

Short communication

## Abuse liability of buprenorphine–naloxone tablets in untreated IV drug users<sup>☆</sup>

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### Abstract

Buprenorphine (Subutex<sup>®</sup>) is widely abused in Finland. A combination of buprenorphine plus naloxone (Suboxone<sup>®</sup>) has been available since late 2004, permitting a comparison of the abuse of the two products among untreated intravenous (IV) users. A survey was distributed to attendees at a Helsinki needle exchange program over 2-weeks in April, 2005. At least 30% were returned anonymously. Survey variables included: years of prior IV opioid abuse, years of buprenorphine abuse, frequency, dosage, route of administration and reasons for use, concomitant IV abuse of other substances and amount paid on the street for both buprenorphine and buprenorphine + naloxone. Buprenorphine was the most frequently used IV drug for 73% of the respondents. More than 75% said they used IV buprenorphine to self-treat addiction or withdrawal. Most (68%) had tried the buprenorphine + naloxone combination IV, but 80% said they had a “bad” experience. Its street price was less than half that of buprenorphine alone. The buprenorphine + naloxone combination appears to be a feasible tool, along with easier access to addiction treatment, for decreasing IV abuse of buprenorphine.

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### 1. Introduction

The abuse potential of buprenorphine (Subutex<sup>®</sup>) has been recognized since its clinical introduction (Strang, 1985). Reports of misuse have been published in several countries including Finland, France, Great Britain, and Australia (Sakol et al., 1989; Obadia et al., 2001; Jenkinson et al., 2005; Partanen et al., 2004a). Buprenorphine was registered in Finland in 2002 for use in tightly controlled opioid maintenance programs. A buprenorphine + naloxone combination drug (Suboxone<sup>®</sup>) became available in late 2004. Reports from the EMCDDA (2004) have established a steady increase in buprenorphine abuse throughout Finland (Partanen et al., 2004a; Virtanen et al., 2005). It is

believed that most of illicit buprenorphine comes from abroad (Hakkarainen et al., 1996; Hakkarainen and Tigerstedt, 2004).

Demand for buprenorphine treatment surpassed availability especially in the Helsinki area where there now are 12–18 months long waiting lists to gain entrance into opioid maintenance treatment programs. Only about 10% of the estimated 4000 opioid-dependent persons in the area are in the programs (Partanen et al., 2000; Partanen et al., 2004b).

Having both buprenorphine and buprenorphine + naloxone available provides an opportunity to assess the extent to which the two products are abused. This study was conducted to evaluate the current status of intravenous use of buprenorphine and other opioids in the Helsinki metropolitan area.

### 2. Method

A questionnaire consisting of six multiple-choice and ten fill-in-the-blank questions was distributed to all attendees at a needle exchange program in the Helsinki area over 2-weeks in April, 2005. Survey completion was voluntary and anonymous; the return or non-return of the survey in no way influenced services provided by the program. A total of 589 surveys were distributed and 176

<sup>☆</sup> This study was conducted at: Vinkki and Vantaa and Needle Exchange Centers, Espoo, Vantaa and Helsinki, Finland.

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returned. The actual return rate, however, is probably higher than 30% because the same person may have been present at more than one meeting and thus received two or more copies, but they were instructed to return only one copy.

All surveys had an informed consent attached to the survey, telling why the information was being collected. Needle exchange personnel did not receive completed surveys but directed participants to place surveys in a box accessible only to the investigators. No identifying information was obtained.

### 2.1. Data analysis

Group comparisons were done with *t*-tests when examining ratio data and with Chi square tests for nominal data. The number of respondents differs from question to question as participants were free to complete any or all portions of the survey. Some survey questions required two-part responses; if only one part was completed, neither part was included in the analysis.

### 2.2. Ethical conduct of study

The study was conducted according to the EU and Finnish regulations (KL 7/2004 and 2/2004) on clinical research, with notification to the ethical committee filed on 13.12.04 as number KTL 6/2004 and approved. The study protocol was in accord with the Personal Data Protection rule of National Public Health Institute.

## 3. Results

### 3.1. Buprenorphine (Subutex) use

Data from 131 male (74%) and 45 female (26%) participants were examined. Among all responders only three persons indicated that they were currently in a maintenance treatment program, one specifically with methadone. The average ( $\pm$ S.D.) age of all respondents was  $27.8 \pm 6.9$  years, with males being slightly older at  $28.1 \pm 6.8$  years than females at  $26.8 \pm 7.3$  years (range 18–49 years for the whole population).

