A Five-Year Follow-up of Buprenorphine Abuse Potential

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Abstract

Background: Mono-buprenorphine has been the most abused intravenous opioid in Finland since 2001. A buprenorphine/naloxone combination drug intended to lower the risk of abuse became already available in Finland in 2004. In 2008 the mono-buprenorphine product was placed under special license (for pregnancy only). The availability of both drug preparations provides an opportunity to assess the extent to which the two products are abused and street priced. The main aim of this study was to evaluate five-year trends of abuse pattern, dosage and street price of illicit opioid abuse in the Helsinki metropolitan area.

Methods: A questionnaire consisting of multiple-choice and fill-in-the-blank questions was distributed to all attendees at all the 10 harm reduction (needle exchange) units in the Helsinki area over 2-week periods from 2005-2008 and in 2010.

Results: In 2007, 60.2% of the respondents claimed heroin or morphine as their first injected drug. This percentage had declined to 51.3% in 2010, but in contrast the incidence of buprenorphine as the first injected or abused drug by the study population increased from 30.5% (2007) to 44.4% (2010). Among all drugs mono-buprenorphine was the most frequently used primary illicit drug (68.2-77%), followed by amphetamine. In 2005, the street price of buprenorphine/naloxone was 50% lower than that of mono-buprenorphine and this price difference has remained constant during the evaluation period. The respondents bought their buprenorphine from several sources, primarily street dealers, but they also received/bought buprenorphine/naloxone from patients in maintenance treatment.

Conclusions: Buprenorphine is still the most commonly used illicit opioid in Finland. Restrictions on the access of mono-buprenorphine and the lower street price of buprenorphine/naloxone did not significantly alter the illicit use of this drug over several years of its availability on the street.

Keywords: Buprenorphine; Naloxone; Opioids; Intravenous; Polysubstance abuse

Introduction

Buprenorphine is a mu-opioid receptor partial agonist and partial kappa-opioid receptor antagonist. The high-dose sublingual mono-buprenorphine tablet formulation (Subutex®) is used worldwide as an effective treatment for opioid dependence [1-3]. The abuse potential of buprenorphine has been recognized since its introduction, and Finland, France, Australia and the UK have reported its abuse [4] as also in the United States and Asia [5-7]. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 12 out of 17 member states of the European Union reported the abuse of legal buprenorphine in 2004 [4,8]. The current rates of abuse of medication for treatments of opioid dependence, mainly buprenorphine and methadone, in subjects involved in the open drug scene range from 5.6% in Portugal [9] to 73% in Finland [10] and over 50% for slow release morphine in Austria [11].

The prevalence of opioid abuse in Finland is approximately 0.5%, and the majority of abusers are located in the Helsinki metropolitan area [12], though the majority of drug is imported from other countries, notably France [13]. Since 2001, mono-buprenorphine has been the most abused opioid by the intravenous route in Finland [10,12,14]; the incidence of its abuse in Finland is different than in many other countries. This difference has also been observed in the number of heroin-related deaths, which have decreased rapidly since 2000 [15]. Unfortunately however, a simultaneous increase has been observed in the number of deaths related to combinations of tranquiliizers, alcohol and buprenorphine [16,17].

In Finland, opioid maintenance treatment (OMT) has been available since 1995 based on the Ministry of Social Affairs and Health recommendations, and the latest decree was introduced in 2008. Criteria for access to treatment are restrictive, and the treatment is strictly controlled. The buprenorphine/naloxone combination drug (Suboxone®) designed to lower the risk of abuse was introduced into Finland in late 2004. In 2008 the mono-buprenorphine product was placed under special license (for pregnancy only). Currently there are approximately 2450 patients in OMT and the combination product is the most popular prescribed OMT with a rate of use of 55%, 35% of patients are on methadone and 10% on mono-buprenorphine [18].

The first health counseling service for intravenous drug users, which was based on the harm reduction approach, opened in the Helsinki capital region in 1997. The activities began as a response to the social and health authorities’ concern in Finland in the 1990s regarding the spread of contagious blood-borne diseases such as HIV and hepatitis through sharing of needles during intravenous drug use. The services are particularly aimed at active intravenous drug users, and to receive services, the users do not have to commit to stopping drug use or even present any plans for quitting. In addition to the exchange of syringes
and needles, users receive help and support on social and health care issues. In 2009 there were harm reduction units (i.e. needle exchange units) in over 35 municipalities with approximately 13000 different users and over 3.1 million syringes were exchanged [19].

