Univerzita Karlova v Praze

1. lékařská fakulta

Disertační práce

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

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Content

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.

Abstract

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.

1. Introduction

This section describes an investigative framework and rationale for planning and implementing a multi-phase research endeavour.

First mention of buprenorphine (Subutex®) injection in Georgia occurred in 2003 Annual Drug Situation Report (Gamkrelidze et al., 2004). By the time of defendant's PhD study initiation the problem had grown into a serious public health issue, with buprenorphine (Subutex®) overtaking the heroine on a black market and being responsible for 40% of inpatient drug treatment admissions in the country (Gamkrelidze et al., 2005). Therefore, this new and unstudied issue was selected as a topic for PhD research. Following the careful consideration a multi-phase research plan was developed and agreed with mentors.

The initial step was describing and understanding the drug situation in Georgia. It was obvious that the spread of buprenorphine injection was not simply related to the attractive physiological effects of the medication; rather, it was a result of variety of factors not necessarily associated with pharmacological characteristics of the preparation. Analyzing the drug situation we were focusing on social, economic and cultural factors in which drug use occurs in Georgia. Availability and accessibility of prevention and treatment programs, legal environment and law enforcement practice were also examined. This information allowed us to assess complex set of factors surrounding the studied phenomena and discuss options for prospective interventions.

At the following stage extensive literature review has been conducted. We aimed at collecting information from different locations that would help us to better understand the phenomena – prevalence of non-medical use, socio-demographic characteristics of misusers, factors that could have been associated with (or lead to) buprenorphine misuse, reported reason for misuse, complications of injection use of buprenorphine and so on. We wanted to gather and analyze maximal volume of relevant information to be able later compare (or align) findings of other colleagues with what we intended to examine in

Georgian setting. Search for thematic research publications and reports was permanent and the latest referred article dates as late as the end of 2012. In a situation when international literature on buprenorphine non-medical use was very scarce and fresh publications have been appearing during the conduct of our research, this approach allowed us to stay updated and well informed on the most recent developments and findings from other countries and settings.

The next step was to describe buprenorphine misuse in Georgia. For this purpose, we designed and conducted an exploratory descriptive study with Georgian drug injectors – clients of needle/syringe exchange programs. Simple, self-administered questionnaire allowed us to collect self-reported information related to socio-demographics, drug use initiation and history, buprenorphine injection, preference of buprenorphine or other drugs. The major research question for this survey for us was to understand **why buprenorphine injection became so popular and widespread among drug injectors in a country where this medication was not registered in a medical system and was not legally available.**

The last phase of the research was a logical culmination of the previous efforts – we implemented a randomized clinical trial (RCT) and examined acceptability and efficacy of two treatment options for buprenorphine injectors in Georgia. Abstinence oriented drug free treatment in Georgia is not sufficiently developed and so far did not implement the paradigm of continuum of care and treatment planning. It usually consists of two-week drug-free detox with no follow-up. Drop-out rates are high and effectiveness of this treatment, as well as patients' willingness to engage remain low. Findings of earlier phases allowed us to carefully plan, design and implement a pilot study with opioid full agonist methadone and agonist/antagonist Suboxone® (combinatory sublingual pill containing 80% of buprenorphine + 20% of naloxone). To our knowledge, this RCT is the first trial focusing the injectors of Subutex® - the sublingual tablet formulation of buprenorphine. The only identified previous intervention study with buprenorphine injectors targeted misusers of injectable formulation of buprenorphine (J. Ahmadi, Ahmadi, & Ohaeri, 2003). We hope that the pilot data comparing the relative benefits and acceptability of these two treatment options (methadone and

Suboxone®) has provided sufficient new information on their potential impact for treating buprenorphine abuse, a problem highly relevant for Georgia and several other countries including the Czech Republic.

2. Drug Situation in Georgia

Brief country information

Figure 1: Schematic Map of Georgia (Source: Wikipedia)

Georgia is a presidential republic located in the South Caucasus. The country consists of 9 regions and one autonomous republic. Two regions of the country – Abkhazia and South Ossetia – are cut off from the rest of the country as a result of internal conflicts since the early 'nineties and further after the war with the Russian Federation and the subsequent *de facto* Russian occupation of these Georgian territories in 2008. Approximately 288,000 persons are internally displaced in Georgia, and another 118,000 persons are Georgian refugees in Russia. Tbilisi is the capital of the country, with a population of 1,253,000. The principal towns are: Kutaisi (241,100), Rustavi (158,000), Batumi (137,100), Zugdidi (105,000), Chiatura (70,000), Gori (70,000), and Poti (50,900). The state language is

Georgian, and, in the territory of Abkhazia, Georgian and Abkhazian. The main religion is Georgian Orthodox; other confessional groups include Shiite and Sunni Muslims (in the Pankisi Gorge), Armenian Gregorians (in the Javakheti region of Georgia), Catholics, Baptists, and Jews.

The Republic of Georgia has experienced rapid economic, political and social changes since gaining independence from the Soviet Union in 1991. With the relaxation of political, social and trade control since the fall of the dictatorship, the scale of the illicit drug market has increased, drug use has become more common, and the citizens' attitude towards drugs has diversified.

A number of factors contribute to the illegal drug trade in Georgia, three of which the principal ones considered to be:

- the Republic of Georgia and the whole South Caucasus is a natural trafficking corridor from Asia to Europe for different commodities, including drugs;
- the two unresolved inter-ethnic conflicts limit Georgia's capacity to control its own territory and borders;
- the heritage of the Soviet repression-based approach of organising public life and the related social inertia slows down and complicates efforts to create a balanced pragmatic drug strategy and, subsequently, a sustainable system of interventions and responses.

Table 1: Key Figures

Indicator	Year	Georgia	Source
Surface area	2013	69 700 sq km	National Statistics Office of Georgia
Population	2013	4 497.6 m	National Statistics Office of Georgia
GDP per capita in PPS	2012	3 508 USD	National Statistics Office of Georgia
GINI Index	2010	42.1	World Bank
Unemployment rate	2012	15.1%	National Statistics Office of Georgia
Prison population rate (per 100,000 of national population)	2013	200	International Centre for Prison Studies

Drug use in the general population and young people

There are currently no reliable data indicating the extent of different patterns of illegal drug use in Georgia, with some limited exceptions relating to injecting/problem drug use (see below). The figures that are occasionally found in the media are unrealistically high, suffer from ambiguous case definitions and are not based on transparent data or a sound estimation method. So far, no survey on drug use has been conducted in the general Georgian population – neither nationwide, nor limited to some city or area.

The drug survey of young people in Georgia that consistently followed international standards was conducted by the National Centre for Disease Control (NCDC) in the framework of the Southern Caucasus Anti-Drug Programme (SCAD)[1] (Baramidze & Sturua, 2009). Using the ESPAD survey methodology and a questionnaire that was adjusted to Georgian terminology and the local cultural environment, the study found that in the capital city, Tbilisi, in February 2009, 17% of the adolescents who were surveyed reported having used marijuana at least once in their lifetime. After cannabis, ecstasy was the most available drug for the young people who were surveyed, its use at least once in their lifetime being reported by 7.5% of the respondents; the lifetime prevalence for amphetamine-type stimulants was about 2%. Lifetime experience with crack cocaine was reported by fewer respondents (1.1%) and the rate for heroin was still lower (1%). Lifetime powder cocaine experience was reported by 0.6% of the survey respondents. Just as few reported experience of GHB and anabolic steroids or drug use by intravenous administration. Of the sample that was representative for Tbilisi, the lifetime prevalence for any illegal drug was 20% in the study (33% of males; 8% of females) (Baramidze & Sturua, 2009).

The survey of young people was implemented in Tbilisi and the results obtained reflect the situation that is characteristic of Tbilisi youngsters. Stemming from this fact, the study results could not be extrapolated to the whole Georgian youth population.

[1] Data were collected during February 2009 and the target population was Tbilisi students in the 10th grade (93% born in 1992), with a mean age of 16.1 years at the time of the data collection.

Problem drug use

As was noted in the previous section, the numbers on the extent of (different patterns of) drug use appearing in public debates in Georgia have been extremely flawed, with no transparent methodology until very recently. The first attempt to avoid mere guessing and to arrive at an expert consensus on the number of injecting drug users in the country occurred with the Consensus Meeting of experts in the field of drug demand reduction that took place on April 21, 2009. The meeting, which was organised by the Country Coordinating Mechanism on HIV/AIDS (CCM) critically reviewed the results of the "Study Estimating the Prevalence of Injecting Drug Use in Georgia Using the Multiplier/Benchmark Method" conducted within the framework of a programme funded by the EU and implemented by UNDP, "South Caucasus Anti-Drug Programme" (SCAD). Combining different estimation methods, the Consensus Meeting agreed on the estimation of IDUs in the country being approximately 40,000 (95% CI: 39,000-41,000), i.e. 1.5% (1.48%-1.52%) of the population aged 15-64 (Sirbiladze, 2010).

Concerning injecting drug use, the most frequent primary drug is of the opioid group, and heroin was the leading drug until the early 2000s. Since 2004, buprenorphine, in the form of the medical drug Subutex®, has become commonly injected (J. Javakhishvili et al., 2006). In Georgia, Subutex® entering the black market from abroad and competing with heroin.

According to data provided by addiction clinics, approximately one third of medically treated injecting drug users (IDUs) asked for treatment because of problems related to the non-medical use of Subutex® in 2007 (D. Otiashvili et al., 2010). Since the end of 2008, field studies have suggested that the overall use of Subutex® is slowly decreasing and other, more readily available injecting drugs are taking over its market share – most commonly home-made stimulants prepared from cough medicines containing pseudo/ephedrine or phenylpropanolamine that are easily available from pharmacies without a prescription (I. Kirtadze, 2010). The final (injectable) product of the preparation contains methamphetamine

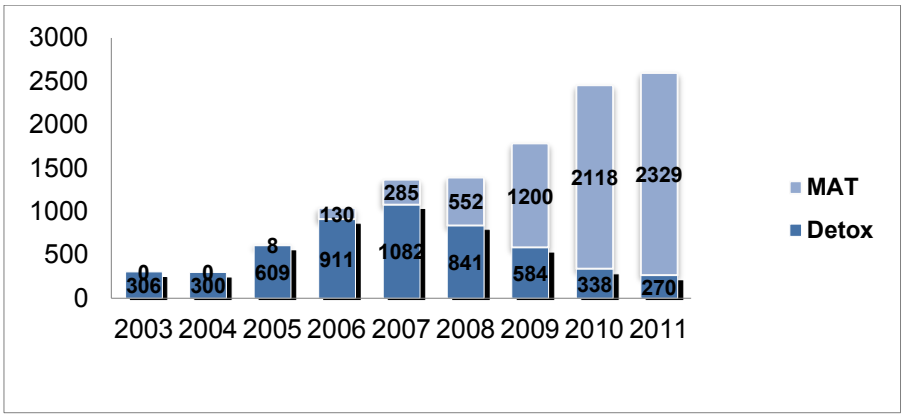
(street name “vint” or “boltushka”: a long-acting stimulant prepared through the reduction of pseudo/ephedrine) or methcatinone (street name “jeff”; a short-acting stimulant prepared through the oxidation of pseudo/ephedrine). The use of cocaine and other amphetamines than the two mentioned above remains very low (J. Javakhishvili & Sturua, 2009).

Treatment demand

As for 2011-2012, the four abstinence oriented treatment institutions function in Georgia are providing both in- and outpatient services. The standards according to which the four clinics are collecting and proceeding the data on the treated patients differ. Thus, reliable and valid national data on patients treated for drug use disorders do not exist in Georgia. In 2011,270 persons (2 females) received abstinence oriented inpatient treatment in the country. Contrary to detoxifications, opioid substitution treatment (OST) has been growing in recent years, providing methadone treatment to 2400 patients in 2012. Since January 2010, substitution treatment with Suboxone® (a composite medical drug, containing buprenorphine and naloxone, intended to lower the risk of injecting use) has been provided to about 80 patients in Tbilisi.

Traditionally, the majority of patients who came to addiction clinics for treatment were opioid users, most of them heroin addicts. In 2008, there was an increase in the number of detoxification patients whose principal drug was home-made methamphetamine and methcatinone (Georgian Research Institute of Addiction and NGO New Way, 2008). Most of the inpatient detoxifications (94.5% in 2009, 97.4% in 2008 and 93% in 2007) were provided in specialised clinics in Tbilisi, whereas only 5.5% (2.2% in 2008, 7% in 2007) were detoxified in the Adjara region.

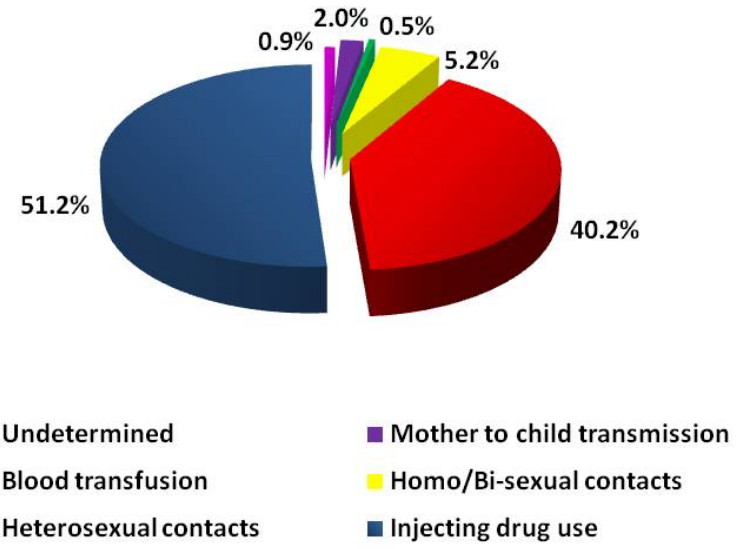
Figure 2: Trends in number of treatment episodes in abstinence-oriented treatment facilities (detox) and medication-assisted treatment (MAT) programs by years (Source: Centre for Mental Health and Prevention of Addiction, 2012)



Drug-related infectious diseases

By December 2013, the Infectious Diseases, AIDS and Clinical Immunology Research Centre (henceforth the AIDS Centre) had registered 4,131 cases of HIV, including 3,031 men (73%) and 1,099 women (27%). Most patients (60%) were 29 to 40 years of age at the time of diagnosis. Altogether, 2,483 reached the AIDS stage of the infection, and 896 of them died. Injecting drug use is the most frequent route of HIV transmission among all registered people living with HIV (51.2%). Other transmission routes include heterosexual transmission (40.2%), mother to child (2.0%), homosexual transmission (5.2%) (Georgian AIDS and Clinical Immunology Centre, 2013). Among IDUs, HIV prevalence rates range from 1.5% to 4.5%, depending on the locality (Chikovani, Chkartishvili, Gabunia, Tabatadze, & Gotsadze, 2010).

Figure 3: Cumulative distribution of HIV cases by routs of transmission (AIDS Centre, Tbilisi 2012)



Traditionally, injecting drug use has been the most frequent route of HIV transmission in Georgia (as in many other Eastern European countries), the second most prevalent route was heterosexual contacts. From 2002 this trend started to change. According to the data of the AIDS Centre, in the period from 1989 to 2002 the cumulative share of transmission due to IDU was stable - 69%, while starting from 2002 IDU share started to decrease and heterosexual transmission share started to increase. For 2008, IDU share has decreased to 60% while heterosexual transmission increased to 33%. As of May 2012, the cumulative shares of these two routes are correspondingly 54.9% and 38.1% (AIDS Centre, 2012). In 2011, annual incidence rate related to heterosexual contacts was 47.4%, while IDU route's share was 44.6% (unpublished data by NCDC). 42.6% of males and 57.4% of females were infected due to heterosexual contacts.

