences in pain measures but buprenorphine caused significantly less nausea and a lower number of treatment discontinuations due to adverse effects. Compared to morphine, buprenorphine caused significantly better pain control and less constipation as well as fewer cases of treatment discontinuations.

2.2 ABUSE

2.2.1 Definitions of opioid dependence and abuse

Opioid dependence is a complex health condition with social, psychological and biological determinants and consequences (World Health Organization 2004). It develops after regular opioid use and is a chronic disease with relapse and remission phases (World Health Organization 2004, World Health Organization 2009). There are no universally accepted definitions for opioid dependence or abuse. Internationally, two main systems of classification for diagnostic criteria of substance use disorders are used: The International Classification of Diseases (ICD-10) (World Health Organization 1993, American Psychiatric Association 2000) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (World Health Organization 1993, American Psychiatric Association 2000). ICD-10 is published by the WHO and it is the official diagnostic classification in Finland. DSM-IV is preferred within the mental health sector and the USA as well as in international addiction research (Larance et al. 2011c). The diagnostic criteria for opioid use disorders according to these systems are presented in Table 1. The new version of DSM criteria, DSM-V (5th edition) was released in May 2013 with some changes in criteria and terminology for substance-related and addictive disorders (American Psychiatric Association 2013).

There has been controversy surrounding the terms addiction and dependence for decades (O'Brien 2011). Both ICD-10 and DSM-IV used the term dependence even though it has been denoted to refer only to physical dependence which is body's normal physiological response (Larance et al. 2011c). However, in the latest version of the DSM (5th edition), dependence has been replaced with a term 'substance use disorder' in order to

avoid confusion and possible under-treatment of pain due to fear of addiction (O'Brien 2011). In addition, the abuse/dependence dichotomy has been removed and replaced with a single disorder which is measured on a scale from mild to severe (American Psychiatric Association 2013). American Society of Addiction Medicine uses the term addiction and defines it as: “a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations” (American Society of Addiction Medicine 2001). Addiction is characterized by impaired control over use, compulsiveness, continued use despite harm and craving. According to the WHO, dependence syndrome is a phenomenon characterized by: “a strong desire to take the drug, impaired control over its use, persistent use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and a physical withdrawal reaction when drug use is discontinued” (World Health Organization 2012). In this thesis, the term dependence according to the WHO definition has been used when referring to this disorder.

Similarly, various definitions have been used when referring to drug abuse, such as illicit use, misuse, non-medical use, unsanctioned use, extramedical use, harmful use and hazardous use, with some of them being used interchangeably (Larance et al. 2011c). For example, illicit use may be confusing when referring to PO abuse due to their legal status. Larance and colleagues recommended to use either hazardous use, which refers to, “a pattern of substance use that increases the risks of harmful consequences for the user, regardless of a diagnosis of dependence”, or extramedical use which refers to, “use of a medication outside a doctor’s prescription, not excluding the possibility that the user may have medically driven reasons for using the drug” (Larance et al. 2011c). Cicero and colleagues defined abuse as a substance use with the intention to get high, use in combination with other drugs to get high, or use as a substitute for other drugs of abuse (Cicero et al. 2007a). In a study by Katz and colleagues, the term abuse was used interchangeably with nonmedical use, with the latter being defined as, “use of prescription-type drugs not prescribed for the respondent by a physician or used only for the experience or feeling they caused” (Katz et al. 2007). The WHO defined abuse as a pattern of harmful psychoactive substance use causing damage to health (World Health Organization 2012). In this thesis, the terms harmful use and drug abuse are considered synonymous with each other, and the term abuse has been used throughout the text.

Table 1. The diagnostic criteria for opioid use disorders according to the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (World Health Organization 1993, American Psychiatric Association 2000)

ICD-10	Diagnostic criteria
Harmful use	Clear evidence that the substance use was responsible for physical or psychological harm. The nature of the harm should be clearly identifiable. The pattern of use has persisted for at least one month or has occurred repeatedly within a 12 month period. The disorder does not meet the criteria for any other mental or behavioural disorder.
Dependence	Three or more of the following manifestations should have occurred together for at least one month or if persisting for periods of less than one month then they have occurred together repeatedly within a 12 month period. (1) A strong desire or sense of compulsion to take the substance. (2) Impaired capacity to control substance-taking behaviour in terms of onset, termination or level of use. (3) A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome. (4) Evidence of tolerance to the effects of the substance. (5) Preoccupation with substance use (important alternative pleasures or interests being given up or reduced; or a great deal of time being spent in activities necessary to obtain/take the substance, or recover from its effects). (6) Persisting with substance use despite clear evidence of harmful consequences.
DSM-IV	
Abuse	A maladaptive pattern of substance use leading to clinical signs of impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period, and the symptoms have never met the criteria for substance dependence for this class of substance. (1) Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home. (2) Recurrent substance use in situations in which it is physically hazardous (e.g. driving). (3) Recurrent substance related legal problems. (4) Continued substance use despite having persistent/ recurrent social/ interpersonal problems caused/ exacerbated by the effects of the substance.
Dependence	A maladaptive pattern of substance use leading to clinical signs of impairment or distress, as manifested by 3 or more of the following occurring at any time in the same 12 month period. (1) Tolerance defined by either the need for markedly increased amounts of substance or a markedly diminished effect with continued use. (2) Withdrawal, as evidenced by either the characteristic withdrawal syndrome; or the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms. (3) The substance is often taken in larger amounts or over a longer period than was intended. (4) Persistent desire or unsuccessful efforts to cut down or control substance use. (5) A great deal of time is spent in activities necessary to obtain the substance or recover from its effects. (6) Important social, occupational or recreational activities are given up or reduced. (7) Substance use is continued despite of having a persistent/recurrent physical or psychological problems.

2.2.2 Abuse potential of buprenorphine

In general, drugs with abuse potential have reinforcing properties and cause harm to the individual and the society (Lewis 1985). Abuse liability can be defined as a likelihood of a psychoactive drug to sustain patterns of nonmedical self-administration with undesirable consequences (Johnson et al. 2005). The pharmacokinetic properties of a drug generally determine its abuse liability (Schaeffer 2012). Large brain concentration within a short time correlates with the feeling of euphoria. However, formulations without these properties may be tampered with the drug delivery system in order to make them better suited for abuse. In addition, extrinsic factors contribute to the abuse potential, e.g., media attention, peer preferences, cost and availability (Romach et al. 2013). Early studies indicated that buprenorphine did not produce physical dependence and it had low reinforcing efficacy (Martin et al. 1976, Cowan et al. 1977, Jasinski et al. 1978, Lewis 1985). Jasinki and colleagues reported that buprenorphine produced minimal abstinence symptoms and that withdrawal was easily managed. Due to these features as well as partial agonism and slow onset of action, it was assumed that the abuse potential of buprenorphine was low. However, more recent studies have indicated that situation is not that straightforward.

There is evidence of a statistically significant correlation between therapeutic exposure to buprenorphine (measured by filled prescriptions) and the magnitude of its abuse (Cicero et al. 2007b). Authors speculated that the value of a drug for non-therapeutic purposes may determine the level of diversion and, therefore, the rate of abuse can be viewed as an indicator of abuse liability. However, there are specific abuse liability studies which are mainly based on animal or human laboratory testing (Balster & Bigelow 2003). In human abuse liability testing, the drug effects have usually been compared to a known substance, and the most common assessments are subjective ratings of 'liking' of the drug effect supplemented with physiological and behavioural assessments.

Intravenous administration of buprenorphine increased the positive responses of 'feeling the drug' and increased the scores of drug-liking, good effects and euphoria in non-dependent opioid users (n=6) (Pickworth et al. 1993). Other studies examining the effects of sublingual and IM buprenorphine in non-dependent opioid users have reported similar results (Weinhold et al. 1992, Strain et al. 2000, Duke et al. 2010). The results of Duke and colleagues indicated that intramuscularly administered buprenorphine may have greater abuse potential compared to sublingual administration. Buprenorphine (IV and IM administration) also served as a reinforcer among recently detoxified heroin users (Bedi et al. 1998, Comer & Collins 2002). In opioid-dependent volunteers maintained on sublingual buprenorphine (n=8), IM buprenorphine produced agonist-like effects, especially the highest dose (16 mg) (Strain et al. 1997). Intravenous buprenorphine (8 mg) produced similar increased 'drug liking' and 'high' ratings compared to heroin among opioid-dependent heroin users maintained on sublingual buprenorphine (Comer et al. 2010). Eissenberg and colleagues conducted antagonist challenges in opioid-dependent persons maintained on sublingual buprenorphine and measured the effects by subject and observer ratings as well as physiological measures (Eissenberg et al. 1996). The authors concluded that buprenorphine can produce physical dependence in humans. For methadone-maintained opioid users, buprenorphine seems to have lower abuse potential because IM administration produced mild antagonist-like effects (Strain et al. 1995). Another study compared the abuse liability of different POs in morphine-maintained heroin-dependent volunteers (n=8) (Comer et al. 2008). Despite statistically significant increases in the ratings of 'drug liking' and 'good drug effect' from IV buprenorphine, it was not self-administered by study participants and it precipitated mild withdrawal symptoms. As a conclusion, buprenorphine seems to have abuse potential, especially in non-dependent opioid users.

Nevertheless, relying solely on subjective 'drug liking' ratings when measuring abuse potential, may be insufficient.

2.2.3 Epidemiology of buprenorphine abuse

2.2.3.1 International studies

The first reports of buprenorphine abuse emerged in the early 1980s in New Zealand, Australia and the United Kingdom (UK) (Harper 1983, Quigley et al. 1984, Strang 1985, Rainey 1986). At this time, buprenorphine was marketed as a low-dose product for the treatment of pain (Temgesic®). Low-dose buprenorphine refers to buprenorphine products used for pain treatment and high-dose buprenorphine to products used for the treatment of opioid dependence. In 1986, Robertson and Bucknall highlighted the extensive abuse of buprenorphine in Edinburgh and advised doctors to be aware of the dangers of prescribing it (Robertson & Bucknall 1986). Another study reported a marked increase in the number of buprenorphine users presenting for substance abuse treatment in Ireland between 1986 and 1987 (O'Connor et al. 1988). During the same time period, a 9% increase in the proportion of new clients using buprenorphine was detected in an outpatient clinic in Glasgow, Scotland (Sakol et al. 1989). The first report about the dependence potential of buprenorphine was published by Gray and colleagues (Gray et al. 1989). More than half (58%) of the new clients referred to their Glasgow clinic during a 6-month period reported that buprenorphine was their preferred drug. Low-dose buprenorphine was the most frequently abused drug among IV drug users in Glasgow between 1989 and 1990 (Lavelle et al. 1991). Due to these reports, restrictions on prescribing of buprenorphine were introduced in Glasgow in September 1989 but this led only to a moderate drop (20%) in incidence of abuse cases which started to rise again after few months (Stewart 1991). Reports from India (Nizamie & Sharma 1990, Chowdhury & Chowdhury 1990, Singh et al. 1992) and Spain (San et al. 1993) also indicated increasing abuse of buprenorphine. In 1989, the WHO Expert Committee on Drug Dependence recommended the inclusion of buprenorphine in Schedule III of the Convention on Psychotropic Substances 1971 (World Health Organization 1989). Schedule III substances are under international control (International Narcotics Control Board 2010). In addition to buprenorphine, for example pentazocine and flunitrazepam are included in the list. The first report of abuse of buprenorphine by snorting was published in 1991 (Strang 1991). In New-Zealand, low-dose buprenorphine was withdrawn due to abuse in 1991 and replaced by a buprenorphine-naloxone combination product (0.2 mg buprenorphine + 0.17 mg naloxone) (Robinson et al. 1993). The proportion of clinic patients self-reporting buprenorphine abuse in New Zealand dropped from 81% in 1990 to 57% in 1991-1992 indicating lower but still existent IV abuse potential of the combination product.

French general practitioners (GPs) have been able to prescribe high-dose buprenorphine to patients for the treatment of opioid dependence since 1996 (Thirion et al. 2002). Since then the abuse of buprenorphine has been widely documented in France. Obadia and colleagues reported that 24% of their injecting drug user (IDU) sample injected only buprenorphine and 34% injected it occasionally in parallel with other drugs (Obadia et al. 2001). Another French study reported similar results, with 27% of their IDU sample using only buprenorphine and 37% being poly-drug users (Moatti et al. 2001). Valenciano and colleagues reported even higher proportions as 45% of needle exchange program (NEP) clients (n=1,004) were categorized as main buprenorphine users and 73% had used buprenorphine in the last month (Valenciano et al. 2001). Falsified prescriptions to obtain buprenorphine from community pharmacies have been detected in France (Baumevieille et al. 1997). Around the same time, buprenorphine abuse has also been reported in Nepal (Shrestha et al. 1998) and India (Kumar et al. 2000). A rapid assessment conducted in

Madras, India revealed that 42% of IDUs interviewed (total n=100) used buprenorphine as their primary drug of abuse in 1998 (Kumar et al. 2000). Another Indian study reported that buprenorphine abuse increased rapidly until 1994 and then started to gradually decrease (Sharma & Mattoo 1999).

More recently, buprenorphine abuse has been documented all over the world, such as in Australia, in the USA and in many European and Asian countries (Yokell et al. 2011). The main studies examining buprenorphine abuse published within the last 10 years have been summarized in Table 2. In Australia, high-dose buprenorphine products have been available since 2000 (Jenkinson et al. 2005). In a survey conducted in 2002, 57% of IDUs (total n=156) reported life-time use of buprenorphine and 37% reported life-time injecting of buprenorphine (Jenkinson et al. 2005). Aitken and colleagues conducted a similar survey with IDUs in Melbourne in 2005-2006 (n=316) and reported that 32% (n=101) had injected buprenorphine during the previous 3 months and 10% (n=33) were primary buprenorphine users (Aitken et al. 2008). Buprenorphine injecting has also been reported in Malaysia (Bruce et al. 2008) and Nepal (Aich et al. 2010). Among Indian IDUs, buprenorphine was the second most commonly injected drug in 2005-2006 (Solomon et al. 2010). Buprenorphine abuse has caused large-scale public health problems in Singapore (Chua & Lee 2006, Winslow et al. 2006) and in the south Caucasus state of Georgia (Parfitt 2006). In 2005, 39% of patients treated in Georgian detoxification units were seeking treatment due to buprenorphine abuse (Parfitt 2006). In 2007, buprenorphine was the most commonly abused IV drug among IDUs (n=381) using NEP services in Georgia (96% reporting lifetime injecting and 75% reporting last-month injecting) (Otiashvili et al. 2010). Despite the high prevalence of abuse, only 13% of respondents reported buprenorphine as their favorite drug. There were at least 3,800 buprenorphine users in Singapore in 2006 (Lee 2006). As a countermeasure for large-scale abuse, Singaporean authorities tightened buprenorphine controls, prohibited buprenorphine from being dispensed as take-home doses and forbade GPs to start any new patients on buprenorphine.

A systematic literature review examining the abuse of medicines in the countries of European Union (EU) indicated that buprenorphine was one of the most abused medicines in this area (Casati et al. 2012). However, there were regional differences across the EU region. In Sweden, 89% of heroin users and 24% of amphetamine users visiting a NEP had used buprenorphine during the last year in 2004 (Hakansson et al. 2007). Intravenous abuse was reported by 43% altogether. According to a recent qualitative study, buprenorphine abuse was not generally perceived as a widespread problem among Swedish adolescents (Richert & Johnson 2013). A Norwegian multi-indicator model which utilized data from seizures, treatment units, pharmacy sales, helplines, key informants and media monitoring indicated increasing illicit use of buprenorphine between 2002 and 2006 (Mounteney & Haugland 2009). France was the first country to introduce a generic buprenorphine product in April 2006 (Nordmann et al. 2012). In 2008, 32% of clients entering drug addiction treatment centres were consuming generic buprenorphine (Nordmann et al. 2012). The studies mentioned above refer to the abuse of high-dose buprenorphine. The abuse of low-dose buprenorphine has been reported in the South Asia region (Larance et al. 2011a). Data about opioid abuse and injecting from this region are not complete but buprenorphine abuse has been reported in Bangladesh, India, Nepal and Pakistan. In Bangladesh and Nepal, buprenorphine has been reported to be the most favored drug among IDUs (Larance et al. 2011a).

The USA research has predominately highlighted the abuse of oxycodone and hydrocodone (Cicero et al. 2005) while the abuse of buprenorphine has remained low (Cicero & Inciardi 2005, Cicero et al. 2007c, Hughes et al. 2007). According to poison centre data collected between 2002 and 2003, hydrocodone and oxycodone had the highest abuse

rates in the USA (3.75 and 1.81 per 100,000 population, respectively) (Hughes et al. 2007). A study utilizing poison centre and prescription database information in 2003-2005 reported a low abuse rate of buprenorphine (Smith et al. 2007). The average quarterly abuse ratio per 1,000 prescriptions dispensed was 0.08 for the single-ingredient buprenorphine (BUP) and 0.16 for the BNX. In 2005, only 1% of PO users enrolled in OST reported recent abuse of buprenorphine (Rosenblum et al. 2007). Among a sample of street drug users in New York City (n=586) in 2004 to 2006, buprenorphine products were the least used POs (0.2% of the sample) (Davis & Johnson 2008).

However, according to more recent data from drug screens and interviews conducted in parole and probation units, buprenorphine abuse increased in the USA between 2005 and 2010 (Wish et al. 2012). A post-marketing surveillance study using data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Programs reported similar findings (Dasgupta et al. 2010). Nevertheless, the rates of methadone abuse and diversion were significantly higher than those for buprenorphine. From 2005 to 2009, the different measures of diversion and abuse of buprenorphine (user and physician surveys, exposures to buprenorphine reported to Poison Control Centres, seizures, emergency department visits) all steadily increased (Johanson et al. 2012). In 2007, Stimmel speculated that buprenorphine abuse would increase in the USA as a consequence of the growing number of people for whom buprenorphine is prescribed (Stimmel 2007). The USA Food and Drug Administration (FDA) approved buprenorphine (both BUP and BNX) for the treatment of opioid dependence in 2002, later than in many European countries or Australia.

Buprenorphine abuse by OST patients has been widely reported. Approximately half of 404 buprenorphine-maintained OST patients in France reported ever injecting buprenorphine (Vidal-Trecan et al. 2003). Factors associated with buprenorphine injecting were IV use of some other substance (OR 13.18, 95% CI 5.36-32.42), cannabis use (OR 2.34, 95% CI 1.51-3.63), having another source of income than salary (OR 1.58, 95% CI 1.02-2.45) and heroin use (OR 0.23, 95% CI 0.09-0.61). Another French study reported that 36% of buprenorphine-treated OST patients (n=142) injected buprenorphine during the previous month which was a considerably higher proportion than methadone patients injecting methadone (less than 1%, $p< 0.01$) (Guichard et al. 2003). Factors associated with injecting among buprenorphine patients were unstable housing (odds ratio OR 4.3, 95% confidence interval CI 1.6-11.5) and high buprenorphine dosage (OR 6.2, 95% CI 2.0-19.7). Roux and colleagues found out that 32% of buprenorphine-treated OST patients (n=111) reported buprenorphine injecting after treatment initiation (Roux et al. 2008a). Patients who reported inadequate buprenorphine dose (OR 2.7, 95% CI 1.1-7.0) or an experience of suicide ideation or suicide attempt (OR 2.6, 95% CI 1.2-5.7) had a significantly increased risk of injecting. In the same study population, 30% of patients reported intranasal use of buprenorphine after the initiation of OST (Roux et al. 2008b). Authors speculated that this behaviour may be a response to dissatisfaction with treatment. Besides France, other countries have also reported buprenorphine abuse among OST patients. In Italy, 23% of OST patients (total n=307) had injected buprenorphine and injecting was more common among those treated with buprenorphine compared to methadone-treated patients (35% vs. 18%, $p<0.001$) (Moratti et al. 2010). Approximately one quarter (27%) of buprenorphine-treated OST patients had ever injected buprenorphine in 2005 (Winstock & Lea 2010). In Australia, current OST was significantly associated with buprenorphine injection among IDUs (OR 10.7, 95% CI 4.5-25.9) (Aitken et al. 2008). Contrary to these results, a recent German study reported that injecting OST medicines (buprenorphine or methadone) was more common among study participants currently in OST compared to users who abused buprenorphine/methadone but were not in OST ($p<0.001$) (Schmidt et al. 2013). Life-time

prevalence of buprenorphine/methadone abuse was 61.8% among OST patients and 70.3% among other study participants. In 2008, among 440 Australian OST patients, 18% reported having ever inhaled (smoked or snorted) buprenorphine (Horyniak et al. 2011). Other studies have also reported intranasal use of buprenorphine (i.e. snorting, inhaling and sniffing) (Roux et al. 2008b, Daniulaityte et al. 2012).

Table 2. Summary of main human studies published in 2004 or later examining the abuse of buprenorphine

Authors (year), country	Study design	Setting	Study period	Data source	Number of subjects	Sample characteristics	Main findings
Aich et al. (2010), Nepal	Cross-sectional survey + one-year follow-up	A de-addiction center in Bhairahawa	January 2003–December 2004	Semi-structured questionnaire	n=76 (males)	Clients with opioid abuse/ dependence (both IDUs and non-IDUs)	A history of buprenorphine injecting was reported by 42%. Poly-substance abuse was common (76%). IDUs had more problematic abuse patterns.
Aitken et al. (2008), Australia	Cross-sectional survey	NEP and 'streets' in Melbourne	July 2005-May 2006	Interviewer-administered questionnaire	n=316	Street-recruited current IDUs	For 10% BUP was the drug they most often injected, 32% had injected BUP during the previous 3 months. Needle sharing (mean 4.9 vs. 2.1 times/3 months) and current OST (OR 10.7) were associated with BUP injection.
Alho et al. (2007), Finland	Cross-sectional survey	NEP in Helsinki	April 2005	Semi-structured questionnaire	n=131	NEP clients (IDUs)	Buprenorphine was the most frequently used IV drug (73%). More than 75% used it for self-treatment. The majority (68%) had tried BNX injecting and 80% considered it as a "bad" experience.
Bazazi et al. (2011), the USA	Cross-sectional survey	NEP and community outreach site in Rhode Island	August - November 2009	Self-administered questionnaire	n=100	Adults who self-reported opioid use in the previous 30 days (both IDUs and non-IDUs)	The majority (76%) reported having obtained BNX illicitly. More IDUs reported the use of BNX than non-IDUs. Self-treatment of withdrawal (74%) was the most common reason for BNX abuse.

Table 2 continues

Table 2 continued

Authors (year), country	Study design	Setting	Study period	Data source	Number of subjects	Sample characteristics	Main findings
Bruce et al. (2008), Malaysia	Cross-sectional study	NEP in Kuala Lumpur	2006	Qualitative interviews	n=19	IDUs who self-reported buprenorphine use[a]	BUP was injected to avoid withdrawal symptoms. No significant harmful health effects were reported. Co-administration with benzodiazepines was common.
Bruce et al. (2009), Malaysia	Cross-sectional study	NEP in Kuala Lumpur	2007	Structured face-to-face interviews	n=41	Individuals who self-reported buprenorphine injection (IDUs)[a]	During the nationwide transition from BUP to BNX, 44% increased their daily buprenorphine dose, IV related risk behaviour did not change and the development of opioid withdrawal symptoms was common.
Cicero et al. (2007c), the USA	Cross-sectional survey	Substance abuse treatment centres in the USA	2005-2007	Mail survey	n=264 (BUP users) n=799 (PO users)	Clients who abused POs and had a DSM-IV diagnosis for opioid abuse	The proportion of clients who abused BUP varied between 20-35% of all PO users in 2005-2007. The abuse of BUP as a primary drug was rare (<3%).
Daniulaityte et al. (2012), the USA	Cross-sectional survey + qualitative interview	Community sample of PO users from Ohio	2009-2010	Qualitative interviews	n=396	Young adults (18-23 years old) who abused POs[b]	White ethnicity, intranasal inhalation of POs, symptoms of opioid dependence, and a greater number of POs used in lifetime were predictors of illicit buprenorphine use.

Table 2 continues

Table 2 continued

Authors (year), country	Study design	Setting	Study period	Data source	Number of subjects	Sample characteristics	Main findings
Degenhardt et al. (2009), Australia	Cross-sectional study + time-series analysis	OST clinics and inner-city drug markets in Australian capital cities	2003-2007	Structured interviews and national sales data	n=513 (IDUs), n=399 (OST clients, only in 2007)	Current OST clients and regular IDUs involved in central inner-city drug markets	Last 6 months injecting of BUP was reported by 23% of IDUs and 30% of OST clients; BNX injecting was reported by 9% of IDUs and 10% of OST clients. The strongest predictor of OST medicine injection was IV use of other POs.
Hakansson et al. (2007), Sweden	Cross-sectional survey	NEP in Malmo	October-December 2004	Interviewer-administered questionnaire	n=350	All NEP clients who lived in Malmo (IDUs)	In the previous year BUP abuse was reported by 89% of heroin users and 24% of amphetamine users. In total, 43% injected BUP. Illicit acquisition was the most commonly mentioned source and self-medication the most common reason for BUP use.
Horyniak et al. (2011), Australia	Cross-sectional survey	OST clinics and community pharmacies in Australia	March – June 2008	Interviewer-administered questionnaire	n=440	Buprenorphine and methadone treated OST clients	Life-time intranasal use of buprenorphine was reported by 18%. Factors associated with intranasal use of buprenorphine were being aged 35 or younger, having ever been in prison and having ever injected buprenorphine.
Jenkinson et al. (2005), Australia	Cross-sectional survey	NEP in Melbourne	June - August 2002	Structured questionnaire	n=156	A convenience sample of regular IDUs	Life-time injecting of BUP was reported by 37% and recent injecting by 33%. Recent BUP injection was associated with the IV use of other drugs, OST, injection-related health problems and crime.