The 2000-2002 Riski study [14] of intravenous drug users visiting harm reduction units describes the users’ background and drug use on the basis of baseline interviews. In this study a total of 494 baseline interviews were conducted in two harm reduction units in Helsinki and one each in Turku and Tampere. The respondents’ median age was 27.5 years, and 70% were male; their drug use began at approximately 15 years of age. According to the results, only 6% of the opioid users had started injecting mono-buprenorphine as their first injected drug. Approximately half of the opioid abusers had injected heroin 1 year prior to starting mono-buprenorphine use, approximately one-third had started injecting heroin during the same year they began abusing mono-buprenorphine, and 15% began using heroin only after regular mono-buprenorphine abuse.

Buprenorphine has been for more than a decade the most abused opioid in Finland. The long history of abuse provides a unique opportunity to assess the trends and patterns of opioid abuse. Primary outcomes of this study were a) first intravenously abused opioid, b) duration of mono-buprenorphine and buprenorphine-naloxone abuse, c) changes in abused buprenorphine prevalence and d) changes in buprenorphine street prices.

Methods

A questionnaire consisting of multiple-choice questions was distributed to all attendees at the 10 harm reduction units (i.e. needle exchange units for untreated drug abusers) in the Helsinki metropolitan area during annual 2-week period in years 2005-2010, excluding 2009. Survey completion was voluntary and conducted anonymously, and the services provided were not influenced by whether the attendees completed the surveys. All surveys included an informed consent document that explained the voluntary basis on 12.13.04 (reference number KTL 6/2004). The study protocol was notified to the ethical committee of the study approval was filed in accordance with the Personal Data Protection rule of the National Public Health Institute.

The annual survey contained 12 identical questions. In addition four extra questions were added in 2007 and three in 2010. The annual questionnaire included:

- Background questions (gender and age),
- Two questions on the patterns of drug use:
  i) What is currently the drug you most frequently use?  
  ii) Which drugs did you use in addition to the previously-mentioned drug?  

These responses were categorized into seven subgroups:

  a) all buprenorphine products,  
  b) all amphetamine/ methamphetamine drugs,  
  c) heroin or morphine,  
  d) MDMA, MDA, MDEA, MBDB or ecstasy,  
  e) cocaine,  
  f) oxycodin, and  
  g) other drug (benzodiazepines and others not included into classes’ a-f).

- Two questions on the willingness to enter the treatment:
  i) Are you currently in an OMT program in Finland or Are you currently in an OMT program in another country?  
  ii) Would you like to be in an OMT program?  

- Several questions on the duration (years) on intravenous abuse, frequency and dose of abuse and the route of abuse which were surveyed separately for both mono-buprenorphine and buprenorphine/naloxone.

- The street price paid for an 8 mg mono-buprenorphine or buprenorphine/naloxone tablet was also asked.

The additional questions were concerning:

  i) On the first intravenously abused drug and opioid,  
  ii) The onset of Hepatitis C in years 2007-2010, and  
  iii) In 2010 only from where the buprenorphine was obtained/bought.

Data analysis

The number of respondents per question differs because the participants were free to complete any or all portions of the survey. The numbers of answers obtained for individual questions are reported in the result section. The results are analyzed by Student’s t, chi2, df and p-value (one-sided test) and were calculated by using the SPSS, Survo version 3.35 program and then analyzed using Microsoft Excel in calculating mean values and SD.

Ethical conduct of study

The study was conducted according to EU and Finnish regulations (KL 313/2004 and 295/2004) regarding clinical research, and a notification to the ethical committee of the study approval was filed on 12.13.04 (reference number KTL 6/2004). The study protocol was in accordance with the Personal Data Protection rule of the National Public Health Institute.

Results

A total of 1507 individuals completed questionnaires (yearly 2005: 176; 2006: 260; 2007: 411; 2008: 384 and 2010: 276), 1023 respondents (68%) were male, and 478 (32%) were female. The mean response rate was 50.8% (calculated as the return rate % of the individuals who visited the service units during the study period) and ranged from 45.4% (2008) to 58.2% (2005). The average respondent’s age in 2005