Prevalence of the hepatitis C virus (HCV) among HIV positive patients is as high as 48.6 %. In the study, HIV+ men were more likely to be co-infected with HCV than HIV+

women (60.8% and 18.0%, respectively). The prevalence of HCV among HIV+ injecting drug users was 73.4%. The odds of being HCV infected were 3.25 (95% CI; CL--1.89-5.26; p<0.01) for HIV+ injecting drug users (IDUs) compared to non-IDUs. The prevalence of viral hepatitis B antibodies (anti-HBV) among HIV positive people was 43.42% (76/175) in the study, and the prevalence of chronic HBV infection (HBsAg positive) was 6.86% (12/175). The prevalence rate of HBsAg was 8.51% in IDUs and 5.26% in non-IDUs. Triple infection (HIV, hepatitis C and chronic hepatitis B) was found in 9 patients (5.14%). Infections were associated with injecting drug use (88.88%) and were mainly related to the sharing of needles/syringes and other injecting medical paraphernalia (Badridze, Chkhartishvili, Abutidze, Gatserelia, & Sharvadze, 2008).

Treatment responses

After the collapse of the Soviet system, the first two narcological clinics providing residential treatment of addiction emerged in the early 1990s, although both had very limited capacities: the Georgian Research Institute for Addiction's clinic with 25 beds, and the Bemoni clinic with 6 beds. Since then, treatment capacity has increased in the country: there are presently five clinics with 60 beds and the capacity to detoxify more than 1000 patients in one year while offering both in- and out-patient treatment.

Treatment is usually limited to a 2-week detoxification (either pharmacologically assisted or completely drug-free), followed by discharge to individual and group outpatient therapy that is provided for 1-6 months. Till now treatment approach follows the heritage of Soviet biomedical narcology, stressing the patients' control, with little attention being paid to the psychological, behavioural, social and spiritual dimensions of addiction and ignoring the phenomena of non-addictive use. Most patients drop out of treatment during the first month since they believe the mere detoxification is sufficient for them, and because the cost of the outpatient therapy is extremely high: on average 2000 GEL per month (4 times the average salary in the country). As a result, the abstinence-oriented treatment as provided in Georgia

has a very limited and short-term impact; it does not support the recovery process, and the rate of relapse is high.

Almost all treatment procedures provided by the narcological clinics are paid for by patients directly and are prohibitively expensive, with the cost ranging from about $1000-1500 per detoxification period. In 2009, the state budget covered the treatment of only 78 patients (Chikovani, et al., 2010).

Opioid substitution treatment (OST) was introduced in 2005, when it was fully funded by a grant of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM); given the grant support, it has been the only addiction treatment that was provided free to the patients. Acknowledging the importance and positive impact of this treatment modality, the Georgian government started to co-fund OST in 2008. In the governmentally supported programmes, the cost of the methadone is covered by the state and patients pay for the services of the staff; the cost of such treatment is 150 GEL per month. This has resulted in a rapid expansion and increased availability of the treatment; as of 1st January 2012, there were 16 programmes operating throughout 8 regions of the country (and one OST was established in a prison in Tbilisi, providing treatment to 1200 patients (see above). About 800 patients receive treatment in state co-funded programmes and 400 receive it in GFATM-funded programmes.

Currently, GFATM maintains OST programmes in Tbilisi, in Gori, and in the prison facility; all of the GFATM-funded programmes are provided 100% free of charge. The governmental programmes are operating in Tbilisi and in seven regions of the country providing treatment for 150 GEL.

Harm reduction interventions

Harm reduction is a relatively well-developed approach in the country. This has happened as a result of the attention of international donors (Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), other UN agencies, the European Union and its Member States, the Open Society Institute). In 2006, 7 national non-governmental organizations established Georgian

Harm Reduction Network (GHRN) and by the end of 2013 the Network united 24 organizations working in the field of HIV/AIDS prevention, substance abuse treatment, and human rights.

GFATM is a single major donor providing funding for harm reduction services. In 2012 these programs served more than 5,000 beneficiaries. Harm Reduction services in the country include distribution of injecting equipment, condoms, information materials; voluntary counselling and testing (VCT) on HIV, BHV, CHV, and syphilis; peer to peer education. By the end of 2013, there were 12 HR sites of combined type (clients could receive both sterile equipment for injection and VCT in the same site) run by members of GHRN. Three sites are located in Tbilisi, and one in Batumi, Rustavi, Telavi, Gori, Kutaisi, Samtredia, Poti, Zugdidi and Sokhumi.

Coverage of harm reduction programs remains still very low despite seemingly remarkable expansion of harm reduction services in Georgia. Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users (WHO, UNODC, INAIDS, 2009) defines coverage of NSP and VCT programs as a low if less than 20% are covered and as an average if 20-60% are covered. The same guide suggests that 200 and more syringes should be distributed per year per IDU to ensure high coverage. Based on available data coverage of NSP in Georgia barely reaches 10% and highest number of syringes per year per IDU was 26 in 2010. Therefore, the full potential of this otherwise effective and cost-effective HIV prevention intervention is not utilized.

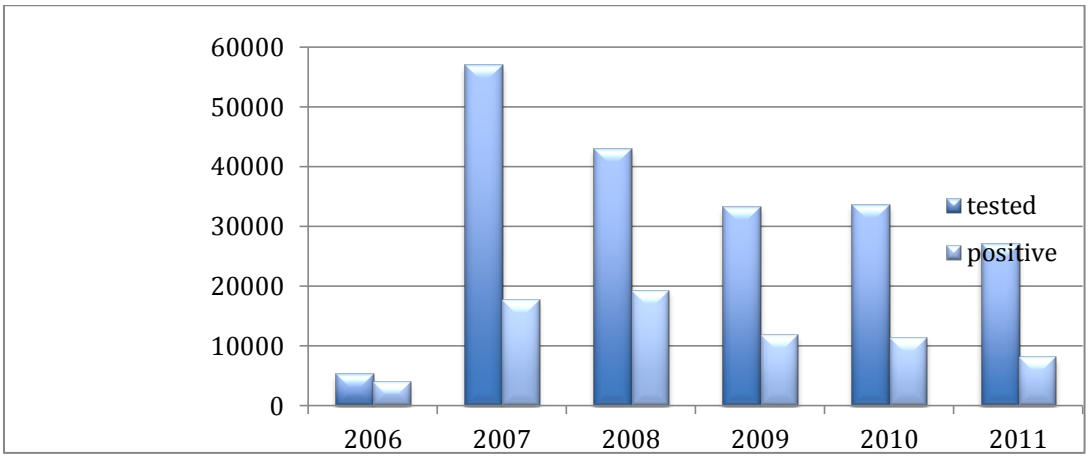
National drug laws

According to existing Georgian legislation, drug use is an administrative offence with a mandatory penalty of GEL 500 (approximately EUR 220) (Article 45 of the Administrative Code of Georgia). However, the same person apprehended as a drug user for a second time within one year after his/her first drug use offence bears criminal responsibility. In this case, the punishment can be either imprisonment or a fine of at least GEL 2000 (Article 273 of the Criminal code of Georgia). Given that the maximum fine is not defined by the criminal code,

the decision is at the discretion of the judge. As a result, there are cases of fines as high as GEL 4000 (approximately EUR 1800) imposed by courts for a positive urine test for inactive metabolites of illegal drugs.

Court judgments for drug use offences are mostly based on rapid (stripe) test results (positive urine test for inactive metabolites of illicit drugs) conducted by the expert-criminalistic laboratory of the MOIA, with no confirmatory laboratory methods used (except cases of appeal from plaintiff's side) applicable for administrative or criminal proceedings in the developed countries. On the basis of Article 45 of the Administrative Offences Code of Georgia, Minister of Internal Affairs together with the Minister of Labour, Health and Social Affairs issued a joint order N1049-233n in 2006, which stipulates rules for drug testing in case of a suspicion that a person is under influence and/or has consumed drugs without doctor's prescription, while the "Law on Police" stipulates that a police officer can demand from a person to follow him for the drug/alcohol testing if he/she is considered to pose a threat to himself/herself or others. Since then, street drug testing became a widespread practice in Georgia and number of people tested randomly in streets augmented in tenth fold. Number of people tested in 2007 was 10 times higher than in 2005 with positive findings as low as 30% (D. Otiashvili, Kirtadze, Tsertsvadze, Chavchanidze, & Zabransky, 2012). Though the numbers have been slowly decreasing in next years, ration between positive and negative test results still remains 1/3.

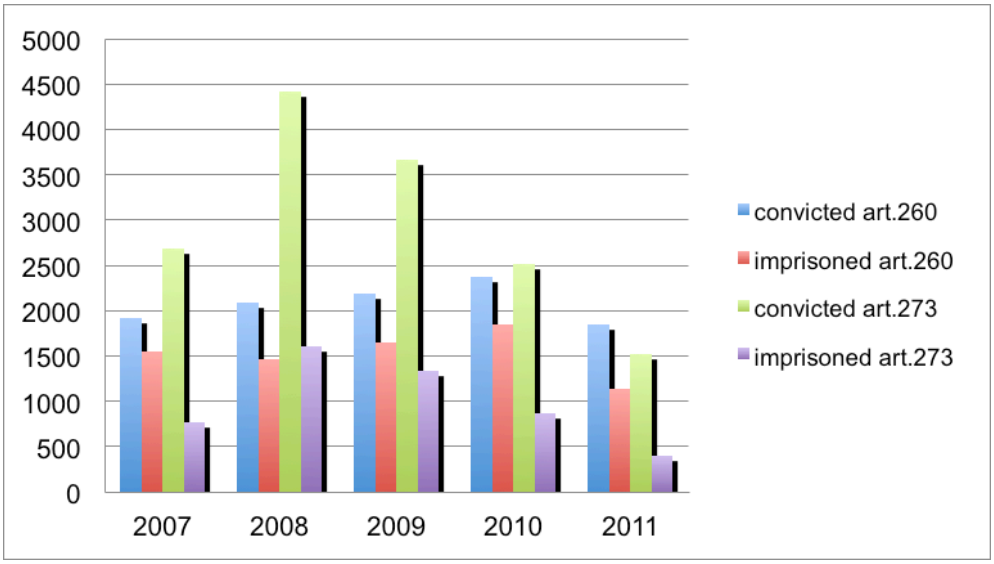
Figure 4: Trends in cases of drug testing in the country (Source: Ministry of Internal Affairs)



The Criminal Code of Georgia (Article 260) does not differentiate between the illicit manufacture,

production, purchase, storage, transportation, reselling and market sale of narcotic drugs or their analogues or precursors. All those criminal activities are defined under one paragraph/definition of crime, which makes it impossible to employ a differentiated approach to different drug offences.

Figure 5: Trends in drug-related convictions and imprisonment (Article 260 and Article 273 of the Criminal code of Georgia) (Source: Supreme Court of Georgia)



Since 2008, several initiatives where undertaken for amending national drug legislation. 2 draft bills were submitted to Georgian Parliament for changes and amendments to existing drug laws. First one was initiated by the Vice-speaker of Parliament and prepared by the Global Fund facilitated group (GFTAM, 2008), while the second one was prepared by Georgian Harm Reduction Network (www.ziani.ge) and initiated with the signatures of 58 000 citizens. Both initiatives stipulated decriminalization of drug use, definition of amounts for all illegal psychoactive substances as well as differentiation of possession of drugs for personal versus selling purposes.

Until recently none of the packages went through hearings in Parliament, but the beginning of 2012 was marked with increased interest towards the issue of drugs and drug related problems, legislation being among one of them. During the first half of 2012 active

debates were held around the first legislative package with parliamentary hearings and a final adoption of the draft bill at the end of May 2012. However, the new bill was not adopted entirely, only several laws have been adopted, setting aside crucial issue of decriminalization for future discussions.

Hopefully, as of end of 2013 major policy reform is discussed – Drug Policy Coordination Council has been established and drug related legislative initiatives have been reviewed in the Parliament. Importantly, this process has been inclusive and transparent enough and has engaged all major stakeholders - policy-makers, service providers, field experts, and representatives of affected groups. It is hoped that newly elected government will be committed to recalibrate current drug policy regime and build a system in which tolerance and care for those in need, effectiveness of interventions and evidence-driven decision-making will be prioritized.

3. Non-medical use of buprenorphine: review of available evidence

Despite variety of measures to control legal turnover and prescribing practices, majority of psychotropic medications is used non-medically (UNODC, 2011). This might range from unsanctioned use by patients who are prescribed the medication to diversion of the medication to illegal market and nonmedical use by those who do not have any prescription for it, and to online sale of opioids (Forman, 2003). This is truth for sedatives, tranquilizers, prescription painkillers, including opiates and others. The World Drug Report 2010 indicates that *"the misuse of prescription drugs, including opioids, benzodiazepines and synthetic prescription stimulants, is a growing health problem in a number of developed and developing countries"* (UNODC, 2010). Existing available information about the non-medical use of prescription drugs is insufficient to estimate the scale of the problem accurately. Prescription drugs are legally prescribed to patients to treat medical disorders and conditions, such as pain and numerous psychiatric conditions. It is of no surprise that these medications in certain instances might be widely available and accessible to relatively large groups.

In the United States, cannabis is the only illicit drug that is more widely used than prescription drugs (including analgesics, stimulants, sedatives, and tranquilizers) according to the 2009 National Survey on Drugs and Health (UNODC, 2011; Zacny & Lichtor, 2008). The SAHMSA 2009 National Survey on Drug Use and Health in the United States reported that 7 million citizens, or 2.8 per cent of population aged 12 and older, had used prescription drugs for non-medical purposes in the past month: an estimated 5.3 million had used analgesics, 2 million had used tranquilizers, 1.3 million had used stimulants, and 370 thousand had used sedatives non-medically in the past month (UNODC, 2011). There are estimated 4.5 million users of prescription opioids for nonmedical purposes, 1.4 million of whom are estimated to be opioid dependent (Carrieri et al., 2006) – much more than estimated 160,000 heroin users (Substance Abuse and Mental Health Services Administration, 2003).

Like other prescription medications prescription opioids are misused elsewhere they are available for medical use (Davis & Johnson, 2008). Non-medical use of buprenorphine, which is increasingly widely used to treat opioid dependence, as well as for pain relief, has been recently reported from different regions. Some authors have suggested that certain level of diversion and non-medical use are present wherever buprenorphine has been available for addiction treatment (Center for Health Services & Outcomes Research, 2006).

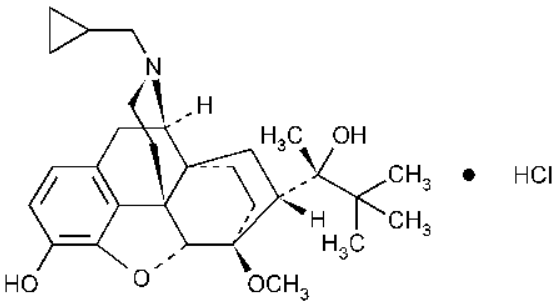
History of buprenorphine, current coverage of maintenance treatment and dispensing systems

Buprenorphine was developed in the 1970s in an attempt to find a ‚non addictive' injectable analgesic and was first registered and made available in the UK under the brand name Temgesic® in 1978 with the sublingual analgesic following in 1982. By 1985, injectable buprenorphine had been marketed for analgesic applications in 29 countries and the sublingual tablet in 16 countries (Campbell & Lovell, 2012). The sublingual pill Subutex® was developed in the mid-1990s and first registered for the treatment of opiate dependence in France in 1995, followed by the UK in 1999, Germany and Australia in 2000 (Verster & Buning, 2005). High-dose buprenorphine tablets are currently approved for use in 44 countries worldwide, with increasing international adoption reflecting the growing appreciation of the safety and effectiveness of substitution therapy (Carrieri, et al., 2006).

