AUTOFERERÁT

PRESENTATION OF THE DOCTORAL THESIS

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<u>Title of dissertation</u>

Non-medical use of buprenorphine in Georgia: prevalence, socio-demographic and environmental correlates, treatment and policy options

Extramedicínské (zne)užívání buprenorfinu v Gruzii a efektivní léčebná intervence

Content

1. Abstract / Abstrakt

Background

Since early 2000s, the nonmedical abuse of buprenorphine (Subutex®) tablets, presumably smuggled from EU countries, has represented major phenomena of the problem drug scene in the Republic of Georgia. In a country with relatively high level of injecting drug use (estimated 40,000 persons, i.e. 1.5 % of population aged 15-64, of whom over 50% inject buprenorphine), this represent a major public health problem that needs detailed description and comprehensive set of interventions.

Aim

(i) To describe the extent of nonmedical buprenorphine ab/use in the Republic of Georgia, the characteristics of the nonmedical ab/users and their motivations for seeking and using the black market buprenorphine. Subsequently, (ii) to plan and pilot-test a treatment intervention that would be more specific and effective than the simple detoxification and/or harm reduction modalities available in Georgian on a routine basis.

Setting

Four regional centres of Georgia were included into the descriptive part of the study: the cities of Tbilisi, Gori, Zugdidi, and Batumi. The intervention (sub)study was conducted in one Tbilisi addiction treatment clinic.

Participants and methods

For the descriptive part of the study, convenience sample of 500 drug users was administered a self-fill questionnaire covering socio-demographic characteristics, drug use and motivations to it, and engagement into risky behaviours. For the intervention part of the study, 80 buprenorphine injecting users were randomized into two treatment groups. The control group was treated using opioid agonist methadone, which is already a well-established treatment modality in Georgia. The intervention group received a comprehensive treatment using Suboxone®, a composite buprenorphine-naloxone pharmaceutical, which is novel in the Republic of Georgia.

Results

Descriptive survey showed that pharmaceutical buprenorphine in the form of Subutex® was the most commonly injected drug in terms of lifetime (95.5%) and last month (75%) prevalence of use. 48% of

those study participants who had injected Subutex® at some point reported having used it to cope with withdrawal or to give up other opioids. 90.5% of Subutex® injectors used 1–2 mg as a single dose, and the mean frequency of its injection was 6 times per month.

Within the intervention (sub)study, out of 80 patients (4 females) randomly assigned to either group 68 (85%) completed 12-week treatment, and 37 (46%) were still in treatment at 20-week follow-up. In both study arms treatment participation resulted in dramatic reduction in opioid and other drugs injection, reduction in opioid craving, and reduction or elimination of unsafe injection behaviour.

Conclusion

While widely misused by Georgian drug injectors, Subutex® is neither the principal nor the favourite drug, and it is rather used for self-medication purposes. The results of both (sub)studies show that buprenorphine injection users can be effectively engaged and retained in treatment. The results also suggest that increasing availability and accessibility of opiate agonist treatment both with methadone and buprenorphine might be an effective public health approach to address non-medical use of buprenorphine. The appropriate coverage of patients, in particular those who inject buprenorphine for self-treatment, can significantly reduce the street demand for it and cut down its illegal market. Carefully planned and organized treatment process, and adequate pharmacological and psychological aid should be offered to all patients with buprenorphine abuse. In the case of Georgia, there is an appealing need to scale-up and increase access to free opioid substitution treatment for people who inject buprenorphine and other opioids.

Abstrakt

Úvod

Jedním z nejdůležitějších jevů drogové scény v Gruzii je od počátku tisíciletí nemedicínské (zne)užívání tablet buprenorfinu (vesměs ve formě preparátu Subutex®), jež jsou podle převažujícího mínění pašovány ze zemí EU. Pro zemi, kde je relativně vysoká prevalence injekčního užívání drog (cca 40 000 osob, tj. 1,5 % populace ve věku 15-64 let; z nich zhruba 50 % užívá buprenorfin) to představuje zásadní veřejnozdravotní problém. K jeho zvládnutí je třeba podrobného popisu a vývoje komplexní intervence.

Cíle

(i) Popsat rozsah nemedicínského užívání v Gruzii, charakteristiky uživatelů a jejich motivaci k vyhledávání a užívání buprenorfinu z černého trhu. Následně (ii) vyvinout a pilotně otestovat léčebnou intervenci, jež by byla specifičtější a efektivnější než v zemi běžně dostupná prostá detoxifikace a/nebo intervence typu snižování škod (harm reduction).

