

ILLICIT USE OF HIGH-DOSAGE BUPRENORPHINE IN TUNISIA

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ABSTRACT

In Tunisia, dependence to high-dosage buprenorphine (HDB) is expanding since the uprising of 2011, driving the epidemics of blood-borne infections among people who inject drugs. Only one rehabilitation center (Thyna center), run by the Tunisian Association for the Prevention of Drug Use is still operating in the country and accepting to treat patients. The aim of this study is to provide evidence-based solutions for the mitigation and prevention of HDB illicit use in Tunisia through the analysis and discussion of the results of a cross-sectional survey conducted to describe the socio-economic, the medical characteristics, the substance use patterns, and the treatment outcomes of patients seeking treatment at the Thyna rehabilitation center during the year 2013. The results of this survey showed that main demographic characteristics of the patients using illegal HDB were single men, unemployed and from low-income urban areas. The intravenous use was privileged and incarceration recurrences ($p < 0.05$), alcoholism ($p < 0.01$) and migration ($p < 0.01$) were associated with daily dosage of HDB. Most of the patients dropped out of treatment within the first month at the center. The analysis reveals the unmet needs of the people who inject drugs in terms of prevention and treatment and identifies opioid maintenance therapy within a psychosocial rehabilitation program framework as a good alternative to the current available health services for people who use drugs in Tunisia. Future research areas will explore the social factors behind substance use and substance injection in Tunisia among out-of reach groups of women and adolescents; as such data is needed to develop efficient policies.

Keywords: Injecting drug use, opioid, maintenance therapy, drug policy

Illicit drugs dependence has direct and indirect adverse consequences on individuals and on populations. In 2010, it

was estimated to account for almost 1% of global all-cause Disability-Adjusted Life Years (DALY) (Degenhardt et al., 2013).

A particular aspect of drug dependence is Injecting Drug Use (IDU), mainly opioids that derive from opium e.g. heroine, morphine. Opioid dependence is the largest contributor to the global burden of disease causing 9.2 million DALY globally (Degenhardt et al., 2013). Countries with the highest burden are mainly countries in Europe and North America, nonetheless, recent reviews suggest that illicit substance use is quickly expanding across Africa and the Middle-East (Dewing, Plüddemann, Myers, & Parry, 2006). A literature review on IDU in six African countries showed that high-risk behaviors among people who inject drugs are potentially contributing to the spread of Human Immunodeficiency Virus (HIV) in the continent (Dewing et al., 2006). This high risk is imputable to direct transmission of the virus through the sharing of injecting equipment, such as syringes (“People who inject drugs, HIV and AIDS,” 2015). Furthermore, IDU alone as a risk factor accounts for 2.1 million DALY globally (Degenhardt et al., 2013) and is considered as an important factor driving the HIV epidemics in African countries (Horton & Das, 2010).

Tunisia, a North African country, is no exception. While transmission of HIV in the general population is still limited, the highest infection rates are registered among high-risk groups such as people who inject drugs. In 2011, a study conducted in Tunis, capital city of Tunisia, estimated that almost 25% of HIV infections are imputable to IDU and that 2.4% of people who inject drugs are HIV positive (Rahimi Movaghar, Amin Esmaeili, Aaraj, & Hermez, 2012). The Tunisian National AIDS Strategy includes people who inject drugs as a key target population. Yet, it is hard to assess the general prevalence of

IDU in the country, and harm reduction and preventive services are solely provided by non-profit, private organizations (“Bénéficiaires principaux Sida,” n.d.). Finally, rehabilitation options are very limited in the public sector and Opioid Maintenance Therapy (OMT) medication are not available in Tunisia (Skhiri, Zalila, Zid, & Boukassoula, 2014).

OMT offers a long-term treatment of opioid dependence with replacement medication such as Methadone or High-Dosage-Buprenorphine (HDB) to decrease the withdrawal syndrome after opioids cessation (Bart, 2012). Buprenorphine is a semi-synthetic opioid formulated in sub-lingual, highly-dosed tablets to be prescribed as part of OMT (Khanna & Pillarisetti, 2015). Although HDB is not legally accessible in Tunisia, neither in hospitals nor in pharmacies, the sub-lingual tablets could be obtained illegally on the black market since the early 2000. Back in 2008, a hospital-based study, described HDB intravenous use as “an emerging reality” in the Tunisian society (Becheikh, Ghachem, Zalila, & Boussetta, 2008). After the 2011 Revolution, its trade and use have expanded and have not been effectively addressed since (Belarbi et al., 2014). Today it is considered to be the first IDU substance (Skhiri et al., 2014).

Overall, drug use and injection are extremely criminalized by the law in Tunisia and people who inject drugs are marginalized from the rest of the society (Rahimi Movaghar et al., 2012). Men and women who inject drugs also face limited treatment options and insufficient prevention services, in addition to incarceration. Efforts to mitigate and prevent are limited and coverage is low as only six free and safe needle exchange facilities exist on the national territory (Rahimi Movaghar et al.,

2012). The growing non-medical and illicit use of HDB as a risk factor behind the growing hepatitis and HIV epidemics in Tunisia (Kilani et al., 2007; Mumtaz et al., 2014), is a Public Health concern. Despite this reality, the legislation and national policies are lagging behind the emerging social trends. The few rehabilitation clinics available in Tunis have shut down in recent years. Moreover, harm reduction centres and rehabilitation services depend on external funding as they are not government-based. The political transition of 2011 has affected the development of their activities, and in some cases they were completely ceased. Only one rehabilitation center has been operating and accepting patients from all regions of the country (Skhiri et al., 2014). This center is managed by a non-governmental organization, the Tunisian Association for the Prevention of Drug Use, named ATUPRET and located in Thyna, near the city of Sfax.