Buprenorphine's Effects

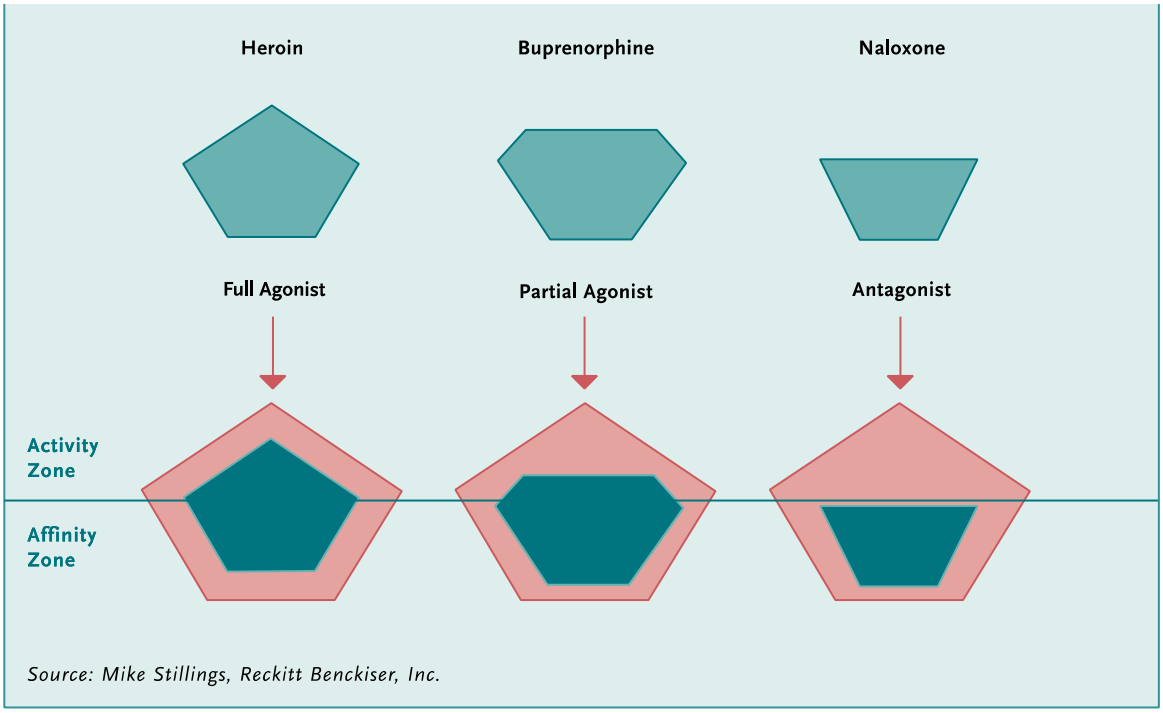
Buprenorphine is chemically an opioid.

Figure 6: Buprenorphine hydrochloride



Like other opioids, it produces most of its important effects by interacting with a structure on nerve cells called the mu opioid receptor (see Figure 7).

Figure 7: Heroin, Buprenorphine, and Naloxone Effects at the Mu Opioid Rece Heroin, Buprenorphine, and Naloxone Effects at the μ Opioid Receptor (Source: Mike Stillings, Reckitt Benckiser, Inc.)



Heroin, buprenorphine, and naloxone (represented above by blue polygons) produce contrasting effects because they interact differently with the brain's mu opioid receptors (red pentagons).

First, the chemicals differ in how much each stimulates the receptors (represented above by the percentage of receptor "activity zone" each fills). The stronger the stimulation, the more pronounced will be the opioid effects of pain relief, feelings of well-being, respiratory depression, and so on. Heroin, classified as a full receptor agonist (stimulator), nearly fills the activity zone. Buprenorphine, a partial receptor agonist, fills a smaller portion of it. Naloxone does not stimulate the receptor at all.

Second, each chemical binds to the receptors more or less strongly (represented above by the percentage of receptor "affinity zone" it fills). A chemical that forms a tighter bond can push one with a weaker bond off the receptors and take its place. Thus, buprenorphine can push heroin off the receptors, and in doing so replace heroin's full receptor stimulation with its own partial stimulation. Buprenorphine also binds more tightly than naloxone.

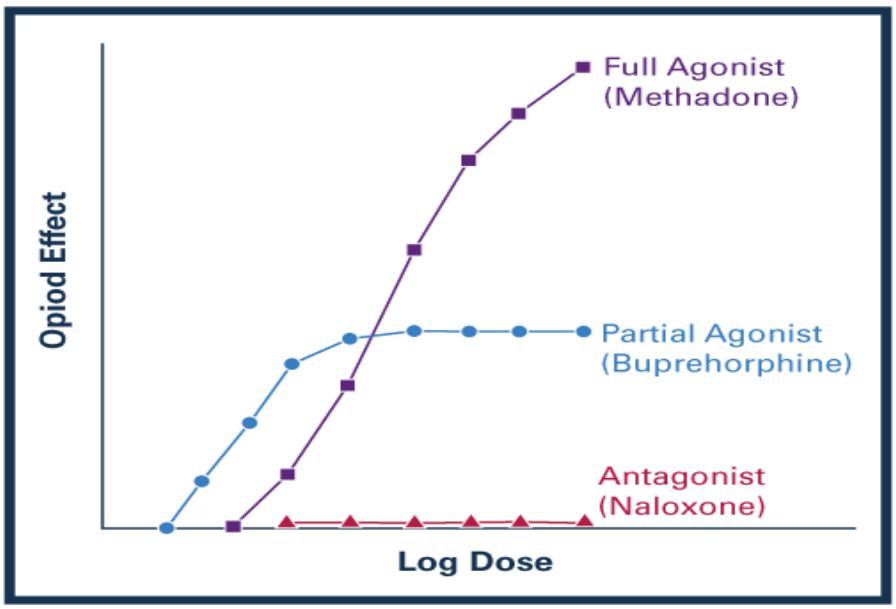
Naloxone can compete with heroin for the receptors. Because naloxone can block heroin and other opioids from stimulating the receptors while not itself stimulating them, it can precipitate opioid withdrawal and is classified as an opioid receptor "antagonist."

The special characteristics that distinguish buprenorphine from other opioids and make it useful for helping people overcome opioid addiction result from the unique ways it interacts with this receptor:

"Buprenorphine is a partial agonist at (i.e., stimulator of) the mu (μ) receptor. Stimulation of mu receptors result in the most of familiar opioid effects, for example, pain reduction, feelings of wellbeing or pleasure, and respiratory suppression. By stimulating the receptor only partially, buprenorphine yields those same effects, but with less intensity than heroin, morphine, or methadone, all of which stimulate the receptor fully (R.E. Johnson & Strain,

1999). While those drugs can cause powerful euphoria, motivating continued abuse, buprenorphine provides a positive but moderate psychoactive effect that reduces craving and helps patients comply with their medication regimens (Jasinski, Pevnick, & Griffith, 1978; Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). Buprenorphine also has a "ceiling effect" whereby increased doses of the drug do not produce increased effects after a certain point" (Jones, 2004)

Figure 8: Dose associated effects of different opioid agonists and antagonists, conceptual representation of opioid effect vs log dose for opioid agonists, partial agonists, and antagonists (Centre for Substance Abuse Treatment, Clinical Guidelines for the Use of Buprenorphine in the Treatment for Opioid Addiction, Treatment Improvement Protocol (TIP) Series 40, 2004, US Substance Abuse and Mental Health Services Administration)



- *" Buprenorphine has high affinity for the mu receptor. That is, buprenorphine binds tightly to mu receptors, more so than abused opioids and methadone do. Consequently, if a patient takes an abused opioid on top of buprenorphine, the medication will block it from reaching the receptors and producing the desired strong effects. Moreover, if buprenorphine is given to an individual who has already taken another opioid, it displaces the other opioid from the receptors. Depending on the dosage of buprenorphine, the patient's level of physical dependence, and when he or she last administered an abused opioid, the abrupt stripping of the other opioid from the mu receptor can precipitate withdrawal.*
- *Buprenorphine disassociates (detaches) from the mu opioid receptor slowly. This*

characteristic probably accounts for buprenorphine's long duration of action in the treatment of opioid dependence. While buprenorphine's manner of interacting with the mu receptor gives rise to its most important attributes and advantages in addiction treatment, the medication also has a significant action at a second receptor:

- *Buprenorphine is an antagonist (i.e., prevents stimulation) of the kappa opioid receptor. Stimulation of the kappa opioid receptor plays a role in producing some of the major symptoms associated with opioid withdrawal, such as chronic depression. By attaching to the kappa receptor and slowing its activity, buprenorphine may induce positive mood and feelings of wellbeing."* (Jones, 2004)

There are two formulations of buprenorphine for treating opioid dependence, a single-substance pill containing buprenorphine hydrochloride (HCl) tablet, marketed as Subutex® and Temgesic®, and a combination tablet Suboxone® containing buprenorphine HCl plus naloxone HCl in a ratio of 4:1 (Fudala, Yu, Macfadden, Boardman, & Chiang, 1998; Mendelson & Jones, 2003; Mendelson et al., 1996; Mendelson et al., 1999). Both tablets produce similar clinical effects when administered sublingually (Stoller, Bigelow, Walsh, & Strain, 2001). Suboxone was developed because buprenorphine alone has potential for abuse (Pickworth, Johnson, Holicky, & Cone, 1993; Strain, Walsh, Preston, Liebson, & Bigelow, 1997) and has been abused in a number of countries (P. G. O'Connor et al., 1998; Varescon, Vidal-Trecan, Nabet, & Boissonnas, 2002). Unlike buprenorphine, naloxone is poorly absorbed and has little effect when taken sublingually (Chiang & Hawks, 2003; Preston, Bigelow, & Liebson, 1990); however, when injected by an opioid-addicted person, naloxone can precipitate an opioid withdrawal syndrome - a strong deterrent to diversion of Suboxone® and its abuse by injection (O'Brien, Greenstein, Ternes, & Woody, 1978).

Table 2: Buprenorphine's relevant properties (Ford, Morton, Lintzeris, Bury, & Gerada, 2004)

Time to peak concentration	90-150 minutes after sublingual administration
Time for peak clinical effects	1-4 hours post dose
Duration of action related to dose	Low dose e.g. 2-4 mg exerts clinical effects for up to 12 hours Higher doses e.g. 16-32 mg can exert effects for up to 48-72 hours
Metabolism	Principally in the liver via two hepatic pathways: glucuronide conjugation and N-dealkylation by the CP450 enzyme system
Excretion	Principally in the faeces and urine
Elimination half-life	20-37 hours
Blockade dose	Maximal above 12-16 mg daily
Maintenance doses	Between 8-32 mg daily

As noted above, buprenorphine is characterized by a sustained duration of action, and it reduces craving, alleviates opiate withdrawal symptoms, and blocks the euphoric effect of opioids (Jones, 2004; Lintzeris, Bammer, Rushworth, Jolley, & Whelan, 2003; Sporer, 2004). Buprenorphine was prescribed to 152,000 patients in 18 European countries in 2011 (EMCDDA, 2011). The widest application of buprenorphine for the treatment of opioid addiction is to be found in France, where it is prescribed for 100,000 patients (Diaz-Gomez et al., 2010), which represents prevalence 0.15 per 10,000 population. In the US, buprenorphine is prescribed to 640,000 patients in the office based settings (W. H. Clark, 2010) which represents prevalence 0.2 per 10,000 population.

Generally, three treatment models, or combinations of them, have emerged. In the United States and France, general practitioners and drug dependence specialists are the major prescribers; in Australia, community-based pharmacies supervise dispensing and work closely with primary care physicians or specialised centers; and in Italy, Germany, Ukraine and Georgia specialist clinics or combinations of these systems dispense and prescribe buprenorphine. In Italy, buprenorphine is dispensed from specialised centers, whereas in Germany buprenorphine is available through physicians and specialist clinics, although uptake of all doses must be supervised for the first 6 months (Carrieri, et al., 2006). Georgia

and Ukraine are probably the examples of strictest control application for buprenorphine dispensing – the medication is provided in specialized addiction clinics on a daily bases under the direct control of the staff. No take homes are allowed (D.J. Javakhishvili, Sturua, Otiashvili, Kirtadze, & Zabransky, 2011; Schaub, Subata, Chtenguelov, Weiler, & Uchtenhagen, 2009).

Notably, none of the available dispensing systems provide safeguards for prevention of non-medical use. Even though buprenorphine uptake in Australia is supervised, there have been reports of both diversion and injection. More than 30% of IDUs in some locations have injected buprenorphine (Jenkinson, Clark, Fry, & Dobbin, 2005), and pharmacists now routinely crush all buprenorphine tablets before dispensing them (Lintzeris et al., 2004).

Abuse potential of buprenorphine

Similarly to other opiates, buprenorphine has potential for misuse (Comer & Collins, 2002; Comer, Sullivan, Whittington, Vosburg, & Kowalczyk, 2008; Pickworth, et al., 1993; Zacny, Conley, & Galinkin, 1997). When administered intravenously its clinical effects are comparable to those of morphine and heroin (Sporer, 2004) and it can produce reinforcing and subjective effects similar to methadone (Comer, Sullivan, & Walker, 2005). Despite its relatively safe properties, the combined use of buprenorphine with sedatives (alcohol, tranquillisers, barbiturates) can cause respiratory depression and overdose. The majority of cases of non-medical use have involved diluting the pills in water and injecting the preparation (Chua & Lee, 2006; Jenkinson, et al., 2005; D. Otiashvili, et al., 2010; Singh, Grover, & Basu, 2004) which may cause serious medical complications, such as abscesses, celullitis, myofasciitis, polyneuritis, septic sacroiliitis, thrombosis, and phlebitis, including overdose death (Ho, Ho, & Mak, 2009; Kintz, 2001; Loo, Yam, Tan, Peng, & Teoh, 2005; Pickworth, et al., 1993; Sharma, Vasoo, & Ong, 2005; Yang & Lee, 2008). Sniffing of the crushed tablets was also reported, particularly in France (Roux, Villes, Bry, et al., 2008)

Buprenorphine/naloxone combination

Increased concern over the abuse of buprenorphine has led to the development of Suboxone® – a combination of buprenorphine and opioid antagonist naloxone. Though the combination product seems to have a less abuse potential than buprenorphine alone (Simojoki, Vorma, & Alho, 2008), there are isolated reports about injecting abuse of combined formulation Suboxone®, which do not allow for drawing any conclusions. For this purpose we concentrate on the misuse of Subutex® in this report.

One study that examined abuse of Subutex® and Suboxone® by untreated injection drug users found a strong preference for the formulation without naloxone. Most subjects in this study (68%) had tried the Suboxone® formulation, but a large majority (4 out of 5) said it produced a "bad" experience (Alho, Sinclair, Vuori, & Holopainen, 2007; Center for Health Services & Outcomes Research, 2006). Work of the Comer and Collins (2002) suggests that buprenorphine/naloxone combination might be as attractive as buprenorphine alone for recently detoxified heroine abusers, i.e. for those who have experience of opioid dependence and who are on a low dose currently (Comer & Collins, 2002). There are some data indicating that Suboxone® can precipitate withdrawal symptoms in high doses but can be abused by individuals who are addicted to low doses of opiates. Some reports indicate that Suboxone® is being abused successfully when snorted (National Drug Intelligence Center, 2004), or when injected gradually in a small doses or mixed with benzodiazepines (Vicknasingam, Mazlan, Schottenfeld, & Chawarski, 2010). Also, both buprenorphine alone and buprenorphine/naloxone may be diverted to nonmedical use by the sublingual route in individuals who are not physically dependent on opioids (Strain, Stoller, Walsh, & Bigelow, 2000), as well as by the intravenous route in patients who have recently undergone detoxification (Carrieri, et al., 2006; Comer, et al., 2005).

Certainly, although buprenorphine/naloxone has lower abuse liability than buprenorphine alone, the extent to which the combination formulation is likely to mitigate abuse or diversion of buprenorphine may be limited. Introduction of buprenorphine/naloxone combination for

example did not result in reduction in illicit use in Malaysia (Bruce, Govindasamy, Sylla, Kamarulzaman, & Altice, 2009).