<table>
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<tr>
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<td>Mean age</td>
<td>27.8 (SD ± 6.9)</td>
<td>29.7 (SD ± 8)</td>
<td>30 (SD ± 7.8)</td>
<td>31 (SD ± 8)</td>
<td>31.9 (SD ± 8.6)</td>
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<td>years of opioid iv abuse</td>
<td>7.3 (SD ± 4.9)</td>
<td>7.6 (SD ± 4.53)</td>
<td>8.8 (SD ± 6.67)</td>
<td>8.8 (SD ± 6)</td>
<td>9.8 (SD ± 6.66)</td>
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<td>Years of mono- buprenorphine iv abuse</td>
<td>4.2 (SD ± 2)</td>
<td>4.8 (SD ± 2.5)</td>
<td>5.4 (SD ± 3.13)</td>
<td>5.5 (SD ± 3)</td>
<td>7.2 (SD ± 4.03)</td>
<td>&lt;0.001</td>
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<td>Years of buprenorphine/naloxone iv abuse</td>
<td>N.A.</td>
<td>1.7 (SD ± 1.7)</td>
<td>1.8 (SD ± 0.9)</td>
<td>2.4 (SD ± 2.2)</td>
<td>4.0 (SD ± 3.4)</td>
<td>&lt;0.001</td>
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Table 1: Demographics.
Heroin/morphine was the third most abused intravenous substance of multiple drugs in 2005 and even 74.8% by 2010. In 2005 and 2006, a total of 48.4% of the respondents reported the abuse of buprenorphine and amphetamine as a most frequently used service (the needle exchange services) which was 5.5 years (SD ± 3.1) in 2007 and 6.9 years (SD ± 3.9) in 2010.

Years of buprenorphine abuse

The mean duration of intravenous mono-buprenorphine abuse was 4.2 (SD ± 2) years (n=173) and 7.2 (SD ± 4) years in 2005 and 2010, respectively (compared to 2005, t=-8.954 df=372 P<0.001). The mean duration of intravenous buprenorphine/naloxone abuse was 1.7 years in 2006 (SD ± 1.7) and four years (SD ± 3.4) in 2010 (compared to 2006, t=-4.928 df=153 P<0.001). In 2006 buprenorphine/naloxone was tried at least once by 23.4%, more than twice by 35.8% and frequently by 8.1%. In 2010 (n=174) correspondingly once 8%, twice 56.7% and frequently by 14.4% of the responders (Chi²=27.2508 df=3 P<0.001). The percentage of respondents who had never abused buprenorphine/naloxone was 31% in 2005 (n=46) and 19.5% in 2010 (n=34) (Chi²=6.24875 df=1 P<0.001).

Primary drug (most frequently used)

Buprenorphine was the most frequently abused primary intravenous drug in all survey years (2005: 68.2% and 2010: 77.9%), followed by amphetamine/methamphetamine (2005: 22.7% and 2010: 67.8%, Table 2). In 2005, the primary drug was the only drug used by 39.4% of the respondents (n=157) and in 2010, the percentage of respondents who reported their primary drug as the only drug of used dropped to 23.8%. However, in all survey years the primary drug adds up to more than 100% of the responders, for example in 2010 up to 146%, thus approximately 46% of the responders were considering both buprenorphine and amphetamine as a most frequently used drug. Indeed, a total of 48.4% of the respondents reported the abuse of multiple drugs in 2005 and even 74.8% by 2010. In 2005 and 2006, heroin/morphine was the third most abused intravenous substance and was abused in 2005 by 2.3% of the respondents; this level increased to 11.7% in 2007 and then declined to 8.3% in 2010 (compared to 2007, Chi²=49.6211 df=20 P<0.001). The category “other drug”, which includes benzodiazepines, surpassed heroin/morphine in 2007 with yearly frequencies varying between 21.3% and 44.9%, as most frequently abused drug (Table 2). The abuse of ecstasy, MDMA etc. designer drugs and cocaine as primary drug remained in small numbers and did not significantly increase during the years surveyed 2007-2010 (Table 2).

First opioid of use

Since 2007 the survey asked respondents to identify the first intravenous opioid that they abused. In 2007, 60.2% (n=344) of the respondents identified heroin or morphine as the first opioid abused, and buprenorphine was identified as their first intravenous drug by 30.5% of the responders. In 2010, the percentage of respondents who named heroin or morphine as their first intravenous drug fell to 51.2% (n=234), and the percentage of those who identified buprenorphine as their first intravenous drug increased to 44.4% (increase Chi²=14.81 df=3 P=0.0020). In 2007, 9.2% of the respondents identified another drug (non-opioid) as their first drug; this percentage decreased to 4.3% in 2010 (Chi²=0.736671 df=1 P=0.3907) (Table 3).

Buprenorphine abuse pattern

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

The abuse method of buprenorphine/naloxone changed throughout the duration of the study. In 2005 (n=111) 60.4% misused intravenously, 4.5% nasally and 13.5% sublingually while 21.6% reported mixed ways (asked only in 2006). This was changed by 2010 (n=140) when 69.3% misused intravenously, 24.3% nasally and only 6.4% sublingually (change of routing, Chi²=40.87666 df=12 P<0.001).