Geografické pokrytí

Do deskriptivní fáze studie byla zařazena čtyři regionální centra: Města Tbilisi, Gori, Zugdidi a Batumi. Intervenční substudie probíhala na jedné z adiktologických klinik v Tbilisi.

Výzkumný vzorek a metody

V deskriptivní části studii vyplnilo 500 osob vybraných pomocí nenáhodného vyčerpávajícího výběru dotazník pokrývající sociodemografické charakteristiky, užívání drog a jeho motivace, a rizikové chování při užívání. V intervenční části studie bylo 80 injekčních uživatelů buprenorfinu rozděleno do dvou léčebných skupin. Kontrolní skupina byla léčena s využitím metadonu, opioidového agonisty běžně používaného v Gruzii pro substituční léčbu opioidové závislosti. Intervenční skupina byla léčena v komplexním programu za využití Suboxone®, kompozitního léku s obsahem buprenorfinu a naloxonu, který v Gruzii dosud nebyl zaveden pro standardní léčbu.

Výsledek

Deskriptivní studie prokázala postavení Subutexu jako nejrozšířenější injekční drogy co do celoživotní prevalence (95,5 % účastníků studie) a co do prevalence užití v posledním měsíci (75 %). Celkem 48 % probandů, kteří někdy v životě užili Subutex, tak učinili s cílem zvládnout abstinenční příznaky nebo s cílem přestat užívat jiné opioidy. 90,5 % injekčních uživatelů Subutexu obvykle užila v jedné dávce 1-2 mg; průměrná frekvence injekčního užívání byla 6x měsíčně.

V intervenční studii z 80 pacientů (4 ženy) náhodně rozdělených do dvou skupin, dokončilo dvanáctitýdenní léčbu celkem 68 osob (85%, a 37 osob (46 %) bylo v léčbě ještě po 20 dalších týdnech. V obou skupinách došlo k dramatickému snížení injekčního užívání opiodů a jiných drog, k redukci cravingu („bažení"), a k redukci či naprostému vymizení vysoce rizikových způsobů injekčního užívání.

Závěr

Subutex je sice gruzínskými uživateli drog široce zneužíván, nejedná se však ani o primární, ani o nejoblíbenější drogu; je užívána spíše k autoterapeutickým účelům. Výsledky obou substudií našeho projektu nasvědčují tomu, že injekční uživatelé buprenorfinu mohou být úspěšně zapojeni do léčby a udrženi v ní. Výsledky také ukazují, že by zvýšená dostupnost a přístupnost léčby agonisty opiátů – jak metadonem, tak buprenorfinem – mohla být úspěšným veřejnozdravotním řešením problému nemedicínského zneužívání buprenorfinu. Řádné pokrytí potenciálních pacientů – zejména těch, kteří užívají buprenorfin jako automedikaci – může významně snížit poptávku po ilegální droze a eliminovat černý trh s ní. Léčebný proces by měl být pečlivě naplánován a organizován tak, aby byla léčba dostupná všem uživatelům nelegálního buprenorfinu. Konkrétně v Gruzii situace vyžaduje zvýšení počtu programů a úpravu vstupních kritérií do bezplatných programů substituční léčby zneužívání buprenorfinu a dalších opioidů.

2.   Introduction

Buprenorphine is available for opioid addiction treatment as a sublingual tablet (Subutex[®]), or a sublingual tablet or film composed of 4 parts buprenorphine to one part naloxone (Suboxone[®]); one or more of these products is available in at least 44 countries (Carrieri et al., 2006). The buprenorphine-naloxone combination was developed to reduce diversion and injecting use and it appears to have had that effect (Simojoki, Vorma, & Alho, 2008), however, these problems continue to occur (Bruce, Govindasamy, Sylla, Kamarulzaman, & Altice, 2009; Vicknasingam, Mazlan, Schottenfeld, & Chawarski, 2010). In the US, almost all addiction treatment is done using Suboxone[®] and approximately 640,000 patients received it in 2009, mostly in office based settings (Clark, 2010). In France, where Subutex[®] has been the main product used in addiction treatment, more than 100,000 patients have received it (Diaz-Gomez et al., 2010).