Reported prevalence of non-medical use of buprenorphine

We identified first recorded report on the injecting misuse of buprenorphine (Temgesic®) in Dublin, Ireland, as early as in 1986 (J. J. O'Connor, Moloney, Travers, & Campbell, 1988). The same form of the medication (Temgesic®) was reportedly injected in late 1980-early 1990 by drug users in Glasgow (Stewart, 1991), London (Strang, 1991), and Manchester (Strang, 1985). Buprenorphine misuse has been reported in at least twelve European countries (EMCDDA, 2005); however, this problem is not equally severe in each of them.

Some countries report a significant proportion of treatment demands relating to opioids (including buprenorphine) other than heroin. Buprenorphine misuse is reported as the main reason for entering treatment by 40% of all clients in Finland and 8% of clients in France. In Latvia and Sweden, between 5% and 8% of drug clients report primary use of opioids other than heroin or methadone: mainly buprenorphine, painkillers and other opioids (EMCDDA, 2008). In 2005 in Georgia 40% of clients in detox clinics reported Subutex® as a primary drug of dependence (J. Javakhishvili, et al., 2006). Cicero and colleagues showed that about 22% of people seeking drug treatment due to prescription drug abuse used buprenorphine during the last months and for about 2% of them buprenorphine was the primary drug of dependence (Cicero, Surratt, & Inciardi, 2007). 59% of problem opiate users in the Czech Republic (6,300 out of 10,600) are Subutex® users (Mravčík et al., 2013).

In Australia, eleven percent of the national sample reported recent injection of licit (prescribed to them by physician) buprenorphine and 20% reported injection of illicit buprenorphine. Again, there were jurisdictional variations in the proportion of IDU reporting injection of licit and illicit buprenorphine. For example, Western Australia reported the highest level of injecting illicit buprenorphine with 31% injecting in the last six months (O'Brien et al., 2006).

Bangladesh (where data is based on treatment demand) and Singapore also report the non- medical use of buprenorphine (UNODC, 2009). In Bangladesh, India, and Nepal, the illicit use of injected buprenorphine is common. In India, buprenorphine is the main drug of injection in most areas of the country (UNODC, 2007).

Characteristics of misusers and related factors

There are only a few studies attempting to study the factors promoting buprenorphine injecting, the circumstances associated with its use, its negative effects, and preventive or treatment programmes designed to address it (J. Ahmadi & Ahmadi, 2003; J. Ahmadi, et al., 2003; M. Ahmadi, Maany, & Ahmadi, 2003; Tacke, 2002). It has been suggested that non-medical use of buprenorphine is associated with poor social conditions, such as unstable housing or/and on-going (poly)substance use (Center for Health Services & Outcomes Research, 2006; Guichard et al., 2003; National Medicines Information Centre, 2002; Obadia, Perrin, Feroni, Vlahov, & Moatti, 2001; Roux, Villes, Blanche, et al., 2008). It is also reported that, compared with other opiate users, buprenorphine users are of a younger age, start injecting earlier, and apply for treatment sooner (Varescon, et al., 2002). In contrast, Yokell and authors reported older age of buprenorphine misusers in their sample in New York (Yokell, Zaller, Green, & Rich, 2011). Based on the available studies we could probably identify three different groups of buprenorphine injectors: 1) those trying to give up heroin and other opiates and using buprenorphine for self-treatment purposes, 2) those using buprenorphine as a principal drug of misuse in order to get pleasure, and 3) those who experiment with it (Alho, et al., 2007; EMCDDA, 2005; Hakansson, Medvedeo, Andersson, & Berglund, 2007; D. Otiashvili, et al., 2010; Yokell, et al., 2011).

Reported purpose of buprenorphine injecting

Available data show that significant portions of the people who inject Subutex® use it for self-medication purposes. Self-treatment was reported as the main reason for the non-prescription use of buprenorphine by significant portion of the respondents in Finland (Alho, et al., 2007), France (EMCDDA, 2005), Sweden (Hakansson, et al., 2007), Singapore (Winslow, Ng, Mythily, Song, & Yiong, 2006) and the US (Center for Substance Abuse

Research, 2011; Monte, Mandell, Wilford, Tennyson, & Boyer, 2009) - see table 4. Notably buprenorphine is rarely the preferred drug but in many places is used in absence of another (traditional) drug, or to cope with withdrawal symptoms, and not because of its reinforcing effect (Daniulaityte, Falck, & Carlson, 2011; J. J. O'Connor, et al., 1988).

Dosage of injected buprenorphine

The average dose and frequency of buprenorphine injection varies significantly between countries and apparently reflects complex set of contributing factors, such as availability of the medication as a medical treatment, price of the tablet on illegal market and others. Price of illegal Subutex® was reported in a range from IR£2-5 for 2 mg in Ireland in 1987 (J. J. O'Connor, et al., 1988; Strang, 1991) to $25-50 in the USA (National Drug Intelligence Center, 2004), and more than $100 in Georgia (D. Otiashvili, et al., 2010) for one 8 mg tablet.

4. Non-medical use of buprenorphine among Georgian IDUs

Introduction

As noted earlier, there are only a few studies attempting to study the factors promoting buprenorphine injecting, the circumstances associated with its use, its negative effects, and preventive or treatment programmes designed to stop it (J. Ahmadi, et al., 2003; M. Ahmadi, et al., 2003; Tacke, 2002). According to the existing data, the non-medical use of buprenorphine is more characteristic among people with unstable housing or homeless residents of marginalised urban regions and it is often combined with the use of other narcotic or psychotropic substances (Guichard, et al., 2003; National Medicines Information Centre, 2002; Obadia, et al., 2001; Roux, Villes, Blanche, et al., 2008). It is also suggested that, compared with other opiate users, buprenorphine users are of a younger age, start injecting earlier, and apply for treatment sooner (Varescon, et al., 2002). Some authors identify two different groups of buprenorphine injectors: 1) those trying to give up heroin and other opiates and using buprenorphine for self-treatment purposes, and 2) those using buprenorphine as a principal drug of misuse in order to get pleasure (Alho, et al., 2007; EMCDDA, 2005; Hakansson, et al., 2007). All the cited papers refer to the misuse of buprenorphine in countries where the drug is available for treatment. We were unable to identify any studies dealing with the injecting use of buprenorphine in a setting where it is not legally available, as it is the case in our study.

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. At the time of the data collection methadone maintenance treatment (MMT) was provided with the support of the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) to 230 patients only (Georgian Research Institute of Addiction and NGO New Way, 2008). 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).

In our very recent study we found a 100% lifetime prevalence of buprenorphine injection among participants (not-in-treatment opioid-dependent men) and 55% of the study sample named buprenorphine as a principal drug at the time of their entering the study (D. Otiashvili, Kirtadze, O'Grady, & Jones, 2012). Despite clear indications of the increasing injecting misuse of buprenorphine, so far there have been no peer-reviewed publications exploring this phenomenon in Georgia.

It should be emphasized that at the time the study was conducted buprenorphine was not a registered medication and thus it was not legally available for healthcare in the Republic of Georgia. It has entered the country only illegally, available exclusively in the form of buprenorphine tablets; subsequently, it is used in Georgia by injecting, similarly to the majority of other illegal opioids. So far, no pattern of buprenorphine use other than injecting was reported in Georgia (Gamkrelidze, et al., 2004; Gamkrelidze, et al., 2005; J. Javakhishvili, et al., 2006). Thus, we designed the exploratory part of our study to understand what the prevalence and patterns of the non-medical injecting use of buprenorphine among drug injectors in Georgia are.

Methods and Participants

Method: We designed a self-administered questionnaire study to describe the prevalence and patterns of buprenorphine injection among Georgian IDUs. Additionally, we sought to understand the reasons why IDUs start and/or continue injecting buprenorphine. Questionnaire was developed through the focus group discussions with (1) key informants (addiction specialists, staff of low threshold services who are in contact with drug users on a daily bases) and (2) drug users recruited by the outreach workers of the low threshold programs. To ensure that questions are properly and understandably formulated and cover all the important for the study themes draft version of the questionnaire was piloted for validation with ten injecting drug users in Tbilisi. Final version represents a short and easy-to-fill-in questionnaire with 13 questions (9 of them multiple-choice). The questions cover topics related to drug use career, patterns (frequency, history, dosage), and reasons for the use of buprenorphine (see attachment 1).

Study sites and sampling: The survey was conducted 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.

Ethical issues: The study questionnaires included information related to the purposes of the study, and an informed consent form was signed by the study participants. Participation was voluntary and anonymous, and no personal information except for gender and age was collected. Participation or non-participation in the study did not affect the provision of any services to the clients of the programmes. The protocol of the survey was approved by the Bio-Ethics Committee/IRB at the HIV/AIDS Patients Support Foundation of Georgia.

Statistical analysis: Non-parametric statistical procedures were used in all the analyses. 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).

Findings

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. As shown in Table 3, buprenorphine was the most prevalent drug injected at least once in the previous month.

Table 3: Lifetime and last-month prevalence of use of different drugs

Pattern of use	Buprenorphine	Opium	Heroine	Home-made pseudo/ephedrine	Sedatives	Medical opiates other than	Painkillers	Coaxil	Heroin with cocaine	Meth/amphetamine in tablets	Crack	Cocaine
Lifetime prevalence (%)	95.5	84.2	80	67	68	75	67.4	16	30	22.3	5.8	14
Last month prevalence (%)	75	42	53	43	39	32	29	6	3	2	1	1
Last month cumulated days	1,77	1,70	1,47	1,87	1,45	650	413	82	30	20	7	4

One of the aims of the study was to better understand why Georgian drug users inject buprenorphine. Five alternative categories were identified during the discussions in focus groups and included in the questionnaire:

1. To get high, pleasure
2. Self treatment, to get off drugs
3. To coup with withdrawal
4. It's easy to get Subutex
5. Other…….

Distribution of responses is presented in the Table 2. 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 4). 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 4: Reported reason for buprenorphine injection

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. We also looked at the age-related distribution of different patterns of buprenorphine injection. For this purpose, two age groups were analysed – young people of 10-24 years of age (as defined by the UN system), and participants above 24 years of age. 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. On the other hand, we found no significant age-related differences in terms of favouring buprenorphine, with 14.6% [4.2, 24.9] of the younger injectors and 12.7% [9.0, 16.3] of the older injectors reporting buprenorphine as their favourite drug.

Interestingly, frequency of buprenorphine use was positively correlated with the frequency of heroin use in the same period [95% CI: 0.08, 0.24], but negatively with the frequency of the use of opium [95%CI -0.26, -0.15].

We found no significant differences in the amount of money that drug users would pay for a single dose of different opioid-type drugs. Respondents would pay a mean of 48 GEL (SD 27.3) for a single dose of heroin, 43 GEL (SD 23.6) for a single dose of buprenorphine, and 45 GEL (SD 33.8) for a single dose of opium (€ 1 was 2.1 Georgian Lari at the time of the study). The average single dose of buprenorphine reported by the respondents was low compared to what is generally considered as the average therapeutic/effective dose (Campbell & Lovell, 2012; H. W. Clark, 2010; National Medicines Information Centre, 2002). 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 (D. Otiashvili et al., 2008). 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.

Discussion

Buprenorphine is abused in different setting, regardless whether it is available in medical system or not. Our findings in Georgia reported 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 at the time of referred study. The prevalence of lifetime and recent Subutex® injection use found in our study sample was the highest among all the reported cases known to us from any country worldwide - 95.5% of the sample had injected Subutex® at some time in their life and 75% had injected it in the last month. In both cases Subutex® was the most prevalent of all injected drugs. However, drawing a comparison between countries and studies is difficult, as they are carried out in different settings and employing different designs. Furthermore, available studies mainly focus on buprenorphine misuse by clients who are in treatment.

Significant proportion of drug users combined Subutex® with benzodiazepines and other sedatives (Alho, et al., 2007; Jenkinson, et al., 2005; Ng, Mythily, Song, Chan, & Winslow, 2007; Nielsen, Dietze, Lee, Dunlop, & Taylor, 2007; Obadia, et al., 2001; D. Otiashvili, et al., 2012; David Otiashvili, Kirtadze, O'Grady, & Jones; D. Otiashvili, et al., 2010). French authors have suggested that the concurrent use of benzodiazepines was more common among those with low prescription doses of buprenorphine (De Ducla, Gagnon, Mucchielli, Robinet, & Vellay, 2000; Fatseas & Auriacombe, 2007). In the Georgian setting benzodiazepines and other sedatives are thought to be added to the preparation in order to increase the potency and duration of effect of a small dose of buprenorphine. In addition to the concurrent use of benzodiazepines, the use of other opiates and home-made stimulants was common in our sample. Even if poly-drug use is a well-known phenomenon in the region and is confirmed by other authors (Booth, Lehman, Dvoryak, Brewster, & Sinitsyna, 2009; Booth et al., 2008; Kruse et al., 2009), our findings indicate a scenario of even more chaotic drug use in the study sample. The reasons for unsystematic (unstructured) poly-drug use (mixing together buprenorphine with other sedatives, and with pseudo/ephedrine-based stimulants at the same time) might be the fluctuating availability of particular substances, the high price of all illegal drugs on the Georgian black market compared to local income levels, and users' attempts to combine different drugs in order to increase the euphoric effects,

potency, and duration of effect of the preparation. Obviously, these are questions to be explored in future research.

Although buprenorphine accounts in our sample for the highest lifetime and last-month prevalence, overall it is by far not the favorite drug of those who inject it. Only 13% of respondents claim that it is their favorite 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.

It has been argued that the relatively long-lasting effect of buprenorphine injection (compared to heroin or opium) and less obvious external signs of intoxication might be important reasons for its popularity in the Georgian drug-using setting (J. Javakhishvili, et al., 2006). Recently there has been a dramatic increase in police activity aimed at random street searches and (urine) testing of young people for drugs, which, in the event of a positive result, leads to harsh penalties (D. Otiashvili, Sárosi, & Somogyi, 2008). Thus, buprenorphine might attract drug users because of its moderate clinically (externally) visible signs after its intake. Furthermore, for a long period the police did not check suspects for the presence of buprenorphine in their urine, but rather concentrated on the traditional opium and heroin. This could in fact have added to the “attractiveness” of buprenorphine for local drug users; however, in our Georgian study we did not investigate this factor.

The average dose and frequency of drug injection was low in our sample. More than 90% of buprenorphine injectors use 1-2 mg as a single dose and the mean frequency of its injection was 6 times per month. Our findings were consistent with previous reports reporting that an 8 mg tablet of buprenorphine is usually injected by a group of 4-8 people in Georgia (J. Javakhishvili, et al., 2006). In contrast with our findings, the dose of buprenorphine injected by drug users in Western Europe and elsewhere is reported to be much higher, between 6 and 10 mg per injection (Alho, et al., 2007; De Ducla, et al., 2000; Nielsen, et al., 2007; Winstock, Lea, & Sheridan, 2008). The low dosage in our sample can most probably be explained with economic reasons. One 8mg tablet of buprenorphine costs about €73 on

the Georgian black market (according to the State Department of Statistics, the average salary in Georgia is about €143) and the typical drug user can only afford to pay for a relatively small part of one such tablet in Georgia. Regardless of the reasons, the low dosage also suggests that the euphoric effects are less important for Georgian buprenorphine users than simply coping with withdrawal and – possibly – social factors.

Limitations of the study

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 (I. Kirtadze, Otiashvili, & Chavchanidze, 2008). In contrast, the mean age of this group was at least 5 years higher than the mean age of the "random" sample of IDUs recruited for other study using respondent driven sampling technique (Dershem et al., 2004). 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.

Concerns were raised about the reliability of the reporting of drug use practice by the clients of treatment programmes (they might not want to report their misuse while in detoxification treatment) (Darke, 1998; Magura & Kang, 1996); other concerns with possible over-reporting of drug use that are often raised by Georgian addiction treatment staff, suggesting that clients may simulate severe addiction in order to increase their chance of being included into the "highly competitive" methadone maintenance treatment programme (MMT) in Georgia [personal communication with Dr. Sikharulidze, Uranti MMT programme].