Street price of buprenorphine

All annual questionnaires inquired the street price and daily dosage of buprenorphine used: 1) How much did you pay for 8 mg of Subutex® or Suboxone®? 2) What is your current daily dose of Subutex®/Suboxone® and 3) from where did you obtain/purchase your buprenorphine? In 2005 (n=176), the mean street price for a single dose of 8 mg mono-buprenorphine was 28 Euros (Figure 1). The price increased by 53.2% to 42.9 Euros in 2010. Inflation in Finland during...
this time period accounts for less than 2.75 Euros of the increase [20]. The corresponding average price of buprenorphine/naloxone was 12.3 Euros in 2005 and it increased by 103.2% to 25 Euros in 2010. However, the price of buprenorphine/naloxone was 36% lower than that of mono-buprenorphine in 2005, and this price difference had declined to 41.4% by 2010 (Figure 1).

Between 2006 and 2010 the daily average dose of IV abused mono-buprenorphine decreased by 22.9% from 7.0 mg to 5.5 mg/day. During the same time period the average daily dose of buprenorphine/naloxone decreased by 36.6% from 8.2 mg to 5.2 mg (Figure 1).

**Route of illicit buprenorphine purchase**

Participants were asked in 2010 only where they obtained/purchased their buprenorphine. Several options were possible to choose from and thus the added percentages can be over 100%. For mono-buprenorphine (n=161), the majority (91.3%) reported buying it from a street dealer, 22.4% from a person attending official opioid maintenance treatment, and 8.7% imported it themselves from abroad. For buprenophrine/naloxone (n=125), the corresponding numbers were 68.8% bought from a dealer, 49.2% from a person in substitution treatment, and only 2.4% brought it abroad (compared to mono-buprenorphine, Chi²=24.3302 df=2 P<0.001).

**Demand for entering opioid maintenance therapy (OMT) programs**

In 2005, 141 respondents (80.1%) answered these questions, and 192 respondents (69.6%) answered them in 2010. In 2005, 8 respondents (5.7%) were in treatment in Finland, and 21 (14.9%) were in treatment abroad. In 2010, 29 (18.8%) were in treatment in Finland, and only 2 (1.3%) were in treatment abroad.

The number of respondents who desired to enter OMT programs was 43% in 2005 (n=112) and 64.1% in 2010 (n=123) (increase Chi²=9.84766 df=3 P=0.0199). In 2010, of the remaining 84 participants informed that they had been on OMT assessment and 45.2% had fulfilled the criteria for treatment but were lined up, 26.2% had not been accepted for treatment, and 28.6% had repeatedly attempted to enter treatment but had not fulfilled the criteria.

**HCV infection prevalence**

The prevalence and duration of hepatitis C virus (HCV) were surveyed in 2007-2010. In 2007 (n=401), 66.3% (n=266) of participants reported having diagnosed HCV infection, on average for 7 years (SD ± 5.2). In 2008 (n=372), 69% (n=257) were diagnosed for HCV on average for 7.44 years (SD ± 5.88). In 2010 (n=271), 65.8% (n=179) were HCV positive on average for 9.3 years (SD ± 6.95).

**Discussion**

The study population consisted primarily of untreated (94%) street drug abusers in the Helsinki metropolitan area and does not represent the entire Finnish drug abuser population. Around half of the opioid abusers do live in the metropolitan area [12] and the harm reduction services do also reach a substantial proportion of the abusers [21]. In this study the target population was intravenous drug abusers, who are the main customer group of Finnish, harm reduction units. The main goal of these centers is in hepatitis/HIV prevention and helping users to seek treatment.

The variation of the annual response rate creates bias and is one of the limitations of this study. However, the exact estimation of the return rate was impossible to calculate because both the service and the surveys were anonymous. The aim of the study design was to limit multiple survey copies from same individual. Generally, our results on drug abuse patterns, especially on opioid and buprenorphine abuse are in agreement with previous studies on treatment seeking intravenous drug users in Finland [21-23].