Table 2 continues

Table 2 continued

Authors (year), country	Study design	Setting	Study period	Data source	Number of subjects	Sample characteristics	Main findings
Larance et al. (2011b), Australia	Several cross-sectional studies	Australian post-marketing studies	2004-2009	IDU and OST client interviews, sales data, prescriber survey	n=881-943 (IDUs), n=440 (OST clients), n=291 (prescribers)	Regular IDUs, current OST clients, authorized OST prescribers	IDUs injected BNX less commonly than BUP. Among OST clients, 28% injected recently BUP and 13% BNX. Street price for both products was similar. Diversion was reported by 28% of OST clients.
Lofwall & Havens, (2012), the USA	Prospective nested cohort study	Appalachian Kentucky county	Not mentioned	Interviewer-administered questionnaire	n=503	Past 30 day non-medical drug users[b]	Failing to access OST predicted the use of diverted buprenorphine (OR 7.3). Daily buprenorphine use was reported by 9.6% and buprenorphine use to get 'high' by 70% of users.
Moratti et al. (2010), Italy	Cross-sectional survey	Addiction treatment centre in Udine	March 2009	Self-administered questionnaire	n=307	Buprenorphine or methadone-treated OST clients	BUP injection was reported by 23% of clients and it was more common among BUP compared to methadone clients ($p<0.001$) and in younger clients. The most common reason for IV-use was self-treatment (51%).
Nordmann et al. (2012), France	Cross-sectional study + time-series analysis	Specialised substance abuse treatment centres in France	2006-2008	Self-administered questionnaire	n=1,311 (in 2006), n=1,688 (in 2007), n=1,696 (in 2008)	Clients who used buprenorphine and were included in the annual OPPIDUM survey[c]	During the study period, the mean age ($p=0.007$) and employment levels increased ($p<0.0005$), the daily buprenorphine dose ($p=0.02$) and the proportion of IV users ($p=0.002$) decreased. Abuse of generic buprenorphine increased in 2006-2008.

Table 2 continues

Table 2 continued

Authors (year), country	Study design	Setting	Study period	Data source	Number of subjects	Sample characteristics	Main findings
Otiashvili et al. (2010), Georgia	Cross-sectional survey	NEPs in Georgia	August-September 2007	Self-administered questionnaire	n=381	IDUs who used NEP services	Both lifetime (96%) and last-month (75%) BUP injecting was common. BUP was used for self-treatment of withdrawal symptoms by 48%. One-fifth of younger users started IV-use with BUP.
Roux et al. (2008a), France	Cross-sectional study with six-month follow-up	GP offices in France	2004	Structured phone interview	n=111	Buprenorphine-treated OST clients	32% of clients had injected buprenorphine during the OST. Injecting was associated with inadequate buprenorphine dose (OR 2.7) and experience of suicide ideation/ attempt (OR 2.6).
Schuman-Olivier et al. (2010), the USA	Cross-sectional study + longitudinal cohort	Outpatient OST clinic in New England	2009	Different questionnaires Beck Depression Scale, urine screens	n=78 (cross-sectional study), n=42 (follow-up)	Treatment seeking (new intakes) and existing OST clients	Buprenorphine was used by 61% of treatment seeking clients and 32% OST clients. Most study participants (92%) used it to reduce cravings.
Simojoki & Alho, (2013), Finland	Annual cross-sectional surveys	NEPs (n=10) in the Helsinki area	2005-2008, 2010	Self-administered questionnaire	n=1,507	NEP clients (IDUs)	Buprenorphine was the most commonly used IV drug in all surveys (68-78% of clients). In 2010, 44% of clients reported that they started injecting with buprenorphine. The street price for BNX was 50% lower than for BUP.
Vicknasingam et al. (2010), Malaysia	Two-wave survey + focus group interviews	Three Malaysian cities (Kuala Lumpur, Penang, Johor Bahru)	2006-2007	Structured interviews (+ qualitative interview in focus groups)	n=276 (1st wave), n=204 (2nd wave)	Current/lifetime BUP/BNX IDUs	Concurrent heroin/ benzodiazepine abuse was common. BNX was less desirable than BUP but naloxone did not prevent abuse.

Table 2 continues

Table 2 continued

Authors (year), country	Study design	Setting	Study period	Data source	Number of subjects	Sample characteristics	Main findings
Winslow et al. (2006), Singapore	Cross-sectional survey	Inpatient and outpatient substance abuse treatment clinics in Singapore	February 2005 - January 2006	Interviewer-administered questionnaire	n=120	Clients who abused BUP and met the DSM-IV criteria for opiate dependence	Clients were mainly males (90%), 53% were employed, and BUP was the first IV drug for 53%. Poly-substance abuse was reported by 82%, and 61% obtained BUP from GPs.
Winstock et al. (2008), Australia	Cross-sectional survey	Community pharmacies providing OST in Australia	2005	Self-administered questionnaire	n=508	Buprenorphine and methadone-treated OST clients attending supervised dosing in community pharmacies	Of buprenorphine clients, 24% had diverted their medication during the previous 12 months compared to 2% of methadone clients. Recent injecting was reported by 9% of buprenorphine and 17% of methadone clients.
Winstock & Lea, (2010), Australia	Cross-sectional survey	Public OST clinics in Australia	2005	Interviewer-administered questionnaire	n=448	Buprenorphine and methadone-treated OST clients who received supervised dosing	Life-time injecting of OST medicine was reported by 27% of buprenorphine and 66% of methadone clients. Last 12-month diversion was reported by 15% of buprenorphine and 4% of methadone clients. Methadone street availability was considered better than buprenorphine.

BUP: single-ingredient buprenorphine, BNX: buprenorphine-naloxone combination product, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th version, GP: general practitioner, IDU: injecting drug user, IV: intravenous, NEP: needle exchange program, OR: odds ratio, OST: opioid substitution treatment, PO: prescription opioid, the USA: United States of America

Studies were not considered for inclusion if they were published prior 2004, if they were not published in English, if the main focus of article was not on buprenorphine abuse, and if study design was case report/series, systematic review or time series (trend) analysis (no individual-level data included). If the same data were reported in separate articles the more extensive/ recent one was included.

[a] Modified snowball recruitment strategy was used for recruitment.

[b] Respondent driven sampling was used for recruitment.

[c] Cross-sectional, nationwide, multi-centre survey investigating psychoactive drug consumption in patients entering specialised care centres dedicated to drug dependence.

2.2.3.2 Finnish studies

Until the 1990s, drug abuse was generally small-scale in Finland (Hakkarainen & Tigerstedt 2005). The availability and abuse of drugs, including cannabis, stimulants and heroin, started increasing from the early 1990s. The number of 'problem drug users' in Finland was estimated to be 11,500-16,400 in 1998 (Partanen et al. 2000). 'Problem drug users' refer to amphetamine and opioid users who have experienced social and/or health harms due to their drug abuse and, therefore, have been in contact with some authorities. In 2005, the number had increased to 14,500-19,000 persons, of whom about 80% were estimated to be amphetamine users and the remainder used opioids (Partanen et al. 2007). About half (50-60%) of problem drug users lived in Southern Finland and more than half of them in the Helsinki metropolitan area.

The first reports of buprenorphine abuse in Finland date back to the late 1990s (Partanen et al. 2004). Partanen and colleagues interviewed 494 NEP clients in the three largest cities of Finland between 2000 and 2002 (Partanen et al. 2004). Fifty-nine percent had injected buprenorphine in the previous month and 78% reported life-time injecting. Thirty-three percent of respondents injected buprenorphine on a daily basis and daily/extensive abuse was more common among young users (less than 25 years old). About one-third had injected both buprenorphine and amphetamine, and one in seven had injected buprenorphine, amphetamine and heroin concurrently in the previous month. Some respondents (6%) had started injecting drugs with buprenorphine. In the early 2000s, buprenorphine-trafficking from France was relatively common among Finnish drug users (Tacke 2002). After the Schengen regulations, this kind of 'medication tourism' has been less popular (Varjonen et al. 2012). Currently, it is believed that most illicit buprenorphine is smuggled into Finland but there are also leakages from legal OST programs (Skretting & Rosenqvist 2010). In 2005, buprenorphine was the most frequently used IV drug for 73% of IDUs using NEP services (n=131) in the Helsinki area (Alho et al. 2007). Another study examined NEP clients in the Helsinki metropolitan area annually between 2005 and 2010 (excluding 2009) and reported that buprenorphine was the most frequently used IV drug during the study period (68-78% of clients) (Simojoki & Alho 2013). Aalto and colleagues interviewed 30 consecutive clients entering to OST in Kotka between 2004 and 2005 and found that 97% (n=29) used buprenorphine as the primary opioid of abuse (Aalto et al. 2007). All, except two participants, used buprenorphine intravenously. Even though 97% of clients reported life-time use of heroin, 30% (n=9) had started opioid abuse with another opioid than heroin. Buprenorphine abuse was the main reason for treatment seeking in 33% of all clients with substance use disorders in Finland in 2009 (Forsell et al. 2010) and in 35% in 2011 (Varjonen et al. 2012). In 2011, those seeking treatment for buprenorphine abuse were mainly injecting it (86%) and almost half (44%) used buprenorphine on a daily basis (Forsell 2012). Clients seeking treatment for buprenorphine abuse represented 82% of all clients seeking treatment for opioid abuse. In 2009, Tammi and colleagues conducted a structured interview study among 100 drug users from the Helsinki metropolitan area (Tammi et al. 2011). Sixty percent of participants had used buprenorphine in the previous month and 39% reported using BNX. Injecting was the most commonly mentioned route of self-administration (93% and 72%, respectively). Almost 50% of buprenorphine users used it on a daily basis. Illicit drug market was the most commonly mentioned source of both BUP and BNX. Malin and colleagues conducted a qualitative interview study among 12 buprenorphine users (Malin et al. 2006). Even though study participants used buprenorphine mainly intravenously, they considered their abuse as self-medication and thought that buprenorphine enabled their functioning in everyday life. Poly-drug abuse

was common among study participants, especially the abuse of benzodiazepines (BZDs), amphetamine and alcohol. Frequent poly-drug abuse has been highlighted in other Finnish studies as well (Partanen et al. 2004, Tammi et al. 2011, Forsell 2012).

The magnitude of buprenorphine abuse can be indirectly estimated via poisoning data. Buprenorphine was the most frequent cause of fatal poisonings among drug users in Finland in 2007 (25% of all intoxications) (Simonsen et al. 2011). These abuse patterns in Finland were different from other Nordic countries, but buprenorphine intoxications have increased in Sweden and Norway as well. The number of buprenorphine findings in forensic post-mortem investigations has increased from less than 10 cases in 2000 to 156 cases in 2010 (Varjonen et al. 2012). However, the detection of buprenorphine from post-mortem samples does not mean that buprenorphine has necessarily caused the death. In 2010, buprenorphine was the underlying cause of death in 46 cases. Fatal buprenorphine poisonings were usually associated with concurrent use of BZDs and alcohol (82% and 58% of buprenorphine poisonings in Finland from 2000 to 2008, respectively) (Häkkinen et al. 2012).

2.2.4 Abuse of the buprenorphine-naloxone combination product

A combination product of buprenorphine and naloxone in a 4:1 ratio (Suboxone®) was developed to prevent diversion and reduce the abuse potential of buprenorphine (Johnson et al. 2003). Naloxone is an opioid antagonist which has poor sublingual bioavailability and, therefore, the combination product produces only buprenorphine effects when taken sublingually (Mendelson & Jones 2003). However, when injected by an opioid-dependent person naloxone can precipitate withdrawal symptoms and reduce the re-enforcing effects of buprenorphine. The 4:1 ratio of buprenorphine and naloxone has been demonstrated to be better than the 8:1 ratio in reducing abuse and better than the 2:1 ratio in producing shorter-term withdrawal symptoms. Stoller and colleagues reported that IM buprenorphine-naloxone precipitated withdrawal symptoms in heroin-dependent individuals (n=10) (Stoller et al. 2001). Other studies have reported similarly that subcutaneously or intravenously given BNX produced antagonist-like effects in opioid-dependent individuals including both methadone/morphine-maintained individuals and those not in maintenance treatment (Bigelow et al. 1987, Preston et al. 1988, Mendelson et al. 1996, Mendelson et al. 1997a, Fudala et al. 1998). Similar results have been reported in non-dependent opioid users (IM administration) indicating low abuse potential (Weinhold et al. 1992). However, controversial results have also been published. Buprenorphine and buprenorphine-naloxone produced similar opioid agonist-like effects in non-dependent opioid users when taken sublingually (n=7) (Strain et al. 2000) or intramuscularly (n=8) (Duke et al. 2010). In opioid-dependent individuals maintained with buprenorphine (n=9), BUP and BNX produced similar modest agonist-like effects (sublingual and IV administration) (Harris et al. 2000). Comer and Collins demonstrated that IV buprenorphine produced higher positive subjective ratings compared to the combination product in recently detoxified heroin users (n=6), however, both products served as reinforcers and were self-administered by study participants (Comer & Collins 2002). Buprenorphine-maintained heroin users (n=12) self-administered buprenorphine-naloxone intravenously less frequently than buprenorphine or heroin ($p<0.0005$) and reported lower subjective ratings for ‘drug-liking’ and ‘desire to take again’ ($p=0.0001$) (Comer et al. 2010). These studies indicate that the BNX has a lower IV abuse potential than BUP. The reinforcing effect of the combination product seems to depend on an individual’s opioid tolerance. It may be abused by less-frequent opioid users and by detoxified or buprenorphine-maintained opioid users. Regular buprenorphine users can probably use it

without marked withdrawal symptoms and even heroin users are not totally deterred from injecting BNX (Mammen & Bell 2009).

Several studies have examined the abuse potential of BNX under real-life conditions (Alho et al. 2007, Degenhardt et al. 2009, Bruce et al. 2009, Vicknasingam et al. 2010, Larance et al. 2011b, Smirnov & Kemp 2012). In general, they have reported lower abuse potential compared to BUP but the addition of naloxone has not been able to completely prevent IV abuse of buprenorphine. Alho and colleagues reported that 68% of IDUs using NEP services in the Helsinki area in 2005 had tried IV use of BNX and 80% described it as 'a bad experience' (Alho et al. 2007). Respondents were also willing to pay more for an 8 mg BUP tablet compared to an 8 mg BNX tablet ($p < 0.0001$). Similarly, Degenhardt and colleagues found that combination product was injected less frequently and less commonly than BUP among both regular IDUs (9% and 23% during the previous 6 months, respectively) and OST patients (10% and 30% during the previous 6 months, respectively) (Degenhardt et al. 2009). Differences were especially notable when the availability of both products was taken into account. Larance and colleagues examined current OST patients in Australia and found that significantly fewer BNX patients reported recently injecting their medicine compared to BUP patients (13% vs. 28%) (Larance et al. 2011b). Similarly removing supervised doses (i.e. secreting medicine out of the dosing site instead of ingesting) was less common among BNX patients compared to BUP patients (22% vs. 35%). Thirty-eight percent of BNX patients reported 'not liking' the drug effect compared to 18% of BUP patients. These findings are in agreement with the level of injecting among regular IDUs (adjusted for the volume of sales) which indicated a lower level of BNX injecting compared to BUP in 2008-2009. Despite these differences, the street price of BNX and BUP was similar ($35 for an 8 mg tablet in 2008, $28-30 in 2009). Smirnov and Kemp reported consistent results from the Brisbane area in Australia, indicating lower rates of abuse of the combination product compared to BUP and methadone (Smirnov & Kemp 2012). In addition to Australia (Larance et al. 2011b), BNX diversion has been recently reported from the USA as well (Johanson et al. 2012). In the USA, the abuse rate of BNX was slightly higher compared to BUP between 2003 and 2005 (0.16 and 0.08 abuse cases per 1000 prescriptions dispensed, respectively) (Smith et al. 2007). This difference probably reflects the more frequent therapeutic use of BNX than BUP in the USA.

In Malaysia, BNX was introduced in December 2006, and since this time physicians have only been able to prescribe the combination product for the treatment of opioid dependence (Bruce et al. 2009). However, this action did not reduce the IV abuse of buprenorphine or related risk behaviours and resulted in an increase in the mean daily dose of buprenorphine among IDUs (n=41). Nevertheless, the combination product was not as desirable as BUP among buprenorphine IDUs (Vicknasingam et al. 2010). In addition, daily buprenorphine injecting was more common before the introduction of the combination product than after among regular IDUs (daily BUP injecting 63%, daily BNX injecting 34%). In focus group discussions, participants explained that they divided BNX tablets into small portions or combined them with heroin or BZDs in order to minimize naloxone effects and enhance positive effects. Buprenorphine-naloxone may also be used intranasally (Horyniak et al. 2011). Compared to sublingual administration, intranasal BNX had greater bioavailability and a faster onset of effects (Middleton et al. 2011). The bioavailability of naloxone was relatively high, 24-30% after intranasal administration compared to 10% after sublingual administration (Harris et al. 2000), and this may deter the likelihood of intranasal abuse by some users.

2.2.5 Characteristics of buprenorphine users

Basu and colleagues conducted one of the first studies examining the characteristics of buprenorphine users. They described the characteristics of 94 clients seeking treatment for buprenorphine dependence in India between 1987 and 1993 (Basu et al. 2000). All clients were men, on average 26 years old, 45% were married and one-third unemployed. All had used another substance, most commonly alcohol (100%) or heroin/other opioids (75%) before switching to buprenorphine. Polydrug abuse was common as 90% of participants used some other substance concomitantly to buprenorphine. Further studies have now investigated the characteristics of buprenorphine users in Singapore, Malaysia, and the USA. People abusing buprenorphine were mostly males (90-98%) (Winslow et al. 2006, Vicknasingam et al. 2010), 53-76% were employed (Winslow et al. 2006, Cicero et al. 2007c, Vicknasingam et al. 2010, Lofwall & Havens 2012), and 20-25% were married (Winslow et al. 2006, Lofwall & Havens 2012). Homelessness has been reported to be associated with buprenorphine injecting among French IDUs (Blanchon et al. 2003). A French OPPIDUM survey examined the changes in the profile of buprenorphine users (sample included also OST patients) between 2006 and 2008 (Nordmann et al. 2012). The mean age of users had increased ($p=0.007$), the proportion of users with an occupation had increased ($p<0.0005$), and the daily buprenorphine dose ($p=0.02$) as well as the proportion of IV users ($p=0.002$) had decreased. The frequency of daily buprenorphine abuse varies according to the study population (ranging from 9.6% to 100%) (Kumar et al. 2000, Vicknasingam et al. 2010, Lofwall & Havens 2012). The most commonly mentioned sources of buprenorphine have been medical prescribers (57%) (Cicero et al. 2007c), friends (32-81%), and dealers (59%) (Larance et al. 2011b, Lofwall & Havens 2012). In the USA study by Bazazi and colleagues, 76% of participants (n=100) reported obtaining BNX illicitly from the street and that it was easy or very easy to get access to BNX (Bazazi et al. 2011). According to a recent study, availability of illicit buprenorphine from the Internet seems to be relatively poor and prices high (Bachhuber & Cunningham 2013).

Compared to other PO users, buprenorphine users were more commonly white (OR 3.19, $p<0.01$), younger (31 vs. 35 years old, $p<0.01$), more highly educated (OR 1.72, $p<0.01$) and more commonly employed (OR 1.63, $p<0.01$) (Cicero et al. 2007c). Another US study reported similar results among young (18-23 years old) PO users (Daniulaityte et al. 2012). Factors associated with buprenorphine abuse were white ethnicity (OR 19.7, 95% CI 2.5-159.0), intranasal use of POs (OR 3.8, 95% CI 1.5-9.3), symptoms of opioid dependence (OR 3.5, 1.1-10.7), and a greater number of illicit POs used during lifetime (OR 1.4, 95% CI 1.1-1.8). The qualitative interviews with a representative sub-sample of study participants indicated that buprenorphine users were usually more experienced users and they used buprenorphine mainly orally or by intranasal route while injecting was relatively uncommon. Similarly, other studies have reported that the most common routes of administration have been sublingual or per oral (87-100%) (Cicero et al. 2007c, Schuman-Olivier et al. 2010). However, a high frequency of buprenorphine abuse via injecting has been reported in many studies (Jenkinson et al. 2005, Alho et al. 2007, Aitken et al. 2008, Aich et al. 2010), as described in Chapter 2.2.3.1. Syringe/needle sharing was significantly associated with buprenorphine injecting among Australian IDUs (4.9 vs. 2.1 times/previous 3 months) (Aitken et al. 2008). In contrast to these findings, an Indian study reported that buprenorphine users were less likely to share injecting equipment compared to other IV users (Solomon et al 2010). Buprenorphine injecting can cause various complications, such as soft tissue infections, peripheral ischemia of limbs (Loo et al. 2005, Winslow et al. 2006, Ho et al. 2009, Partanen et al. 2009) and even endocarditis (Chong et al. 2009).

Concurrent abuse of BZDs is common among buprenorphine users (46-89% of users) (Basu et al. 2000, Ahmed & Ara 2001, Winslow et al. 2006, Nielsen et al. 2007b, Otiashvili et

al. 2010, Vicknasingam et al. 2010, Lofwall & Havens 2012). Forty-six percent of buprenorphine-treated OST patients (total n=170) used BZDs during the previous month (Lavie et al. 2009). Thirty-one percent met the DSM-IV criteria for BZD abuse or dependence. A US study reported similar findings, showing that 47-56% of patients receiving buprenorphine filled prescriptions for BZDs (Mark et al. 2013). High levels of psychological disorders such as depression and anxiety may explain the BZD use among opioid users (Lintzeris & Nielsen 2010). Opioid users may also use these anxiolytics in order to relieve abuse-related symptoms or to increase the euphoric effects of opioids (Sharma & Mattoo 1999, Bruce et al. 2008, Lintzeris & Nielsen 2010). Concurrent BZD use is alarming because it increases the risk of fatal buprenorphine poisoning (Häkkinen et al. 2012). Buprenorphine users with concurrent BZD abuse have been shown to be more commonly IV users ($p=0.001$), share syringes ($p=0.02$) and be seropositive for hepatitis C ($p=0.04$) (Ng et al. 2007). Schuman-Olivier and colleagues found no differences in OST retention or illicit opioid use between buprenorphine-treated OST patients with or without BZD use (Schuman-Olivier et al. 2013). Patients with BZD prescriptions had more emergency department visits during OST compared to patients without BZD prescriptions ($p<0.001$) regardless of history of BZD abuse. In addition to BZDs, other concurrent substance abuse has been reported among buprenorphine users. Current heroin abuse was common (62-64%) among IDUs using buprenorphine in Malaysia (Vicknasingam et al. 2010). Lofwall and Havens reported that 64-86% of buprenorphine users had used another opioid in the previous 30 days; marijuana use was reported by 64% and cocaine use by 27% (Lofwall & Havens 2012).

Self-treatment has been defined as “any attempt to provide an appropriate therapeutic strategy for oneself in the absence of professional advice or consent” (Schuman-Olivier et al. 2010). Self-treatment of opioid withdrawal symptoms and/or dependence is the most common reason users give for their buprenorphine abuse (48-92% of users) (Alho et al. 2007, Hakansson et al. 2007, Otiashvili et al. 2010, Schuman-Olivier et al. 2010, Moratti et al. 2010, Larance et al. 2011b, Bazazi et al. 2011). The same applies to the abuse of BNX (Vicknasingam et al. 2010, Bazazi et al. 2011). However, other reasons which do not support the self-treatment hypothesis have been reported as well. Among 120 buprenorphine users in Singapore, 33% initiated buprenorphine abuse out of curiosity and 33% switched to buprenorphine injecting to get an extra ‘high’ (Winslow et al. 2006). Using buprenorphine to ‘get high’ or experience pleasure has been reported by 42% of Malaysian IDUs (Vicknasingam et al. 2010), 32% of US IDUs, 69% of non-IDUs (Bazazi et al. 2011), and 70% of US PO users (Lofwall & Havens 2012). The cheaper price of buprenorphine compared to heroin has also been mentioned as a reason for buprenorphine abuse (Ahmed & Ara 2001, Aitken et al. 2008). Otiashvili and colleagues (2010) reported that 27% of young buprenorphine users (10-24 years old) reported buprenorphine as the first drug of getting addicted to. In the study by Winslow et al. (2006), 53% of buprenorphine users had started IV-drug use with buprenorphine. A Finnish study reported that 44% of NEP clients had started IV drug use with buprenorphine in 2010 (Simojoki & Alho 2013). Another explanation for buprenorphine use may be the self-treatment of depression which was reported by 30% of participants (both illicit and licit buprenorphine users) in the study by Schuman-Olivier et al. (2010). There is evidence from small open-label clinical studies and surveys that buprenorphine may alleviate depressive symptoms (Kosten et al. 1990, Schuman-Olivier et al. 2010, McCann 2008). Anti-depressive effects may tentatively be attributable to buprenorphine’s kappa receptor antagonism (Gerra et al. 2006).