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 study of this design.

Conclusion

This sub-study assessed the extent and patterns of buprenorphine misuse in a setting where this medication was neither available for medical purposes nor for any other legally legitimate purposes. The study findings suggest that illegal buprenorphine has considerable potential for non-medical use. A remarkable portion of Georgian young drug injectors started their injecting career with buprenorphine. The reported reasons of its use and the public health risk involved in its mode of injection, which appears exclusive for illegal buprenorphine use in Georgia, may suggest that introduction of legally available medical treatment with buprenorphine-containing medicals is worth considering by public health authorities in Georgia. Further research is needed to understand the personal, psychological and social factors (characteristics) associated with/leading to buprenorphine injection and
to assess the related health and social risks.

5. Methadone and Suboxone® for HIV risk reduction in Subutex® injectors

Specific Aims

Overall: A problem found in Georgia and a few other countries is that *more than half of all opioid addicted patients have or are currently injecting buprenorphine*. The formulation used is Subutex® that is smuggled into the country from Western Europe (as it was not approved for addiction treatment in Georgia at the time of study launch). Unlike other parts of the former Soviet Union where injecting drug use, particularly heroin, has been associated with the spread of HIV, the prevalence of HIV among Georgian IDUs is less than 5% even though 50% or more are positive for hepatitis C and sharing injection equipment is common (Curatio International Foundation & Public Union Bemoni, 2009). However, 54.4% of known cumulative cases of HIV in the country are associated with injection drug use (D. J. Javakhishvili, et al., 2012). This situation is one where HIV can spread rapidly unless effective treatment and prevention programs are developed and expanded.

This study addresses this problem by obtaining pilot data on the impact of a 12-week course of daily, observed Suboxone® or methadone on HIV risk, injecting use, treatment acceptance and other addiction treatment outcome measures. It also obtains data on patient status at week 20 when subjects have either completed a 3-week dose taper, transferred to a local methadone or residential treatment program, or dropped out of treatment. Patients were 80 opioid dependent patients (40/group) who have injected Subutex® 10 or more times in the past 30 days. The study was done in the methadone program at the medical center Uranti in Tbilisi. Uranti is the second largest addiction treatment program in Georgia and affiliated with the Addiction Research Center, Union Alternative Georgia, also in Tbilisi.

Primary aims of this randomized clinical trial were to:

1) Obtain and analyse pilot data on the impact of a 12-week course of daily, observed Suboxone® and methadone treatment on HIV injecting risk behaviour and opioid use, particularly that associated with injecting use of buprenorphine (mainly Subutex®)
2) Obtain and analyse pilot data on the degree to which the target population accepts treatment with daily observed Suboxone® and methadone

Background and Significance

Few persons addicted to opioids receive any form of treatment in Georgia. If received, it is usually limited to a 2-week inpatient detoxification with clonidine followed by discharge to outpatient individual and group therapy for 1-6 months. Most drop out of treatment during the first month as they believe detoxification is adequate, and relapse is high. Oral naltrexone has been tried but unlike Russia (Krupitsky et al., 2004; Krupitsky et al., 2006), has not been successful. Though methadone maintenance reduces opioid use and HIV risk (Metzger, Navaline, & Woody, 1998; Metzger et al., 1993), it was not legal in Georgia until 2003.

The first methadone program opened in 12/05 *and 9 were operating in 2009, four in Tbilisi and five in other regions, and treating a total of 700 patients*. The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) provided free of charge treatment for 300 patients. The Ministry of Labor, Health and Social Affairs provided co-funding for methadone treatment in private clinics with 150 GEL (about $100/month) to be covered by patients. According to Georgian policy and regulations, patients aged 25 and above with a minimum five years of opioid addiction are eligible for methadone maintenance, however those younger than 25 are permitted if HIV+.

Internationally, there are only a few studies of factors promoting buprenorphine injecting and the circumstances associated with its use, and on prevention or treatment programs to stop it (Tacke, 2002). According to existing data, it is more often seen among homeless, urban residents (National Medicines Information Centre, 2002) and often combined with other

psychotropics (Obadia, et al., 2001). It has also been reported that, compared with other opioid users, buprenorphine users are younger, apply for treatment earlier, and start using at an earlier age (Varescon, et al., 2002).

Only a few papers have been published on treatment for buprenorphine addiction. An Iranian study 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 group had the best retention, followed by sublingual buprenorphine that was in turn followed by naltrexone (J. Ahmadi & Ahmadi, 2003). In another study both sublingual buprenorphine and oral methadone were equally acceptable and effective (M. Ahmadi, et al., 2003).

Unique Features of the Study: Injecting buprenorphine with HIV risk behaviours are problems in several countries and may increase in the U.S. after generic buprenorphine is introduced. Georgia is an excellent place to explore ways to treat it as Georgia has a high concentration of buprenorphine injectors who are on waiting lists for treatment. There is a great need for research that focuses on buprenorphine injectors, particularly treatment research that focuses on reducing its use, preventing the associated HIV injecting risks, and educating patients about how to minimize the risks.

Considering the high level of prejudice in Georgia against all kinds of “narcotics”, the introduction of treatment using daily, observed Suboxone® with its built-in safeguards against diversion, overdose and abuse is a concept that is likely to be acceptable to policymakers and society. Because most persons who need HIV treatment in Georgia are IDUs, positive results from methadone or Suboxone® treatment might help expand the number of persons eligible for antiretroviral therapy (ART) and facilitate adherence to ART since uncontrolled addiction typically excludes persons from ART and negatively effects adherence.

Preliminary Studies

Uranti staff work closely with the Addiction Research Center of the Union Alternative Georgia (ARC), have studied outcome from their methadone program, and found that it is well accepted with 92 % of patients reporting they are satisfied with treatment. Among 85

patients enrolled for one year, only 10 left the program, 4 due to incarceration. Mean age of participants was 40, mean history of drug use 15.3 years, 16.7% were positive for hepatitis B, 80% for hepatitis C, and 11.7% for HIV. This 11.7% with HIV is because HIV+ patients are immediately accepted into the program resulting in a much higher proportion in treatment than among an unselected sample of injecting users. Outcomes showed a significant reduction (68%) in illicit opioid use and injecting risk behaviour at five months, though the data did not include an examination of buprenorphine injecting (Gambashidze, 2007; Piralishvili, Gambashidze, & Sikharulidze, 2008).

There were two relevant research projects at the ARC implemented in recent years. The first is: "Engaging Non Treatment Seeking Drug Abusing Georgian Men", P.I. Dr. Hendree Jones. Data show a 100% lifetime prevalence of Subutex injecting among opioid dependent men not in treatment, and 55% name it as a primary drug (D. Otiashvili, et al., 2012). A second study: "Tbilisi Urban Health Study: Assessment of HIV Risk Factors among IDUs and MSM in the Republic of Georgia" is being done in collaboration with the CFAR at the University of North Carolina and RTI International. Preliminary data show a 100% lifetime prevalence of buprenorphine injection with mean days of Subutex use in the past 30 as 11 (max 28, min 0).

Though heroin and Subutex® are the opioids being injected in Georgia, homemade methamphetamine is also being used, either mixed with opioids or injected alone. According to Otiashvili et al, up to 11% of participants in a recent study reported injecting homemade methamphetamine ("vint") (D. Otiashvili, et al., 2012). Though neither methadone nor Suboxone® directly address stimulant injecting, either medication may reduce it indirectly since stimulants are often used to accentuate opioid effects and the reduction in opioid use typically seen with Suboxone® or methadone treatment, combined with drug counseling, is likely to reduce methamphetamine use as well.

Research Design/Methods

The City

Tbilisi has 1.3 million inhabitants, accounts for approximately ¼ of the country's population, and probably has a substantial proportion of its drug users, as all capitals do. It is well served by public transportation and connected by telephone and e-mail with access to high speed Internet at both study sites and other locations.

Research sites/organizations

The University of Pennsylvania, Addiction Research Center at the Union Alternative Georgia and the Medical Center "Uranti" collaborated on this study.

The Addiction Research Center is a non-governmental, not-for profit organization involved in public health research with a focus on addiction and HIV prevention and treatment

Overview of study design

We randomized 80 consenting, treatment-seeking opioid dependent individuals who report injecting Subutex® 10 or more times in the past 30 days to a 12-week treatment course of involving daily supervised medication with methadone (group 1) or Suboxone® (group 2). Randomization was stratified according to male/female, and over 30/under 30. All patients were offered weekly group therapy and individual drug counselling. A 3-week inpatient or outpatient dose taper, or transfer to the Uranti methadone program, residential treatment, or inpatient detoxification were offered to all patients at the end of the 12-week study treatment period. Comprehensive assessments were done at baseline and at weeks 4, 8, 12 and 20; brief assessments were done weekly during the 12 weeks of active treatment.

Probands

Inclusion criteria: Opioid dependent with physiological features for past three or more years according to ICD-10*; between 25 and 50 years of age; 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 and not planning to move; Home or cellular telephone number where can be reached+; Able to provide name of

family member who knows where can be reached; Willingness and ability to give informed consent and otherwise participate

Exclusion criteria: Currently dependent on alcohol, benzodiazepines or other CNS depressants; Legal charges with impending incarceration; Plans to move from Tbilisi within the next 6 months; Concurrent participation in another treatment study; Advanced neurological, cardiovascular, renal, hepatic or other medical disorder that would seriously impair or make hazardous patient's ability to participate; Active tuberculosis; Currently psychotic, homicidal, or suicidal; Have an uncontrolled seizure disorder.

Notes: patients whose urine test is negative for buprenorphine or other opioids but clearly dependent (e.g. report Subutex or heroin injecting with "tracks", puncture marks, and signs of withdrawal) will be eligible for enrolment.

Persons who fail screening for any reason can be re-screened after 4 weeks if it is likely that the reason they failed was transient.

Procedures

Screening and enrolment: All screening, assessment and follow-up evaluations were done in offices at the Uranti program during evaluations for methadone treatment. A three step process was used: 1) Provision of detailed information about the study to persons who appear to meet entrance criteria along with an opportunity to ask questions about the study. If interested, patients were asked to review, discuss and sign the informed consent and take a 10-item quiz testing their understanding of the study; 2) Upon signing the informed consent and passing the quiz, behavioural assessments were completed along with a history and physical examination including tests for HIV and hepatitis B and C with pre-test counseling; and, 3) HIV/hepatitis B/C post-test counselling, final eligibility, and randomization completed in 3-5 days.

The consent included information about the pharmacology of methadone and Suboxone® including the fact that Suboxone® can precipitate withdrawal if dissolved and injected by someone addicted to heroin, the possibility of overdose if either medication is used with high doses of alcohol, benzodiazepines or other CNS depressants, the importance of taking

medication as prescribed and keeping appointments, the conditions under which medication will be stopped, reimbursements for completing assessments, and the times when assessments are needed.

Patients were told that urine and alcohol breath test results will be shared with clinical staff since they are directly relevant to patient care. The consent informed patients that contact information might be shared with research staff to help locate them for follow-up evaluations, and the conditions under which they may be discharged from the study. Patients who missed more than one question on the 10-item quiz testing understanding of the study were given two chances to retake it and those who cannot answer 9 of the ten questions correctly after three tries were considered ineligible and referred to other locally available treatment programs.

HIV and hepatitis B/C counselling were modelled after US CDC guidelines for personalized risk reduction and were part of staff training. Pre-test risk reduction counselling addressed mechanisms of transmission of HIV, HBV, and HCV and result in a personalized risk profile highlighting behaviours most commonly practiced or difficult to control for the patient. Risk reduction strategies were reviewed and patients counselled about the possibility of infections, adverse drug reactions, and overdoses from illicit drug use. At the end of this visit, patients were scheduled for a return appointment in 3-5 days to receive their HIV and hepatitis test results, complete post-test counselling, and were randomized.

At the post-test visit patients were referred for treatment or followup of associated problems that were present but could not be addressed in the addiction program. AIDS treatment is free to all patients in Georgia and paid by the Global Fund. The AIDS Center is very convenient as it is located in a building adjacent to Uranti. Patients must pay for hepatitis treatment. All patients received printed information about HIV and hepatitis B and C and the need to reduce behaviours that could lead to infection or spread to others.

Administering methadone: Methadone was administered 7 days/week under direct observation; no take-home doses were permitted. The first dose was 20-30 mg and patients returned for a second

dose not to exceed 10 mg on day one if they continued to show signs of withdrawal three or more hours after the first dose. Dose increases of 5-10 mg every 1-7 days were permitted as clinically needed; there is no upper limit on methadone doses in Georgia. Staff and patients were informed of the delayed onset of methadone so as to avoid an overly rapid dose increase that could cause over-medication. Stabilization was achieved when the study physician judged that the patient has few or no signs or symptoms of sedation or withdrawal during the 24-hour dosing interval. For patients who choose to detoxify, a slow taper of 5-10 mg every 2-5 days began at the completion of the 12-weeks of study medication and scheduled to end in 21 days.

Administering Suboxone®: Study personnel recorded the history of current use and did a brief clinical examination prior to administering the first dose to document the time and date of last opioid use and verify that the patient is in withdrawal. Patients were told to keep the medication under the tongue until it is dissolved. An explanation of dosing was provided so the patient understood that the medication will be inactivated if swallowed and that it is likely to cause withdrawal if dissolved and injected by someone on a full agonist such as methadone or heroin. Suboxone® was administered under direct observation throughout the study, and the first dose was 4-8-mg (expressed as buprenorphine). A second dose of 2 to 6 mg was given if withdrawal signs or symptoms continue for three or more hours.

Patients returned on day 2 and received the whole dose that they received on day one unless overmedicated or having some other medication-related adverse event (in which case it was reduced), or had the dose adjusted upwards by 2-6 mg if continuing to experience withdrawal. Similar procedures were followed on day 3 and thereafter until the physician judged that the patient had few or no signs and symptoms of sedation, withdrawal or other opioid or medication-related adverse events during the 24-hour dosing interval and appeared to be responding to treatment. The target dose was 12-18 mg per day. Patients who elect to be treated on the methadone program at the end of the 12-weeks of study treatment were switched to methadone 24-48 hours after receiving their last dose.

Individual drug counseling: Individual counseling sessions lasted approximately 45 minutes and were delivered by trained and experienced staff guided by a drug counseling manual that has been modified for opioid use from the one available on the NIDA web site: http://www.nida.nih.gov/TXManuals/IDCA/IDCA1.html). The manual emphasizes involvement in 12-step programs and, though they have not been very successful in Georgia, we think it is worth mentioning them even if only as an introduction as they seem helpful in other countries.

The overall counselling approach consisted of three components: 1) working with the physician to adjust the Suboxone® or methadone dose so the patient feels comfortable over the 24-hour dosing interval; giving advice, support and clinical management aimed to maintain abstinence from opioids and other substances; 2) adherence enhancement to encourage keeping appointments, taking medication as prescribed, getting treatment for associated problems, and the need to stop using all abusable substances including alcohol; and 3) reviewing behaviours that are likely to spread HIV and counselling how to stop them.

Interventions that focus on the first component involved providing an acceptable level of clinical management with a supportive relationship including having the patient see the physician if dose adjustments are needed; helping the patient begin thinking about how to address cravings and associated psychiatric, medical, social and legal problems; teaching ways to avoid people, places and things associated with drug taking; teaching skills to avoid managing stress without using drugs; and encouraging abstinence from abused substances including alcohol.

Group drug therapy: Weekly group therapy was part of the Uranti methadone program and were done by the same therapists who do individual counselling. The counsellors read the individual drug counselling manual and used similar techniques in the groups, however the groups provided an environment where patients can obtain additional support from peers that included having unhealthy behaviours (lying, “conning”, denial, not changing life styles, etc) pointed out by peers and receive constructive input on how to change them.