Like other opioids, buprenorphine has reinforcing and subjective effects similar to methadone (Comer, Sullivan, & Walker, 2005) with the potential for abuse and addiction (Comer & Collins,

2002; Comer, Sullivan, Whittington, Vosburg, & Kowalczyk, 2008; Pickworth, Johnson, Holicky, & Cone, 1993; Zacny, Conley, & Galinkin, 1997), particularly when administered intravenously where its effects are comparable to those of morphine and heroin (Sporer, 2004). Most cases of non-medical use have involved crushing Subutex[®], mixing it with water and injecting it (Chua & Lee, 2006; Jenkinson, Clark, Fry, & Dobbin, 2005; Otiashvili et al., 2010; Singh, Grover, & Basu, 2004). However, inhaling crushed tablets has also been reported, particularly in France (Roux et al., 2008). Following the expansion of Subutex[®] treatment in Europe after France introduced it in 1995 (Verster & Buning, 2005), non-medical use has been reported in at least twelve countries (EMCDDA, 2005) and identified as the main reason for entering treatment by 40% of opioid addicted patients in Finland and 8% in France (EMCDDA, 2008). 59% of problem opiate users in the Czech Republic (6,300 out of 10,600) are Subutex[®] users (Mravčík et al., 2013). In Australia, 11% of a national sample of injecting users reported recent injection of prescribed Subutex[®] and 20% reported injecting illicitly-obtained buprenorphine (O'Brien et al., 2006). Though these data are of concern, studies have also shown that significant portions of Subutex[®] injectors use it to cope with withdrawal and not primarily for its reinforcing effects (Daniulaityte, Falck, & Carlson, 2011; O'Connor, Moloney, Travers, & Campbell, 1988; Uosukainen et al., 2012). For example, self-treatment was reported as the main reason for non-prescription use of buprenorphine by 77.7% of users in Finland (Alho, Sinclair, Vuori, & Holopainen, 2007), 57% in France (EMCDDA, 2005), and 87% in Sweden (Hakansson, Medvedeo, Andersson, & Berglund, 2007).

Subutex[®] injection in Georgia

In the Republic of Georgia, heroin and home-made opium were the main drugs used in the country during the late 1990s (Gamkrelidze et al., 2004). According to official statistics, 1092 people were admitted in 2007 for inpatient drug-free detoxification treatment that was followed with rehabilitation care only very rarely. By the end of 2008, several new MMT programmes had been launched with a total of about 600 slots for clients after government started to participate in the funding. In 2012, the total number of patients in MMT at the time reached 1800 (D. J. Javakhishvili et al., 2012).

In 2004, there occurred a sudden change in the Georgian opioid black market, resulting in a quick and significant increase in the

proportion of buprenorphine users in the population of all users of different drugs that were registered in the *Narcological Register* (Gamkrelidze et al., 2005). In 2004, the number of buprenorphine users increased substantially, also among patients in narcological clinics (specialized medical facilities providing treatment for substance use disorders – in the overwhelming majority of cases simple detoxification) and reached 30%, whereas in 2003 it was only 4.5% (Gamkrelidze, et al., 2004). In 2005, the share of buprenorphine injectors among drug users admitted for in-patient drug-free treatment reached 39% (J. Javakhishvili et al., 2006).

Treatment of buprenorphine-addicted injectors
Despite a growing number of reports about buprenorphine addiction there have been only a few reports focusing on its treatment. One was an Iranian study that compared 50 mg of daily methadone to 5 mg of daily sublingual buprenorphine or 50 mg of daily oral naltrexone over 24 weeks and found that the methadone had the best retention, followed by sublingual buprenorphine, followed by naltrexone (J. Ahmadi, Ahmadi, & Ohaeri, 2003). In another study patients were randomized to 40 mg of methadone, 4 mg of buprenorphine, or 0.4 mg of daily clonidine and outcomes measured over 12 weeks (M. Ahmadi, Maany, & Ahmadi, 2003) and retention on methadone was significantly better than buprenorphine. However both medications were well accepted by buprenorphine injectors and outcomes on both were significantly better than if treated only with clonidine. In Finland, a naturalistic follow-up study found an 83% retention rate in opioid dependent patients that were injecting buprenorphine and treated with sublingual buprenorphine (Aalto, Visapaa, Halme, Fabritius, & Salaspuro, 2011).

3.   Aims

1) To describe the extent of nonmedical buprenorphine ab/use in the Republic of Georgia, the characteristics of the nonmedical ab/users and their motivations for seeking and using the black market buprenorphine. Subsequently, 2) to plan and pilot-test a treatment intervention that would be more specific and effective than the simple

detoxification and/or harm reduction modalities available in Georgian on a routine basis.