2.2.6 Prescription opioid abuse in general

Prescription drug abuse has grown worldwide (Kuehn 2007). In the USA, the abuse of prescription drugs is more prevalent than the abuse of any illicit drug, except cannabis (International Narcotics Control Board 2013). Abuse of POs has become a significant problem in the USA, South Asia, some parts of Europe and to lesser extent in Canada, Australia and New Zealand (Degenhardt et al. 2008). At the same time, the abuse of heroin has decreased (Fischer et al. 2006, Fischer & Rehm 2007, Holmes 2012). The most commonly used prescription or pharmaceutical opioids include buprenorphine, methadone, codeine, morphine, dextropropoxyphene, oxycodone, fentanyl, pethidine (meperidine), hydrocodone, propoxyphene, and hydromorphone (Degenhardt et al. 2008). The populations abusing POs can be very different across countries. In some countries, e.g., India and Australia, POs are abused by IDUs whereas in the USA, PO abuse is relatively common among the general population. The abuse of POs can be highly prevalent in subsamples of the general population, e.g., aboriginal populations in Canada where more than 50% of adults abuse POs (Webster 2013).

In the USA, PO abuse has increased markedly during the last decade and has become a significant public health problem (Compton & Volkow 2006a, Compton & Volkow 2006b, McCarthy 2007, Mendelson et al. 2008, Office of Applied Studies 2010, Fischer et al. 2013b). In 2008, 14% of the general population in the USA self-reported life-time illicit use of POs (Substance Abuse and Mental Health Services Administration 2009). Treatment admissions to substance abuse treatment services due to PO abuse increased from 2% in 2000 to 9% of all admissions in 2010 (Substance Abuse and Mental Health Services Administration 2012). Among 5,663 opioid dependent persons enrolling in OST in the USA, POs were abused by 67% and 38% indicated that a PO was their primary drug of abuse (Rosenblum et al. 2007). Among street drug users in New York City (i.e. drug users recruited in public settings), PO abuse was also common and methadone was the most commonly abused PO (72% of the sample) (Davis & Johnson 2008). In Canada, the number of PO-related admissions to addiction treatment services rose by 60% in 2004-2009 and the prevalence of problematic PO use for the five-year study period was 12.3% (Fischer et al. 2010). In the general population within Canada, the prevalence of past year PO abuse was 15.5% in students and 5.9% in adults (Fischer et al. 2013a). In the UK, there was a growing trend in the number of PO related deaths in 2001-2011 (Giraudon et al. 2013). The abuse and injection of POs has also increased in the South Asia region while the use of heroin has declined (Larance et al. 2011a). India is thought to account for extensive diversion of POs in this area but there is a paucity of empirical data across the South Asia region (Larance et al. 2011a). In India, the abuse of natural opioids, such as opium and poppy husk, has decreased with a concomitant increase in the abuse of POs such as buprenorphine, codeine and dextropropoxyphene between 1978 and 2008 ($p<0.001$) (Basu et al. 2012).

There is a significant correlation between the therapeutic use of POs and the magnitude of their abuse (Cicero et al. 2007b, Unick et al. 2013). It has been suggested that increased availability along with greater social acceptability and a perception that licit drugs are safe contribute to the rise of PO abuse (McCarthy 2007). A relationship between opioid prescribing and opioid overdoses has also been reported (Bohnert et al. 2011). A growing abuse problem has led to several negative consequences. Overdose deaths involving opioid analgesics have increased throughout 1997-2007 in the USA (Paulozzi et al. 2011). Between 1999 and 2002, the number of opioid analgesic poisonings increased by 91% (Paulozzi et al. 2006). Between 1999 and 2009, the PO-related overdose death rate increased almost fourfold and POs accounted for the highest relative increase in death rates (Calcaterra et al. 2013). In New York City, PO related overdose deaths showed an increasing trend from 1990 to 2006 ($p<0.01$) with an almost sevenfold increase in death rate (from 0.39 to 2.7 per 100.000

persons) (Cerda et al. 2013). Hospitalizations for poisonings by POs, sedatives and tranquilizers increased by 65% in the USA from 1999 to 2006 (Coben et al. 2010). Women seem to be especially susceptible to PO abuse (Green et al. 2009, Tkacz et al. 2012) and abuse-related hospitalizations (Coben et al. 2010, Unick et al. 2013). However, contrasting results have also been reported. In the USA general population (n=55,023), women were less likely to abuse POs than men in 2003 (past-year prevalence 4.5% vs. 5.2%, p=0.0098) (Tetrault et al. 2008).

Spiller and colleagues reported four-year trends from different US states and showed that there was a consistent, increasing trend between poverty and unemployment rates and PO abuse rate (Spiller et al. 2009). Various studies have examined the characteristics of PO users (sociodemographics, social and health factors, substance abuse behaviour, treatment-related factors) (Brands et al. 2004, Sigmon 2006, Rosenblum et al. 2007, Moore et al. 2007, Subramaniam & Stitzer 2009, Green et al. 2009, Fischer et al. 2010, Katz et al. 2013). Fischer and colleagues examined PO-related treatment admissions in Ontario, Canada between 2004 and 2009 (n=61,509) and found that approximately 60% of PO users were younger than 34 years old, 29% were married, 27% were employed, about half received income from social assistance or insurance programs and less than half (47%) self-referred to treatment (Fischer et al. 2010). Concurrent substance abuse was common (75%). Similarly, other studies have reported that concurrent substance abuse is common among PO users (Subramaniam & Stitzer 2009, Green et al. 2009). Injecting the primary drug of abuse was relatively uncommon (11-33%) in PO users (Rosenblum et al. 2007, Office of Applied Studies 2010, Cicero et al. 2011b). In the study by Fischer et al. (2010), 24% of PO users had injected drugs in the past year. The most commonly mentioned source of POs has been a dealer (50-86%) (Rosenblum et al. 2007, Cicero et al. 2008, Cicero et al. 2011b). Other commonly mentioned sources have been friends/relatives (68%) and physicians (63%) (Cicero et al. 2008). Reasons for abuse of POs include easy access, legal status, greater social acceptability compared to illicit drugs, high purity and predictable dose and, therefore, increased safety (Cicero et al. 2007a). POs may also be used to self-treat pain or dependence, to seek euphoria or to substitute for illicit substances when their availability is poor (Degenhardt et al. 2008). The high prevalence of psychiatric disorders among PO users has been documented in many studies (Cicero et al. 2008, Wu et al. 2010, Wu et al. 2011a, Fischer et al. 2012). In the general population reporting PO abuse, a pooled prevalence of any mental health symptoms was 32% (95% CI 24-40) (Fischer et al. 2012). The lifetime prevalence of any DSM-IV mood disorder or personality disorder was 48% and 40%, respectively (Wu et al. 2011a). Both comorbid mental and physical disorders can increase the risk of PO abuse and dependence (Katz et al. 2013).

Several studies have compared the characteristics of heroin and PO users (Sigmon 2006, Rosenblum et al. 2007, Moore et al. 2007, Fischer et al. 2008, Nielsen et al. 2011, Wu et al. 2011a, Wu et al. 2011b, Tkacz et al. 2012). Compared to heroin users, PO users have been reported to be younger (Sigmon 2006, Moore et al. 2007, Rosenblum et al. 2007, Fischer et al. 2008, Wu et al. 2011b), more commonly white (Sigmon 2006, Moore et al. 2007, Rosenblum et al. 2007, Fischer et al. 2008, Tkacz et al. 2012), and more commonly have pain problems and less experience with substance abuse treatment (Sigmon 2006, Moore et al. 2007, Rosenblum et al. 2007). Daily use has been reported to be more common among heroin users (71%) compared to PO users (61%) (Office of Applied Studies 2010). Heroin users were more likely to report lifetime/recent IV drug use (range 61–92%) compared to PO users (range 0–67%) (Brands et al. 2004, Sigmon 2006, Rosenblum et al. 2007, Fischer et al. 2008, Office of Applied Studies 2010). Tkacz and colleagues reported that PO users were more likely to be married (34% vs. 16%) and had more years of education (13.1 vs. 12.3 years) compared to street users of heroin (current or life-time) (Tkacz et al. 2012). PO users

have also been reported to earn more income, have fewer years of opioid use, and be less likely to have Hepatitis C antibodies ($p<0.05$) (Moore et al. 2007). PO users had improved treatment response in terms of retention (21.0 vs. 14.2 weeks), opioid-negative urine samples (56.3% vs. 39.8%) and completing the treatment (59% vs. 30%) compared to heroin users. Certain socio-demographic and clinical characteristics may be associated with a successful treatment outcome among PO users (Dreifuss et al. 2013). Dreifuss and colleagues examined PO dependent patients treated with BNX (n=360) and reported that age (OR 1.3, 95% CI 1.0-1.6), lifetime major depression (OR 1.8, 95% CI 1.2-2.9), route of use other than oral or sublingual (OR 0.5, 95% CI 0.3-1.0), and prior opioid dependence treatment contacts (OR 0.6, 95% CI 0.4-1.0) were significantly associated with successful treatment outcome (Dreifuss et al. 2013).

However, among PO users there are distinct groups differing from each other in key variables such as age, gender, ethnicity, education, concurrent substance abuse, duration of abuse, familial substance abuse, psychiatric disorders, treatment history, and in risk for adverse events (Martins et al. 2009, Green et al. 2011, Wu et al. 2010). An example of distinct user groups was reported in an Australian study which compared the characteristics of heroin and PO users (Nielsen et al. 2011). Clients seeking treatment for heroin or PO abuse were relatively similar in demographics as well as health and injecting-related factors. Nevertheless, there was a distinct group of PO users who did not inject, initiated opioid use as a treatment for pain and had poor physical and mental health status.

2.3 THE USE OF BUPRENORPHINE IN OPIOID SUBSTITUTION TREATMENT

2.3.1 Definition of opioid substitution treatment

According to the WHO, OST 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” (World Health Organization 2009). In general, the aims are to reduce the illicit use of opioids and mortality and morbidity related to it, reduce criminal behaviour, reduce injecting and associated risk behaviour, improve physical and psychological health and social functioning, and enable employment and/or education and, hence, reintegration into the society (World Health Organization 2004, World Health Organization 2009). Aiming to achieve a drug-free state is the ultimate goal of OST but it is not feasible for everyone (World Health Organization 2004). Therefore, it is not considered as one of the primary goals of OST. Opioid agonists methadone and buprenorphine are the most commonly used medicines in OST (World Health Organization 2009). Dole and Nyswander demonstrated the use of methadone in the treatment of heroin dependence in the 1960s (Dole & Nyswander 1965). They concluded that methadone was able to reduce narcotic hunger and block the euphoric effects of heroin leading to marked improvements in patients’ functioning and social abilities. According to a review of the history of buprenorphine development, buprenorphine was developed in 1966 and its potential in the treatment of opioid dependence was discovered soon after (Campbell & Lovell 2012). However, the use of buprenorphine as an OST medicine started officially in the 1990s.

Gerra and colleagues pointed out that methadone and buprenorphine should not be considered as substitutes for the euphoric effects of heroin but instead medicines which can control addictive behaviour in individuals with opioid dependence (Gerra et al. 2009). Authors speculated that the term ‘substitution’ oversimplifies their actions and contributes to the misunderstanding of this treatment approach. The WHO utilizes the term ‘maintenance treatment’ when referring to the treatment of drug dependence by a

substitute drug whose action is based on cross-dependence or cross-tolerance (World Health Organization 2012). In Finland, opioid agonist treatment was originally divided into 'substitution treatment' which aimed at rehabilitation and abstinence and 'maintenance treatment' which aimed mostly towards harm reduction (Hermanson 2008). These categories were removed when the new Decree of the Ministry of Social Affairs and Health on the detoxification and substitution treatment of opioid addicts with certain medicinal products (33/2008) came into effect in February 2008. Decree 33/2008 defines substitution treatment as: "treatment of an opioid addict by using medicinal products containing buprenorphine or methadone in which the objective is either, rehabilitation and a lifestyle free of illegal drugs, or harm reduction and improved quality of life of the patient" (Ministry of Social Affairs and Health 2008). As this is currently the official definition used in Finland, this thesis uses this definition and the term 'opioid substitution treatment' when referring to this treatment.

2.3.2 Efficacy and safety of buprenorphine

2.3.2.1 Single-ingredient buprenorphine

It was suggested as early as in the 1970s that buprenorphine may be a potential drug in the treatment of opioid dependence due to its long duration of action, low potential for producing physical dependence and low toxicity (Jasinski et al. 1978). It has been shown that buprenorphine can suppress the self-administration of other opioid agonists and block their effects (Martin et al. 1976, Jasinski et al. 1978, Bickel et al. 1988, Mello et al. 1982). Currently it is known that buprenorphine can produce dependence as well (Eissenberg et al. 1996) but most early research into the potential use of buprenorphine in OST programs is still valid.

The majority of prominent studies examining the effects of buprenorphine in the treatment of opioid dependence were published in the 1990s (Johnson et al. 1989, Fudala et al. 1990, Lange et al. 1990, Johnson et al. 1992, Johnson et al. 1995b, Ling et al. 1998, Johnson et al. 2000). They led to the conclusion that buprenorphine is a safe and effective medicine in the treatment of opioid dependence. Johnson and colleagues reported that buprenorphine-treated patients were more likely to remain on their initial dose and less likely to request dose changes compared to placebo (Johnson et al. 1995b). Ling and colleagues conducted a multicentre randomized clinical trial evaluating the safety and efficacy of sublingual buprenorphine (1-16 mg/day) in the treatment of heroin dependence (Ling et al. 1998). The authors concluded that buprenorphine was effective in retaining patients in treatment, decreasing the number of opioid-positive urine samples and reducing heroin craving as well as ratings for the severity of drug problems when given in an adequate dose (8 mg statistically more efficient than 1 mg/day). Buprenorphine treatment has also been shown to improve patients' clinical status, social adjustment and quality of life (Maremmani et al. 2007). Mattick and colleagues reported that buprenorphine improved patients' self-reported HIV-risk behaviour and physical as well as psychological health and also reduced criminal activity (Mattick et al. 2003). A large multicentre clinical trial comparing buprenorphine (alone and in combination with naloxone) to placebo in the treatment of heroin dependence had to be terminated early because active treatment had markedly better efficacy than placebo in terms of opiate craving, patients' overall status and opioid-negative urine samples (Fudala et al. 2003). Similarly, the study by Schottenfeld and colleagues was terminated earlier than planned because the outcomes of buprenorphine treatment were superior compared to placebo and naltrexone, an opioid antagonist which can be used for the treatment of opioid dependence (Schottenfeld et al. 2008). Most commonly mentioned side-effects related to buprenorphine treatment include sedation,

constipation, decreased libido, headache, withdrawal symptoms, pain, and insomnia (Mello et al. 1982, Lange et al. 1990, Fudala et al. 2003). Ling and colleagues reported that most adverse effects seen in their clinical trial were typical side effects of opioid treatment (Ling et al. 1998).

Kakko and colleagues compared OST with buprenorphine to placebo in heroin users (n=40) and reported 1-year treatment retention in the buprenorphine group to be 75% compared with 0% in the placebo group (p=0.0001) (Kakko et al. 2003). Other studies have reported generally lower retention rates which have varied between 38-62% (Johnson et al. 1992, Strain et al. 1994, Ling et al. 1998, Fischer et al. 1999, Johnson et al. 2000, Pani et al. 2000, Petitjean et al. 2001, Ahmadi 2002, Mattick et al. 2003, Cozzolino et al. 2006, Soyka et al. 2008, Leonardi et al. 2008, Haddad et al. 2013). Various factors, such as buprenorphine dose, length of study, inclusion criteria and other treatment given (e.g. psychosocial support) may have a substantial impact on retention. Maremmani and colleagues reported 12-month treatment retention of 78% but they did not include the first 3 months of treatment which can be a critical period for retention (Maremmani et al. 2007). A Finnish study (n=30) examined the effectiveness of buprenorphine-based OST in buprenorphine users and reported a 3-month retention of 100% (Aalto et al. 2011). At 12 months the retention rate was 83%. Contrary to previous studies, study participants were dependent on buprenorphine, not heroin as in most other studies. Studies comparing the effects of different buprenorphine doses have usually indicated that larger doses produce better treatment outcomes in heroin-dependent patients (Ling et al. 1998, Ahmadi 2002, Ahmadi 2003).

Compared to methadone, studies have shown that buprenorphine is equally effective (Strain et al. 1994, Strain et al. 1996, Johnson et al. 2000, Ahmadi 2003, Vigezzi et al. 2006, Maremmani et al. 2007, Soyka et al. 2008) or that methadone is more effective than buprenorphine in retaining patients in treatment (Kosten et al. 1993, Ling et al. 1996, Fischer et al. 1999, Pani et al. 2000, Petitjean et al. 2001, Mattick et al. 2003). Outcome measures other than retention (e.g., opioid-positive urine samples, self-reported drug abuse, heroin craving) have usually shown similar results between buprenorphine and methadone treated patients (Pani et al. 2000, Petitjean et al. 2001, Mattick et al. 2003). Fischer and colleagues reported lower retention ($p<0.05$) but otherwise better treatment outcomes (lower level of illicit opioid use, $p=0.04$) in the buprenorphine group compared to the methadone group (Fischer et al. 1999). It has been speculated that high attrition rates (44-53%) in buprenorphine-treated patients may reflect inadequate dosing (Pani et al. 2000, Petitjean et al. 2001). Lower induction doses of buprenorphine have been associated with higher relapse rates (51% with 2 mg of buprenorphine vs. 21% with 10 mg dose) (Leonardi et al. 2008). Soyka and colleagues conducted a randomised clinical study with a flexible dosing regimen and found no differences in outcomes between methadone and buprenorphine-treated patients (retention rates 55% vs. 48%, $p=0.42$) (Soyka et al. 2008). Other possible reasons for lower retention in buprenorphine treatment include too slow induction and patients being able to terminate buprenorphine treatment more easily on their own compared to methadone due to milder withdrawal symptoms (Jones 2004). Lower retention in buprenorphine treatment may be explained by differences in the effects of buprenorphine and methadone, i.e., buprenorphine is a less reinforcing drug and supresses withdrawal symptoms less completely compared to methadone (Bell 2012). A systematic literature review examined the effects of buprenorphine in comparison to placebo and methadone and concluded that buprenorphine was significantly more effective in retaining patients in treatment compared to placebo but less effective than methadone when administered at adequate doses (Mattick et al. 2008). Nevertheless, buprenorphine may be more suitable in some settings due to its safety and the possibility of alternate-day

administration (see 2.3.3). Buprenorphine is not very likely to cause overdoses due to the ceiling effect on respiratory depression (Dahan 2006).

2.3.2.2 Buprenorphine-naloxone combination product

The buprenorphine-naloxone combination product has been reported to be equally effective and safe compared to BUP (Harris et al. 2000, Fudala et al. 2003). A large, multicentre study found that both BUP and BNX decreased opioid craving (Fudala et al. 2003). The rates of adverse effects were similar and no differences in the proportions of opioid-negative urine samples were detected between BNX and BUP-treated patients (18% vs. 21%). Buprenorphine-naloxone reduced the reinforcing and subjective effects of heroin (BNX doses 8/2 and 32/8 mg per day) and was well-tolerated among heroin-dependent individuals (n=7) (Comer et al. 2005). A US study reported 2-year retention of 38% in office-based BNX treatment (Fiellin et al. 2008). No serious adverse events directly related to BNX were reported during the follow-up period over 2-5 years. A nationwide prospective surveillance study in Germany reported high effectiveness and safety of BNX in routine care (Apelt et al. 2013). The 12-month treatment retention was 57% and rates for serious and non-serious adverse events were low (1.2% and 17.5%, respectively). Other studies have similarly shown that BNX is a suitable treatment option in the primary health care setting (Finch et al. 2007, Mintzer et al. 2007). Naloxone can produce dose-dependent sympathetic activation with increases in heart rate, blood pressure and respiratory rate, which may be unpleasant but are not dangerous (Mendelson & Jones 2003). Because buprenorphine's half-life is markedly longer than naloxone's half-life (32 h vs. 1 h) and naloxone is poorly absorbed when taken sublingually, buprenorphine effects dominate when the combination product is taken sublingually (Chiang & Hawks 2003). However, there is evidence that sublingual naloxone may precipitate withdrawal in heroin users and methadone-maintained OST patients, at least in large doses (up to 8 mg, which is equivalent to 32 mg of BNX) (Preston et al. 1990).

Compared to methadone, BNX produced similar treatment outcomes in terms of opioid-negative urine samples, retention, concurrent drug abuse, medication compliance and overall functioning (Kamien et al. 2008). An Italian 1-year follow-up study (n=3,812) reported that retention in methadone vs. buprenorphine-naloxone treatment was similar ($p=0.369$) but a higher percentage of BNX-treated patients was married, had higher educational levels and lower rates of illicit drug abuse ($p<0.001$) (Curcio et al. 2011). However, selection bias may have affected the results because it is possible that more stable patients were selected to receive BNX. Buprenorphine-naloxone and methadone were highly and equally effective in retaining patients in the treatment (retention rate 62-68%) and reducing heroin abuse in a naturalistic study conducted in the UK (McKeganey et al. 2013). Methadone and stepped treatment using both BNX and methadone were equally efficient in a 6-month follow-up study (overall retention 78%) but only 46% of patients in the stepped care group remained on BNX while others were switched to methadone (Kakko et al. 2007). In stepped treatment patients started taking BNX with flexible doses but they could be transferred to methadone if necessary. BNX has been linked to better cognitive functioning compared to methadone, at least in the early phase of OST (Rapeli et al. 2007). However, it should be taken into consideration that in the study by Rapeli and colleagues, most study participants reported buprenorphine as their primary opioid of abuse whereas in other studies participants have been mainly heroin users, if not otherwise stated.

Originally, OST was developed for the treatment of heroin dependence but more recently its efficacy in the treatment of PO dependence, including buprenorphine, has been demonstrated (Ahmadi et al. 2003, Moore et al. 2007, Aalto et al. 2011). Findings from a large randomized controlled trial suggest BNX treatment can assist PO users to reduce their

opioid abuse (Weiss et al. 2011). However, when tapering off buprenorphine-naloxone, the rate of unsuccessful outcomes was shown to be high (exceeding 90%).

Switch from BUP to BNX has been shown to be well-tolerated and adverse effects, including withdrawal symptoms, were mild and relatively rare in the observational study conducted in Italy (n=77) (Magnelli et al. 2010). The average buprenorphine dose increased from 7.3 mg/day to 12.7 mg/day. Other studies have reported similarly positive outcomes related to the switch from BUP to the combination product (Bell et al. 2004, Stimolo et al. 2010, Montesano et al. 2010, Daulouede et al. 2010). However, dose adjustments may be needed and both dose increases (Bell et al. 2004, Magnelli et al. 2010) as well as reductions (Simojoki et al. 2008) have been reported. Amato reported that the switch was associated with no problems in 50% of patients and that most patients (78%) did not experience any withdrawal symptoms related to the combination product (Amato 2010). In the study by Simojoki and colleagues, 50% of patients experienced adverse effects during the 4-week follow-up period after the medication switch (Simojoki et al. 2008). However, during the 4-month follow-up, only 27% reported adverse effects. A French trial examined medication preferences among OST patients and reported that 54% of patients who switched to BNX from BUP preferred BNX and 71% wished to continue treatment with it (Daulouede et al. 2010). Other studies have reported similarly high patient satisfaction with BNX treatment in the office-based setting (Barry et al. 2007, Fiellin et al. 2008).

2.3.3 Clinical use of buprenorphine and OST practices

OST practices and delivery models vary from country to country due to different social, political and professional determinants (Farrell et al. 2000, Fischer et al. 2002, Carrieri et al. 2006, Skretting & Rosenqvist 2010). In some jurisdictions, GPs and community pharmacies have major roles whereas others rely mainly on specialized substance abuse treatment units. In some countries, such as Russia, opioid agonist-based treatments are prohibited (Carrieri et al. 2006). OST practices may change over time, e.g., in Nordic countries official OST guidelines have become less strict in the recent years (Skretting & Rosenqvist 2010). The WHO has given minimal as well as best practice recommendations for the provision of OST in different settings (World Health Organization 2009). Due to its complex nature, opioid dependence usually requires long-term treatment (World Health Organization 2004). Certain single treatment modalities are not effective for everyone and therefore, different treatment options should be available. The efficacy and safety of buprenorphine (both BUP and BNX) have been demonstrated and it has been shown to have great relevance for clinical practice (Soyka et al. 2011). Buprenorphine established its position as OST medicine rapidly since its launch to the market in the late 1990s and early 2000s (Jenkinson et al. 2005, de Wet et al. 2005). For example, in England the number of buprenorphine prescriptions increased from 13% in 2001 to 23% of the total number of opioid prescriptions for OST or opioid withdrawal treatment in 2003 (de Wet et al. 2005). In the USA, the number of buprenorphine prescriptions increased from 48,000 prescriptions in 2003 (the year when buprenorphine products were launched to the USA market) to 1,911,000 prescriptions in 2007 (Mark et al. 2009). In 2005, BUP (Subutex®) had been approved for the treatment of opioid dependence in 44 countries worldwide (Carrieri et al. 2006). In March 2005, buprenorphine was added to the WHO list of essential medicines (14th Model List of Essential Medicines LEM) (Herget 2005). Nevertheless, the majority of OST patients in Europe received methadone (60%), although variation between countries exists (range between 19.3% of OST patients in Austria and 75.4% of OST patients in the UK) (Dale-Perera et al. 2012).