The mean duration for IV use of opioids by all respondents, 7.3 years (range, 0–25 years; median, 6; mode, 4 years; S.D., 4.9 years for all subjects), was significantly longer than the mean duration of IV buprenorphine use, 4.2 years (range, 0–12 years; median, 4 years; mode, 4 years; S.D., 2.1 years) ( $t[152] = 9.29, p < 0.0001$ ). There were no significant differences between males and females regarding age, years of IV drug abuse, or years of IV buprenorphine abuse.

Respondents used on average 7.0 mg of buprenorphine IV per day (range, 0–40; median, 6; mode, 8; S.D., 5.4). Among the 148 subjects saying how frequently they used IV buprenorphine, 81.8% said daily; 9.5% reported 2–3 times per week, and 8.8% less often. When using ( $n = 161$ ), 9% injected once daily, 26.1% injected twice daily, 41.6% 3 or 4 times a day and 12.4% more often and the remaining 10.6% reported some other pattern.

Overall, 73.2% of the participants reported that their most frequently used IV drug was buprenorphine, 24.4% reported amphetamine or methamphetamine and 2.4% reported other opioids. For the 111 respondents who reported using buprenorphine most frequently, the mean daily IV dose was  $7.7 \pm 5.4$  mg. Table 1 presents the choices selected as the main reason for IV use of buprenorphine.

IV use of only buprenorphine was reported by 44 (28%) of 157 respondents while the remaining 113 (72%) reporting polydrug abuse; 62 respondents (54.9%) reported IV use of

Table 1

Self-reported reason for IV use of buprenorphine answer selected for “The most important reason for Subutex IV usage:”

	Number of respondents	Percentage of respondents (%)
“euphoria, pleasure”	18	10.5
“to treat my addiction”	124	72.5
“to enhance the effect of other drugs”	4	2.3
“to alleviate withdrawal signs of opiates”	5	2.9
“to alleviate withdrawal signs of other drugs”	4	2.3
“other reason”	13	7.6
“I do not know why”	3	1.8

stimulants including amphetamine or methamphetamine; and one reported use of cocaine. Thirty-two (28.3%) reported use of several substances of abuse in addition to buprenorphine: 11 (9.7%) reported use of other substances such as benzodiazepines or other “medicines”; and only 7 respondents (6.2%) reported IV use of other opioids. Benzodiazepines and buprenorphine were used together, either alone or in conjunction with other substances of abuse by 28 respondents (24.8%).

### 3.2. Buprenorphine plus naloxone (Suboxone) use

The buprenorphine + naloxone combination drug was also frequently misused. Of 145 respondents to this question, 99 (68.3%) reported having used the combination IV; 65 (44.9%) had used it more than once; 12 (8.3%) reported frequent or regular use of IV buprenorphine + naloxone.

A total of 111 responded to the question concerning the ways in which they had used buprenorphine + naloxone; 67 (60.4%) reported they had tried it intravenously, 15 (13.5%) had used it sublingually, 5 (4.5%) nasally, and 24 (21.6%) had used it both intravenously and orally.

### 3.3. Buprenorphine versus buprenorphine plus naloxone use

One means for measuring a drug’s “value” to subjects is to determine the street price of the drug. Respondents were asked to report the maximum amount that they had paid for an 8 mg tablet of buprenorphine or buprenorphine + naloxone on the street. Fig. 1 presents the results from the survey respondents.

Respondents were willing to pay, on average,  $\text{€}28 \pm 4$  for each 8 mg tablet of buprenorphine (range  $\text{€}20\text{--}40$ ), whereas 8 mg tablets of buprenorphine + naloxone could be obtained for an average of  $\text{€}12 \pm 7$  (range  $\text{€}0\text{--}25$ ). The difference was significant:  $t(230) = 21.9, p < 0.0001$ . For comparison, the average daily dose of heroin, in Finland, would cost between  $\text{€}80$  and  $120$  and amphetamine(s) between  $\text{€}40$  and  $50$  (data obtained from patients in treatment with the authors).