4.   Methods and participants

For the descriptive (sub)study we conducted a survey in four regional centres (cities) of the Republic of Georgia: Tbilisi, Gori, Zugdidi, and Batumi. The regions were chosen on the basis of the availability of needle and syringe exchange programmes (NEPs) and previously reported relatively high levels of drug use and HIV rates. The sample consisted of IDUs using services provided by the needle exchange programmes. We did not consider recruiting respondents from opiate substitution programs. Even if certain portion of MMT clients does continue using street drugs, due to antagonistic properties of buprenorphine it is highly unlikely that person on methadone would use it. Client of the needle exchange programs who were willing and able to respond to the questions were included in the study. Persons below the legal age (18) or with major psychical impairment, that would prevent them to properly understand or respond to the questions, were excluded from the sample. Questionnaires were distributed to clients by the staff members of the NEPs and were filled in by participants directly on-site, or were returned within the next few days. The data collection took place in August-September 2007.

The intervention (sub)study, a Randomized Clinical Trial, was done at the Addiction Research Centre, Alternative Georgia, a independent non-profit research institution located in Tbilisi and its partner Centre for Medical, Socio-economic and Cultural Issues - Uranti, the second largest addiction program in the country and one that provides in-patient detoxification, psychosocial-based outpatient treatment, and methadone maintenance. Patients were recruited through word of mouth, fliers and advertisements in addiction clinics, harm reduction programs, and other facilities frequented by injection drug users. All screening, assessment and follow-up evaluations were done at Uranti. Eligibility criteria included: Opioid dependent with physiological features for the past three or more years according to ICD-10; age 25 or above as per Georgian regulations; injecting Subutex[®] 10 or more times in the past 30 days; buprenorphine and/or opioid positive urine test; not on methadone maintenance in last 4

weeks; stable address within Tbilisi area and not planning to move; home or cellular telephone number at which the participant can be reached; and willingness and ability to give informed consent and otherwise participate, including daily clinic attendance since take-home dosing is not permitted by Georgian law. The data collection took place between January 2011-March 2012.

Following the randomization, methadone and Suboxone[®] were administered 7 days/week at Uranti under direct observation and patients were offered weekly individual drug counseling and group therapy. At intake each patient had a physical examination that included a CBC, glucose, bilirubin, liver enzymes, ECG, testing for HIV and hepatitis B and C; a urine drug screen using an on-site kit that tested for opioids, benzodiazepines, amphetamine, buprenorphine, methadone and THC; the Addiction Severity Index (ASI) 5th edition (McLellan et al., 1992); a timeline follow-back (TLFB) for self-reported drug use with a timeframe of past 30 days (Sobell & Sobell, 1992); a visual analogue scale for current opioid craving (0-100; 0=not at all, 100=very much); and the Risk Assessment Battery (RAB), a self-reported measure of drug and sexual HIV risk behaviors using the timeframe of past six months.

Urine drug screens, opioid craving and the TLFB with a timeframe of past 7 days were repeated in weeks 1-12 and at week 20. The ASI and RAB were repeated at weeks 4, 8, 12 and 20 using the timeframe of past 30 days.

Interviews and assessments were conducted in Georgian. Study instruments were translated into Georgian and back translated into English to ensure correct interpretation in the Georgian language and that the Georgian and English case-report forms matched each other. Data were entered into a web-based system developed by the data management unit at the Penn/VA Center for Studies on Addiction and analyzed by study statistician in Tbilisi. Buprenorphine and other opioid use, study retention, and HIV drug risk behavior were the focus of the analyses presented here.

Institutional Review Boards at the University of Pennsylvania and the Georgian National Council on Bioethics approved the study.

Statistical analysis

For the descriptive (sub)study a non-parametric statistical procedures were used. Missing values (non-reported variables) were omitted and

the given observation was dropped for the respective analysis. Standard deviations or 95% confidence intervals for proportions were calculated. Classified data from two independent populations were compared by Fisher's exact tests, and p values < 0.05 are considered statistically significant. For all the analyses, the Stata software package was used (Stata Corp: Stata Statistical Software: Release 9.2, Stata Corporation, College Station, TX, 2007).

Statistical analysis for the clinical trial was performed using statistical package SPSS 20.0. The study was designed to have 80% power to detect an effect size of Cohen's d=0.7 at a two-sided significance level of 0.05. For a comparison of binary outcomes, 80% power was set to detect a difference of about 30% in rates of use. For the quantitative endpoints the Student's t test (for the comparison of two groups) or ANOVA or Univariate General Linear Model approach (for more than two groups) were used. The categorical endpoints were compared using x^2 test or Fisher's exact test (where appropriate according to the size of the outcome).