Besides specialised substance abuse treatment units, buprenorphine is efficient and safe in primary health care and office-based settings (Fiellin et al. 2002, Lintzeris et al. 2004,

Carrieri et al. 2006, Fatseas & Auriacombe 2007, Fiellin et al. 2008, Gunderson & Fiellin 2008, Hersh et al. 2011, Kraus et al. 2011, Haddad et al. 2013). This enables new types of clients to enrol into treatment and improves the flexibility of treatment. However, office-based treatment is not suitable for all opioid users (Bell 2012). Opioid users with complex problems require more structured treatment and possibly a more reinforcing medicine (methadone). The longest experience of office-based buprenorphine treatment comes from France where all GPs have been able to prescribe buprenorphine without any special education since 1996 (Fatseas & Auriacombe 2007). In France, the introduction of buprenorphine led to an increase in the number of OST patients (from 14 to 69%) and a decrease in the number of IDUs (from 55 to 22%) between 1995 and 1997 (Thirion et al. 2001). At the same time, the number of overdose deaths declined by 79% (Auriacombe et al. 2001). A review summarizing the French experience with office-based buprenorphine treatment since its introduction until the early 2000s concluded that there are more societal and individual-level benefits than problems related to it (Auriacombe et al. 2004). In Sweden, the drug policy was liberalized in 2005 (Romelsjö et al. 2010). As a consequence, the sales of OST medicines and number of patients increased more than three-fold and opioid-related mortality and the number of hospitalizations reduced 20-30% between 2000 and 2006. However, buprenorphine/methadone related mortality increased from 9 cases in 1998 to 49 cases in 2006.

In Finland, OST programs with methadone and BUP were officially started in 1997 (Hakkarainen & Tigerstedt 2005). The buprenorphine-naloxone combination product was first marketed in 2006. Since December 2007, it has been the only licit high-dose buprenorphine product since BUP was withdrawn from the market due to widespread abuse. In 2010, 60% of Finnish OST patients (estimated n=2000) were treated with BNX and the rest were in methadone treatment (Varjonen et al. 2012). Single-ingredient buprenorphine is used only for OST in pregnant women by special permission from the Finnish Medicines Agency. OST services are regulated by the Decree of the Ministry of Social Affairs and Health on the detoxification and substitution treatment of opioid addicts with certain medicinal products (33/2008) (Ministry of Social Affairs and Health 2008). OST can be started in a person with opioid dependence (F11.2x according to ICD-10), if detoxification treatment has not been successful. Treatment begins with the assessment of the treatment needs which can be done in either an outpatient or inpatient setting (Varjonen et al. 2012). According to the Decree 33/2008, treatment can be initiated and provided at a municipal health care centre, substance abuse treatment unit or prison health care unit. Usually more demanding patients are treated in specialised health care and others in the primary health care units (Varjonen et al. 2012). Often assessments and treatment initiations are done in specialised health care units even though Decree 33/2008 recommends that only the 'more demanding cases' should be treated there. Because OST is long-lasting, treatment should be provided close to patient's place of residence. OST should be based on an individual treatment plan which specifies the pharmacotherapy, other medical and psychosocial treatment as well as rehabilitation and treatment follow-up (Ministry of Social Affairs and Health 2008). Unobserved doses to a maximum of 8 daily doses (for special reasons up to 15 daily doses) can be given to patients showing good treatment compliance.

Buprenorphine-based OST is started with an individually-tailored dose (most commonly 4 mg) which depends on the level of tolerance, the half-life and amount of opioids used and the time since the most recent use (Johnson et al. 2003, World Health Organization 2009). It has been recommended that patients should be in moderate withdrawal state before the first buprenorphine dose is given (Kraus et al. 2011). The stabilization phase concentrates on finding the optimal dose. Generally most patients can be stabilized on a dose of 8-24

mg/day which is usually an adequate maintenance dose as well (World Health Organization 2009, Kraus et al. 2011). The dose may need to be increased if illicit opioid abuse continues (World Health Organization 2009). A survey was conducted among French GPs in 2002, and it revealed that untrained GPs were especially prone to prescribing doses of buprenorphine that were commonly ineffective (too low) (Feroni et al. 2005a). Authors highlighted the need for clear guidelines and improved training for GPs. Buprenorphine is also suitable for alternate-day or thrice-weekly dosing with similar retention compared to daily dosing regimen (Johnson et al. 1995a, Schottenfeld et al. 2000, Mattick et al. 2003, Marsch et al. 2005). Less-than-daily dosing has been associated with better compliance and retention in buprenorphine treatment compared to daily dosing (Leonardi et al. 2008). Amass and colleagues demonstrated the acceptability and efficacy of alternate-day dosing of BNX as well (Amass et al. 2000). There is no information about the optimal duration of OST but it can be long-term, even life-long (Kraus et al. 2011). Dose reductions should be done gradually in order to prevent withdrawal and illicit use, and assure retention (Johnson et al. 2003). Possible dose reduction schedules include equal reduction, such as 2 mg, or 50% dose reductions every 4-7 days or slower. Buprenorphine can also been safely used in the treatment of certain subpopulations such as people with concurrent psychiatric disorders, adolescents, older people, and people with HIV and liver disease although further research is needed (Kraus et al. 2011). For pregnant women, buprenorphine without naloxone is a safe and effective treatment option (Kraus et al. 2011, Jones et al. 2012).

Pharmacological treatment should be combined with psychosocial interventions, such as cognitive and behavioural therapy and contingency management, or at least patients should be offered the possibility to receive psychosocial treatment as well (World Health Organization 2009, Soyka et al. 2011, Kraus et al. 2011). According to Finnish legislation, psychosocial treatment is an essential part of OST (Ministry of Social Affairs and Health 2008). In international studies, the proportion of patients given/willing to receive psychosocial support ranges between 24-100% (Leonardi et al. 2008, Amato 2010, Dale-Perera et al. 2012, Haddad et al. 2013). Psychosocial support can improve the treatment outcomes in terms of less craving and better retention (Leonardi et al. 2008, Haddad et al. 2013). However, no difference in treatment outcomes were detected between standard medical management and standard treatment plus opioid dependence counseling among outpatient PO users treated with BNX (n=653) (Weiss et al. 2011). A systematic Cochrane review reported that extra psychosocial interventions did not offer benefits compared to standard treatment in terms of retention (risk ratio RR 1.03, 95% CI 0.98-1.07), opioid abstinence during the treatment (RR 1.12, 95% CI 0.92-1.37) or any other outcome measures used in the review (Amato et al. 2011). These results may be explained by the fact that standard treatments already offer routinely counseling in addition to pharmacotherapy.

2.3.3.1 Unobserved dosing

Unobserved dosing in relation to OST refers to the daily administration of OST medicines without direct supervision by treatment staff (Bell et al. 2004). It does not mean that patients' treatment is not supervised or monitored otherwise. A pilot study on unsupervised BNX treatment showed that the combination product was well tolerated, 6-month retention was high (88%) and unobserved dosing did not attenuate patients' stability (Bell et al. 2004). However, strict inclusion criteria were applied including at least part-time employment and, therefore, only a small proportion of patients was eligible for the study. According to a large European study which examined OST practices in 10 countries, 41.9% of OST patients were under daily supervision (range 15.0-77.9%) (Dale-Perera et al. 2012). Methadone-treated patients were more commonly supervised daily (48.2%) compared to BUP or BNX-treated patients (42.4% and 22.8%, respectively).

Unobserved dosing can offer substantial advantages compared to observed dosing such as increased accessibility to OST (Bell et al. 2004, Gunderson et al. 2010), positive effect on social and occupational rehabilitation, and less stigma related to OST (Bell et al. 2004, Anstice et al. 2009). Daily visits to treatment centres can be problematic, especially for persons living in rural, remote areas where travel distances to treatment centres are long (Farrell et al. 2000, Webster 2013). Some patients want to isolate themselves from their previous 'drug using life' and, therefore, find it difficult to meet other OST patients or former peers at the addiction clinics (Treloar et al. 2007, Anstice et al. 2009). Studies comparing observed and unobserved dosing have found no differences in treatment-retention or substance abuse (Fiellin et al. 2006, Bell et al. 2007, Moore et al. 2012). Holland and colleagues found out that retention was better among those not supervised (89%) compared to daily supervision (75%) even though all patients collected their medications daily from community pharmacies (Holland et al. 2012). Bell and colleagues conducted a cost-effectiveness analysis in conjunction with their clinical trial (Bell et al. 2007). Authors concluded that as there were no differences in outcomes, simply the cost of treatment matters, and unsupervised treatment was less costly compared to supervised treatment. In the study by Barry and colleagues, patients who received weekly dispensing had a higher mean overall satisfaction score on a 5-point scale compared to those receiving thrice weekly dispensing (mean difference 4.9, p=0.03) (Barry et al. 2007). Other studies have not shown statistically significant differences in treatment satisfaction (Holland et al. 2012, Moore et al. 2012) or quality of life scores (Bell et al. 2007) between unobserved and observed dosing conditions. OST patients valued take-home allowances because of enhanced personal freedom and flexibility, as well as convenience in terms of less travelling and better employment opportunities (Stone & Fletcher 2003, Treloar et al. 2007, Madden et al. 2008). Patients thought that unobserved dosing gave them the sense of being normal and 'trusted' and increased their treatment compliance. In general, OST patients considered the possibility of unobserved dosing as an essential part of OST.

For long, direct observation of OST medication dosing has been the principal feature of OST programs (Farrell et al. 1994, Bell et al. 2007). This was done in order to prevent the abuse (e.g., injecting) or diversion of medicines. In France, the lack of supervision has been associated with more illicit drug use and psychotropic drug use compared to a strict treatment protocol among buprenorphine clients (Barrau et al. 2001). In order to reduce the risk of diversion, the UK national guidelines directed GPs to utilize arrangements for instalment dispensing and supervision of consumption in the late 1990s (Strang et al. 2007). Between 1995 and 2005, the mean number of dispensings per week increased from 3.3 to 4.7, and the proportion of buprenorphine prescriptions dispensed supervised increased from 0% to 26%. Diversion by selling may be tempting for OST patients as a way to get more income. For example, Finnish street buprenorphine users were willing to pay on average €28 (±4) for one 8 mg buprenorphine tablet (Alho et al. 2007). On the other hand, some OST patients do not want to receive take-home allowances presumably due to a fear that medicines could be stolen or that they would be put under pressure to share their medicines with or sell to other users (Stone & Fletcher 2003). Several studies have shown the association between methadone take-home doses and diversion (Darke et al. 1996, Lintzeris et al. 1999, Darke et al. 2002, Ritter & Di Natale 2005, Duffy & Baldwin 2012). Ritter and Di Natale found a clear association between methadone injecting and less strict jurisdictional methadone take-away policies between different Australian states (Ritter & Di Natale 2005). However, authors stated that besides take-away policies, many other things influence injecting, such as drug preference and availability as well as treatment access. In addition, all the above mentioned studies concerned methadone, not buprenorphine. Winstock and colleagues examined the prevalence of self-reported

diversion among OST clients receiving their medicines from community pharmacies and found out recent diversion was more than 10 times higher among buprenorphine clients compared to methadone clients (Winstock et al. 2008). Authors speculated that this may be due to relative ease of diverting a tablet compared to liquid, difficulties in supervising the consumption of a sublingual tablet as well as less strict take-away policies concerning buprenorphine compared to methadone. However, another Australian study reported that entitlement to take-away doses did not predict injecting of BUP (OR 0.9, 95% CI 0.8-1.1) or BNX (OR 1.1, 95% CI 1.0-1.2) among OST patients (Degenhardt et al. 2009).

Bell and colleagues reported that withdrawal of unobserved dosing as a punishment due to violations against treatment guidelines can lead to significant drop-out from treatment (6-month retention 22%) (Bell et al. 2008). French experience reveals that daily supervised dosing for 6 months compared to 2 weeks at the beginning of buprenorphine-based OST may result in better retention (80% vs. 46 %) and lower proportion of opiate-positive urine samples (14% vs. 18%) (Fatseas & Auriacombe 2007). Therefore, the manner in which take-away doses are introduced to patients may have a substantial impact on treatment outcomes. According to the Australasian clinical guidelines, appropriate patient selection, transparent treatment guidelines and clinical monitoring are the key issues for successful unobserved OST dosing (Winstock & Bell 2006). Take-away doses are only suitable for patients in a stable clinical situation which includes social, personal and physical functioning, as well as stability of psychosocial conditions, medicines and substance abuse behaviour. Providing take-away doses to unstable patients is detrimental in terms of patients' treatment outcomes, and it can increase diversion and negative public opinion on OST services. However, relapses are common among drug-dependent individuals and, therefore, in case of instability, supervised dosing should be reintroduced. Involving patients in all treatment-related decisions may reduce challenging clinical situations and improve patients' treatment compliance. Clinical guidelines defining the risk management measures needed for prescribing take-away doses can be used to harmonize treatment practices between different treatment providers (Bell 2010). They may also be efficient in reducing diversion.

In recent years, there has been a trend towards less restrictive treatment policies. In Finland, the decree regulating OST services was amended in February 2008 to become less restrictive in order to improve access to OST, shorten waiting times and enable patients to live as normal as possible (Hermanson 2008). Swedish drug policy was liberalized in 2005 and as a result, the use of take-away doses increased (Romelsjö et al. 2010). In addition, less strict national guidelines resulted in an increase of OST and reductions in opioid-related mortality and inpatient care while retention in treatment was unchanged. The decline in mortality and inpatient care was especially pronounced in Stockholm County which had the least restricted treatment policy. In the USA, the federal opioid treatment program regulations were amended in the beginning of 2013 (Substance Abuse and Mental Health Services Administration & Department of Health and Human Services 2012). This allows programs to dispense buprenorphine more flexibly, since take-home doses of buprenorphine can be dispensed to patients without temporal restrictions on treatment duration. Authorities acknowledged the possibility of additional risk of diversion but concluded that benefits of increased flexibility and access to treatment outweigh possible risks.

2.3.4 Diversion

2.3.4.1 Definition and frequency of diversion

There are various definitions of diversion. Carrieri and colleagues applied a broad definition for buprenorphine diversion involving diversion to the black market, non-adherence to physicians' recommendations about the dose or the concurrent use of other substances, and the use of buprenorphine by injection or snorting (Carrieri et al. 2006). Dasgupta and colleagues defined diversion as "wilful illegal removal of a controlled substance from the distribution chain or storage of the patient for whom it was prescribed, for the purpose of distribution or sale, including acts by the patient" (Dasgupta et al. 2010). Similar definitions have been used in other studies (Inciardi et al. 2007, Degenhardt et al. 2008, Larance et al. 2011b, Larance et al. 2011d). Stockpiling medicines for later use has also been regarded as diversion (Bell 2010). Larance and colleagues reviewed different definitions used for diversion in the scientific literature (Larance et al. 2011c). They concluded that defining diversion as 'not taking medicines as directed' or 'not complying with all OST constraints' is problematic because these definitions would not be exactly the same everywhere due to variations in treatment guidelines. In addition, these definitions do not separate situations where patients are noncompliant voluntarily (e.g., lack of commitment, desire to divert) or due to service constraints. Authors recommended that diversion should be defined as: "unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended" (Larance et al. 2011c). This definition has been used in this thesis.

Diversion can also occur during supervised dosing and it has been defined as "a client removing or attempting to remove a supervised methadone or buprenorphine dose from the dosing site before the dose has been fully absorbed by the client" (Winstock et al. 2009b). Winstock and colleagues examined diversion methods and motivations at OST clinics in Australia and found out that there seemed to be a misunderstanding between clinicians and patients to what constitutes diversion (Winstock et al. 2009a). Authors highlighted the need of consistent definition of diversion of supervised OST medicines and recommended the term 'non-adherence' with dosing instructions to be used when referring to diversion of supervised doses.

Winstock and colleagues examined 71 episodes of diversion during supervised dosing at OST clinics in Sydney, Australia (Winstock et al. 2009a). Removal of buprenorphine from the mouth (n=35) and secretion of buprenorphine in the mouth (n=32) were the most common methods of diversion. In almost half of the episodes (45%), patients denied the diversion. The most commonly mentioned motivations for diversion were stockpiling for later use (n=15) and discarding buprenorphine (n=11). Diversion as a form of 'spit backs' has been reported in another Australian study as well (Aitken et al. 2008). The risk of microbiological contamination is especially high for this kind of diversion. In another Australian study, 18% of buprenorphine-treated OST patients (n=98) reported ever diverting their supervised buprenorphine dose and 15% reported doing it during the previous 12 months (Winstock & Lea 2010). Diversion of supervised doses was more common among buprenorphine patients compared to methadone patients. In an Australian pharmacy survey, 46% of community pharmacies with buprenorphine clients reported incidents of attempted diversion of supervised buprenorphine (Winstock et al. 2009b).

Diversion has always been a part of OST (Bell 2010). Historical overview of OST and diversion indicates that opioid diversion occurs in proportion to the unobserved dosing of opioids and in inverse proportion to the availability of heroin. Diversion is associated with severe adverse consequences including fatal overdoses, increased prevalence of dependence, injection-related harms like infectious diseases and vascular and soft tissue

damage as well as negative public attitude towards OST (Degenhardt et al. 2008). According to a large European study, 24.0% of OST patients reported ever having diverted their OST medicines (range 15.6-39.1% of patients in different countries) (Dale-Perera et al. 2012). In the USA, all survey respondents who were aware of BNX (n=49) diverted it and 61% obtained the drug from an individual with legal prescription for it (Monte et al. 2009). Twenty-eight percent of Australian OST patients (n=440) reported having diverted their medicines during the previous 6 months (Larance et al. 2011b). There were no differences between patients receiving methadone, BUP or BNX. Contrary to these findings, Winstock and colleagues found that buprenorphine patients reported diverting their medicines significantly more often during the previous 12 months compared to methadone patients (23.8% vs. 2.2%) (Winstock et al. 2008). In legislation with buprenorphine by prescription, buprenorphine diversion has been shown to be associated with social vulnerability and prescriptions from multiple GPs (Carrieri et al. 2006).

Prescribers found it difficult to assess abuse and diversion among OST patients (Larance et al. 2011d). About half (54%) were confident in assessing the risk of injection and even less (37%) the risk of diversion. Prescribers perceived that diversion and IV-use were relatively uncommon among buprenorphine patients (2-20% and 5% of patients, respectively). The most commonly mentioned sources of information about diversion were patients' self-report (51%) and pharmacist reports (49%). In the USA, physicians were more sceptical since 46% of physicians believed that BNX is diverted and sold on the street and 53% thought that the source of illegal BNX is OST patients (Johanson et al. 2012).

Doctor-shopping can be regarded as a subtype of diversion and it means that OST patients turn to several prescribers in order to get more buprenorphine than the prescribed dose (Feroni et al. 2005b). This is possible in countries such as France where GPs can prescribe buprenorphine and patients collect their medicines from community pharmacies. A French study revealed that OST patients had on average 3.1 prescribers over the last 12 months in 2001 (Feroni et al. 2005b). However, consultations of several prescribers were mostly successive rather than concomitant. Pradel and colleagues reported that the majority of buprenorphine-treated OST patients (75%) had no overlapping prescriptions from different physicians indicating no doctor-shopping behaviour (Pradel et al. 2009). It has been estimated that about 13% of reimbursed buprenorphine prescriptions were obtained by doctor-shopping in France in 2006 (Pauly et al. 2011). Nevertheless, high-dose buprenorphine was most likely to be obtained through doctor-shopping and the second most likely to be obtained by forged prescriptions compared to other opioid analgesics, BZDs and methadone in France over 2006-2008 (Pauly et al. 2012).

2.3.4.2 Methods to prevent diversion

Besides supervision, various approaches have been suggested and used as ways to reduce opioid diversion (Fudala & Johnson 2006, Katz et al. 2007, Bell 2010). These include both general wide-ranging actions, such as educational programs for physicians, abuse-deterrent formulations, prescription monitoring programs, supply chain interventions, and restrictions on use, as well as patient-orientated approaches, such as careful screening and monitoring of patients, urine drug screens, patient education, and the assessment and treatment of comorbid conditions (Katz et al. 2007). Restrictions on use can refer to tightening of regulatory controls or prescribing guidelines or restricting the use to supervised settings (Fudala & Johnson 2006). Practical, traditional methods include tablet counts, patient diaries and interviews, random drug testing and contracts between patients and physicians (Fishman et al. 2000). According to a US survey, most pharmacies (74%) were willing to conduct buprenorphine pill counts and five pharmacies were already performing pill counts (Lofwall et al. 2010). In relation to buprenorphine, a widely used

method to minimize diversion is 'off-label' crushing of buprenorphine tablets (Muhleisen et al. 2003, Winstock et al. 2009b, Simojoki et al. 2010). According to Simojoki and colleagues, there were no differences in serum buprenorphine or norbuprenorphine levels or in clinical effects between crushed and whole tablets (Simojoki et al. 2010). A Finnish research group recently developed a new analysis method for BNX in urine (Heikman et al. 2013). Authors suggest that it may be possible to differentiate sublingual therapeutic use of BNX from its parental use when analysing naloxone residual concentration and naloxone/buprenorphine ratio in urine. In the future, this method could be used in detection of noncompliance among BNX-treated OST patients. Non-compliance could serve as an indicator for intention to diversion. In methadone treatment, dilution of methadone liquid is an easy way to discourage injecting and indirectly also diversion (Bell 2010). Winstock and Lea highlighted better supervision, standardized administration procedures and education as ways to reduce buprenorphine diversion (Winstock & Lea 2010). The need of personnel and time resources, as well as patient acceptability should be taken into account when planning new attempts to prevent diversion.

Abuse-deterrent formulations (ADFs) are drug formulations developed to prevent the tampering and abuse of drugs (Schaeffer 2012). Schaeffer (2012) divided ADFs into four categories: physical or mechanical barrier, aversion or the addition of a noxious component, agonist-antagonist combinations, and pro-drugs. Mechanical or physical barriers refer to solid physical barriers which cover the tablets (e.g., extended release oxycodone) and to viscous or semisolid gel formulations (e.g., controlled release oxycodone). These usually prevent the release of active substances if tablets are crushed, chewed or attempting an extraction (Katz et al. 2007, Schaeffer 2012). Manufacturers have added aversive components and antagonists to products in order to make their abuse less rewarding (Schaeffer 2012). The buprenorphine-naloxone combination product is an example of an agonist-antagonist combination. Naloxone has also been combined with pentazocine, tilidine, oxycodone and methadone (Fudala & Johnson 2006, Katz et al. 2007, Schaeffer 2012). An example of a product, which utilizes aversive components, is an immediate release oxycodone which is formulated with several possibly aversive or irritating components creating e.g., a burning sensation if snorted (Romach et al. 2013). Pro-drugs are biologically inactive before being metabolized to the active form in the body (e.g., lisdexamphetamine for attention deficit/hyperactivity disorder). ADFs have been shown to deter drug abuse; however, there are also reports of disadvantages, such as increased risk of adverse effects for compliant patients and problems to swallow the tablets (Romach et al. 2013). Other drug formulations, such as transdermal or injectable sustained-release formulations can also possibly decrease the abuse liability and diversion (Fudala & Johnson 2006). Buprenorphine films and implants have been developed as countermeasures against abuse and diversion (Ling et al. 2010, Soyka 2012, Lintzeris et al. 2013). Whether these formulations reduce the risk of diversion needs further studies.

More sophisticated methods include the use of radio frequency identification (RFID) technology (Fudala & Johnson 2006). RFID technology can be used to track medicines in the supply chain or individual dosage units given to end users. Similar technology has been used in electronic adherence monitoring devices which usually contain microprocessors to record the openings of devices in real time (Fishman et al. 2000). The most commonly known device is MEMS (Medication Event Monitoring System) by Aprex Corp. These kinds of devices provide information about container openings but not about ingestion or other possible routes of administration or the number of tablets (dose) taken. There are few publications about the use of electronic monitoring devices as part of OST but they have used devices in collecting reliable adherence data and have not aimed towards preventing diversion or abuse (Arnsten et al. 2001, Fiellin et al. 2006, Sorensen et al. 2007). A small

Finnish study (n=12) found that electronic monitoring devices were well-accepted among OST patients, they increased treatment compliance and three patients reported that devices had prevented them from diverting BNX (Tacke et al. 2009).

Possible strategies to prevent diversion in countries where buprenorphine prescribing is possible include increased patient monitoring, shorter duration of prescriptions and enhanced training of GPs (Carrieri et al. 2006). Training as a means to prevent diversion was examined in the study by Lofwall and colleagues (Lofwall et al. 2011). They demonstrated that physicians' knowledge about buprenorphine pharmacology and OST legislation was poor but improved markedly during an educational intervention. Authors speculated that improved OST practices may result in decreased risk of diversion but this was not examined in the study per se. There is evidence that a prescription monitoring program implemented in the French region of the Bouches-du-Rhône in 2004 was able to decrease doctor-shopping quantity and ratio, which were used as indicators to measure the impact of program (Pradel et al. 2009). French authorities have successfully used doctor-shopping indicator and clustering method in the surveillance of buprenorphine abuse and diversion in the population level (Pauly et al. 2011). In the USA, monitoring programs utilizing data from poison centres and emergency departments have been successfully used as indicators for PO abuse (Hughes et al. 2007). However, their ability to serve as an indicator of diversion is unclear. The company marketing buprenorphine products (Reckitt Benckiser Pharmaceuticals Inc.) has a risk management program which aims to monitor and prevent the diversion of buprenorphine in the USA (McCormick et al. 2009). The program includes monitoring the distribution of buprenorphine products, educational activities and different surveillance methods. Risk management aims to minimize harms associated with the use of opioids while maintaining the requisite access to treatment at the same time (Katz et al. 2007). A sample of US physicians who had prescribed buprenorphine was asked what steps they had taken to reduce the abuse and diversion (Yang et al. 2013). Respondents reported taking a mean of 4.4 steps from a pre-specified 12-steps list. Most commonly mentioned steps were limiting 30-day prescriptions to compliant patients (72%), prescribing the lowest effective dose (61%) and requiring regular drug screening (59%). Actions which required coordination with other staff or units, e.g., counseling, were underutilized. In addition, authors highlighted that methods included in the list have not been scientifically proven to reduce diversion.