Encouraging Adherence: Patients began medication Monday through Friday. Patients were introduced to their individual counsellor on the first visit when they made appointments for individual and group therapy. Efforts were made to establish positive, helping relationships to facilitate adherence to counselling and medication. Stabilizing patients on medication and forming a positive relationship were a focus of both individual and group therapy, particularly during the initial phase. Though therapy emphasized stopping use of opioids and other substances including alcohol, aggressive confrontation was avoided. Staff reminded patients of the 4, 8, 12 and 20-week evaluations prior to their scheduled time, and of the option for dose taper or transfer to methadone or other treatment prior to the end of the 12-week dosing period.

Missed visits and termination: Methadone or Suboxone® were stopped if patients miss 3 or more consecutive days of medication and were restarted if they return within 7 days. The restart dose was half the previous dose. Patients who missed 7 or more consecutive days were not eligible to restart study medication but were encouraged to continue counselling. Patients who were intoxicated by alcohol or sedatives (slurred speech, difficulty with coordination, alcohol on breath) were not dosed and were asked to return for further evaluation in two or more hours, or on the next day, prior to continuing methadone or Suboxone®.

Assessments: Some instruments needed to be translated into Georgian; others have been translated and used in previous Georgian studies.

Drug and Alcohol Use:

- *Confirm opioid addiction and the presence/absence of other substance use disorders*:

  Done at baseline using the substance use disorders section of the Composite International Diagnostic Interview, version 2.1 (CIDI-2.1). The CIDI is a standardized instrument that was developed for epidemiological studies and can be administered by lay interviewers to diagnose psychiatric disorders with reliability and validity. It provides lifetime and current diagnoses for substance use disorders according to DSM-IV and ICD-10 criteria.

- *Urine drug testing:* Done at baseline, weekly at random, and at week 20 using a kit manufactured by Biothechnostix (http://www.btnx.com/category.aspx?cat=3) that tests for opiates, benzodiazepines, methamphetamine, buprenorphine, methadone and THC.

- *Alcohol Breathalyzer testing*: Done at baseline, weekly at random at the time of the urine drug test, and week 20.
- *Addiction Severity Index (ASI):* The ASI is a structured interview that assesses the range of problems seen in persons with substance use disorders over their lifetime and the past 30 days. It combines objective and subjective data to produce ratings of problem severity in seven areas: medical, employment/support, drug use, alcohol use, legal status, family/social relations, and psychological status. It produces severity ratings and composite scores in each of these seven areas and has high levels of inter-rater, test-retest, and concurrent reliability (McLellan, Luborsky, Woody, & O'Brien, 1980). It was revised in 1992 into a 5th edition which contains items to assess route of administration; illegal activities; emotional, physical, and sexual abuse; quality of the recovery environment; and history of close personal relationships. This 5th edition resulted in no changes in the composite scoring so that comparability can be maintained with previous editions (McLellan et al., 1992) and will be used for this study. It has been translated and used in Georgia, and was done in our study at baseline, and repeated at weeks 4, 8, 12 and 20 using only questions addressing the past 30 days.
- *Time Line Follow-Back (TLFB; full*): This instrument assesses use of specific substances over a specified period of time. It was used to assess drug and alcohol use during the past 7 days and past 30 days at the baseline and 20-week assessments. Questions were added to assess days of Subutex® use (heroin and other opiates [not buprenorphine] are included in the current version), and number of times that Subutex® and heroin were injected during the past 7 and past 30 days.

- *Time Line Follow-Back (TLFB; brief)*: Same questions as the TLFB full, but used to assess drug and alcohol use during the past 7 days at weeks 1-12 with questions added to assess days of Subutex® use, and number of times that Subutex® and heroin were injected during the past 7 days..
- *Opioid craving:* Was measured using a visual analogue scale at baseline, weekly during the 12-weeks of study treatment, and at the 20-week followup.

Medical Evaluations

- Medical history and physical examination: Done at baseline as part of routine care. History is done using a standardized for approved by the Ministry of Health and Social Affairs of Georgia. The physical exam includes height; weight; pulse; temperature; blood pressure; head, eye, ears, nose and throat (HEENT); chest; abdomen; extremities.
- *Routine laboratory tests*: Patients applying for methadone treatment at Uranti must bring copies of current (past month) laboratory tests that include CBC, glucose, bilirubin, liver enzymes, and an ECG. The program does not have funding to do these tests and patients obtained them from their primary care provider. This requirement has not been a barrier to enrolment in methadone treatment.
- *HIV, hepatitis B & C tests*: Done at baseline and week 12 with pre and post-test counselling
- *Count of fresh puncture marks and scabs from healing punctures on arms, legs, feet, neck, groin*: We developed a CRF with three parts: a count of fresh puncture marks, a count of scabs from healing punctures, and an overall count of fresh marks + scabs. Though these counts will not differentiate between types of drugs injected, they should demonstrate trends in injection use by showing decreases (or increases) in the number of fresh marks and scabs over time. Punctures usually heal and the scabs fall off in 7-10 days, thus a count of fresh marks and scabs should provide an objective measure of trends in injection use to supplement the self-reports. Medically

trained staff (nurses, physicians) did these counts at baseline, and at weeks 1-12, and 20.

HIV/Hepatitis B/C Risk

- *Risk Assessment Battery (RAB):* Provides a self-report measure of drug use, injection related behaviour and sex risk behaviours (Navaline et al, 1994), and can be adjusted to assess risk over various periods of time. For this study, the timeframes was past three months and past 30 days. The RAB has 38 closed end items that cover issues of recent substance use including frequency, needle sharing and cleaning, and condom use. Responses on the RAB have been equivalent to those collected by personal interview and scores were able to discriminate between cocaine and opioid abusers as well as those who converted to HIV+ from those who remained HIV- (Metzger et al, 2001). The RAB has been translated into Georgian and was administered at baseline and at 12 and 20 weeks.

Psychiatric Assessments

- *Global Assessment Form (GAF):* This assessment of overall function comprises Axis V in the DSM-IV and will be translated into Georgian. GAF scores range from 0 to 100. A reasonably well-functioning person scores above 70; serious impairment is below 50; scores of 30 or below are generally associated with inpatient treatment. A psychiatrist administered it at baseline, and at 4, 8,12 and 20 weeks.
- *Beck Depression Inventory (BDI):* This 21-item questionnaire takes about 10 minutes and will be self-administered but can also be completed as a clinical interview (Beck, et al., 1961). It has been found to validly and reliably assess depression in many cultures and patient groups including substance abusers. It was administered at baseline, and at 4, 8,12 and 20 weeks.

Compliance

- *Study Medications:* Recorded weekly using Uranti dispensing records
- *Therapist Contact Log:* The number and duration of treatment sessions since the last visit were recorded weekly and at each evaluation point.

- Self-help group attendance: Collected weekly and at week 20.
- Non-study medical services and medications received: Medications or treatments received since the last study visit that were prescribed or administered outside the assigned treatment condition will be recorded at weeks 4, 8, 12 and 20.

Others

- *Adverse Event Report Form (AERF):* Patients were asked weekly about adverse events since their last visit and reports were categorized as Adverse Events (AE) or Serious Adverse Events (SAE) and followed up to determine their outcome.
- *Endpoint Rating Form (ERF):* Research staff completed an endpoint rating form when the patient leaved treatment to document the reason for termination (e.g. finished treatment, dropout, relapse, symptomatic failure, failure to comply with medication).
- *Patient Satisfaction (PS*): At the end of treatment a self-report was completed by all patients on their satisfaction with treatment, the degree of change in their condition and their perception of the helpfulness of the medication and the psychosocial therapy they received

Assessment Windows: Weekly assessments had a window of +/- two days; monthly assessments had a window of +/- one week; the 20-week assessment had window of +/- 3 weeks.

Follow-up: To maximize chances for completing assessments, each research assistant were assigned patients for whom they are responsible. The research team met weekly to discuss study activities including follow-up adherence and strategies for locating difficult to find patients. At the time of enrolment, the follow-up schedule for that patient was automatically produced. Patients were reminded of their assessments prior to the scheduled due date.

Full schedule of assessments is shown in Table 5

Data Analyses

Hypotheses for Primary Aims:

1) Patients in each study arm will significantly reduce HIV injecting risk as measured by the drug use section of the RAB
2) Patients in each study arm will significantly reduce Subutex® and heroin injecting as measured by the drug use section of the ASI, the TLFB, and weekly counts of puncture marks and scabs
3) Patients in each study arm will significantly reduce the rate of opioid positive urine tests provided in each arm of the study after week 4
4) The target enrolment will be met and 90% of patients will continue on methadone or Suboxone® for 12 weeks

Additional hypotheses:

1) There will be significant improvement on the illegal, employment and psychiatric subscales of the ASI in each study arm at the 4, 8 and 12 week outcomes
2) There will be significant improvement on the GAF and BDI in each study arm at the 4, 8 and 12 week outcomes
3) By week 20, 75% or more of patients will either have relapsed or be in treatment
4) HIV will be found in 1% of patients, hepatitis B in 50%, and hepatitis C in 75% at baseline

General Considerations in Data Analyses

Important: It should be emphasized that this study purposely designed as a basic feasibility study. The project was considered a success if we were able to recruit the proposed number of patients, collect at least 80% of all proposed measures at each data collection point, show that each medication substantially reduces injection use and HIV risk, retains patients in treatment, has no SAEs attributable to it, and gains treatment research experience for the Georgian staff. Analyses have purposely been tailored to address these aims.

Statistical power for the primary outcomes: The focus of the study was on the collection of preliminary data, but the sample was large enough to detect 'moderate to large' effects of the Suboxone® treatment. We considered two-sided tests at a 5% significance level, and

assumed a 15% loss to follow-up. For a comparison of a continuous outcome across two groups (e.g. the RAB drug risk change score) we had 80% power to detect an effect of Cohen's d=0.7. For a comparison of binary outcomes, we had 80% power to detect a difference of about 30% in rates of use. For the repeated measures analyses, the minimal detectable effects are slightly smaller than for these univariate summaries, but remain in the 'moderate to large' range.

Descriptive Analyses: Summary statistics (e.g., means, SDs) were computed and distributional properties assessed (e.g., histograms, normality plots) for all key variables to screen for outliers and determine if remedial measures such as power transformations or non-parametric statistical methods were required. Analyses for Primary Responses: We compared the groups on the change in RAB Drug Risk scale between baseline and 12 weeks, using a t-test on the change scores. The other primary outcomes were addressed using mixed effects. We used a mixed effects model with group, time, and group by time interaction effects to compare the course of ASI drug scores between the groups, across the 4, 8, and 12-week time-points. For the TLFB self reports, we used a logistic mixed effects model to compare weekly reports of use/no-use across the 12 weeks of the treatment phase. We compared the rates of opioid positive urines across weeks 4, 8, and 12 using a logistic mixed effects model.

Analyses for Secondary Responses: We again used mixed effects models to compare the groups on illegal, employment and psychiatric subscales of the ASI, and on the GAF and BDI scales, across the 4, 8 and 1- week outcomes. We note that our group sizes of 40 are large enough for reliable estimation of the coefficients in these mixed effects regression models. However, as the sample is somewhat small, and some of the response may have very skewed or zero-inflated distributions, we performed supplementary analyses on univariate summaries for each of the main responses. Thus, we calculated overall summaries based on each of the repeated responses, and compare the groups on change from baseline to 12 weeks on those measures. While these analyses are less susceptible to

problems with small samples, they are less robust to non-ignorable dropout, so we regard the repeated measures models described above as the primary focus of the grant.

Human Subjects

Protection of Human Subjects*:* Safety assessments included a baseline psychiatric examination to rule out patients who are suicidal, homicidal, psychotic, or addicted to alcohol, benzodiazepines or other CNS depressants; and a physical examination to rule out patients with medical problems that may make it difficult or impossible to participate, or a safety risk. Additional safety checks were daily visits to receive study medication where patients were observed by clinical and research staff, and weekly urine drug screens, alcohol breath tests, and assessments for adverse events. Inpatient treatment is available at Uranti. Risks includeed those related to methadone or Suboxone®; distress if found positive for HIV or for hepatitis B and/or C; and distress associated with asking personal questions in the behavioural ratings.

Methadone Risks: Methadone has been administered to tens of thousands of opioid dependent and pain patients throughout the world without serious adverse events other than those related to diversion or an overly rapid dose increase. There is evidence that it prolongs the QT interval but the clinical significance of this finding seems minimal or absent based on the very small number of reports where it might have been a problem and the very the large number of patients that have been treated with methadone at doses ranging from 60-120 mg/day or more for 40+ years.

Other possible side effects include constipation; sedation; excess sweating; peripheral edema; physical dependence; overdose if taken with high doses of alcohol or other sedatives; abuse if multiple doses are taken simultaneously or diverted to substance abusing individuals; and accidental use of take home doses by children or other non-tolerant individuals. Each of these potential problems were explained in the consent and reviewed verbally with the patient. Uranti physicians have experience treating patients with methadone and Dr. Woody reviewed dosing guidelines as part of the training procedures. Georgian regulations do not permit take-home dosing, thus minimizing the chances for diversion and

accidental overdose by children or non-tolerant individuals. A description of possible side effects was in the consent form and reviewed with the patient prior to beginning the study.

Suboxone® Risks: Possible side effects include sedation; physical dependence; precipitation of withdrawal if taken by persons dependent on full agonists and if not in withdrawal at the time of initial dosing; and overdose if taken with high doses of benzodiazepines, alcohol or other sedatives. Each of these potential problems were explained in the consent and reviewed verbally and in writing with the patient. Precautions against entering subjects who are abusing benzodiazepines or other sedative type drugs, or of continuing patients on Suboxone® who develop benzodiazepine, alcohol or other sedative drug dependence have been described.

HIV Testing: Risks include violation of confidentiality or severe emotional reactions including suicidal ideation or attempts upon if found to be HIV+. All efforts were made to minimize these risks by providing pre and post-test counselling and referral to the most appropriate treatment resources available in Tbilisi.

Hepatitis B and C Testing: Risks are similar to those associated with HIV. Pre and post-test counselling included education about what hepatitis does to the body, how it is transmitted, how to protect oneself from being infected or infecting someone else, and referral to the most appropriate treatment that is available if testing positive.

Behavioural Ratings: Risks are minimal and limited to violation of confidentiality or becoming anxious or embarrassed by some of the questions that are asked.

Recording and Reporting Adverse Events (AEs) and Serious Adverse Events (SAEs): AEs and SAEs were noted on Adverse Event Forms similar to those used in the CTN study of Suboxone® treatment for opioid addicted youth. Medical staff evaluated the intensity, seriousness, and causal relationship of the AE or SAE to study medication.

Patient Reimbursement: Follow-up data are extremely important and patient reimbursements for time spent doing evaluations have been calculated to serve as incentives for compliance and reimburse them for the time spent doing assessments. We paid patients

the Georgian equivalent of 15 US$ for the time spent completing the baseline assessment and measures at 4, 8, 12 and 20 weeks. No reimbursements were given for the weekly assessments, as they were relatively brief. The total amount that participants earned if they completed all assessments was 75 US$.

Consenting Procedure: Research staff explained the study to potential subjects including its potential risks, benefits, and options for alternative treatment. Patients were encouraged to ask questions about the study and their understanding will be tested by a 10-item true/false quiz that was given after the study was explained and the patient read the consent and had a chance to discuss it with research staff. Patients must have answered 9 of the 10 questions correctly in order to qualify for enrolment. Patients who fail the quiz were given two additional chances to pass it and those who were unable to pass were referred to other available treatments. Randomization to one of the two medication conditions was done after completion of these consenting procedures and the baseline assessment to confirm that all study admission criteria are met.