5.   Results

Descriptive (sub)study

Five hundred questionnaires were distributed and 401 were collected back. Twenty of them were excluded because of missing data and/or inconsistencies in responses. Thus, the final effective response rate was 76.2%, with questionnaires filled in by 368 male and 13 female injecting drug users that were further analysed. The mean age of the participants was 32.6 (SD 7.6). The mean history of regular (at least twice a week) injecting use of any drug was 98 months (median 84 months) and was significantly longer than the mean buprenorphine injecting career, which was 32.5 months (median 30). Of the sample, 95.5% (N=364; 95% CI [93.4, 97.6]) of respondents had used buprenorphine, 84.2% (N=321; 95% CI [80.6, 87.9]) had used opium, and 80% (N=305; 95% CI [76.0, 84.1]) had used heroin ever in their life.

One of the aims of the study was to better understand why Georgian drug users inject buprenorphine. Distribution of responses is presented in the Table 1. We compressed all those reasons into the

three major categories: (1) coping with withdrawal or giving up other opioids *; (2) to get high/pleasure **; and (3) high availability of buprenorphine ***. As a result of such interpretation 48% [42.1, 53.9] of the study participants who have used buprenorphine reported injecting it mostly to cope with withdrawal or give up other opioids and the same proportion of respondents (48%) reported injecting it to get high and gain pleasure (see Table 1). The remaining 15 injectors (4%) report the high availability of the drug as their reason for using it. Of those whose first drug of dependence was buprenorphine, 77% inject it to get high/pleasure.

Table 1. Reported reason for buprenorphine injecting

What is the main (leading) reason for you to inject buprenorphine?	Freq.	Percent	Cumulative
It's easy to get buprenorphine***	12	3.32	3.32
Self treatment, to get off drugs*	21	5.82	9.14
To coup with withdrawal*	151	41.83	50.97
Because of free time***	2	0.55	51.52
For fun***	1	0.28	51.80
For stimulation**	1	0.28	52.08
To coup with depression*	1	0.28	52.35
To get high, pleasure**	172	47.65	100.00
Total	361	100.00	

*- interpreted as "coping with withdrawal or giving up other opioids"
** - interpreted as "to get high/pleasure"
*** - interpreted as "high availability of buprenorphine"

Only 10% [7.5, 13.6] of respondents had used a single type of injection drug within the month prior to the study, and more than 66% had used three or more drugs. Out of 279 respondents who had injected buprenorphine during the previous month, 96% [92.9, 97.9] had injected other drugs as well and 75% [70.7, 79.4] had used two or more other drugs. Of those who had injected buprenorphine in the previous month, 46% [40.0, 51.8] combined it with benzodiazepines or other sedatives, and 45% [38.9, 50.7] combined it with home-made stimulants. The other main drugs concurrently used by buprenorphine injectors were opium, heroin, and pharmaceutical opiates.

In sharp contrast with the high values of prevalence indicators, only 11.5% [8.2, 14.7] of the sample quote buprenorphine as their historically first drug of dependence, and 13% [9.5, 16.3] report buprenorphine as their favourite drug. Out of the group of younger injectors 27% report buprenorphine as the first drug they have ever been addicted to, compared to 9.2% of the older injectors, which represents a strongly significant statistical difference (p=0.001), suggesting relatively recent appearance of the drug in the market and its increasing popularity.

The average single dose of buprenorphine reported by the respondents was low compared to what is generally considered as the average therapeutic/effective dose [3, 4, 28, 38, 39]. Of those who have used buprenorphine, 44.7% [39.6, 49.9] inject 1 mg of buprenorphine (1/8 of an 8mg tablet of buprenorphine) as their usual single dose, 45.8% [40.7, 51.0] inject 2 mg of buprenorphine (¼ of a tablet), and 9% [5.9, 11.8] inject 4 mg. Only 2 respondents (0.56%) reported 1 full tablet as their usual dose.

In this study we found unexpectedly high rates of injecting of home-made ephedrine- and pseudoephedrine-based preparations, that are, supposedly, mainly methamphetamine and methcathinone [40]. 67.2% of respondents have ever used home-made stimulants and 43% did so in the month prior to the survey. Home-made stimulants were injected the most often compared to other drugs - on average 11.5 times during the last month.

Randomized clinical trial
In total, 112 potential subjects were screened between January 25 and September 27, 2011, of which 80 (4 females) were randomly assigned to methadone or Suboxone®. Of the 112 that were screened, 32 were excluded from study participation for different reasons.

Subjects were all Caucasian; average age was 34; mean years of opioid injection use was 5.8 (SD4.6); and heroin, Subutex®, other opioids (opium, desomorphine) and home-produced amphetamine type stimulants were the main drugs reported to have been injected. Injecting more than one drug was reported by 68.4% of methadone patients and 72.5% of Suboxone® patients. None were HIV positive however 73.4%were positive for hepatitis C. There were

no significant differences in socio-demographic and clinical characteristics between two groups (Table 2).