The most common reason for taking diverted buprenorphine or methadone was self-treatment of withdrawal symptoms or opioid dependence due to not being able or willing to get into treatment (Gwin Mitchell et al. 2009). In the study by Lofwall and Havens, inability to access buprenorphine treatment was a predictor of diverted buprenorphine use (OR 7.3, 95% CI 2.1-25.8) (Lofwall & Havens 2012). In a qualitative study done in New York City, NEP clients felt that the lack of access to buprenorphine treatment was a reason for buprenorphine diversion from treatment programs (Sohler et al. 2013). To address the barriers to OST entry (e.g., lowering the threshold of treatment, shortening the waiting time, reducing the costs of treatment) may serve as a way to prevent diversion (Gwin Mitchell et al. 2009, Lofwall & Havens 2012).

The battle against diversion is ongoing and there are no easy answers. Approaches which are too controlling or restrictive will compromise the acceptance of treatment and in the opposite situation, the harms of diversion will be predominant (Bell 2010). The prevalence of drug abuse as a medical condition in society is likely to remain relatively constant (Romach et al. 2013). When restricting the availability or abuse potential of one substance, it will be replaced by another substance with lower cost and better availability (Cicero et al. 2012, Unick et al. 2013). This has been the case in the USA, where abuse-deterrent formulation of oxycodone reduced the abuse of oxycodone and, as a consequence,

heroin abuse has increased (Cicero et al. 2012). Therefore, as long as opioids are used, there will be diversion, especially when dosing is not directly supervised (Bell 2010). The key is to find the balance between benefits and harms in consensus with all parties involved.

2.3.5 The role of community pharmacies in OST provision

Community pharmacies have been involved in methadone dispensing to OST clients in Denmark in the late 1960s (Farrell et al. 2000). Since the late 1960s, there have also been small community pharmacy-based methadone programs in the USA and Australia (Bowden et al. 1976, Berbatis et al. 2005). Bowden and colleagues described a one-year follow-up of 96 clients who received their methadone from community pharmacies in San Antonio, US between 1970 and 1971 (Bowden et al. 1976). The authors concluded that treatment outcomes were similar compared to traditional programs, 1-year retention was 70% and methadone security was not a problem. More recently, pharmacies are involved in OST provision in Canada (Buxton et al. 2010), the USA (Gunderson & Fiellin 2008), New Zealand (Walters et al. 2012), Australia (Lawrinson et al. 2008, Chaar et al. 2011) and many European countries such as Belgium, Germany, the UK, Ireland, Spain, France, and Austria (Farrell et al. 2000). Services provided by pharmacies include dispensing, supervising consumption, counseling, monitoring treatment, identifying problems and reporting them to physicians (Farrell et al. 2000). However, there are differences in the role of community pharmacies in provision of these services between countries (Berbatis et al. 2005). In some countries, such as the USA, pharmacies concentrate purely on dispensing whereas pharmacies have more clinical duties in some other countries, such as France, the UK and Australia (Berbatis et al. 2005, Gunderson & Fiellin 2008). Pharmacy-based OST provision offers many advantages such as reduced costs and work load in treatment units, increased capacity for new clients, convenient location with flexible dosing and reduced stigma (Chaar et al. 2011).

The main pharmacy surveys examining community pharmacy-based OST services which were published within the last 10 years have been described in Table 3. Most of these studies were conducted in the UK and Australia. Experience from these countries suggests that the number of clients per pharmacy was usually relatively low (<10) (Nielsen et al. 2007a, Sheridan et al. 2007, Lawrinson et al. 2008), however, some pharmacies have larger OST programs, e.g., the mean number of OST clients per pharmacy was 24-26 in Victoria, Australia (Nielsen et al. 2007a, Winstock et al. 2010). The number of pharmacies providing OST and the number of clients using these services have been on the increase (Sheridan et al. 2007, Matheson et al. 2007). In England, the proportion of community pharmacies dispensing OST medicines had increased from 51% to 62% between 1995 and 2005 ($p<0.0001$) (Sheridan et al. 2007). The mean number of clients per pharmacy had increased from 5.9 in 1995 to 9.2 in 2005 ($p<0.0001$). In Scotland, the proportion of pharmacies dispensing OST medicines had increased from 59% in 1995 to 83% in 2006 (Matheson et al. 2007). In Switzerland and Australia, almost 70% of OST clients were treated in community pharmacies (Samitca et al. 2007, Lawrinson et al. 2008). In 2003, 81% of Swiss pharmacies in the Canton of Vaud were providing OST (Samitca et al. 2007). However, only 10% of Portuguese pharmacies were involved in OST in 2008 (Torre et al. 2010). There are also differences in medications pharmacies are allowed to dispense. For example, in Australia and the UK, both methadone and buprenorphine can be dispensed (Sheridan et al. 2007, Lawrinson et al. 2008), whereas in the USA only buprenorphine (mostly BNX) can be dispensed from community pharmacies (Gunderson & Fiellin 2008).

In Finland, dispensing of BNX from community pharmacies has been possible since February 2008 (Ministry of Social Affairs and Health 2008). According to the Decree 33/2008, clients need to sign a contract which compels them to be prescribed by a single

physician and for all OST medicines to be dispensed from the same pharmacy. Physician can determine the time intervals between medication supplies and information on treatment can be exchanged between physician and pharmacy. If problems occur, clients can be reassigned to their treatment service units for supervised or unsupervised treatment. Pharmacists do not supervise the consumption of BNX. In August 2009, OST clients collecting BNX from community pharmacies were entitled to receive a reimbursement by the Social Insurance Institution of Finland (SII). The number of clients entitled to this reimbursement increased from 31 in 2009 to 135 in 2012 (Social Insurance Institute 2013).

Winstock and colleagues examined OST-related problems experienced by community pharmacies in Australia (Winstock et al. 2010). During the previous month, 41% of respondents had refused to dose a client for any reason and 14% had terminated a client's treatment. Most commonly reported reasons were inappropriate behaviour, missed doses and non-payment of dispensing fees. In general, the most commonly mentioned problems were difficulty contacting prescriber and giving take-away doses to unstable clients (21% and 19%, respectively). Contrasting results regarding OST-related problems in community pharmacies have been published. In the USA, 85% of pharmacists reported that BNX clients had not caused problems in pharmacies (Raisch et al. 2005). Contrary to these findings, a Swiss study reported that 83% of pharmacists had experienced some problems related to methadone treatment supervision (Samitca et al. 2007). The most commonly mentioned problems were lack of follow-up by physicians (50%), time needed for supervision (41%) and difficult relationships (32%). In the study by Lawrinson and colleagues, the most commonly mentioned problems related to OST were argumentative behaviour (50%), disturbances by clients (46%), thefts (38%) and aggressive behaviour (38%) (Lawrinson et al. 2008). Thirty percent of pharmacists had detected diversion of methadone or buprenorphine. In the study by Nielsen and colleagues, the most commonly mentioned concern about OST was related to diversion (Nielsen et al. 2007a). The rate of suspected diversion was 33 per 100 clients per month. The most commonly mentioned reason clients gave for diversion was saving the dose for later use (60%). The number of OST clients served by a pharmacy seems to be associated with the frequency of problems and diversion (more clients, more problems) (Winstock et al. 2010, Lawrinson et al. 2008).

About 70% of pharmacists in Australia and Scotland have received OST training (Matheson et al. 2007, Lawrinson et al. 2008). However, in other countries, pharmacists' need for more training related to OST and/or other services for drug users has been identified as a target for development (Samitca et al. 2007, Torre et al. 2010). A study conducted in the USA revealed that 68% of pharmacists had received two hours or less of addiction education during their studies (Lafferty et al. 2006). Their knowledge of addiction and substance abuse was relatively poor but improved with more education. Training was also associated with the frequency of counseling individuals with substance abuse problems. In New Zealand, an online training program turned out to be a feasible method for improving pharmacists' knowledge about OST (Walters et al. 2012). Lack of training may have a negative impact on pharmacies' willingness to provide OST services (Chaar et al. 2013).

Supervised methadone consumption was provided by 19% of pharmacies in Scotland in 1995 (Matheson et al. 1999). In 2005, the proportion had increased to 72% (Matheson et al. 2007). In 2005, 59% of community pharmacies in the UK were involved in supervising the consumption of OST medicines (Sheridan et al. 2007). In addition, 82% of pharmacists considered supervision as an appropriate task for pharmacists. Some respondents were also supportive for newer roles, such as supervising medications for comorbidity or providing hepatitis B vaccinations (48% and 25%, respectively). According to OST clients, pharmacists usually require them to stay at the pharmacy until the dose is absorbed but do not check

their mouth before leaving (50%) (Lea et al. 2008). Pharmacists in a Swiss study perceived that they have a central role in the supervision of OST, as well as the assessment of clients' compliance, health and wellbeing (Samitca et al. 2007). However, pharmacists felt that they were not fully integrated with the care providers and would like to contribute even more to the treatment of drug users. Difficulties in contacting the prescriber and problems with communication have been reported in both Switzerland and Australia (Samitca et al. 2007, Winstock et al. 2010).

Pharmacists had generally positive attitude towards OST services and 64% of them were willing to take new OST clients in an Australian study (Lawrinson et al. 2008). As the provision of OST has expanded, pharmacists' attitudes towards this service have improved (Matheson et al. 2007, Sheridan et al. 2007). McCormick and colleagues have reported similar results (McCormick et al. 2006). In addition, those pharmacists providing OST services had significantly higher attitude scores compared with those not involved in OST ($p<0.05$) (Matheson et al. 2007, Luty et al. 2010). The attitudes of treatment staff have been shown to be associated with OST practices and clients' outcomes in substance abuse treatment centers (Gjersing et al. 2010). A Scottish study revealed that other pharmacy customers have expressed generally supportive opinions on drug misuse services provided by community pharmacies considering that there was a private area for drug consumption (Lawrie et al. 2004). Clients of these services were also worried about privacy in the pharmacy (Lea et al. 2008). Other commonly mentioned problems were the high cost of treatment and not being treated the same as other pharmacy customers. Problems with privacy and concerns about pharmacists' knowledge were the main barriers OST clients mentioned for accessing help from pharmacists (Sheridan et al. 2005). Nevertheless, clients were generally satisfied with OST services (mean score 8.1/10, 10=excellent) (Lea et al. 2008). Ezard and colleagues have reported similar results (Ezard et al. 1999). Pharmacy dispensing fees may be an important barrier for OST clients accessing treatment (Chaar et al. 2011). Winstock and colleagues examined the dispensing fees related to community pharmacy-based OST and found that dispensing fees for methadone and buprenorphine were similar, even though buprenorphine clients had a lower frequency of dosing (Winstock et al. 2007). However, the length of time needed for consumption should also be taken into consideration. Disintegration time of BNX tablet can take up to 20 minutes (Tacke et al. 2009). Seventy percent of pharmacists responded that the time needed to supervise dosing was a negative aspect of buprenorphine treatment (Nielsen et al. 2007a).

Table 3. Summary of pharmacy surveys published in 2004 or later examining the provision of opioid substitution treatment services in community pharmacies

Authors (year), country	Study design	Setting	Study period	Study population and data source	Outcome of interest	Main results
Lawrinson et al. (2008), Australia	Cross-sectional survey	Community pharmacies providing OST in Adelaide, Australia	Not mentioned (probably around 2005)	Structured phone interviews with pharmacy staff	OST practices, problems related to OST, attitudes towards OST, future intentions in relation to the provision of OST	Pharmacies were supportive of OST and had generally positive attitude towards it. 64% were willing to take more clients (90% in rural pharmacies). Most common problems were argumentative behaviour (50%), disturbances (46%), thefts (38%) and aggressive behaviour (38%).
Matheson et al. (2007), Scotland	Cross-sectional survey	Community pharmacies in Scotland	2006 (+ a comparison to surveys done in 1995 and 2000)	Postal survey to pharmacy staff	Involvement in OST services, OST practices and training levels, provisions of needle exchange services, pharmacists' attitudes	Methadone was dispensed by 79.1% of respondents, and 90.9% supervised self-administration. A quarter dispensed buprenorphine. Attitudes improved but training levels remained similar compared to 2000 (about 70% received training).
McCormick et al. (2006), New Zealand	Cross-sectional survey	Community pharmacies in New Zealand	2001	Postal survey to pharmacy staff	OST practices, training levels, attitudes towards OST and drug users	53% worked in the pharmacy that offered OST services. 26% had received training on OST and training was associated with improved attitudes. Attitudinal factors related to OST may be more complicated than previously assumed.
Nielsen et al. (2007a), Australia	Cross-sectional survey	Community pharmacies providing OST in VIC, Australia	2005	Postal survey to pharmacy staff	Issues affecting the provision of buprenorphine in the community pharmacies, pharmacists' perceptions of buprenorphine diversion	Concerns over diversion were common among pharmacists. The rate of suspected diversion was 33/100 clients per month. Option to attend less than daily was the most commonly mentioned positive aspect of buprenorphine (65% of respondents).

Table 3 continues

Table 3 continued

Authors (year), country	Study design	Setting	Study period	Study population and data source	Outcome of interest	Main results
Raisch et al. (2005), the USA	Cross-sectional survey + interviews	Community, outpatient hospital, and clinic pharmacies in the USA	Not mentioned (probably around 2002)	Postal/phone survey to pharmacy staff and follow-up interviews	Pharmacists' attitudes and perceptions about OST in general and OST clients in pharmacies	Most pharmacists had positive attitudes towards OST and OST clients and attitudes improved when pharmacists were more involved in OST. Most (85%) reported that OST clients did not cause problems in their pharmacies.
Samitca et al. (2007), Switzerland	Literature review	Community pharmacies and NEPs in Vaud, Switzerland	1991-2003	Postal surveys to pharmacies, semi-structured interviews with pharmacists, NEP and OST statistics	Pharmacists' role in OST and harm reduction, changes in pharmacists' role during the study period	Pharmacies have important role in OST and needle exchange but they do not feel integrated enough. In 2003, 81% of pharmacies provided OST, 66% of OST clients were supervised in pharmacies. Problems were experienced by 83% of pharmacies. The most commonly mentioned problem was the lack of follow-up by physicians (50%).
Sheridan et al. (2007), the UK	Cross-sectional survey	Community pharmacies in England	2005 (+ a comparison to a survey done in 1995)	Postal survey to pharmacy staff	Changes in community pharmacy practice, involvement in OST services, pharmacists' attitudes	The number of clients, proportion of pharmacies providing OST and provision of supervised consumption increased in 1995-2005. Attitudes were more positive in 2005 compared to 1995.
Winstock et al. (2007), Australia	Cross-sectional survey	Community pharmacies providing OST in NSW, Australia	Not mentioned (probably around 2006)	Postal survey to pharmacy staff	OST medicine dispensing fees in community pharmacies	92% of pharmacies charged a flat fee for methadone and 75% for buprenorphine. Fees were similar for both medicines, despite, the differences in the frequency of supervision.

Table 3 continues

Table 3 continued

Authors (year), country	Study design	Setting	Study period	Study population and data source	Outcome of interest	Main results
Winstock et al. (2010), Australia	Cross-sectional survey	Community pharmacies providing OST in NSW and VIC, Australia	2006	Postal survey to pharmacy staff	Problems pharmacists have experienced in relation to OST and their responses to these situations	During the previous month, 41% of respondents had refused to dose a client and 14% had terminated a client's treatment, most commonly due to inappropriate behaviour and missed doses. Most commonly mentioned problems were difficulty contacting the physician and dosing unstable clients (21% and 19%).

NEP: needle exchange program, NSW: New South Wales, OST: opioid substitution treatment, the UK: The United Kingdom, the USA: The United States of America, VIC: Victoria
Studies were not considered for inclusion if they were published prior 2004, if the main focus of article was not on OST provision from community pharmacies, and if study design was not pharmacy survey (exception: Samitca et al. (2007) was included even though it was a review because it included the results of pharmacy surveys not published elsewhere).

2.4 Rationale of the study

The abuse potential of buprenorphine has been demonstrated in several studies. In addition, the abuse of buprenorphine has been reported in many countries. However, studies examining the characteristics of buprenorphine users have been small, cross-sectional or had short follow-up periods. Several studies have concentrated on the abuse of buprenorphine merely among patients receiving buprenorphine for the treatment of opioid dependence. Previous internationally published studies examining buprenorphine abuse in Finland are relatively scarce. Social, health and treatment-related characteristics of persons who abuse buprenorphine are not well established. Characteristics of heroin users and PO users have been examined extensively; however, there is evidence that different subgroups of users exist, even within the group of PO users. Clinical characteristics of persons with substance abuse problems may be associated with successful treatment outcome. Exploring the changes in characteristics can provide information on drug use trends. Therefore, examining the characteristics of buprenorphine users is important for both clinicians and policy makers.

The provision of OST carries the risk of abuse and diversion of OST medicines, especially if unobserved doses are granted. On the other hand, providing the possibility for take-home dosing is an important part of OST and supports the social and occupational reintegration of patients into society. The challenge is to provide take-home doses in a safe and monitored manner. The feasibility of novel methods such as electronic devices in resolving clinical challenges related to unobserved dosing should be examined. Community pharmacies offer a possibility for less restricted provision of OST. In many countries community pharmacies have major involvement in the treatment of opioid dependence. Community pharmacy -based provision of OST has not been studied in Finland.

3 Aims of the Study

The general aim of this thesis was to explore and describe the abuse of buprenorphine in Finland and possibilities for improving unobserved buprenorphine dosing in OST. This thesis examined the characteristics of persons who sought treatment for buprenorphine abuse. In addition, the thesis explored possibilities for improved unobserved dosing in OST with electronic medicine dispensers and the provision of OST from Finnish community pharmacies.

The specific aims of the study were:

1. To explore the trend in proportions and characteristics of clients seeking treatment for buprenorphine abuse and compare them to those seeking treatment for heroin and amphetamine abuse (I)

2. To examine the social, health and treatment-related factors associated with buprenorphine compared to amphetamine abuse (II)

3. To investigate whether electronic medicine dispensers can reduce the diversion of take-home buprenorphine-naloxone in OST patients in a medium-sized Finnish city (III); and

4. To explore the buprenorphine-naloxone dispensing practices, service experiences, problems encountered and opportunities for future development in Finnish community pharmacies (IV)

4 Methods

The thesis utilized a range of data collection methods (Table 4). Studies I and II were based on the data collected at the Helsinki Deaconess Institute between January 31, 1997 and August 31, 2008. Study III was an open-label clinical study with a four-month follow-up period. Study III also included a survey which was conducted in the local needle exchange service during the two-week periods in August 2010 and December 2010. Information on the drug screens taken at the Kuopio University Hospital was collected between July 2010 and April 2011. Study IV was a cross-sectional postal survey to Finnish community pharmacies in August 2011.

Table 4. Summary of study designs, study participants, data collection methods and study periods included in the thesis

Study	Design	Study period	Study participants	Data collection method
I	A descriptive study over a 12-year period	January 31, 1997 - August 31, 2008	Clients seeking treatment for buprenorphine (n=780), amphetamine (n=1249) or heroin (n=598) abuse	Structured clinical interviews (The Huuti study)
II	A cross-sectional study	January 1, 2001 - August 31, 2008	Clients seeking treatment for buprenorphine (n=670) or amphetamine (n=557) abuse	Structured clinical interviews (The Huuti study)
III	An open-label clinical study[a]	September 2010-January 2011 (intervention) August and December 2010 (NEP survey) July 1, 2010-April 30, 2011 (drug screen data collection period)	BNX-treated OST patients eligible for take-home dosing (n=37)	Questionnaires Drug screen data from the Kuopio University Hospital
IV	A cross-sectional survey	August 2011	Finnish community pharmacies that had dispensed buprenorphine-naloxone to OST clients (n=54)	Questionnaire

BNX: buprenorphine-naloxone combination product, NEP: needle exchange program, OST: opioid substitution treatment
[a] In addition to the study intervention, data were collected from the needle exchange service and the Kuopio University Hospital.

4.1 HUUTI STUDY (I, II)

4.1.1 Description of the study

The Huuti study is a large consortium project examining drug abuse and addiction in Finland. The epidemiological part of Huuti study utilizes data collected at the Helsinki Deaconess Institute (HDI) between January 31, 1997 and August 31, 2008. It contains information on all clients seeking treatment during this time period (n=4,817). Originally data were collected for the purposes of clinical practice. The HDI is a large public utility foundation that provides inpatient and outpatient treatment services for persons with alcohol and other substance abuse disorders. Services are provided to clients from the greater Helsinki metropolitan area, including Espoo, Vantaa and eight other nearby municipalities (Kerava, Kirkkonummi, Porvoo, Nurmijärvi, Järvenpää, Lohja, Hyvinkää, and Tuusula). Overall population of this area is estimated to be 1.3 million. Clients of the HDI were self-referred, referred by, or transferred from other treatment units. These data were used in two publications (studies I and II).

4.1.2 Data collection

All clients were interviewed as part of routine clinical practice by specialist physicians and nurses. Data were collected using a structured questionnaire at each client's initial visit to HDI. The Huuti questionnaire included adapted versions of the European Addiction Severity Index (EuropASI) and Treatment Demand Indicator. The EuropASI is a European version of Addiction Severity Index (McLellan et al. 1980, Blacken et al. 1994). The Treatment Demand Indicator is used by the European Monitoring Centre for Drugs and Drug Addiction (Simon et al. 1999, European Monitoring Centre for Drugs and Drug Addiction 2000). The Huuti questionnaire included questions regarding each client's demographics, substance abuse behaviour, social and health conditions and treatment-related factors. If the questionnaire was not fully completed during a client's initial visit, missing data were collected during a client's subsequent consultations if they occurred within the following three months of the initial consultation. Data pertaining to each client's age, current substance abuse behaviour and health and social state were only recorded during the initial visit. Each client was included in the analyses only once even if they had repeat consultations at the HDI.

4.1.3 Study population

Each client's primary drug of abuse was defined using the Treatment Demand Indicator definition as the drug causing the client the most problems. This was defined by clients themselves or by diagnoses based on ICD-10. According to the primary drug of abuse, clients were categorized as buprenorphine, amphetamine or heroin clients. These substances were selected because they caused most substance abuse problems in Finland and formed the largest client groups in the data. The users of BUP and BNX could not be separated from each other and, therefore, the group of buprenorphine clients encompassed all buprenorphine users. Study I included clients seeking treatment for buprenorphine (n=780), amphetamine (n=1249) or heroin (n=598) abuse between 1997 and 2008. For study II, clients seeking treatment for buprenorphine (n=670) or amphetamine (n=557) abuse between January 1, 2001 and August 31, 2008 were included. The study sample was restricted to this time period because more comprehensive data collection was conducted from 2001 onwards. In addition, the number of buprenorphine clients increased sharply in 2000. Amphetamine was the most commonly used illicit drug among Finnish problem drug

users in 2005 (80% of all problem drug users) (Partanen et al. 2007) and, therefore, amphetamine users were selected as the comparison group. Comparisons to other opioid users were not possible due to low number of clients seeking treatment for abuse of other opioids between 2001 and 2008 (heroin users n=95, other opioid users n=32).

4.1.4 Measures and definitions

For the purposes of this thesis, the terms abuse and harmful use were considered as synonymous with each other. The WHO defines harmful use as a pattern of harmful psychoactive substance use causing damage to health (World Health Organization 2012). The detailed descriptions and categories of variables used in the analyses are shown in Table 5. Clients were asked to report primary and secondary drugs of abuse at the time of the interview as well as other concurrent substance abuse over the past month. Substance categories were alcohol, opioids (heroin, opium, morphine, ethylmorphine, codeine, oxycodone, methadone, buprenorphine, pethidine, tramadol, fentanyl, dextropropoxyphene, pentazocine, other opioids), stimulants (cocaine, amphetamine, metamphetamine, MDMA, other stimulants), cannabis and prescription medicines (barbiturates, BZDs, neuroleptics, other hypnotics and sedatives). The source of substances was not defined (e.g. legal prescription, street market). Psychiatric symptoms were assessed according to clients' self-report and clinical diagnosis by treatment staff. Validated scales were not used consistently because data were collected as part of clinical practice. Medical comorbidity was assessed according to clients' self-report and staff evaluation based on client's blood pressure, pulse, weight, infections, temperature, and condition of skin. Based on the information from the interviews, clients were referred to appropriate treatment either in HDI's treatment facilities (outpatient or inpatient care) or in alternative treatment units.

Table 5. The description of variables included in the Huuti questionnaire

Variables	Descriptions
Demographics	
Sex	Male, female
Age	Age at the time of interview
Nationality	Finnish, other
Housing	Being able to report address (yes vs. no)
Marital status	Married (including those cohabiting) vs. non-married (single, divorced, separated, widowed)
Children under 18 years	Yes vs. no
Educational level	Basic (elementary school or less) vs. higher (high school, vocational training, university)
Vocational status	Employed vs. not employed (unemployed, student, housewife/husband, retired)
Main source of income	Salary vs. social benefits (pension, income support, unemployment benefit)
Substance abuse behaviour	
Route of administration[a]	Intravenous vs. other (oral, intranasal, smoking)
Frequency of use[a]	Daily vs. non-daily (2-6 times per week, once per week or less, no use during the previous month)
Age when started drug abuse	Age when started the primary drug of abuse, age when first used drugs/medicines
Concurrent substance abuse	Last month (yes vs. no), drugs used
Injecting	Life-time, last month (yes vs. no)
Sharing needles/syringes	Life-time (yes vs. no)
Number of drug free months	During last year (0-12)
Duration of primary drug abuse	The difference between the onset of primary drug abuse and the initial visit to HDI (years)
Social and health conditions	
Threat of violence	Threatened by violence by anyone (yes vs. no)
Smoking	Current status (yes vs. no)
Psychotic symptoms	When using drugs, at other times presently or during the previous 3 months (yes vs. no)
Depressive symptoms	Presently or during the previous 3 months (yes vs. no)
Suicidal thoughts	Presently or during the previous 3 months (yes vs. no)
Suicide attempts	Life-time (yes vs. no)
Medical comorbidity	No vs. yes (i.e. having an acute or chronic disease)
Treatment-related factors	
Guidance for treatment	Self-referred vs. by family/friends vs. by authorities (health/social care unit, police or employer)
Main reason for seeking treatment	Substance abuse vs. other (physical, psychiatric, social)
In treatment currently elsewhere	Yes vs. no
Referral to treatment	Outpatient, inpatient vs. other (consulting, guided elsewhere)

HDI: Helsinki Deaconess Institute
[a] Separately for primary and secondary drug of abuse.