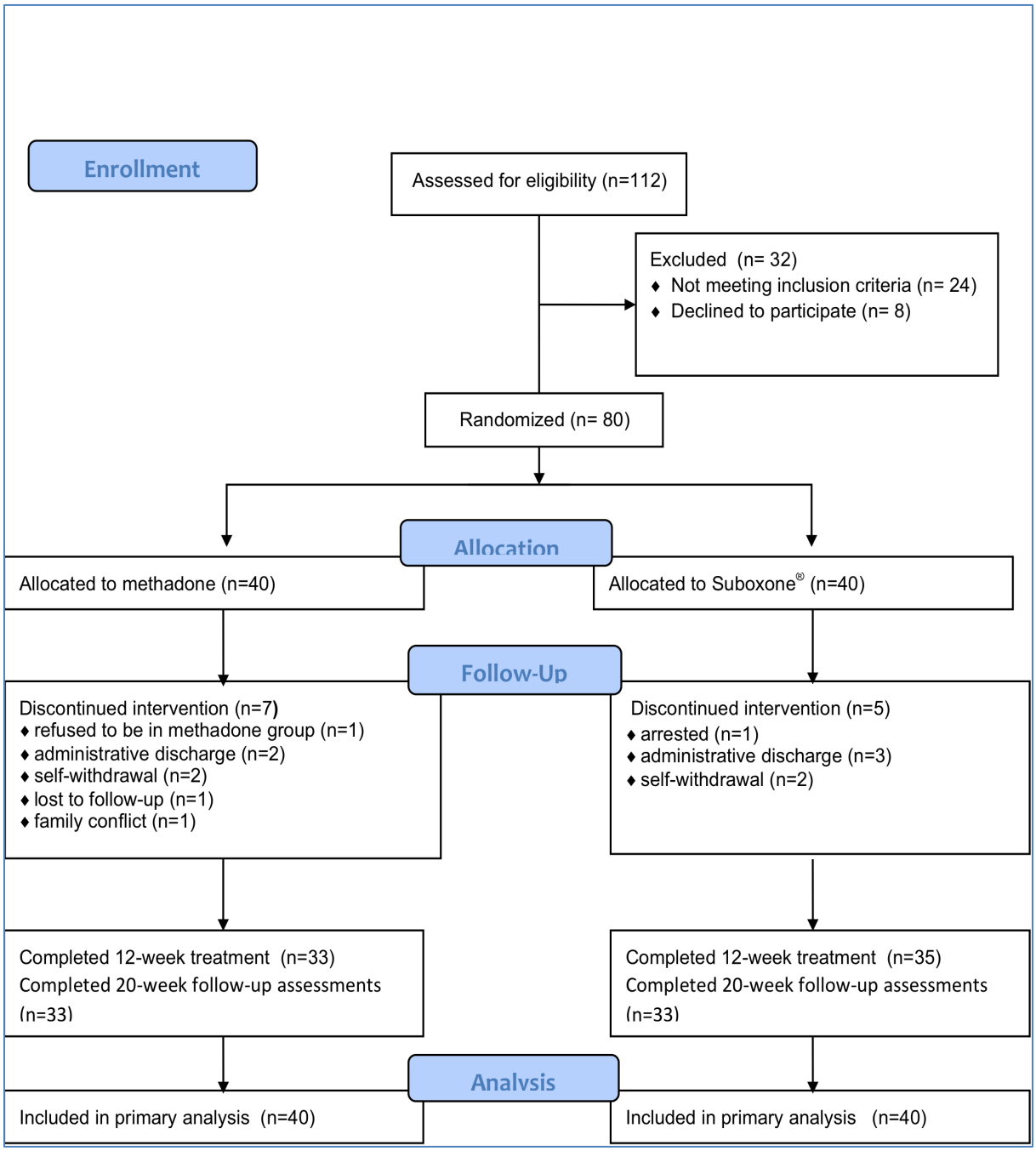
IRB Approvals: The study was approved by IRB's at the University of Pennsylvania, Uranti and the Union Alternative Georgia prior to receiving NIH funding. The Union Alternative Georgia has an IRB at the HIV/AIDS Patients Support Foundation (IRB00001495) and a Federal Wide Assurance (FWA00009897) that apply to studies done at Uranti. The Georgian investigators took the NIH web-based course on human patients.

Results

Participant characteristics

112 potential participants were screened between January 25 and September 27, 2011, of which 80 (4 females) were randomly assigned to methadone or Suboxone® (see Figure 9).

Figure 9: Study Flow Chart



Study subjects were all white, predominantly young, with almost two thirds (72.5%) being in the range 24-35. Mean history of opioid injection use was 5.77 (SD4.6) years, and heroine, Subutex®, other opioids (row opium, desomorphine) and home-produced meth/amphetamine type stimulants were main drugs injected in the last 30 days prior to randomization. Concurrent use of sedatives (benzodiazepines) was also common. None of participants was

HIV positive and 73.4% were infected with hepatitis C. There were no significant differences in socio-demographic and clinical characteristics between two groups (see Table 5).

Table 5: Study participants' background characteristics

1 – data provided for 79 participants, 1 refused testing

	Total sample (n=80)	Met (n=40)	Sub (n=40)	Test statistics	*p*
Male, *n (%)*	76 (95)	37 (92.5)	39 (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 (2.73)	14.7 (3.07)	t=0.33	0.74
Unemployed, *n (%)*	46 (57.5)	24 (60)	22 (55)	χ^2=0.51	0.47
Married, *n (%)*	38 (47.5)	20 (50)	18 (48)	χ^2=0.08	0.78
Drug use history (years), *M (SD)*	5.77 (4.6)	6.21 (5.3)	5.35 (3.8)	t=0.83	0.41
Days drugs used in last 30 days (self reported), *M (SD)*					
Heroine	3.18 (5.85)	3.37 (5.9)	3 (5.8)	t=0.27	0.78
Subutex®	15.18 (5.86)	15.34 (6.6)	15 (5.0)	t=0.24	0.81
Other opioids	10.18 (10.35)	10.6 (10.3)	10.5 (10.2)	t=0.40	0.70
Stimulants	1.56 (2.43)	1.45 (2.3)	1.67 (2.5)	t=0.41	0.68
Benzodiazepines	4.26 (7.33)	3.76 (7.2)	4.73 (7.5)	t=0.58	0.56
Marijuana	2.14 (6.21)	0.8 (1.7)	3.43 (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	58 (73.4)	33 (84.6)	25 (62.5)	χ^2=4.95	0.03
Negative	21 (26.6)	6 (15.4)	15 (37.5)		

Outcomes

Out of 80 participants enrolled in the study 68 (85%) completed 12-week treatment (Figure 1). 5 and 7 participants left treatment prior to study completion in methadone and Suboxone® groups respectively. There was no significant difference in number of days in treatment over 12 weeks between two groups (Table 2). Mean dose of methadone prescribed to study participants at treatment midpoint (six weeks) was 39 mg (SD17.8; 17 to 80) and the mean dose of Suboxone® was 8.5 mg (SD3.5; 4 to 16). Mean number of counselling sessions attended by participants was equal for both groups (Table 2). In total 37 (56%) respondents – 21 (63%) for methadone group and 16 (48.5%) for Suboxone® group - who showed up for 20 week follow-up were still in methadone treatment.

Overall 837 weekly random urine samples were collected and tested over 12-week treatment. During this period there were 123 of 960 (12.8%) urine samples missing, with 74 of 480 (15.4%) missing in methadone group and 49 of 480 (10.2%) missing in Suboxone® group. 108 samples were missing because of participants early termination. With overall low level of urine samples positive for monitored substances, there were significantly more urine samples positive for opioids in methadone group (p=0.03). There were significantly more urine samples positive for amphetamines and marijuana in Suboxone® group (Table 6).

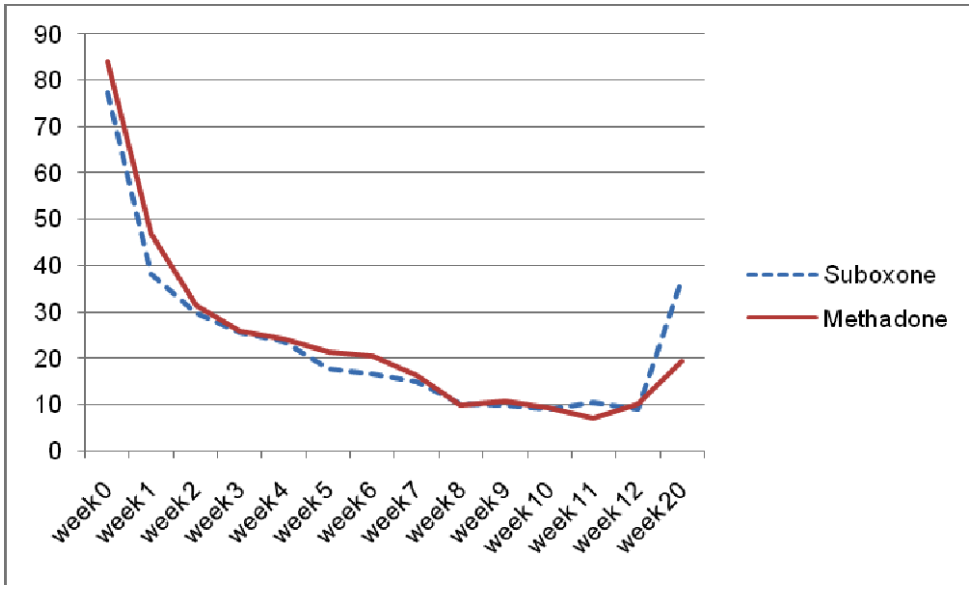
Table 6: Treatment impact

	Met (n=40)	Sub (n=40)	Test statistics	*P*
Assessments conducted, *n (%)*				
0 week	40 (100)	40 (100)		
4 week	34 (85)	38 (95)		
8 week	35 (87.5)	36 (90)	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)*	85.37 (34.25)	88.8 (26.57)	t=0.5	0.6
Counselling sessions attended, *n*	414	443		
Sessions attended per participant, *M (SD)*	13.78 (5.24)	13.85 (5.41)	t=0.05	0.96
Urine samples collected (1-12 weeks), *n*	406	431		
Opioid positive urine samples, *n (%)*	6 (1.5)	1 (0.2)	χ^2=4.87	0.03
Buprenorphine positive urine samples[1], *n (%)*	3 (0.7)	--	--	--

1 - Buprenorphine positive urine samples not shown for Suboxone® group.

Overall 843 weekly TLFB responses were obtained, of which 836 matched with urine sample tests performed (same patient, same week). Of those 836 urine test results and TLFB responses 96.7% were in agreement. Proportion of patients reporting injection of opioids, Subutex®, amphetamine-type stimulants and benzodiazepines was dramatically reduced by the end of treatment, with no significant difference between two groups (Table 2). There was dramatic reduction in opioid craving, again, with no significant difference between two study arms (see Figure 9: Study Flow Chart).

Figure 10: Mean change from baseline in craving



There was significant reduction in unsafe injection behaviour over the 12-week treatment period in both groups, with improvements persisting by the 20-week follow-up. In most cases unsafe behaviour was virtually eliminated (Table 7).

Table 7: Change in injection risk behaviour

	Met (n=40)[1]	Sub (n=40)	Test statistics	*P*
Shared needles or works: never or no shot up[2], *n (%)*				
0 week	35 (91.2)	35 (87.5)	0	1.00
4 week	34 (100)	38 (100)	2.22	0.14
8 week	35 (100)	36 (100)	0.13	0.72
12 week	33 (100)	34 (100)	0.09	0.76
20 week	33 (100)	33 (100)	0	1.00
Shared cooker: never or no shot up, *n (%)*				
0 week	24 (63.2)	22 (55)	0.20	0.65
4 week	34 (100)	37 (97.4)	0.44	0.51
8 week	35 (100)	36 (100)	0.13	0.72
12 week	33 (100)	34 (100)	0.09	0.76
20 week	32 (97)	32 (97)	0	1.00
Shared cotton: never or no shot up, *n (%)*				
0 week	30 (78.9)	33 (82.5)	0.67	0.41
4 week	34 (100)	37 (97.4)	1.13	0.29
8 week	35 (100)	36 (100)	0.13	0.72
12 week	33 (100)	34 (100)	0.09	0.76
20 week	33 (100)	33 (100)	0	1.00
Divided or shared drugs with others by using one syringe: never or no shot up, *n (%)*				
0 week	9 (23.7)	5 (12.5)	1.39	0.24
4 week	33 (97.1)	35 (92.1)	0.39	0.53
8 week	34 (97.1)	35 (97.2)	0.11	0.75
12 week	32 (97)	34 (100)	0.35	0.56
20 week	28 (84.8)	28 (84.8)	0	1.00
Never practiced any unsafe injection behaviour or no shot up[3]				
0 week	9 (23.7%)	4 (10%)	2.63	0.1
4 week	33 (97.1%)	35 (92.1%)	0.84	0.36
8 week	34 (97.1%)	35 (97.2%)	0.00	0.98
12 week	32 (97%)	35 (100%)	1.05	0.31
20 week	28 (84.8%)	28 (84.2%)	0.00	1.00

1 - baseline data provided for 38 participants; 2 cases are missing data.
2 – for the purpose of current analyses we focus on four types of injection risk behaviour characteristic to the population studied
3 – presents data on participants who did not practice any of risk behaviours shown in rows above

Statistically significantly more patients in Suboxone® group experienced at least one adverse event than in methadone group (p=0.003) (Table 8). Insomnia, constipation and depression were most frequent adverse events reported in both groups. All 80 adverse events in methadone group and 108 in Suboxone® group were qualified by study physicians as mild or moderate, and in 10 cases adverse events were deemed to be definitely related to study medications. There were no serious adverse events observed; no death, overdose episodes or suicide attempts were reported.

Table 8: Adverse events

	Met (n=40)	Sub (n=40)	Test statistics	*P*
Adverse events, *n*	80	108		
Drug-related adverse event, *n (%)*				
Definitely	5 (6.25)	5 (4.6)	χ^2=0.24	0.62
Possibly	51 (63.75)	54 (50)	χ^2=3.52	0.06
Most frequent adverse events, *n (%)*				
Insomnia	13 (16.25)	12(11.1)	χ2=1.05	0.3
Constipation	23 (28.75)	25 (23.1)	χ^2=0.76	0.38
Depression	18 (22.5)	19 (17.6)	χ^2=0.7	0.4
Participants with at least one adverse event, *n (%)*	23 (57.5)	31 (77.5)	χ^2=9.05	0.003
Participants with >1 adverse event, *n (%)*	10 (25)	13 (32.5)	χ^2=1.55	0.21

In this randomized controlled trial participants - regular Subutex® injectors – well accepted both treatments, with methadone and Suboxone®, and 85% remained in treatment over the 12 week period. 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. There were no statistically or clinically significant differences in outcomes between two treatments. Medications were well tolerated and there were no serious adverse events reported.

Expectedly, the vast majority of the sample used more than one psychoactive substance prior to study inclusion. Phenomenon of poly-drug use has been well documented in Georgia and regionally (Booth, et al., 2009; Booth, et al., 2008; D.J. Javakhishvili, et al., 2011; Kruse, et al., 2009; Tiihonen et al., 2012). It has been suggested that the reason for this unsystematic poly-substance use (mixing buprenorphine and other opioids with sedatives and amphetamine-type stimulants) is ever fluctuating availability and high price of drugs on Georgian black market and attempts of drug users to increase the euphoric effects and the potency of injection preparations (D. J. Javakhishvili, et al., 2012; D. Otiashvili, et al., 2010). Notably, participation in our trial resulted in dramatic reduction in use of all substances that were monitored.

Daily doses of medications prescribed to study participants were comparatively moderate – 39 mg for methadone and 8.5 mg for Suboxone® as mean daily doses, as

measured at six week treatment midpoint. Main reason for that might be overall low doses of illicit drugs used by Georgian drug injectors. In our previous publication we reported the average daily dose of buprenorphine (Subutex®) in the sample of needle exchange program participants as low as 1-2 mg (D. Otiashvili, et al., 2010). In contrast, the daily dose of illicit buprenorphine injected in other countries varies between 6-10 mg (Aitken, Higgs, & Hellard, 2008; Alho, et al., 2007; Winslow, et al., 2006; Winstock, et al., 2008). This could well explain the fact that desirable clinical effects were achieved in our sample with comparatively moderate doses of treatment medications.