Table 2. Background characteristics of RCT participants

	Total sample (n=80)	Met (n=40)	Sub (n=40)	Test statistics	p
Male, n (%)	76.0 (95.0)	37.0 (92.5)	39.0 (97.5)	χ^2=1.05	0.305
Age, M (SD)	33.7 (5.7)	34.3 (6.1)	33.1 (5.2)	t=0.94	0.35
Education (years), M (SD)	14.8 (2.9)	14.9 (2.7)	14.7 (3.0)	t=0.33	0.74
Unemployed, n (%)	46.0 (57.5)	24.0 (60.0)	22.0 (55.0)	χ^2=0.51	0.47
Married, n (%)	38.0 (47.5)	20.0 (50.0)	18.0 (48.0)	χ^2=0.08	0.78
Drug use history (years), M (SD)	5.8 (4.6)	6.2 (5.3)	5.3 (3.8)	t=0.83	0.41
Days drugs used in last 30 days (self reported), M (SD)					
Heroine	3.2 (5.8)	3.4 (5.9)	3.0 (5.8)	t=0.27	0.78
Subutex®	15.2 (5.8)	15.3 (6.6)	15.0 (5.0)	t=0.24	0.81
Other opioids	10.2 (10.3)	10.6 (10.3)	10.5 (10.2)	t=0.40	0.70
Stimulants	1.5 (2.4)	1.4 (2.3)	1.7 (2.5)	t=0.41	0.68
Benzodiazepines	4.2 (7.3)	3.7 (7.2)	4.7 (7.5)	t=0.58	0.56
Marijuana	2.1 (6.2)	0.8 (1.7)	3.4 (8.3)	t=1.9	0.06
Opioid craving scale, M (SD)	81 (20.54)	84(20.46)	77.5(20.35)	t=0.32	0.75
HIV status[1], n (%)					
Positive	0 (0)	0 (0)	0 (0)		
Negative	79 (100)	39 (100)	40 (100)	χ^2=0.00	1.00
HCV status[1], n (%)					
Positive					
Negative	58 (73.4)	33 (84.6)	25 (62.5)	χ^2=4.95	0.03
	21 (26.6)	6 (15.4)	15 (37.5)		

1 – data provided for 79 participants, 1 refused testing

Of the 80 study participants, 68 (85%) completed 12-weeks of treatment; 12 left the study. Average number of days in treatment was 87 and average number of individual counseling sessions attended was 13.8 with no difference between groups. Mean dose of methadone at treatment midpoint (six weeks) was 39mg (SD17.8; 17 to 80) and mean dose of Suboxone® was 8.5 mg (SD3.5; 4 to 16).

Over the 12-week medication phase, 837 weekly, observed urine samples were collected and tested. During this period 123 of the 960 scheduled tests (12.8%) were missing with 74 of 480 (15.4%) in the methadone group and 49 of 480 (10.2%) in the Suboxone® group; 108 of the missing tests were due to early termination. The overall level of opioid-positive urine samples was very low but there were significantly more positive opioid tests in methadone than Suboxone® patients (6 vs. 1, or 1.5% vs. 0.2%; p=0.03) – see Table 3.

Table 3. Treatment impact

	Met (n=40)	Sub (n=40)	Test statistics	P
Assessments conducted, n (%)				
0 week	40 (100)	40 (100)		
4 week	34 (85.0)	38 (95.0)		
8 week	35 (87.5)	36 (90.0)	χ^2=4.95	0.99
12 week	33 (82.5)	35 (87.5)		
20 week	33 (82.5)	33 (82.5)		
Days in treatment over 12 weeks, M (SD)	85.4 (34.2)	88.8 (26.6)	t=0.5	0.6
Counseling sessions attended, n	414	443		
Sessions attended per participant, M (SD)	13.8 (5.2)	13.8 (5.4)	t=0.05	0.96
Urine samples collected (1-12 weeks), n	406	431		
Opioid positive urine samples, n (%)[1]	6 (1.5)	1 (0.2)	χ^2=4.87	0.03
Buprenorphine positive urine samples[1], n (%)	3 (0.7)	--	--	--

Of the 843 weekly TLFB responses on opioid use that were obtained, 836 were matched with urine tests performed on the same patient in the same week and 96.7% were in agreement. Consistent with the reduction in opioid use, there was a marked reduction in opioid craving with no significant difference between groups. There was a significant reduction in reported HIV risk injection behaviors over the 12-week treatment period in both groups, with improvements persisting by the 20-week follow-up. In most cases unsafe injecting risk behavior was virtually eliminated. Sexual risk behavior did not change over the course of treatment with about half of the sample never using condoms during sex, and about a third of participants having 2 or 3 sexual partners over the past 30 days.