4.2 ELECTRONIC MEDICINE DISPENSERS IN OPIOID SUBSTITUTION TREATMENT (III)

4.2.1 Study setting

The study was conducted in Kuopio which is a city of 90,000 inhabitants situated in a predominantly rural area in Eastern Finland. This study was a naturalistic, open-label trial

examining the use of EMDs in OST. There were three treatment units providing OST in Kuopio: the addiction psychiatry outpatient clinic of the Kuopio University Hospital, the Kuopio region addiction services trust, and the health center of the Kuopio municipality. Besides these services, three local community pharmacies dispensed BNX to OST clients. In addition to the trial, a survey was conducted at the local needle exchange service (NEP survey) and drug screens data from the emergency department and the intensive care unit of the Kuopio University Hospital were analysed. The Kuopio University Hospital was the only local provider of acute and emergency services in the study region.

4.2.2 Study participants

All OST patients who were registered at the treatment-services and eligible for the study were asked to participate. Inclusion criteria were the following: (1) diagnosis of opioid dependence (F11.22) according to ICD-10 criteria; (2) a stable dose of BNX; (3) OST started at least 1 month before the initiation of the study; and (4) one or more take-home allowance(s) per week. All patients were asked to give a written informed consent. Patients not meeting the inclusion criteria at the time of study initiation (August-September 2010) were included in the study later, if they became eligible and were willing to participate.

4.2.3 Electronic medicine dispenser

The EMD used in the study was the Med-O-Wheel Smart by Addoz Ltd. Detailed information about the device can be found from company's website (Addoz Ltd. 2013). The device is made from hard plastic and includes a locking system to prevent tampering and access to tablets outside the pre-set time window. BNX tablets were removed from blisters and the daily doses were put into the compartments of the dosage cassettes. A maximum of daily doses for one week was dispensed at once to ensure the stability of BNX tablets. EMDs were loaded and programmed by treatment staff (nurses, pharmacists). These procedures took approximately 5–10 minutes per device, depending on the dose of the individual patient. The compartment with the appropriate daily dose could be moved into the opening position by pressing the cover of the device, which was only possible during a 3-hour time window around the pre-set dosing time. Dispensers were programmed according to patients' individual dosing times. After the time window, the device was "closed" automatically and tablets were inaccessible until the next dosing time. Missed or skipped doses remained locked within the EMD.

4.2.4 Procedures

A diagram of study procedures is shown in Figure 1. In August and September 2010 all eligible patients were asked to participate in the study. Few weeks later, dispensing of BNX take-home doses in EMDs was started and continued for the next 4 months. Aside from this, normal standard care was continued, including the possibility for an increase or decrease in the number of take-home allowances. All study protocol violations such skipped doses or tampering with the device were handled according to unit-specific treatment guidelines. The most usual consequence was the reduction of take-home allowances. In case of revocation of all take-home allowances, EMD dispensing was ceased and reintroduced if take-home allowances were granted again. During the intervention phase, EMDs were provided to all OST patients with BNX take-home doses in the municipality as part of routine clinical care, regardless of their participation in the study per se. This way we ensured that during the intervention phase no unobserved BNX doses were dispensed without EMDs in the city of Kuopio. At the end of intervention period in January 2011, patients were asked to fill in a questionnaire to give their opinions on EMD

use. A slightly modified questionnaire was distributed among treatment staff involved in the study (nurses and pharmacists).

The NEP survey was conducted in the only needle exchange service located in Kuopio. Anonymous questionnaires were handed out in the NEP during the two 2-week periods before EMD use in August 2010 (pre-EMD phase) and during EMD use December 2010 (EMD phase). All clients visiting the service during these study periods were asked to fill in the questionnaire. The questionnaire was developed according to questions used in a previous Finnish study examining buprenorphine abuse among NEP clients (Alho et al. 2007). To ensure the content validity, the questionnaire was developed in close collaboration with service-staff (nurses and physicians).

Information on the drug screens taken at the emergency department and the intensive care unit of Kuopio University Hospital was collected from the time period of EMD use (EMD phase 1.10.-31.12.2010) and control periods before and after the intervention (pre-EMD phase 1.7.-31.8.2010, post- EMD phase 1.2.-30.4.2011). Positive drug screens were regarded as indicators for hospital-treated drug-related health problems. This was based on the assumption that any licit or illicit buprenorphine user in Kuopio with an acute, presumably drug-related health problem requiring hospital treatment would be subjected to a urine drug screen. Drug screens included buprenorphine (with and without naloxone), other opioids (methadone, oxycodone, heroin, codeine, morphine), other illicit drugs (amphetamine, methamphetamine, cannabis, MDMA) and BZDs. Urine-samples were analysed with the Cobas 6000 clinical chemistry analyser (Roche/Hitachi) at the Eastern Finland Laboratory Centre Joint Authority Enterprise. For buprenorphine-analysis CEDIA Buprenorphine Drugs of Abuse Assay reagents (Thermo Scientific) and the kinetic interaction of micro particles in a solution (KIMS) reagents (Roche Diagnostics) were used.

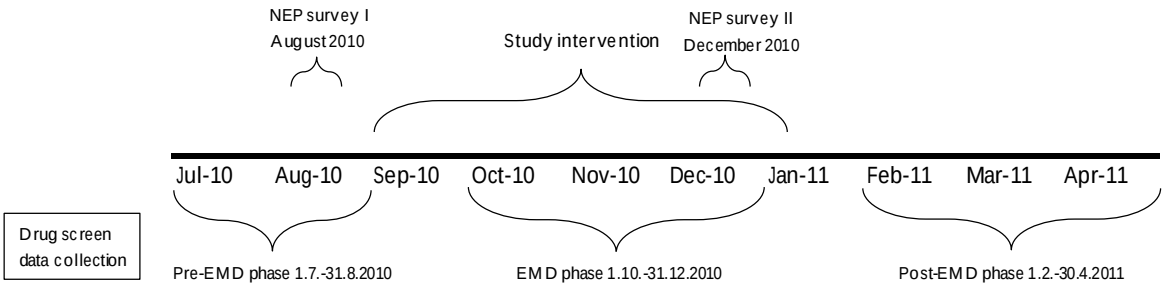

Figure 1. Diagram of the study III procedures

4.2.5 Measures

The variables included in the questionnaire for study participants are described in Table 6. The questionnaire was completed anonymously but participants were asked to provide certain background information about their treatment: duration of OST (less than 3 months, 3-11 months, 1-2 years, more than 2 years) and the number of take-home allowances at the time of completing the questionnaire. The questionnaire for treatment staff requested their opinions on the same issues and whether they thought EMDs could be used as part of routine OST (agree, no opinion, disagree).

The questionnaire used in the NEP survey requested information on the frequency of buprenorphine use during the previous month (none, 1-3 times, once a week, many times per week, daily) and products used during the previous month (BNX, BUP, low-dose buprenorphine product Temgesic®). Respondents were asked to report which of these

products they used most frequently. They were also asked to estimate the amount of money they were willing to pay for one tablet of BUP (8 mg) or BNX (8/2 mg), and the present availability on the local illegal drug-market (good, moderate, poor) as well as origin of BNX they used (OST vs. other). The questionnaire was anonymous and similar in both data collection periods. Respondents were asked to report their gender and age (less than 20 years, 20-29 years, 30-39 years, more than 40 years) for demographic background information.

Table 6. The description of variables included in the questionnaire for OST patients

Variable	Description
The use of EMD	
The effect of EMD on OST	Useful vs. no effect vs. harmful, details[a]
Has EMD prevented diversion	No vs. yes (the number of occasions)
Has EMD prevented other people to get hold of take-home doses	No vs. yes (the number of occasions)
Willingness to use EMD after study period	Yes vs. no, details [a]
Technical properties	
The suitability of 3-hour time window	Too short vs. suitable vs. too long
The ease of use	Yes vs. no, details [a]
Problems with EMD	Yes vs. no, details [a]
Tampering with EMD[b]	Easy vs. difficult vs. impossible
Opinions	
My BNX intakes have been more regular during the study. My life has been more flexible during the study. It feels safer to keep OST medicines in the EMD compared to paper sachet. I have been more involved in treatment during the study. In general EMD can prevent diversion of OST medicines. Reduced supervision may lead to increased abuse in some patients. EMD is difficult to use.	Answer options: strongly agree, agree, neither agree nor disagree, disagree, strongly disagree, don't know

BNX: buprenorphine-naloxone combination product, EMD: electronic medicine dispenser, OST: opioid substitution treatment

[a] Room for open responses and/or possibility to choose from multiple answer options.

[b] Getting access to tablets in the device outside the time window.

4.3 COMMUNITY PHARMACY SURVEY (IV)

4.3.1 Data collection

A cross-sectional postal survey was conducted in all community pharmacies dispensing BNX to OST clients in Finland. A list of all Finnish community pharmacies that had supplied buprenorphine-naloxone since August 2009 was received from the company (Reckitt Benckiser) with the marketing authorization for BNX (n=71). Of these pharmacies, 69 were community pharmacies and they formed the study sample.

Data were collected using a questionnaire which was developed according to previous studies examining community pharmacy based OST services in other countries (Sheridan et al. 1997, Matheson et al. 1999, Raisch et al. 2005, Matheson et al. 2007, Nielsen et al. 2007a, Lawrinson et al. 2008). The face-validity of the questionnaire was pilot-tested in four local pharmacies dispensing BNX to OST clients. According to the feedback received from pilot pharmacies, questionnaire was slightly modified. Pilot pharmacies received the final questionnaire at the same time as other pharmacies. Their initial responses were used merely for pilot testing and they were not recorded.

Prior to mailing the questionnaires, all pharmacies were contacted by phone. This was done in order to inform them about the study objectives as well as to maximize the response rate. In August 2011, questionnaires were mailed together with a cover letter and a prepaid return envelope. The cover letter informed participants about study background

and objectives, and instructed the staff member most familiar with the pharmacy's BNX dispensing practices to complete the questionnaire. Staff members were instructed to discuss their experiences before completing the questionnaire. Responses were anonymous and confidentiality was assured. Return envelopes were coded in order to identify non-respondents, but codes were not connected to the filled questionnaires. In September 2011, non-respondents were contacted again by phone and reminder questionnaires were sent a month after the initial mailing.

4.3.2 Measures

The questionnaire included both closed and open-ended questions. It was divided into five sections: (1) background information, (2) BNX clients and pharmacy resources, (3) problems and co-operation with treatment staff, (4) future development, and (5) sale of injecting equipment (Table 7). Clients who collected their buprenorphine-naloxone from community pharmacies were regarded as BNX clients. If pharmacies did not separate the numbers of current and all BNX clients, the total number of all clients was interpreted as same as the number of current clients. The number of current BNX clients was compared to the number of all buprenorphine-naloxone treated OST patients in Finland. In 2010, there were estimated to be 1,080 patients treated with BNX (Tanhua et al. 2011). The questionnaire included also a section of attitudinal questions on the personal opinions of the staff member filling the questionnaire. These data were not included in this thesis because the focus of the study IV was on the implementation of the new service and attitudinal factors were considered to be beyond the scope of the study.

Table 7. The description of variables included in the pharmacy survey questionnaire

Variables	Descriptions
(1) Background information	
Location	Geographical location within Finland (province) Urban, suburban, outside a city but within a local shopping mall, or rural
Size	Small or large (the annual number of prescriptions dispensed ≤80,000 or >80,000)[a]
(2) BNX clients and pharmacy resources	
BNX clients	The number of current and all BNX clients
Time needed to serve a BNX client (handling the prescription, dispensing, labeling, counseling)	More, less or the same as other clients
Resources	Dispensing fee for BNX clients (yes vs. no) The payer of the medicines (client, social service, SII) Staff received training on OST (yes vs. no) A nominated staff member responsible for OST (yes vs. no) Satisfaction with BNX dispensing (very well, well, poorly, very poorly)
(3) Problems	Has pharmacy experienced problems related to providing OST (yes vs. no; details[b]) Suspicions about diversion/abuse during the previous 6 months (yes vs. no; the number of occasions; consequences[b]) Has/have any BNX client(s) discontinued having BNX dispensed at the pharmacy (yes vs. no; reasons[b])
Co-operation with treatment staff (communication, availability, support)	Contacts with treatment staff (yes vs. no; reasons[b]) Satisfaction with co-operation with treatment staff (well, fairly well, fairly poorly, poorly; details about problems[b])
(4) Future development	
Opportunities for future development	Yes vs. no; details[b]
Willingness to take more BNX clients	Yes vs. no; reasons[b]
Supervised dosing[c]	How well supervised dosing suits Finnish pharmacies (well, fairly well, fairly poorly, poorly; reasons[b])
Importance of pharmacies' roles in different fields of treatment	Paperwork, treatment follow-up, dispensing, health education, medication counseling (scale from 1 'not important at all' to 4 'very important')
(5) Sale of injecting equipment	Do you sell injecting equipment (yes vs. no) How often do you sell injecting equipment (once a week or less often, several times/week, daily) Problems with clients (yes vs. no; details[b]) NEP available in the city (yes vs. no)

BNX: buprenorphine-naloxone combination product, NEP: needle exchange program, OST: opioid substitution treatment, SII: Social Insurance Institute in Finland

[a] Classification was based on dividing pharmacies into two groups of similar size according to the mean number of annual prescriptions in Finland (Association of Finnish Pharmacies 2011).

[b] Room for open responses and/or possibility to choose from multiple answer options.

[c] Pharmacist supervises the consumption of BNX and checks that mouth is empty before a client can leave.

4.4 STATISTICAL ANALYSES

Descriptive statistics were presented as proportions, means, medians and standard deviations (SD). Categorical and ordinal variables were analysed using Pearson chi-square (χ^2) test and Fischer's exact test depending on the number of categories. Statistical

differences in continuous variables were analysed using Mann–Whitney U -test and Kruskal–Wallis test. The assumption of normality was assessed graphically and tested with Kolmogorov-Smirnov test and Shapiro-Wilk test. Significance level of 0.05 was used for all tests. The Statistical Package for the Social Sciences Version 19.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for all analyses.

Study I

Separate analyses were performed for the time periods 1997-2001 and 2002-2008 in order to determine possible changes over time. Buprenorphine (n=197), amphetamine (n=808) and heroin clients (n=577) were all included in the analyses for 1997-2001. Heroin clients were excluded from the analyses in 2002-2008 because the low number of clients (n=21) precluded statistical testing. Changes in the characteristics of buprenorphine clients over time were examined for 1997-2008. Non-parametric tests were used in the analyses of continuous variables because normality assumptions were not met.

Study II

Binomial logistic regression models were used to analyse factors associated with buprenorphine abuse. Clients seeking treatment for amphetamine abuse were considered as a comparison group. The dependent variable in each model was dichotomous (buprenorphine client yes vs. no). Linearity of continuous variables (age, age when first used drugs/medicines) was confirmed. Statistically significant variables (p-value <0.1) in univariate models were included in the multivariate model. Only the clinically most relevant variable of two or more highly correlated predictive variables was selected for inclusion in the multivariate model to avoid multicollinearity. The results were presented as unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Study III

The small sample size limited the opportunity for statistical testing. Results of patient and staff questionnaires were presented descriptively. The data from NEP survey and drug screens were analysed with χ^2 test, Fischer's exact test and Mann–Whitney U –test. Continuous variables were not normally distributed and, therefore, nonparametric tests were used.

Study IV

Characteristics of pharmacies that responded prior to and after the reminder were compared to assess possible response bias. Binomial logistic regression models were used to analyse factors associated with perceived problems related to OST clients and BNX dispensing. Only pharmacies dispensing buprenorphine-naloxone directly to BNX clients were included in the analyses. The outcome measure in each model was dichotomous (experienced problems yes vs. no). Explanatory variables were chosen on the basis of previous studies indicating that they may be associated with problems (Nielsen et al. 2007a, Lawrinson et al. 2008, Winstock et al. 2010). The size and location of pharmacy were assessed as potential confounders. The results were presented as ORs with 95% CIs. Adjusting for the size and location of pharmacy did not affect results and, therefore, only unadjusted ORs were reported.

4.4.1 Missing data

The Huuti study had a considerable amount of missing data. Data pertaining clients' primary drugs of abuse were 100% complete but variables assessing other characteristics of clients contained missing information. Missing values were especially prevalent in the data collected during 1997-2000, but from 2001 onwards data were more complete. Therefore, study II was restricted to clients seeking treatment from 2001 to enable investigation of the associations with a greater range of covariates. Study I included all clients seeking treatment for buprenorphine, amphetamine or heroin abuse from 1997 to 2008. Complete cases analysis was used in study I. Clients with missing information were excluded from the analyses. Complete case analysis may cause bias and loss of power, especially if the amount of missing data is large (Graham 2009). Therefore, only variables with a relatively low amount of missing data (<20%) were included in the analyses. The amount of missing data (range 0-19.5%) was presented as a proportion of all cases for each variable included in the analyses in order to warrant the transparency of analyses. In addition, multivariate analyses were not conducted and, therefore, possible bias and loss of power had minor effect on the results.

Multiple imputation (MI) was used to replace missing values in study II. Therefore, all clients were included in the analyses. Multiple imputation is considered superior to complete case analyses when data are missing at random (MAR) (Baraldi & Enders 2010, Janssen et al. 2010). MAR allows the probability of missingness to depend on the observed data, but not on the missing data (Schafer & Graham 2002, He et al. 2010). Missing value analysis was done to check the MAR assumption. The following variables were associated with missing data for any of the variables of interest: buprenorphine user ($p=0.020$), daily use of the primary drug of abuse ($p< 0.001$), IV use of the primary drug of abuse ($p< 0.001$), method of treatment ($p=0.023$), sex ($p=0.042$) and concurrent use of cannabis ($p=0.012$). These variables were included in the imputation model to make MAR assumption more tenable (Graham 2009, Baraldi & Enders 2010, McPherson et al. 2012). The dependent variable did not contain any missing values. Multiple imputation with five iterations was used to replace missing values in predictive variables (range of missingness 0.2-21.7%). Imputation was done based on the values of other variables of interest and auxiliary variables (concurrent use of cannabis, alcohol or medicines during previous month).

4.5 ETHICAL CONSIDERATIONS

All ethical standards for protecting human participants were maintained in accordance with standards of the appropriate ethics committees and the Helsinki Declaration of 1975. All data analyses were performed anonymously and strict confidentiality was assured. The Huuti study protocol (studies I and II) was approved by the Research Ethics Committee of the North-Savo Hospital District and the Ethics Committee of the Helsinki Deaconess Institute. Permissions to use the data were obtained from appropriate municipal authorities of all communities that clients reported as their places of residence. The Ministry of Social Affairs and Health and the National Data Protection Ombudsman also approved the study protocol. The protocol of study III was approved by the Research Ethics Committee of the North-Savo Hospital District. The Clinical Trials protocol registration number of this study is NCT01182402 (www.clinicaltrials.gov). Written informed consent was obtained from the study participants. Participation was voluntary and decision to participate had no effect on the treatment provided at the treatment units. Ethics approval was not required for the study IV. According to the recommendations made by the Finnish National Advisory Board on Research Ethics, local ethics committee approval is not required for postal surveys

(National Advisory Board on Research Ethics in Finland 2009). The research was conducted in accordance with these guidelines. All potential participants were provided with written information about the study. Return of the completed questionnaire after reading the cover letter was considered as consent to participate.

5 Results

5.1 CHARACTERISTICS OF CLIENTS SEEKING TREATMENT FOR BUPRENORPHINE ABUSE (HUUTI STUDY) (I, II)

There were a total of 780 clients who sought treatment for buprenorphine abuse from the HDI between 1997 and 2008. Between 2001 and 2008, 670 clients sought treatment for buprenorphine abuse. The main characteristics of these clients as well as heroin and amphetamine clients used as comparison groups are shown in Table 8. Study I examined changes in the characteristics of buprenorphine clients over time. In terms of gender, age and the mode and level of buprenorphine abuse, the characteristics remained stable during the study period 1997-2008 ($p>0.05$). Poly-substance abuse behavior changed over the study period. The proportion of buprenorphine clients with concurrent abuse of alcohol ($\chi 2_{[df=4]}=27.0$, $p<0.001$), prescription medicines ($\chi 2_{[df=4]}=40.1$, $p<0.001$) and stimulants ($\chi 2_{[df=4]}=18.8$, $p=0.001$) increased. The proportion of buprenorphine clients abusing heroin concurrently decreased from 60.9% in 1997-2000 to 12.7% in 2007-2008 ($\chi 2_{[df=4]}=98.1$, $p<0.001$). The duration of buprenorphine abuse before seeking treatment from the HDI increased during the study period (Kruskal-Wallis $\chi 2_{[df=4]}=62.4$, $p<0.001$).

The annual proportion of buprenorphine clients increased from 0% in 1997 to 37.6% in 2008 (Figure 2). Since 2002, buprenorphine clients have represented at least half of all opioid users seeking treatment from the HDI (range: 49.3% in 2006, 60.3% in 2008). From 1997 to 2008, there were a total of 598 clients who sought treatment for heroin abuse and 1,249 clients who sought treatment for amphetamine abuse. Until 2000, heroin was the most commonly abused opioid among all clients. The number of heroin clients declined sharply to approximately 1% of all clients seeking treatment from 2000 to 2002 and remained on that level until the end of the data collection period. The proportion of amphetamine clients decreased during the study period (range from 34.2% of all clients in 1998 to 13.9% in 2007-2008).

Table 8. Main characteristics of participants in studies I and II

	Study I (1997-2008)			Study II (2001-2008)	
	Buprenorphine clients (n=780)	Heroin clients (n=598)	Amphetamine clients (n=1,249)	Buprenorphine clients (n=670)	Amphetamine clients (n=557)
Males, n (%)	560 (71.8)	450 (75.3)	826 (66.1)	475 (70.9)	347 (62.3)
Mean age (SD)	25.7 (6.6)	25.6 (7.4)	27.1 (8.1)	25.8 (6.6)	27.6 (8.9)
Finnish nationality, n (%)	753 (96.5)	550 (92.0)	1234 (98.8)	646 (96.4)	552 (99.3)
Homeless, n (%)	212 (27.2)	133 (22.2)	388 (31.1)	183 (27.6)	167 (30.6)
Mean age at the onset of abuse[a] (SD)	21.8 (5.7)	19.9 (5.0)	19.0 (5.3)	21.7 (5.7)	19.0 (5.5)
Daily use[a], n (%)	576 (73.8)	370 (61.9)	418 (33.5)	491 (76.5)	186 (34.2)
Injecting[a], n (%)	629 (80.6)	421 (70.4)	883 (70.7)	538 (82.8)	409 (75.7)

[a] The primary drug of abuse.