Over the last decade, buprenorphine has been cited as the major opioid abused in Finland, and earlier Finnish studies have indicated that the majority of abusers (73%) abuse buprenorphine for the purpose of self-medication, but not to get high [10]. This raises an interesting question, what is the first intravenous opioid abused? This was surveyed for the first time in the current study and it shows that 60% of the respondents in 2007 claimed heroin or morphine as their first intravenous opioid, and that number was reduced to 51% in 2010. Interestingly, the proportion of abusers that started with buprenorphine as first intravenous opiate was 30% in 2007 and increased to 44.4% in 2010. This change was even more profound when compared to the results of the 2002 Riski study [14]. In 2002, less than 10% of respondents identified buprenorphine as the first opioid drug of abuse. One possible explanation for this increase over time is that older abusers, with a longer abuse history started with heroin, whereas the younger generation of abusers started with buprenorphine. Another explanation could be that in 2002 buprenorphine was still relatively new to Finland. The same Riski study indicates that 85% of respondents used heroin within one year prior or after regular use of buprenorphine, which is in line with our results. The duration of regular buprenorphine intravenous abuse was consistently 2.5 to 3 years shorter than total opioid intravenous abuse, which indicates regular abuse of other opioids prior to buprenorphine use. According to the data from the Social Insurance Institution of Finland (KELA), these prior abused opioids could be mainly prescription opioids. The number of patients receiving prescribed opioids in Finland has more than doubled between 2008 and 2011 [24]. It could be possible that prescription opioids are much easier and cheaper to obtain than buprenorphine, and thus could be the main abused opioids in the first years of misuse.

One main study objective was to identify and examine possible trends of abuse in mono-buprenorphine and buprenorphine/naloxone use. Particular areas of inquiry included the street price, the pattern of abuse, and whether buprenorphine was the first intravenous...
opioid used. The number of buprenorphine abusers who cite frequent buprenorphine/naloxone use increased during the study period; however the daily use of buprenorphine/naloxone (14.7%) was significantly lower than that of mono-buprenorphine (74.3%). This is in agreement with recent study reporting that opioid abusers seeking treatment at specialized treatment centers, 92% reports abusing mono-buprenorphine and 8% buprenorphine/naloxone [25]. The street prices of the same milligrams of mono-buprenorphine and buprenorphine/naloxone tablets remained approximately 40% less for buprenorphine/naloxone tablets. The street value could be considered as an indicator for the abuse potential.

There are several studies showing that the combination product does not cause withdrawal in buprenorphine-dependent persons as it does in those dependent on heroin, methadone and other "pure" opiate agonists [26-28]. However, if the main abused opiate is buprenorphine, as in Finland, the abusers do not necessarily experience the negative effects of the naloxone component. Thus, it is possible that the overall prevalence of buprenorphine or buprenorphine/naloxone abuse is not simply a function of the biological properties of these medications, but rather it depends on a variety of social, cultural, political and economic forces [29].

During the study period, the average dose of abused buprenorphine decreased by one-third, which could be partially connected to the increase of the street price, which had risen over 50%. However, we also observed changes in the abuse route of buprenorphine; there was a five-fold increase over the study period into an intranasal abuse. A recent study [30], which indicates that intranasal use produces more potent drug effect than sublingual use, could also explain the observed change of buprenorphine routing and abused dose.

Another interesting finding from the 2010 data emerged from the survey question about where respondents obtained/bought their buprenorphine; the response rate was surprisingly high, considering the delicate nature of the question. The majority of respondents purchased buprenorphine from a street dealer and only a few respondents imported it themselves from other countries. This finding raises the question of the existence of a well-organized illegal drug business. Considering that almost 90% of buprenorphine patients in Finland are using buprenorphine/naloxone [18], we were surprised that nearly 25% of the respondents claimed to have bought mono-buprenorphine from a person undergoing treatment. One explanation for this finding is the possibility that the respondents did not characterize as dealers those people in official treatment that diverted their medication. The percentage of participants who bought street buprenorphine from patients in treatment was 26.8% higher for buprenorphine/naloxone than for mono-buprenorphine. This finding is not surprising because buprenorphine/naloxone is the main medication used in the OMT program in Finland. We did not investigate the question of whether patients receive their medication from outpatient units or pharmacies, and future questionnaires need to more closely examine this issue.

In conclusion our results indicate that during the five-year study period, the drug abusers mean age and length of opiate abuse steadily increased, multidrug abuse became more prominent, and the age of onset of opioid intravenous abuse decreased. The majority of respondents had an HCV infection and a long intravenous drug abuse history, they had not entered an OMT program, even though the majority indicated an interest to enter to the OMT. Approximately 50% of all responders reported that they had tried to enter to the OMT program but were not accepted. These findings indicate a possible need for more OMT treatment options and lower threshold treatments. When opioid abusers are unable to gain access to treatment, despite their interests in and attempts to enter, it may lead to illicit drug abuse, more likely the intravenous route, which often have unwanted consequences for them, their families, friends and society.

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