Sixty-six participants were evaluated at the 20-week follow up and of these, 37 were receiving agonist maintenance with 34 on methadone and 3 on Suboxone[®]. Based on the results of urine tests at this assessment point, significantly fewer participants who remained in treatment used illicit opioids (5.6% vs 27.6%; p<0.001) or used illicit buprenorphine (2.7% vs 13.8%; p=0.005), benzodiazepines (13.5% vs 34.5%; p<0.001), or marijuana (2.8% vs 20.7%; p<0.001, compared to those who were not in treatment.

Significantly more Suboxone[®] than methadone patients experienced at least one adverse event (p=0.003). Insomnia, constipation and depression were the most frequent events reported in both groups and constipation was the event most often judged

possibly related to study medication. All 80 adverse events in the methadone group, and 108 in the Suboxone® group, were judged to be mild or moderate and 10 were deemed to be definitely related to study medication. There were no deaths, overdoses, suicide attempts or other serious adverse events.

6. Discussion

Findings of the descriptive (sub)study report on the misuse of buprenorphine in a setting where it was not available for treatment and the availability of the only existing opiate substitution treatment with methadone was extremely limited. The prevalence of lifetime and recent buprenorphine injection use found in our study sample is the highest among all the reported studies known to us from any country worldwide. However, drawing a comparison between studies is difficult, as they are carried out in different settings and employing different designs. Furthermore, available studies predominantly focus on buprenorphine misuse by clients who are in treatment. In our study, 95.5% of the sample had injected buprenorphine at some time in their life and 75% had injected it in the last month. In both cases buprenorphine was the most prevalent of all injected drugs.

Our findings show that significant portion of the people who inject buprenorphine report its use for self-medication purposes. Almost half of the drug users who admitted buprenorphine injection report that they do so to cope with withdrawal or give up other opioids. Exactly the same proportion reported injecting buprenorphine to get pleasure and only a small proportion of respondents (4%) claimed they injected it because of its easy availability.

Although buprenorphine accounts in our sample for the highest lifetime and last-month prevalence, overall it is by far not the favourite drug of those who inject it. Only 13% of respondents claim that it is their favourite drug. Moreover, 80.2% of buprenorphine injectors use it 10 or less times a month, while the overall injecting frequency for all drugs combined was 28/month. This might support the idea that drug users mostly inject it in the absence of another drug, or to cope with withdrawal symptoms, and not because of its reinforcing effect.

In our randomized controlled trial of opioid addicted individuals that had injected Subutex[®] 10 or more times in the last month, daily observed methadone and Suboxone[®] were well accepted and 85% remained in treatment throughout the 12 week dosing period. In both study arms treatment participation resulted in a marked reduction in opioid use, a reduction in opioid craving, and a reduction or elimination of unsafe HIV risk injecting behaviors. The vast majority of study participants were using more than one psychoactive substance prior to study inclusion, as previously documented in Georgia and regionally (Booth, Lehman, Dvoryak, Brewster, & Sinitsyna, 2009; Booth et al., 2008; D.J. Javakhishvili, Sturua, Otiashvili, Kirtadze, & Zabransky, 2011; Kruse et al., 2009; Tiihonen et al., 2012). It has been suggested that this poly-substance use that involves mixing buprenorphine and other opioids with sedatives and amphetamine-type stimulants is related to the ever fluctuating availability and high price of drugs on the Georgian black market and/or attempts by users to increase the euphoric effects and potency of injection preparations (D. J. Javakhishvili, et al., 2012; Otiashvili, et al., 2010).

One of the most striking findings was the 76% prevalence of hepatitis C but the absence of HIV. Similar to other recent reports (Chikovani, Bozicevic, Goguadze, Rukhadze, & Gotsadze, 2011) direct needle sharing was not high among study participants; the most common unsafe injection behavior at baseline was sharing a cooker and dividing the solution using one syringe. As noted earlier, buprenorphine (Subutex[®]) injection in Georgia generally occurs in groups of 3-4 people who dissolve one 8 mg tablet in a water and then, using a large volume syringe, divide the solution by front- or back-loading into smaller individual syringes (D.J. Javakhishvili, et al., 2011; Otiashvili, et al., 2010). Home preparation of meth/amphetamine type stimulants ("vint" and "jeff") and opioids ("crocodile") both involve using a common cooker to process ingredients through often complicated chemical refinement, and using a large-volume syringe to divide the final product into smaller syringes for injection.