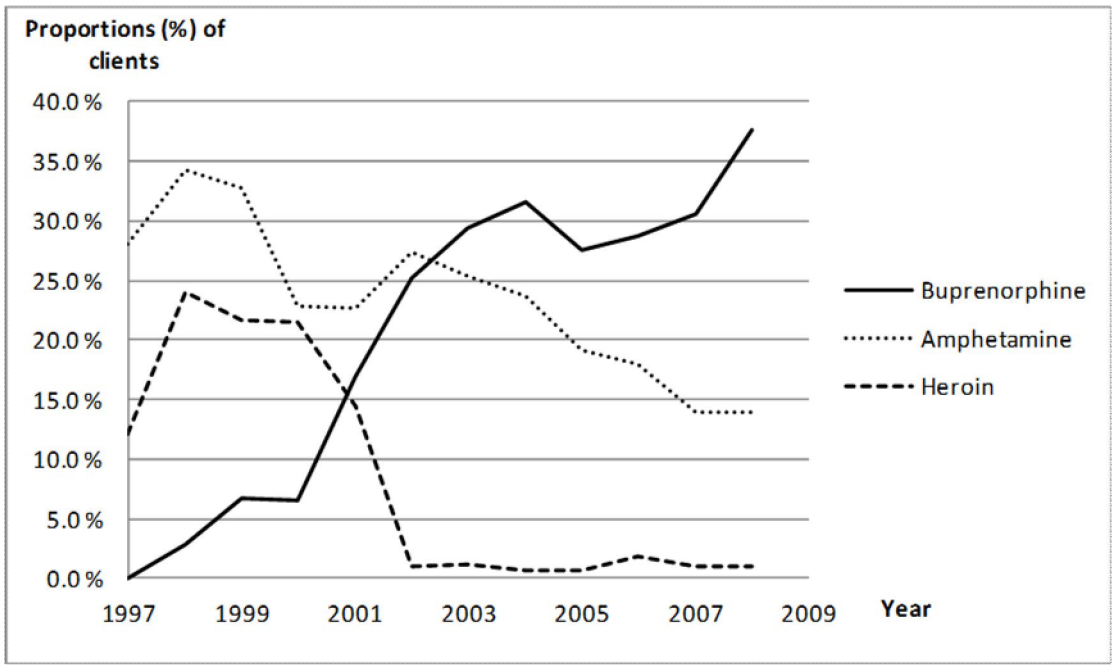

Figure 2. The proportions of clients seeking treatment for buprenorphine (n=780), amphetamine (n=1,249) and heroin (n=598) abuse from all clients (n=4,817) seeking treatment from HDI in 1997-2008

Comparisons between buprenorphine clients and heroin and amphetamine clients were performed separately for 1997-2001 and 2002-2008 (Table 9). Compared to heroin and amphetamine clients, buprenorphine clients were more frequently daily users of their primary drug ($\chi 2_{[df=2]}$=164.9, p<0.001) as well as secondary drug of abuse ($\chi 2_{[df=2]}$=17.0, p<0.001) in 1997-2001. Injecting the primary drug of abuse was more common among buprenorphine clients (83.2%) than among heroin and amphetamine clients (70.0% and 68.4%, respectively) ($\chi 2_{[df=2]}$=13.7, p=0.001). Amphetamine clients were more likely to be concurrent abusers of alcohol ($\chi 2_{[df=2]}$=120.5, p<0.010), while buprenorphine clients were more likely to abuse prescription medicines ($\chi 2_{[df=2]}$=43.8, p<0.001). Prescription medicines (28.9%) were the most common secondary drugs of abuse among buprenorphine clients whereas cannabis was the most commonly abused secondary drug of abuse among heroin and amphetamine clients (33.6% and 45.9%, respectively). The length of primary drug abuse before seeking treatment from the HDI was longest for amphetamine clients (Kruskal-Wallis $\chi 2_{[df=2]}$=151.3, p<0.001). In 2002-2008, buprenorphine clients were compared solely to amphetamine clients. Buprenorphine clients were more likely to be daily users of their primary (p<0.001) and secondary drugs of abuse (p=0.007) compared to amphetamine clients. Concurrent alcohol abuse was more common among amphetamine clients, while buprenorphine clients were more likely to abuse prescription medicines (p<0.001). In 2002-2008, 41.3% of buprenorphine clients reported prescription medicines as their secondary drug of abuse. Cannabis was the most commonly reported secondary drug of abuse for amphetamine clients (37.2%). Nevertheless, concurrent abuse of prescription medicines increased also among amphetamine clients from 30.0% in 1997-2001 to 55.1% in 2002-2008.

Study II included only clients seeking treatment for buprenorphine (n=670) or amphetamine abuse (n=557) in 2001-2008. A minority of buprenorphine clients were employed (12.5%, n=82) and 77.4% (n=499) reported elementary school or lower level of education. Social benefits were the main source of income for the majority of buprenorphine clients (n=503, 83.0%). The majority of buprenorphine clients reported

depressive symptoms (n=447, 73.2%) and psychotic symptoms when using drugs (n=377, 59.5%). Almost all buprenorphine clients were smokers (n=599, 96.0%) and 245 (40.2%) had a medical comorbidity (acute or chronic disease). IV drug use was common (lifetime use reported by 92.1%) and 345 (56.5%) had ever shared needles/syringes. Most buprenorphine clients self-referred to treatment (n=446, 67.8%) and nearly one-third received concurrent treatment from another provider (n=183, 28.3%). Most buprenorphine clients were referred to outpatient treatment services provided by the HDI or some other treatment provider (n=467, 75.8%). In multivariate analyses, factors significantly associated with buprenorphine abuse in comparison to amphetamine abuse were male gender (OR 1.57, 95% CI 1.17-2.09), daily abuse (OR 5.45, 95% CI 4.14-7.18), no drug free months during the last year (OR 1.68, 95% CI 1.23-2.29), self-referral to treatment (OR 1.33, 95% CI 1.01-1.75) and being referred to outpatient treatment (OR 1.40, 95% CI 1.00-1.93) (Table 10). Increasing age (OR 0.95, 95% CI 0.93-0.97 per year) and psychotic symptoms when using drugs (OR 0.33, 95% CI 0.24-0.45) were inversely associated with buprenorphine abuse.

Table 9. Comparison of the characteristics of buprenorphine, heroin and amphetamine clients in 1997-2001 and 2002-2008

	1997-2001					2002–2008				
	Buprenorphine clients (n=197)	Heroin clients (n=577)	Amphetamine clients (n=808)	Missing cases (%)[a]	p value[b]	Buprenorphine clients (n=583)	Heroin clients (n=21)	Amphetamine clients (n=441)	Missing cases (%)[a]	p value[c]
Males, n (%)	139 (70.6)	434 (75.2)	555 (68.7)	0.0	0.029	421 (72.2)	∓	271 (61.5)	0.0	<0.001
Mean age (median)	25.1 (23.0)	25.3 (23.0)	26.7 (25.0)	0.0	< 0.001	25.9 (25.0)	∓	27.7 (25.0)	0.0	0.100
Primary drug abuse										
Daily use [c], n (%)	146 (74.1)	362 (62.7)	260 (32.2)	12.0	< 0.001	430 (73.8)	∓	158 (35.8)	3.6	< 0.001
Injecting, n (%)	164 (83.2)	404 (70.0)	553 (68.4)	5.1	0.001	465 (79.8)	∓	330 (74.8)	3.3	0.076
Mean duration (median)[d]	3.0 (2.0)	5.1 (3.0)	7.6 (6.0)	5.2	< 0.001	3.9 (3.0)	∓	8.5 (6.0)	3.9	< 0.001
Mean age at the onset (median)	21.8 (20.0)	20.0 (18.0)	19.0 (18.0)	4.9	< 0.001	21.8 (20.0)	∓	18.9 (17.00)	3.9	< 0.001
Concurrent drug abuse										
Alcohol, n (%)	46 (23.4)	187 (32.4)	460 (56.9)	0.0	< 0.001	218 (37.4)	∓	232 (52.6)	0.0	<0.001
Cannabis, n (%)	143 (72.6)	430 (74.5)	649 (80.3)	0.0	0.010	395 (67.8)	∓	315 (71.4)	0.0	0.218
Medicines, n (%)	108 (54.8)	193 (33.4)	242 (30.0)	0.0	< 0.001	389 (66.7)	∓	243 (55.1)	0.0	< 0.001
Secondary drug abuse										
Alcohol, n (%)	10 (5.1)	34 (5.9)	151 (18.7)	6.0	< 0.001	39 (6.7)	∓	85 (19.3)	6.2	< 0.001
Cannabis, n (%)	41 (20.8)	194 (33.6)	371 (45.9)	6.0	< 0.001	100 (17.2)	∓	164 (37.2)	6.2	< 0.001
Medicines, n(%)	57 (28.9)	43 (7.5)	72 (8.9)	6.0	< 0.001	241(41.3)	∓	59 (13.4)	6.2	< 0.001
Opiate, n (%)	47 (23.9)	120 (20.8)	107 (13.2)	6.0	< 0.001	45 (7.7)	∓	65 (14.7)	6.2	< 0.001
Stimulant, n (%)	33 (16.8)	131 (22.7)	56 (6.9)	6.0	< 0.001	127 (21.8)	∓	24 (5.4)	6.2	< 0.001
Injecting, n (%)	69 (35.0)	179 (31.0)	94 (11.6)	14.9	< 0.001	141 (24.2)	∓	59 (13.4)	11.1	< 0.001
Daily use, n (%)	58 (29.4)	127 (22.0)	122 (15.1)	19.5	< 0.001	177 (30.4)	∓	100 (22.7)	10.1	0.007

[a] The amount of missing data as percentage (%) of all cases for each variable.
[b] χ^2-test for categorical variables, Kruskal-Wallis test for continuous variables.
[c] Fischer´s exact test for categorical variables, Mann-Whitney U-test for continuous variables.
[d] The difference between the onset of primary drug abuse and treatment seeking from the HDI (years).
∓ Comparison to heroin abusers was not done since there were only 21 primary heroin abusers between 2002 and 2008.

Table 10. Univariate and multivariate analyses of factors associated with buprenorphine abuse

Variable	Unadjusted odds ratio (95% CI)[a]	p value[b]	Adjusted odds ratio (95 % CI)[c]	p value
Male	1.47 (1.16-1.87)	0.001	1.57 (1.17-2.09)	0.002
Age	0.97 (0.96-0.99)	<0.001	0.95 (0.93-0.97)	<0.001
Married	1.26 (0.85-1.88)	0.246		
Homeless	0.87 (0.68-1.11)	0.262		
Children under 18 years	0.78 (0.60-1.00)	0.048	1.02 (0.73-1.42)	0.924
Elementary school or less education	1.24 (0.95-1.61)	0.112		
Employed	1.00 (0.71-1.40)	0.990		
Salary as main source of income	0.87 (0.64-1.18)	0.361		
Thread of violence	0.68 (0.46-1.00)	0.051	0.72 (0.42-1.22)	0.211
Psychotic symptoms (when using drugs)	0.39 (0.30-0.50)	<0.001	0.33 (0.24-0.45)	<0.001
Psychotic symptoms (other times)	0.54 (0.40-0.72)	<0.001		
Depressive symptoms	0.97 (0.75-1.26)	0.824		
Suicidal thoughts	0.70 (0.55-0.88)	0.003	1.02 (0.77-1.35)	0.900
Suicide attempts	0.73 (0.54-0.99)	0.041		
Medical comorbidity	1.05 (0.82-1.35)	0.714		
Daily use of primary drug of abuse	6.27 (4.87-8.07)	<0.001	5.45 (4.14-7.18)	<0.001
IV use of primary drug of abuse	1.55 (1.17-2.06)	0.002	1.23 (0.87-1.75)	0.242
No drug free months during last year	2.11 (1.63-2.73)	<0.001	1.68 (1.23-2.29)	0.001
Age when first used drugs/medicines	0.94 (0.91-0.97)	<0.001	0.97 (0.93-1.01)	0.098
Smoking	1.79 (1.05-3.06)	0.033	1.21 (0.62-2.36)	0.569
IV drug use ever	2.21 (1.53-3.19)	<0.001		
IV drug use last month	1.85 (1.38-2.47)	<0.001		
Shared needles/syringes	1.02 (0.80-1.31)	0.876		
Self-referral to treatment	1.60 (1.26-2.01)	<0.001	1.33 (1.01-1.75)	0.044
Referred to outpatient treatment	1.39 (1.06-1.82)	0.018	1.40 (1.00-1.93)	0.048
Treatment because of drug abuse	1.66 (0.48-5.71)	0.425		
In treatment concurrently elsewhere	1.12 (0.87-1.45)	0.375		

IV: intravenous

[a] Separate unadjusted logistic regression models for each variable (dependent variable buprenorphine client yes vs. no).

[b] Variables with P value < 0.1 were included in the multivariate analysis. In case of highly correlated variables the clinically most relevant variable was chosen to the model. Cox and Snell R Square ranged between 0.239-0.247 according to the imputed dataset.

[c] Adjusted logistic regression model for the other variables in the model.

5.2 THE USE OF ELECTRONIC MEDICINE DISPENSERS IN OPIOID SUBSTITUTION TREATMENT (III)

Study intervention

A total of 37 BNX-treated OST patients participated in the study (participation rate 88%). Twenty-one of them (57%) were males, the mean age was 30.0 years (SD 5.1) and they were all Finnish by ethnic background. The mean duration of OST was 3.0 years (SD 2.9) and the mean daily dose of buprenorphine was 17.2 mg (SD 4.3). In addition to study participants, five patients who refused to participate and three patients who were pregnant during the study got their take-home doses of BNX (and BUP for pregnant women) in EMDs during the study period. Thirty-one patients (84%) completed the questionnaire at the end of the EMD phase. Five patients (16%) reported that the EMD had prevented them from diverting their medicines and 18 patients (58%) thought that EMDs could generally prevent diversion. Seven patients (23%) responded that EMD had prevented others to get hold of their medicines. The majority of patients (n=21, 68%) regarded EMDs as a safer option for the storage of take-home doses than paper sachets which had been used in the routine dispensing practice before the trial. Most participants thought that tampering with the device was impossible (n=18, 58%) or difficult (n=6, 19%).

Treatment staff returned a total of 19 questionnaires (3 from pharmacies, 16 from treatment units). Response rate was estimated to be 84% according to the number of

returned questionnaires and staff involved in the study. The majority of respondents did not think that EMDs could prevent diversion (n=16, 84%). In spite of that, 58% of respondents (n=11) preferred to dispense take-home doses of BNX in EMDs compared to paper sachets and 74% (n=14) reported that EMDs could be used routinely as part of OST.

Needle exchange program survey

For the first survey (pre-EMD phase), 35 responses (response rate 46%) were received and for the second survey (EMD phase) 27 responses (39%) were received. In the first survey, three respondents were not buprenorphine users and they were excluded from the analyses. Respondents were mostly males (56% and 64%, respectively) and younger than 30 years old (56% and 74%, respectively) in both surveys. Almost all respondents abused BNX in both surveys (100% and 96%, respectively), and about half used buprenorphine on a daily basis (47% and 59%, respectively) (Table 11). In the pre-EMD phase, more respondents reported that BNX was the buprenorphine product they used most commonly (n=26, 87%) than in the EMD phase (n=16, 59%) (p=0.033). In the EMD phase, more respondents used illegal BUP compared to the pre-EMD phase (67% vs. 47%, p=0.188) but the difference was not statistically significant. Respondents indicated that the availability of illegal BNX (p=0.371) or its origin from OST (p=1.000) had not changed between the surveys.

Drug screen data

A total of 198 positive drug screen results from 121 individuals were registered during the data collection periods. Overall, there were no statistically significant differences in drug screen results between the data collection phases (pre-EMD, EMD and post-EMD phases) ($\chi 2_{[df=6]}$=1.429, p=0.964). About 10% of the drug screens were buprenorphine-positive during all data collection periods (range 8.8%-11.4%). Positive drug screens for other opioids (range 20.0%-23.8%), BZDs (range 47.9%-53.8%) and other drugs (range 13.8%-18.8%) also remained stable between the study phases.

Table 11. Results of the NEP surveys conducted before the study intervention (pre-EMD phase) and during the intervention (EMD phase)

Variable	Pre-EMD phase (n=32)	EMD phase (n=27)	p value[a]
BNX user, n (%)	32 (100)	26 (96)	0.458
BUP user, n (%)	15 (47)	18 (67)	0.188
Daily buprenorphine user, n (%)	15 (47)	16 (59)	0.435
BNX most commonly used buprenorphine product, n (%)	26 (87)[b]	16 (59)	0.033
Availability of BNX is good, n (%)	6 (19)	8 (30)	0.371
BNX originated from OST, n (%)	6 (19)	5 (19)[c]	1.000
Mean price (€) of one BNX tablet (8/2 mg) (SD)	42.92 (11.67)	43.34 (7.09)	0.943
Mean price (€) of one BUP tablet (8 mg) (SD)	50.71 (14.45)	55.27 (10.23)	0.110

BNX: buprenorphine-naloxone, BUP: single-ingredient buprenorphine, EMD: electronic medicine dispenser, OST: opioid substitution treatment

[a] Fischer´s exact test for categorical variables, Mann-Whitney U-test for continuous variables.

[b] The responses of two persons are missing.

[c] The response of one person is missing.

5.3 BUPRENORPHINE-NALOXONE DISPENSING IN FINNISH COMMUNITY PHARMACIES (IV)

The survey questionnaire was completed and returned by 64 pharmacies (response rate 93%). The characteristics of 12 pharmacies responding after the reminder did not differ statistically significantly from the other respondents indicating no response bias. Of the 64 respondents, 54 pharmacies dispensed BNX directly to clients. The remaining 10 pharmacies dispensed BNX to health care units without having contact with BNX clients. Therefore, these pharmacies were excluded from the analyses. Of the 54 pharmacies included in the analyses, 30 pharmacies (56%) were located in Southern Finland and 32 pharmacies (59%) had the total annual prescription volume of more than 80,000 prescriptions. Twenty-five pharmacies were located in city centres (46%), 24 pharmacies in suburbs or within a shopping mall (44%) and 5 pharmacies in rural areas (9%).

Pharmacies had a total of 155 current or previous BNX clients (range 1–16 per pharmacy). Of the 54 pharmacies, 48 pharmacies had a total of 108 current clients (range 1–13 per pharmacy). Current clients represented 10% of all BNX treated OST patients in Finland. Thirty-six pharmacies (67%) charged a dispensing fee for BNX clients (Table 12). The mean dispensing fee per week was €5.26 (SD 2.59, range €0.67– €11.50). Seventy-eight clients (72%) got SII reimbursement of their BNX expenses. In 14 pharmacies (26%) staff had received training on OST and in 21 pharmacies (39%) there was a nominated staff member responsible for OST. Overall satisfaction with BNX dispensing was high, with all respondents perceiving that dispensing had gone ‘very well’ (n=31, 57%) or ‘well’ (n=21, 39%). Similarly, all respondents perceived that co-operation with treatment staff had gone ‘well’ (n=43, 80%) or ‘fairly well’ (n=9, 17%). In 20 pharmacies (37%), one or more BNX client(s) had discontinued receiving BNX dispensed from that particular pharmacy. Most commonly reported reasons for this included returning to dispensing from an addiction treatment unit (n=11), changing pharmacy (n=9) and completion of OST with successful withdrawal from BNX (n=3).

Fourteen pharmacies (26%) had encountered some problems which were mostly dose timing issues or non-collection of scheduled doses (n=7), confusion with financial obligations (n=5), confusion with prescriptions (n=4) or client’s difficulty paying for the medications (n=3). Diversion had been suspected in 6 pharmacies (11%) and abuse in 4 pharmacies (7%) during the previous 6 months (Table 12). Problems were more likely to occur in pharmacies with more than one BNX client compared to pharmacies with only one client (OR 1.39, 95% CI 1.05-1.86) and in pharmacies where one or more clients had discontinued pharmacy dispensing compared to pharmacies where no clients had discontinued (OR 6.53, 95% CI 1.70-25.03). Most pharmacies recognized opportunities for future development (n=43, 80%), such as financial remuneration for pharmacies (n=32, 74% of those pharmacies which recognized a need for improvements), more training for pharmacists (n=30, 70%) and better co-operation with treatment staff (physicians) (n=15, 35%). Most respondents replied that providing supervised dosing does not suit Finnish community pharmacies (n=43, 80%). Nevertheless, most pharmacies (n=46, 85%) were willing to dispense BNX to more clients in the future.

Table 12. Pharmacies' responses to survey questions and factors related to experiencing problems related to buprenorphine-naloxone dispensing in Finnish community pharmacies

	Total (n=54), n (%)	Pharmacies with problems (n=14), n (%)	Pharmacies without problems (n=37), n (%)	Unadjusted odds ratio (95% CI)[a]	p value
Number of all BNX clients					
One client	22 (41)	1 (7)	21 (57)	Ref.	
More than 1 client	31 (57)	13 (93)	16 (43)	1.39 (1.05-1.86)	0.024
Missing data	1 (2)	-	-		
Pharmacy is charging a dispensing fee for BNX clients	36 (67)	10 (71)	26 (70)		
Staff received training on OST	14 (26)	3 (21)	11 (30)	0.71 (0.16-3.09)	0.647
There is a nominated staff member responsible for OST	21 (39)	5 (36)	16 (43)		
Time needed to serve a BNX client					
More than other clients	20 (37)	7 (50)	12 (32)		
Same as other clients	28 (52)	6 (43)	21 (57)		
Less than other clients	4 (7)	1 (7)	3 (8)		
Don't know/missing data	2 (4)	-	1 (3)		
One or more BNX client(s) discontinued pharmacy dispensing	20 (37)	9 (64)	8 (22)	6.53 (1.70-25.03)	0.006
Overall level of satisfaction with BNX dispensing					
Very well	31 (57)	5 (36)	26 (70)		
Well	21 (39)	9 (64)	10 (27)		
Missing data	2 (4)	-	1 (3)		
Suspicions about diversion	6 (11)	2 (14)	4 (11)	1.38 (0.22-8.50)	0.732
Suspicions about abuse	4 (7)	2 (14)	2 (5)	3.18 (0.40-25.31)	0.274
Opportunities for future development of BNX dispensing	43 (80)	13 (93)	28 (76)	4.18 (0.48-36.53)	0.196
Overall level of satisfaction with co-operation with treatment staff					
Well	43 (80)	9 (64)	32 (86)		
Fairly well	9 (17)	5 (36)	4 (11)		
Missing data	2 (4)	-	1 (3)		
Providing supervised BNX dosing in pharmacies suits to Finland					
Well	9 (17)	2 (14)	7 (19)	Ref.	
Poorly	43 (80)	11 (79)	30 (81)	1.28 (0.23-7.14)	0.776
Missing data	2 (4)	1 (7)	-		
Pharmacy willing to take more BNX clients	46 (85)	11 (79)	33 (92)		

BNX: buprenorphine-naloxone, OST: opioid substitution treatment, Ref: reference category

[a] Separate unadjusted logistic regression models were performed for each factor. Adjusting for the size and location of the pharmacy had no effect on results (data not shown).

6 Discussion

6.1 MAIN FINDINGS

6.1.1 The abuse of buprenorphine (I, II)

The proportion of clients seeking treatment for buprenorphine abuse increased from 0% in 1997 to 38% in 2008 (study I). Treatment seeking for heroin abuse decreased to the level of approximately 1% of all clients after 2001. This shift from heroin to buprenorphine abuse has also been reported in official national reports (Forsell et al. 2010, Varjonen et al. 2012). In Canada, similar opioid abuse trends have been reported (Fischer et al. 2006). Increasing PO abuse has been acknowledged worldwide e.g., (Compton & Volkow 2006b, Degenhardt et al. 2008, Mendelson et al. 2008, Fischer et al. 2013b). However, in other countries the abuse has focused more on other opioids than buprenorphine, such as fentanyl in Estonia (Talu et al. 2010) or oxycodone and hydrocodone in the USA (Cicero et al. 2005). In the USA, buprenorphine is predominately used in OST and not all studies consider it as a PO. The shortage of heroin in the Finnish drug markets since 2001 (Forsell et al. 2010) has probably triggered the increase in buprenorphine abuse. Simultaneously, the access to OST has improved which has led to increased availability of buprenorphine. Increased therapeutic use of opioids seems to be associated with more opioid abuse in the society (Cicero et al. 2007b). Therefore, a possible explanation for the increased abuse of buprenorphine is the increased availability due to expansions in therapeutic use. Another country where buprenorphine abuse has been reported to be high is France (almost 60% of IDUs had injected buprenorphine in the previous 6 months) (Obadia et al. 2001). In France, the availability of buprenorphine has been high since 1996 because all GPs have been able to prescribe buprenorphine for people with opioid dependence. These findings support the role of availability in determining the scale of abuse. However, international differences in treatment practices, take-away policies as well as illegal drug markets shape this association.

According to previous studies, self-medication of withdrawal symptoms and/or dependence has been the most common reason for buprenorphine abuse (Alho et al. 2007, Hakansson et al. 2007, Otiashvili et al. 2010, Schuman-Olivier et al. 2010, Moratti et al. 2010, Larance et al. 2011b, Bazazi et al. 2011). A qualitative Finnish study revealed that study participants regarded their buprenorphine use as self-medication, even though they mainly injected buprenorphine (Malin et al. 2006). Reliance on self-medication indicates a shortage of treatment resources, dissatisfaction with current treatment options or both. That probably explains the increase in abuse in Finland in the early 2000s because OST was still in the state of development. Malin and colleagues reported that their study participants regarded the threshold to get into OST as too high, the number of treatment slots too low and treatment in general too burdensome because of regular visits and drug screens. However, as the provision of OST increased in Finland throughout the 2000s, the lack of treatment seems unlikely to be a major explanatory factor for constantly increasing abuse. Nevertheless, increased provision of OST does not necessarily ensure a quick treatment initiation everywhere. According to a report from 2007, waiting time for OST was more than a year in some Finnish cities (Hermanson 2008). OST legislation has become more liberal which should lower the threshold for seeking and getting into treatment. In previous foreign studies, OST patients have valued the possibility for unobserved dosing and found it to increase their treatment compliance (Stone & Fletcher 2003, Treloar et al. 2007, Madden

et al. 2008). The possibility for community pharmacy dispensing of BNX was intended to help to get more opioid users into treatment. However, this study was not able to take this into account as pharmacy dispensing has been possible since February 2008 and the data collection period of the Huuti study was terminated in August 2008. There is evidence that some users start their IV drug abuse primarily with buprenorphine (Partanen et al. 2004, Winslow et al. 2006, Otiashvili et al. 2010, Simojoki & Alho 2013). This suggests that buprenorphine can also be abused due to its opioid agonist-like effects which may partly explain the scale of the abuse.

The results of this study showed that clients seeking treatment for buprenorphine abuse in Finland had risky abuse patterns. This was evidenced by the fact that the majority of clients injected buprenorphine (81%) and used it on a daily basis (74%). These patterns were constant during the study period from 1997 to 2008. Injecting and daily abuse of both primary and secondary drugs of abuse were more common among buprenorphine clients compared to amphetamine and heroin clients. Compared to users of buprenorphine and POs in other countries, injecting was more common among buprenorphine clients in this study (Cicero et al. 2007c, Degenhardt et al. 2009, Aich et al. 2010). Concurrent abuse of alcohol, stimulants and especially prescription medicines increased among buprenorphine clients during the study period indicating increasing poly-drug abuse. Frequent poly-drug abuse among buprenorphine users, especially BZDs, has been acknowledged in previous Finnish (Partanen et al. 2004, Tammi et al. 2011) and foreign studies as well (Winslow et al. 2006, Nielsen et al. 2007b, Otiashvili et al. 2010, Lofwall & Havens 2012). Concurrent substance abuse complicates the treatment of opioid dependence (Kraus et al. 2011) and increases health risks related to abuse. Concurrent use of BZDs and buprenorphine increases the risk of fatal poisonings (Häkkinen et al. 2012).