The survey asked respondents to compare the experience of IV buprenorphine + naloxone versus IV buprenorphine. Of the 107 answering, 86 (80.4%) reported IV use of buprenor-

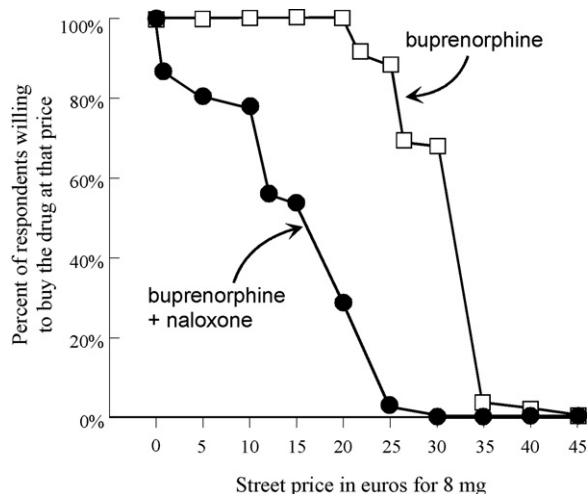


Fig. 1. Higher street price for buprenorphine than for the buprenorphine + naloxone combination. Respondents reported the prices they had paid for 8 mg of the two products. The graph shows the percentage of respondents willing to purchase the drug at a particular price. For example, 89% were willing to pay €25 for 8 mg of buprenorphine but only 3% would pay that much for 8 mg of the combination.

phine + naloxone as a “bad” experience, and only 21 (19.6%) reported that it was similar to their experience with IV buprenorphine. Of the 12 respondents who reported regular and frequent use of IV buprenorphine + naloxone, 4 (33.3%) still reported it as a “bad” experience.

#### 4. Discussion

Our goal was to gather preliminary data on IV drug use among a small sample of IV drug users in the Helsinki area. The number of responders (176) for the survey, though adequate, corresponds only to roughly 5–10% of all IV users in the metropolitan area (Partanen et al., 2004b). The exact value for the return rate cannot be calculated because the same person may have gotten two or more copies but could return only one. It was at least 30%. Conclusions should be viewed as tentative. Further replication is needed.

EMCDDA (2004; Virtanen et al., 2005) data indicate that buprenorphine has replaced heroin as the main injected opioid (73% of all IV drugs). The rise in the use of buprenorphine and deaths associated with its use in the period from 2000 to 2004 has been accompanied by a sharp decrease in the death rates from heroin (Steentoft et al., 2005; Vuori et al., 2003.) The reduction in heroin use probably was not caused by reduced availability (Partanen et al., 2004a) because the street price for heroin in Finland in 2000–2004 did not increase but instead was at its lowest level (United Nations Office on Drugs and Crime, World Drug Report, 2005) averaging only US\$ 181 g<sup>-1</sup> in contrast to an estimate of US\$ 800 g<sup>-1</sup> in 1990. One reason for the reduction in heroin use may be that the addicts were successfully treating their heroin addiction and/or withdrawal by substituting buprenorphine. Support for this conclusion comes also with the finding that the respondents had used other IV opioids significantly longer than IV buprenorphine.

The combination buprenorphine + naloxone was introduced to help eliminate diversion and IV use of buprenorphine. The combination is supposed to have a lower IV abuse potential than buprenorphine alone. A 68% of the respondents had tried IV buprenorphine + naloxone and 66% of those who tried it, took it again or even regularly. This may indicate that combining naloxone with buprenorphine does not block all agonist effects when used IV. However, the continued usage of the combination product might reflect the fact that the study population was from a needle exchange program accustomed to using drugs IV, and the habit may not have been extinguished by a few non-reinforced attempts. The latter conclusion is supported by the finding that 80% reported that they had a “bad” experience with the combination product, while less than 20% reported it “similar” to experiences with IV buprenorphine. Consistent with this finding, respondents were willing to pay a significantly higher street price for buprenorphine than for the combination product.

It is possible that the rigid control of the drug treatment delivery system contributed to these individuals resorting to illicit buprenorphine (Hakkarainen et al., 1996; Partanen and Mäki, 2004). Treating more people within the system, especially with the combination buprenorphine + naloxone, could reduce the number using buprenorphine IV on the street. Thus, it appears that the next logical step in attempting to stop the diversion and misuse of buprenorphine should include both increased availability of treatment programs and increased use of buprenorphine plus naloxone in these programs.

#### Conflict of interest

None.

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