In both cases drug preparation is a group activity with predetermined division of roles and contributions (money, ingredients, space for production) but with little direct sharing of injection equipment, behaviors that could be due to long-term efforts to educate drug users about the risks of direct needle sharing. Nevertheless,

indirect sharing, in this case through use of a common container and common syringe for drug division has not been sufficiently acknowledged and targeted, and may account for the high prevalence of HCV since it is more easily transmitted than HIV (Doerrbecker et al., 2013; Thibault, Bara, Nefau, & Duplessy-Garson, 2011). In addition, given the relatively high mean age of study participants, HCV prevalence is likely a function of sharing injection equipment over their extended injection careers.

Limitations
Main available socio-demographic characteristics of the sample, such as age, drug use history and sex ratio were similar to those found in other studies with the clients of needle exchange programs in Georgia [41]. In contrast, the mean age of this group was at least 5 years higher that the mean age of the "random" sample of IDUs recruited for other study using respondent driven sampling technique [42]. Thus, the study sample might not be representative of all IDUs in Georgia; because of the sampling scheme, the study participants may be more experienced and more socially disadvantaged group of users. In order to increase the response rate in a study with no incentives for participants we did not collect socio-demographic data except for age and sex, and thus we were unable to analyse possible associations between buprenorphine injecting (or any other injecting behaviour) and the socio-demographic characteristics of the respondents. However, our decision to make the questionnaire as short and simple to fill in as possible supposedly facilitated the high rate of return of the survey questionnaire and the low rate of omitted responses / missing variables.

In our understanding, the respondents in our sample had no reasons either to under-report or over-report their drug use, as they were in NEPs because of their injection drug use and there were neither threats nor incentives associated with any distortions of reality in their anonymous reporting. The main limitation in this respect would be the recall bias which is present in any similar design.

Findings of the clinical trial also must be considered in light of some limitations. We could not objectively measure buprenorphine misuse in the Suboxone® group, however in the methadone group only 3 of 406 urine samples were positive for buprenorphine during weeks 1-12 and TLFB data were highly consistent with urine tests

results, a finding supporting the validity of self-reports and the conclusion that non-prescribed use of buprenorphine in both groups was extremely low.

Daily, observed dosing eliminated diversion and ensured medication compliance. Results might be different if take-home doses were allowed. In Georgian real life setting, both methadone and buprenorphine/naloxone are provided in specialized clinics that provide daily-supervised dosing with no take-homes allowed, procedures that raise the cost of both treatments (Kirtadze, Menon, Beardsley, & Forsythe, 2012). With agonist maintenance rapidly expanding, and with data showing that they are highly effective, there is an opportunity to consider how costs might be reduced and treatment expanded while retaining control over diversion.

The sample size was relatively small and not chosen based on a power analysis since this trial was primarily a feasibility study to collect initial data on treatment engagement and retention and its impact on drug injection and risk behavior. Importantly, although we did not focus on retaining participants in maintenance treatment after the study completion, 56% of participants assessed at the 20-week follow-up (46% of the initial sample) were continuing on agonist treatment and assessments showed that significantly fewer patients who remained in treatment had urine samples positive for opioids, and significantly fewer reported HIV risk behavior compared to those who were not in treatment.

7.   Conclusion

Findings of the descriptive (sub)study suggest that illegal buprenorphine has considerable potential for non-medical use. A noticeable portion of Georgian young drug injectors started their injecting career with buprenorphine. However, while widely misused by Georgian drug injectors, Subutex® is neither the principal nor the favourite drug, and it is rather used for self-medication purposes. Results of the clinical trial showed that daily observed methadone and buprenorphine-naloxone were effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior among non-medical buprenorphine and other opioid users in Georgia.

The results of both (sub)studies show that buprenorphine injection users can be effectively engaged and retained in treatment. The results also suggest that increasing availability and accessibility of opiate agonist treatment both with methadone and buprenorphine might be an effective public health approach to address non-medical use of buprenorphine. The appropriate coverage of patients, in particular those who inject buprenorphine for self-treatment, can significantly reduce the street demand for it and cut down its illegal market. Carefully planned and organized treatment process, and adequate pharmacological and psychological aid should be offered to all patients with buprenorphine abuse. In the case of Georgia, there is an appealing need to scale-up and increase access to free opioid substitution treatment for people who inject buprenorphine and other opioids.

8. References

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