Based on the findings of study I, we hypothesised that buprenorphine clients have more social and health-related problems compared to amphetamine clients. However, findings from study II revealed that buprenorphine and amphetamine clients shared similar social, health and treatment-related characteristics, despite the fact that buprenorphine clients reported more intense abuse patterns. As expected, amphetamine clients more commonly reported psychotic symptoms which are a well-known complication of stimulant abuse (Curran et al. 2004, Zweben et al. 2004, Darke et al. 2008, Wang et al. 2012). Otherwise, there were no differences between these groups in social or health-related factors. The higher frequency of psychotic symptoms may explain the finding that amphetamine clients were more commonly referred to inpatient treatment. Another treatment-related difference was the finding that buprenorphine clients were more commonly self-referred to treatment compared to amphetamine clients (OR 1.33, 95% CI 1.01-1.75) or compared to users of buprenorphine and POs in previous studies (Basu et al. 2000, Aich et al. 2010, Fischer et al. 2010). This may be explained by the intensity of abuse among buprenorphine clients. On the other hand, the lack of established pharmacological treatment options for amphetamine dependence may have affected amphetamine clients' willingness to seek treatment. In general, buprenorphine clients reported higher frequency of unemployment, lower educational levels and higher reliance on society benefits compared to users of buprenorphine and POs in other countries (Cicero et al. 2007c, Moore et al. 2007, Fischer et al. 2010, Vicknasingam et al. 2010). Buprenorphine clients in this study seemed to resemble more the characteristics of heroin users entering treatment in terms of injecting, employment status, income sources and poly-drug abuse (Ross et al. 2005). Therefore, our results do not seem to support a perception that abuse of prescription drugs is less dangerous compared to illicit substances (Mendelson et al. 2008, Ling et al. 2011). It has also been hypothesized that PO abuse may offer public health benefits due to a lower prevalence of risk behaviours (Fischer et al. 2009). Possible benefits do not appear to apply

to clients seeking treatment for buprenorphine abuse in Finland. According to our results, we hypothesize that the route of administration may be a stronger determinant of social, health and treatment-related factors than the primary drug of abuse. Both buprenorphine and amphetamine clients in study II were mainly IV-users (83% and 76%, respectively). Similar findings have been reported in an Australian study which found that heroin and PO users with high rates of injecting shared similar socio-demographic and health-related characteristics as compared to PO users not injecting (Nielsen et al. 2011).

6.1.2 Electronic devices as a method to prevent buprenorphine-naloxone diversion (III)

The main finding of the study III was that we were not able to clearly detect that EMDs could prevent the diversion of BNX. Five patients (16%) who took part in the study intervention reported that EMDs had prevented them from diverting their medicines. This represents about half of the proportion of BNX patients who reported diversion (30%) in an Australian study (Larance et al. 2011b). However, these numbers may not be comparable because the extent of unobserved dosing and other treatment practices also affect the frequency of diversion (Bell 2010). Treatment staff also had suspicions about whether EMDs could prevent diversion. This is most likely explained by the fact that treatment staff was aware of some patients tampering with the device (getting BNX from the device outside the dosing window without the possibility to later detect this through visual inspection). However, we have a reason to assume that few patients actually tampered with the device because most patients reported that tampering was difficult or impossible. However, there is a possibility of tampering with monitoring devices when using them in clinical practice. Both patients and treatment staff appreciated the safety of dosing and storage of BNX in EMDs. It is possible that EMDs can reduce the pressure to sell or pass on medicines to other users or dealers.

Changes in the number of hospital-treated buprenorphine-related health problems and the availability of illicit buprenorphine were regarded as indicators of changes in buprenorphine diversion. Despite comprehensive use of EMDs during the trial, there were no reductions in hospital-treated drug-related health problems measured by drug screen results. However, statistical power may have been insufficient, due to small sample size. In addition, since the Kuopio University Hospital is the only emergency hospital for a large catchment area, patients from outside Kuopio may have diluted our results. According to NEP surveys, the availability, price or source of illicit buprenorphine did not change as a consequence of the intervention. However, BNX was the most commonly abused product more often in the pre-EMD phase than in the EMD phase ($p=0.033$) and BUP abuse appeared more common in the EMD phase ($p=0.188$), even though the difference was not statistically significant. Therefore, results indicated a slight shift from BNX to BUP abuse among NEP clients during the intervention. This shift may be explained by decreased availability of BNX as a consequence of the intervention or by better availability of BUP in the EMD phase for reasons unrelated to the trial. It is believed that most illicit buprenorphine is smuggled into Finland from other counties (Skretting & Rosenqvist 2010). Changes in drug supply may not directly impact on the drug prices which can be seen as an indicator of availability (Gibson et al. 2005, European Monitoring Centre for Drugs and Drug Addiction 2010). Therefore, explanations remain speculative because multiple interacting factors influence illegal drug markets (European Monitoring Centre for Drugs and Drug Addiction 2010). Supply-based interventions may lead to a shift in the use of another substance instead of reducing harms (Unick et al. 2013). Therefore, in order to reduce opioid abuse related harms, focusing the prevention resources on treatment and demand-side reduction may be more productive.

6.1.3 Buprenorphine-naloxone dispensing in Finnish community pharmacies (IV)

The results of pharmacy survey indicated that community-pharmacy based dispensing of BNX was still relatively small-scale in Finland but the first experiences have been positive. Most pharmacies providing OST were located in Southern Finland. The geographical distribution of OST pharmacies reflects probably the distribution of pharmacies rather than the availability of OST, which has been acknowledged in previous studies as well (Nielsen et al. 2007a). In addition, the majority of Finnish drug users live in large cities in Southern Finland and, therefore, also treatment services are concentrated on this area (Partanen et al. 2007). About 10% of BNX-treated OST clients had their BNX dispensed from community pharmacy. The proportion of OST clients dispensed at pharmacies was relatively low compared to Switzerland and Australia, where almost 70% of OST clients were treated in community pharmacies (Samitca et al. 2007, Lawrinson et al. 2008). It is possible that the fear of diversion and abuse may partly explain the scale of BNX dispensing in Finnish community pharmacies. In addition, community pharmacy dispensing of BNX was relatively new possibility at the time of the study. Most pharmacies had small OST programs (41% of pharmacies had only one OST client). The number of OST clients was associated with the prevalence of problems (OR 1.39, 95% CI 1.05-1.86). Other studies have reported similarly that more OST clients pharmacies served, more likely they had experienced problems (Lawrinson et al. 2008, Winstock et al. 2010). According to our survey, only 26% of pharmacies had experienced problems, which were mostly technical issues related to dose timing or prescriptions/ financial obligations. Previous studies have reported more serious problems such as argumentative behaviour, disturbances and thefts (Lawrinson et al. 2008), as well as concerns about diversion (Nielsen et al. 2007a). In addition, the prevalence of problems has been higher, e.g. in Switzerland 83% of pharmacies had experienced problems (Samitca et al. 2007), and 41% of Australian pharmacists had refused to dose an OST client during the past month (Winstock et al. 2010). However, there were likely to be differences in how 'problem' has been defined and understood by respondents in different studies (i.e. problems in OST provision from pharmacy in general or related to OST clients per se) (Raisch et al. 2005, Samitca et al. 2007). It is possible that the low frequency of problems in Finnish community pharmacies is explained by the treatment practices since all OST clients are first stabilized in addiction treatment units and carefully selected for suitability for community pharmacy dispensing. According to Australian experience, stabilization of OST clients in specialist clinics has been associated with fewer problems in community pharmacy dispensing (Winstock et al. 2010).

Even though all respondents thought that pharmacy dispensing of BNX had gone well or very well, 80% of them recognized opportunities for future development, most commonly financial remuneration for pharmacies. Finnish community pharmacies do not receive any Government funding to provide OST services. Financial issues should be examined more carefully in case of increasing demand of OST services from pharmacies and, especially, if new responsibilities, such as supervised dosing, will be introduced in the future. Needed improvements cited by the pharmacies were similar to the ones reported in previous studies, such as more training for pharmacy staff (Fleming et al. 2001, Samitca et al. 2007, Torre et al. 2010) and better co-operation and communication with physicians (Samitca et al. 2007, Winstock et al. 2010). Most respondents stated that supervised dosing is not a suitable service in Finnish pharmacies, even though it is a common procedure in many other countries (Matheson et al. 2007, Nielsen et al. 2007a, Samitca et al. 2007). However, these attitudes may reflect the fact that BNX dispensing was relatively novel and unfamiliar to Finnish pharmacy staff at the time of the survey. In England, pharmacists' acceptability of dose supervision has increased as the service has expanded (Sheridan et al. 2007). It is possible that the lack of private area to supervise dosing may have affected

pharmacists' attitudes. Both OST clients as well as other pharmacy customers have expressed their concerns about ensuring the privacy of OST medicine dosing in the community pharmacies (Lawrie et al. 2004, Lea et al. 2008). Despite having expressed a negative attitude towards supervision, most respondents (85%) were willing to accept more OST clients in the future, which was a higher proportion than in previous studies (Lawrinson et al. 2008).

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Study populations

The Huuti studies were based on data collected at the HDI which consists of information about all clients seeking treatment during the data collection period from January 31, 1997 until August 31, 2008. Clients at the HDI were self-referred to the treatment or referred by other clinicians/ treatment units due to their substance abuse problems. In case of later client group, clients may have had more severe substance abuse problems because the physician had regarded it necessary to refer the person to a specialized service. However, the aim of this study was not to select a representative sample of general population with substance abuse problems but to examine characteristics of those who seek treatment for substance abuse. This minimizes the possibility of the presence of selection bias. Substance abuse services of the HDI were relocated to another suburb of Helsinki in 2000 which may have affected the client population. The new location was further from a residential area with a high prevalence of amphetamine abuse. This may partly explain the decrease in the number of amphetamine clients seeking treatment from the HDI during the study period. Some clients had multiple visits to HDI but only the first visit was included in this study in order to ensure the consistency of data. Detailed information on the number of clients receiving OST was not available. These clients may differ from the clients entering treatment for the first time.

The participation rate for the intervention of study III was high (88%) and the study sample can be regarded as a representative sample of BNX treated OST patients in Kuopio. Patients who refused to participate were mainly males (four out of five patients). However, these patients were also obliged to use EMDs as part of their treatment. Therefore, the number of patients not willing to participate in the trial had no effect on the control of BNX take-home dosing or diversion measurements. All clients visiting the NEP service during the data collection periods were asked to fill in the questionnaire. The response rates were relatively low (46%, 39%) but satisfactory considering the target population and similar compared to a response rate in another Finnish survey among NEP clients (30%) (Alho et al. 2007). Nevertheless, the absolute numbers of participants and respondents were relatively low and this limited statistical testing. Hence, there may not have been enough power to detect changes in outcome measures. However, in order to be able to create a study design similar to our study (comprehensive control of BNX take-home doses), a larger multicentre study with possible patients would have been very difficult to conduct.

The list of pharmacies who had supplied BNX was received from the company with the marketing authorization for the BNX product but it is possible that the list has not been all-inclusive. However, there is no evident reason to assume that the amount of possibly missing information was large or differential. The response rate was high (93%) and respondents can be regarded as a representative sample of Finnish community pharmacies with OST clients. Due to low number of non-respondents, the presence of selection bias is unlikely. The characteristics of pharmacies responding after the reminder were similar to other pharmacies indicating no response bias. Similarly to study III, the absolute number of

respondents was low and limited the possibility of statistical testing. Some of the logistic regression models may have been underpowered.

6.2.2 Study designs

Study I was a descriptive study of clients seeking treatment during the 12-year study period. Individual-level follow-up data were not available but characteristics of clients seeking treatment in different years were compared to examine changes over time. This provides more information than studies with merely cross-sectional study designs which are commonly used in studies examining buprenorphine abuse (Table 2, Chapter 2.2.3.1). Studies II and IV were cross-sectional. It is not possible to determine causality with cross-sectional study designs. Study III utilized an innovative study design. A clinical trial was combined with NEP surveys and the review of drug screen data from a large university hospital. The clinical part of the study utilized a naturalistic open-label design without a control group which challenges the reliability of results. However, controlled studies may not provide information about intervention's performance in real-world settings and, therefore, the naturalistic setting can be considered as strength of the study. The duration of the study (four months) may have been too short to detect the impact of EMDs on diversion. It has to be remembered that EMDs could only detect whether tablets were removed from the device, not when the medicine was actually taken or by whom. Stockpiling medicines and diverting little by little has been possible despite the use of devices.

6.2.3 Data collection and measures

Huuti data were mainly based on clients' self-reports which is a possible source of information bias and response bias. Self-reported data may be prone to recall bias. Some clients may have been under the influence of drugs and/or alcohol during their consultation. Clients' desire to receive specific treatments may have affected their self-reporting. Data were not available from urine drug screens to confirm self-reported drug use. However, the validity and reliability of self-reported data on substance use and related behaviour have been established (Darke 1998, Napper et al. 2010, Smith et al. 2010), even though contrasting results have also been published (Chermack et al. 2000). Clients may be more likely to self-report drug abuse at intake into a drug abuse treatment program than at follow-up visits (Wish et al. 1997, Chermack et al. 2000). In addition, the abuse of a drug which is the main reason for treatment seeking may be self-reported more likely than other concurrent drug abuse. The type of substance and the severity of client's drug abuse problems may also influence clients' willingness to report substance abuse. Nevertheless, self-report is the most feasible method for measuring certain aspects of substance abuse such as intensity and route of administration (Smith et al. 2010). Validated assessment tools (e.g., EuropAsi and TDI) were used to ensure the quality of data collection. Psychiatric symptoms and medical comorbidities were clinically diagnosed by specialist physicians in accordance with established criteria. However, depressive and psychotic symptoms were not consistently assessed using validated scales because data were collected as part of clinical practice. Nevertheless, there is evidence that key informants (e.g., drug treatment centre directors and councillors) can provide reliable assessments of their patients' drug abuse problems (Cicero et al. 2011a).

The characterization of clients as buprenorphine, heroin or amphetamine clients was based on clients' self-reported primary drug of abuse. Misclassification is possible because poly-drug abuse is common (Darke & Hall 1995, Partanen et al. 2004, Winslow et al. 2006, Otiashvili et al. 2010, Tammi et al. 2011, Lofwall & Havens 2012). The present availability and price of substances may have an impact on clients' choice of primary drug of abuse.

However, the categorization was performed using a validated assessment tool. In addition, possible misclassification is likely to be non-systematic because there is no reason to assume that clients would have reported another substance as their primary drug of abuse more likely than another. Clients may have been prone to report opioids as their primary drug of abuse if they want to get into OST. However, during the study period OST inclusion criteria were strict and, therefore, this kind of behaviour has been less likely. Underreporting of substance abuse is probably not as likely in treatment seeking drug user population than in general population. Confounding by poly-drug use and uncertainty concerning the actual content of used substances may have also affected clients' self-reported drug abuse. In study I, analyses were performed separately for time periods 1997-2001 and 2002-2008. No further adjustsments were made because the purpose of the study was to describe the characteristics of clients. In study II, the multivariate model was adjusted for factors statistically significant in univariate models including basic demographic characteristics (age, gender) possibly confounding the results. However, there is always a possibility for residual confounding because unmeasured factors cannot be adjusted for.

Study III utilized different data collection procedures. All questionnaires (patients' and staff's questionnaires, NEP surveys) were anonymous and, therefore, it is reasonable to assume that reports were reliable. However, the psychometric properties of questionnaires were not validated. To our knowledge, there were no validated questionnaires suitable for our study and, therefore, we had to develop questionnaires for the purposes of this study. The questionnaire to OST patients was modified from the one used in a previous study (Tacke et al. 2009). However, the questionnaire was not pilot-tested in this previous study. The questionnaire used in the NEP survey was developed in co-operation with service-staff to ensure content-validity. However, NEP survey responses as well as buprenorphine-positive drug screens served as surrogate outcomes for diversion. The results of surrogate outcome measures should be interpreted with caution. The use of drug screen data was based on the assumption that any licit or illicit buprenorphine user in Kuopio with an acute health problem requiring hospital treatment would be subjected to a urine drug screen, if his/ her condition was suspected to be drug-related. It is possible that this assumption was not fully tenable which means results of drug screen data may be underestimations. However, the purpose of the study was to compare the proportions of positive drug screens between trial periods, and not to explore the absolute numbers per se. Therefore, it is unlikely that this had a major impact on the results. Even though several different indicators were used to measure diversion, qualitative measurements could have been used as well.

The questionnaire used in the study IV was developed according to the aims of the study. It was pilot-tested for face-validity and content-validity before the study. However, it is possible that respondents may have misunderstood some questions, because the questionnaire was not formally validated. Staff members were encouraged to discuss their experiences before completing the questionnaire. Despite these instructions, it is possible that responses reflect predominantly the experiences of the individual pharmacist completing the questionnaire. In this case, the presence of problems and the numbers of diversion/ abuse suspicions may have been underestimated. The location and size of pharmacy were assessed as potential confounders. Adjusted models provided similar results compared to unadjusted ones and, therefore, these results were not reported. In addition, the 95% CIs for adjusted ORs were relatively wide, indicating dispersion of values and possible inaccuracy in the parameter estimates.

6.2.3.1 Missing data

The Huuti studies had a considerable amount of missing data, especially for the first four years of data collection. In 2001, data collection process was changed and more comprehensive data were available from then on. Nevertheless, missing data exist throughout the data collection period. There can be various possible explanations for missing data. Data were collected for the purposes of clinical practice. Clinically irrelevant questions may have been skipped, e.g., absence of certain symptoms or clinical findings. It is possible that the data files of clients with more severe abuse problems and/ or those intoxicated during the consultation included more missing information which may have caused information bias. However, the bias caused by missing data was minimized in this study by including only variables with a relatively low level of missing information (<20%) into the analyses of study I and by multiple imputation and restricting analyses to years 2001-2008 in the study II.

6.2.4 Generalizability of findings

Results of the Huuti study can be generalized to those seeking treatment in the Helsinki metropolitan area. It is likely that buprenorphine users in other parts of Finland resemble those from the Helsinki area but generalizing the results should be done with caution. However, as discussed previously people abusing buprenorphine in other countries are different from buprenorphine users in Finland. Buprenorphine is not regarded as a PO in all studies, especially, in those conducted in North America. This means that caution is required when making comparisons to other studies examining PO users. Results may not be generalizable to people not seeking treatment. The data collection period of the Huuti study was in 1997-2008. Availability of different illicit substances changed over time. Single-ingredient buprenorphine was withdrawn from the market in December 2007 and replaced by BNX which may have had impact on abuse patterns among opioid users. In addition, treatment practices have changed over time. The availability of OST has markedly increased in Finland during the previous decade which has probably had an impact on users' willingness to seek treatment.

Results of study III can be generalized to medium-sized Finnish cities with OST practices similar to those in Kuopio. All eligible OST patients were asked to participate in the clinical part of the study and participation rate was high (88%). Therefore, study participants can be regarded as a representative sample of BNX-treated OST patients in Kuopio. In addition, all patients not willing to participate in the trial used EMDs as part of their routine treatment in order to ensure a comprehensive control of BNX take-home dosing. Results cannot be generalized to different treatment settings or other devices than the one used in this trial.

For study IV, sampling was not performed because all community pharmacies that had supplied BNX were contacted. The response rate was high (93%) and therefore respondents can be regarded as a comprehensive sample of community pharmacies providing OST services in Finland. The study took place in August 2011 and presently, two years after the survey, there may be more pharmacies dispensing BNX. The results of this study may have limited generalizability to the present situation. There are substantial differences in pharmacy-based OST services, including medicines dispensed (BNX, BUP, and/or methadone) and the provision of supervised dosing, as well as in pharmacy practices and legislations between countries and, therefore, results may not be generalizable to other countries.

7 Conclusions

Based on the findings of the four studies included in the thesis, the following conclusions were made:

1. The proportion of clients seeking treatment for buprenorphine abuse increased in Finland between 1997 and 2008. Most buprenorphine clients were injecting buprenorphine and using it on a daily basis. Intravenous administration and daily abuse were more common among buprenorphine compared to heroin and amphetamine clients. Concurrent substance abuse, especially the abuse of prescription medicines, increased during the study period.

2. Despite more intense abuse patterns, buprenorphine clients had similar social, health and treatment-related characteristics compared to amphetamine clients. Unemployment, low educational levels and reliance on social benefits were common among buprenorphine clients.

3. The use of electronic medicine dispensers provided a feasible method for improving the safe storage of take-home doses of buprenorphine-naloxone. However, the ability of this method to prevent the diversion of buprenorphine-naloxone could not be demonstrated.

4. Buprenorphine-naloxone dispensing from Finnish community pharmacies has remained small-scale. About 10% of all BNX-treated clients in Finland collected their medicines from a community pharmacy. The first experiences have been positive and only every fourth pharmacy had experienced one or more problems related to OST services.

8 Implications for the Future

8.1 PRACTICE IMPLICATIONS

This study showed a constant increasing trend in treatment seeking for buprenorphine abuse in Finland. Treatment providers and policy makers should take into account that treatment services (e.g. OST) for opioid users in Finland should be targeted specifically for buprenorphine users. Buprenorphine users were commonly IV-users and the frequency of daily use was high. Concurrent substance abuse, social problems such as unemployment and reliance on society benefits, as well as health problems such as depressive symptoms were common. These factors should be taken into account in a comprehensive treatment approach. In addition, this study reported that clients seeking treatment for buprenorphine and amphetamine abuse were relatively similar in terms of social, health and treatment-related factors. These results may imply that the route of administration is a stronger determinant of these characteristics than the primary drug of abuse. It seems that PO abuse does not offer public health benefits, if drugs are injected. It has been suggested that PO abuse can offer public health benefits because PO abuse is associated with a lower prevalence of risk behaviours relevant for morbidity and mortality (e.g., injecting) compared to heroin abuse (Fischer et al. 2009).

The results of this thesis show that new technology such as electronic medicine dispensers can be used as part of OST in a 'real-life' setting. EMDs can improve the safety of take-home dosing from the perspectives of both patients and staff. If EMDs can relieve the external pressure to sell or pass on OST medicines, they can provide clinically significant benefits to OST. However, whether this method can be used in the prevention of diversion in general is unclear. The possibility for tampering with devices should be taken into consideration when using them in clinical practice. Based on the experiences from our trial, the manufacturer of the device made technical changes to make the device more tamper-proof. However, it may not be possible to design a totally tamper-proof device without any pitfalls. Therefore, it should be carefully considered whether attempting to prevent diversion via technical, restrictive methods is reasonable or efficient. It might be more powerful to concentrate on the reasons behind diversion, such as patients' dissatisfaction with treatment, financial problems and offering OST to patients with low treatment motivation.

This thesis includes the first study on OST medicine dispensing by Finnish community pharmacies. The service provision has remained small-scale but first experiences have been positive and problems were rare even though only in one fourth of pharmacies, the staff had received training on OST. The stabilization of OST in treatment units and careful selection of suitable OST clients may be contributing to this success. Therefore, current treatment practices in Finland appear to be functioning well, even though improvements in pharmacy staff's training levels and possible financial remunerations should be considered when developing OST services. The possibility of expanding pharmacy-based OST services without compromising current functionality could be considered in the future. Expanding community pharmacy-based BNX dispensing can release both financial and staff resources in treatment units and assist the rehabilitation of OST clients.

8.2 FUTURE RESEARCH DIRECTIONS

More longitudinal studies on buprenorphine abuse are needed, because most existing studies have been cross-sectional. Reasons behind buprenorphine abuse, whether it is self-medication, euphoria-seeking or other reasons, should be explored in different settings. More studies are needed in order to understand different abuse patterns among opioid users, especially among the evolving group of PO users. Best treatment practices designed specifically for people who abuse buprenorphine should be examined and evaluated. Results from study II implied that the route of administration is a stronger determinant of social, health and treatment-related characteristics than the primary drug of abuse. The validity of this hypothesis could be tested.

Larger controlled studies with more patients and longer follow-up periods are needed to examine the effect of electronic devices on the diversion of OST medicines. Studies should utilize different devices in different treatment settings. The possibility to use other outcomes measures, especially non-surrogate measures, should be considered. Other uses of EMDs could be explored, such as in the treatment of chronic non-malignant pain with opioid-analgesics or as part of BZD detoxification.

Further studies are needed to reflect the current situation with OST provision from Finnish community pharmacies. The number of OST patients has increased in Finland in recent years (Social Insurance Institute 2013, Simojoki 2013) and, therefore, it is likely that the pharmacy dispensing of BNX has grown as well. Studies examining the experiences and opinions of service users, i.e. OST clients collecting their BNX from pharmacies, would be important for the development of community pharmacy-based OST provision. The possibility of providing supervised OST medicine dosing from the Finnish community pharmacies and should be explored.

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Buprenorphine – Features of Abuse and Methods for Improving Unobserved Dosing in Opioid Substitution Treatment

Buprenorphine is an efficient treatment for opioid dependence but its abuse has raised concerns. This thesis examined the characteristics of persons seeking treatment for buprenorphine abuse and possibilities for improving unobserved dosing in opioid substitution treatment (OST). It was shown that clients seeking treatment for buprenorphine abuse had risky abuse patterns in terms of injecting and daily abuse. The ability of electronic medicine dispensers to prevent buprenorphine diversion could not be demonstrated. The first experiences of dispensing buprenorphine for OST from Finnish community pharmacies were positive.

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