Similarly to other recent reports, direct needle sharing was not high in our sample (Chikovani, Bozicevic, Goguadze, Rukhadze, & Gotsadze, 2011). Common unsafe injection behaviour at baseline was sharing a cooker and dividing solution using one syringe. In-debt analysis of drug preparation and division processes provides meaningful explanation for these particular types of risk behaviour. Buprenorphine (Subutex®) injection in Georgian setting occurs as a rule in a group of 3-4 people, who dissolve one 8 mg tablet in a water and then, using large volume syringe, divide solution by front- or back-loading into smaller individual syringes (D.J. Javakhishvili, et al., 2011; D. Otiashvili, et al., 2010). Home preparation of meth/amphetamine type stimulants (vint and jeff) and opioids (crocodile) both involve using common cooker to process ingredients through often complicated chemical refinement, and using large-volume syringe to divide final product into smaller syringes for injection. In both cases drug preparation is a group activity with often predetermined division of roles and contributions (money, ingredients, space for production). It seems that long-term efforts to educate drug users and support behaviour change have resulted in visible reduction in direct needle sharing. Nevertheless, indirect sharing, in this case through common container and common syringe for drug division, has not been sufficiently acknowledged and targeted.

In vast majority of cases reported adverse events were similar to those characteristic to early period of agonist treatment and resolved within reasonable period of time as treatment continued. 7 of 10 adverse events that were considered as medication related

were allergic reactions (swelling, rush, itching). Three of those seven were reported for the same patient in methadone group, and four were reported for three patients in Suboxone® group. All adverse events resolved upon prescription of anti-allergic medications.

Discussion

We could not objectively measure buprenorphine misuse in Suboxone® group. In methadone group only 3 of 406 urine samples were positive for buprenorphine during weeks 1-12. TLFB data were highly consistent with urine tests results, which allow us safely relying on self-reported use. Therefore, we can conclude that non-prescribed use of buprenorphine in both groups was extremely low, as was reported by study participants.

Daily observed dosing ensured participants' full compliance with prescription regime. However, results of the study might be different if take-home doses were allowed and medication intake was less strictly supervised. Additionally, the costs associated with provision of buprenorphine in specialized clinics under the direct observation may be unreasonable, in particular in resource limited settings and in locations where patients must pay for their own treatment, which is the case in Georgia. In this regard, the other day dispensing can be yet another strategy to employ in order to reduce the cost of maintenance treatment with buprenorphine (R. E. Johnson, Strain, & Amass, 2003).

The sample size was not chosen based on a power analysis prior to the conduct of the trial. However, this trial was primary a feasibility study to collect initial data on treatment engagement and retention, and its impact on drug injection and risk behaviour, and should be viewed from this perspective. Larger sample size might have allowed making firmer conclusion about specific advantages of two treatment conditions and explore relations between study outcomes and particular characteristics of participants. Finally, the length of treatment was 12 weeks and the extent to which positive effects produced by two treatments will be translated into long-term improvements are unknown. Importantly, although we did not focus on retaining participants in maintenance treatment after the study completion, 56% of participants assessed at 20-week follow-up (46% of the initial sample) were still in methadone program, to which they transferred at the end of 12-week study treatment period.

Conclusions

The results of this study 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. It has been suggested that in certain locations inaccessibility of buprenorphine treatment contributed to its diversion and injection use (EMCDDA, 2005; Lofwall & Havens, 2012).

6. Conclusions and project implications for policy and research

Given the high morbidity and mortality seen in opioid dependence, the public health challenge is to deliver safe and effective medical treatment to as many patients as can benefit from it, whilst minimizing the risk of diversion of prescribed medication. Thus, variety of considerations need to be taken into account while discussing and developing approaches and interventions to address opioid addiction including non-medical use of buprenorphine. These are, but not limited to, effectiveness, safety, public health impact, and financial considerations.

Our research shows that in Georgia increasing availability of buprenorphine and buprenorphine/naloxone treatment can bring remarkable benefits. The appropriate coverage of patients by buprenorphine treatment can significantly reduce the street demand for it and cut down its illegal market. It has been argued that in some European countries there might be a relationship between the low availability of buprenorphine treatment and its diversion to the black market (EMCDDA, 2005). In US study Lofwall and authors suggested that inaccessibility of buprenorphine treatment contributed to its diverted injection use (Lofwall & Havens, 2012). The French experience with buprenorphine has expanded access to substitution therapy and reduced the overall harm associated with untreated opioid dependence. The benefits were summarized at the 2004 consensus conference: *a 5-fold reduction in the number of deaths attributable to heroin, a 3-fold reduction in the number of prematurely born infants from opioid-dependent mothers, a 6-fold reduction in the number of active IDUs, and ~3500 lives saved* (Carrieri, et al., 2006).

In situations where there is a greater risk of medication diversion, consideration should be given to other treatment options (combination buprenorphine/naloxone or methadone), increased patient monitoring, shorter duration of prescriptions early during treatment, and enhanced training of the clinicians involved in buprenorphine and opioid dependence treatment. Despite existing evidence regarding the non-medical use and diversion of prescription medicine by clients in buprenorphine treatment (Auriacombe,

Fatseas, Dubernet, Daulouede, & Tignol, 2004; Carrieri et al., 2003; Guichard, et al., 2003; Vidal-Trecan, Varescon, Nabet, & Boissonnas, 2003), recent findings indicate that this might be strongly associated with an inadequate (low) dosage of the preparation and unmanaged depression (Center for Health Services & Outcomes Research, 2006; Fatseas & Auriacombe, 2007; Roux, Villes, Blanche, et al., 2008). Methadone, which is a stronger agonist than buprenorphine and has a more controlled mode of prescription, could be more appropriate in certain patients (Center for Health Services & Outcomes Research, 2006; Vidal-Trecan, et al., 2003).

The costs associated with provision of buprenorphine in specialized clinics under the direct observation may be unreasonable in resource limited settings, in locations where patients must pay for their own treatment, or where insurance companies or government agencies are hesitant to burden the extra cost, which is the case in Georgia. The other day dispensing can be yet another strategy to employ in order to reduce the cost of maintenance treatment with buprenorphine (R. E. Johnson, et al., 2003). Engaging GPs in the provision of buprenorphine treatment brings range of advantages related to the flexibility of treatment, less stigmatizing environment and obvious cost savings. Treating a drug dependent patient in a primary care setting is cheaper than treating him in a specialized centre, and can substantially increase the coverage. I tis also truth that *„more clinical research is needed to understand the efficacy, capabilities, and safety and diversion concerns of novel forms of buprenorphine, including subdermal and transdermal patches and implants and Suboxone film"* as suggested by Yokell and authors (Yokell, et al., 2011).

Nowadays opioid dependency represents one of the major problems of public health. Substitution therapy with the use of opioid agonists is acknowledged as an effective intervention in order to reduce morbidity, mortality, criminal behaviour, and public expenditure as an ultimate result. Certain characteristics of buprenorphine – prolonged acting time, lower abuse potential (compared to other opioids), ceiling effect while on high doses that reduces probability of overdose - makes it safe and one of the best fitted medication to treat opioid dependency. Nowadays, buprenorphine easies the lives and brings

benefits to hundreds of thousands of people. Obviously, the benefits are achievable not only in case of those who are undergoing formal treatment, but also for those who are taking buprenorphine illegally, without doctor's prescription (when a person is undergoing self-treatment). Available evidence suggest that illicit use of buprenorphine might bring certain public health benefits when compared to use of heroin or other street opioids – reducing the rates of overdose deaths and reducing the rates of risky injection behaviour associated with transmission of blood borne infections. Carefully planned and organized treatment process, adequate pharmacological and psychological aid should be offered to those persons who use "illegal" buprenorphine for self-treatment.

Rational policymaking should take into account a complex set of considerations. It is important to ensure that attempts to tighten the control over the buprenorphine prescription and dispensing will not result in limited access to this life saving treatment for those who are in need of it. Wide access to buprenorphine treatment for all persons dependent on opioids should be of priority. Striking the right balance between making treatment more accessible and attractive and minimizing diversion should not be allowed to compromise the flexibility of treatment.

7. Attachment: Timetable

	2007	2008	2009	2010	2011	2012
Literature review of scientific publications available online through MEDLINE database						
Descriptive study examining the prevalence and factors associated with buprenorphine injection among 500 Georgian IDUs using structured self-administered questionnaire						
Overview of drug situation in Georgia, including data on buprenorphine use, through revision and adaptation of information collected for country 2010 Drug Situation Summary report						
Randomized controlled clinical trial with 80 buprenorphine (Subutex®) injection drug users in Tbilisi to examine the acceptability and efficacy of methadone and Suboxone® treatment to reduce drug use and HIV risks						

8. Attachment: The questionnaire used in the first sub-study (English transcript)

Subutex injection in Georgia

1. **Age**……..
2. **Sex** 1- male 2-female
3. **Have you ever injected i/venously (check all that apply)**
    1. Buprenorphine (Subutex)
    2. Home made ephedrine (vint, jef, ephedrine+permanganat kali, koldact, efect)
    3. Koaksil
    4. Home made opium (raw opium – black)
    5. Heroin by itself (or mixed with other sedative or antihistamine drugs)
    6. Crack (smokable cocaine)
    7. Powder cocaine (coke)
    8. Heroin and cocaine mixed together
    9. Amphetamines/methamphetamines
    10. Opiates (Morphine, Codeine, methadone, Codilac, etc) that you didn't have a prescription for
    11. Sedatives that you didn't have a prescription for (ksanaks, Valium, diazepam, Sibazon, Radedorm, Reladorm..)
    12. Narcotic painkillers (tramadol, tramal, tetri)
4. **In the past 30 days, how many days did you use each of the following?**
    1. Marijuana/Managua……
    2. Buprenorphine (Subutex) pure, or mixed with sedatives……
    3. Home made ephedrine (vint, jef, ephedrine+permanganat kali, koldact, efect)……
    4. Koaksil……
    5. Home made opium (raw opium – black)…….
    6. Heroin by itself (or mixed with other sedative or antihistamine drugs)……
    7. Crack (smokable cocaine)……..
    8. Powder cocaine (coke)…….
    9. Heroin and cocaine mixed together……..
    10. Amphetamines/methamphetamines……
    11. Opiates (Morphine, Codeine, methadone, Codilac, etc) that you didn't have a prescription for…….
    12. Sedatives that you didn't have a prescription for (ksanaks, Valium, diazepam, Sibazon, Radedorm, Reladorm..)……..
    13. Narcotic painkillers (tramadol, tramal, tetri)……..

5. **For how many years have you been systematically (2-3 times/week) using injecting drugs (summarize)**

   years…….. months……..

6. **What was the first drug you have got dependence on?**

   1. Heroine
   2. Subutex
   3. Vint
   4. Opium
   5. Other (specify)…….

7. **Which one from the list would you prefer, if you have to chose?**

   1. Heroine
   2. Subutex
   3. Vint
   4. Opium
   5. Other (specify)…….

8. **Please circle the maximum amount of money (in GEL) you would pay for one dose of heroine**

   0 20 40 60 80 100 120 140 160 180 200

9. **Please circle the maximum amount of money (in GEL) you would pay for one dose of Subutex**

   0 20 40 60 80 100 120 140 160 180 200

10. **Please circle the maximum amount of money (in GEL) you would pay for one dose of opium**

    0 20 40 60 80 100 120 140 160 180 200

11. **For how long have you been injecting Subutex?**

    Years…….. months…….

12. **What part (dose) of 8 mg pill of Subutex (B8) do you usually inject?**

    1. One eighth
    2. One fourth
    3. Half
    4. Whole pill
    5. Other…….

13. **What is the main (leading) reason for you to inject Subutex?**

    1. To get high, pleasure
    2. Self treatment, to get off drugs
    3. To coup with withdrawal
    4. It's easy to get Subutex
    5. Other…….

9. List of Tables

10. List of Figures

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13. Seznam publikací doktoranda (List of defendant's publications)

1. publikace *in extenso,* které jsou podkladem disertace

a) *s impact factorem (uvést hodnotu IF)*

- **Otiashvili, D.,** Piralishvili, G., Sikharulidze, Z., Kamkamidze, G., Poole, S., Woody, E. G., (2013). Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behaviour - Outcomes of a Randomized Trial. *Drug and Alcohol Dependence, 133*(2), 376-382. (IF= 3.141)
- Lund, I., Kirtadze, I., **Otiashvili, D.,** O'Grady, K., & Jones, H. (2012). Female partners of opioid-injecting men in the Republic of Georgia: an initial characterization. *Substance Abuse Treatment, Prevention, and Policy, 7*(1), 46. (IF= 1.56)
- Kirtadze, I., **Otiashvili, D.,** O'Grady, K. E., & Jones, H. E. (2012). Behavioural Treatment + Naltrexone Reduces Drug Use and Legal Problems in the Republic of Georgia. *The American Journal of Drug and Alcohol Abuse, 38*(2), 171-175. (IF= 1.733)
- **Otiashvili D**., Zabransky T., Kirtadze I., Piralishvili G., Chavchanidze M., Miovsky M., Why do the clients of Georgian needle exchange programs inject buprenorphine? *European Addiction Research,* 2010;16:1-8. (IF= 2.53)

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- Javakhishvili, D. J., Sturua, L., **Otiashvili, D.,** Kirtadze, I., & Zabransky, T. (2011). Overview of the Drug Situation in Georgia. Adiktologie, 11(1), 42-51.

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- **Otiashvili, D.**, Kirtadze, I., O'Grady, K. E., Zule, W. A., Krupitskii, E. M., Wechsberg, W. M., Jones H.E., (2013). Access to treatment for substance-using women in the

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- Kirtadze, I., **Otiashvili, D.,** O'Grady, K. E., Zule, W. A., Krupitskii, E. M., Wechsberg, W. M., & Jones, H. E., (2013). Twice stigmatized: Health service provider's perspectives on drug-using women in the Republic of Georgia. *Journal of Psychoactive Drugs,* 2013; 45(1): 1-9. (IF= 1.176)
- **Otiashvili, D.**, Kirtadze, I., O'Grady, K. E., & Jones, H. E., (2012) Drug use and HIV risk outcomes in opioid-injecting men in the Republic of Georgia: Behavioural treatment + naltrexone compared to usual care. *Drug and alcohol dependence,* 120, 14-21. (IF= 3.141)
- Meyer, William , Costenbader, Elizabeth C. , Zule, William A. , **Otiashvili, David** and Kirtadze, Irma (2010) We are ordinary men: MSM identity categories in Tbilisi, Georgia, *Culture, Health & Sexuality*, 12: 8, 955 -971. (IF= 1.494)
- Costenbader E., **Otiashvili D**., Meyer W., Zule W., Orr A., Kirtadze I., 2009 Secrecy and Risk among MSM in Tbilisi, Georgia, *AIDS Care,* 2009 May; 21(5):591-7. (IF= 1.6)

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- Kirtadze, I., **Otiashvili, D.,** & Javakhishvili, D. J. (2011). Education Needs in the Sphere of Addictology in Georgia. *Adictologie, 11*(1), 52-60.
- **Otiashvili D.**, Gambashidze N., Kapanadze E., Lomidze G., Usharidze D., 2006 Effectiveness of needle/syringe exchange program in Tbilisi. *Georgian Medical News*, 11(140), p. 62-65
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- **Otiashvili D**., 2004 Efficacy of Naltrexone Maintenance Treatment among Opiate Dependence. *Georgian Medical News,* 2 (107), 43-47.
- **Otiashvili D**., Lezhava G., Zurabashvili Zig., Vadachkoria D, 2003 Clasmatosis of neutrofile and lymphocyte nuclei in patients with opiate dependence. *Proceeding of the Georgian Academy of Science*, Biological Series A, 2003, vol. 29, No. 5-6.
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