METHODS

The main objectives of this survey are to describe the socioeconomic and medical characteristics, to identify the consumption patterns and history of dependence, and to look at the correlated factors with HDB use and treatment outcomes of the patients seeking therapy for HDB dependence at the above-mentioned rehabilitation center. The aim is to use the results of the survey and provide evidence-based alternatives from the literature on mitigating the use of HDB in the Tunisian society.

Participants

In this study, the population sample solely includes patients aged at least 18 years old, and admitted for the treatment

of HDB dependence between January 1st 2013 and December 31st 2013 at the rehabilitation center. A total of 167 subjects met these criteria and their records were retrieved.

Data collection

The data collection took place at the center between January and March of 2014 after gaining access to the archived medical records of the year 2013, with an ethical waiver from the association's executive board. After consultations with the medical experts and psychologists at the center, a data collection form was developed by the authors with respects to anonymity and confidentiality. The form helped collecting personal information related to the objectives of this survey. Relevant data included the socioeconomic variables e.g. gender, age, level of education, work and family status, the family history of substance use disorders, the individuals' experience of initiation of substance use, the dosages and means of HDB daily self-administration. Blood-borne infections such as hepatitis C and HIV were reported as part of the medical history. The length of the stay at the clinic and the number of previous rehabilitation admissions, were collected to report on treatment outcomes.

Statistical Analysis

The information extracted was classified and codified into variables. The free software R-GUI was used for the statistical analysis. Frequencies, ranges and standard deviations were determined for socioeconomic characteristics and for variables related to HDB consumption. A chi-square statistical test was conducted for variables related to the daily dosage of HDB and to the duration of HDB intake. Subsequently, a Kendall non-parametric

test was run to identify the correlated variables in the sample.

RESULTS

Patients admitted for HDB dependency in 2013 presented 54% of all the patients admitted that year.

Socioeconomic characteristics

All patients were men and the mean age was 33.5 ± 8.1 years with 95% between 32 and 35 years old. The population characteristics are summarized in Table 1. Among the patients, 73% were single, 60% were unemployed and 51% had completed their primary education or less. The majority of the population (94%) was living in urban areas and 35% came from large families (more than three siblings). More than a quarter (28%) experienced domestic violence and 20% were orphaned at a young age. Family history defined as having any family member with history of substance use disorders was reported for 16%. Furthermore 40% had migrated, mainly to European countries (34%), either legally or through illegal ways. Incarceration rate was at 68% with 44% recidivism rate after the first confinement.

Medical history

On the 167 medical records, 54 indicated infection with hepatitis C, 14 with hepatitis B and 13 reported HIV-positive cases. Among the HIV-positive group, 12 also suffered from hepatitis C (cases of double infection).

History and initiation of substance use

The mean age for the first consumption of a psychoactive substance, was $16.4 \pm$

4.5 years and the mean age for the first injection of an opioid was 24.0 ± 6.1 years. Many subjects initiated drug use by taking multiple products at the same time. For about half (53%), marijuana was the first recreational consumption and for almost the fifth (18%) it was diverted psychotropic medicine such as benzodiazepines. Furthermore, a small proportion of 8% reported glue or other inhalants sniffing before the age of ten years old, whereas use of heroin and cocaine as the first recreational drug was in only 7% of the cases and HDB for a few 2% (Figure 1).

Self-reported causes of initiation were related to peer-pressure in 25%, to feelings of curiosity and thrill-seeking in 21%, in order to escape a harsh reality in 22% and within the illegal emigration context for 16% of the cases. A specific reason for using HDB was the abundance of the substance and the facility of finding and procuring it in comparison to other products such as Heroin, which was the case for 13% of the sample. Less than 1% reported that they have developed an opioid dependence after using prescribed pain killers which led them to the use of DB as a replacement.

Multiple consumptions

Apart from regularly injecting HDB, the majority of the population (98%) was using multiple other dependence-producing substances simultaneously. Harmful alcohol use affected 78% and alcoholism 22%. Tobacco and Marijuana smoking rates were at 86% and 70%, respectively. Moreover, diversion of psychotropic medicine was common with benzodiazepines used by 60% and anxiolytic drugs by 43% of the subjects.

Patterns of HDB intake

The daily intake and dosage of HDB were reported in the medical records in

Table 1. Demographic characteristics and substance use initiation variables

Ages (Years): Mean (\pmSD)	Mean	
Age	33,5(\pm 8,1)	
Age At First Substance Use	16,4 (\pm 4,5)	
Age At First Substance Injection	24,0 (\pm 6,1)	
Mean Duration Of HDB Use	7,5 (\pm 3,7)	
Marital Status	Number	Percentage
Single	122	73%
Married	34	20%
Divorced	9	6%
Widow	2	1%
Place of Living	Number	Percentage
Urban	157	94%
Non-Urban	10	6%
Education	Number	Percentage
Primary School	85	51%
Secondary/High School	66	40%
High School Graduate	13	8%
University	3	2%
Family Environment	Number	Percentage
Parent(S) Deceased	33	20%
Domestic Violence As A Child	46	28%
Large Family	59	35%
Family History Of Substance Use	26	16%
Profession	Number	Percentage
Unemployed	101	61%
Precarious Worker	31	19%
Salarial Work	35	21%
Migration	Number	Percentage
Emigrated	66	40%
Lived In European Country	56	34%
Illegal Migration	33	20%
Legal Migration	33	20%
Detention	Number	Percentage
Incarcerated At Least Once	113	68%
Multiple Incarcerations	74	44%
Drug-Related Felonies	73	44%

Demographic characteristics of the sample of 167 patients show the number and the percentage for each variable. The highest rates are related to being single and unemployed, having a low education level, living in urban areas, and having being incarcerated at least once.

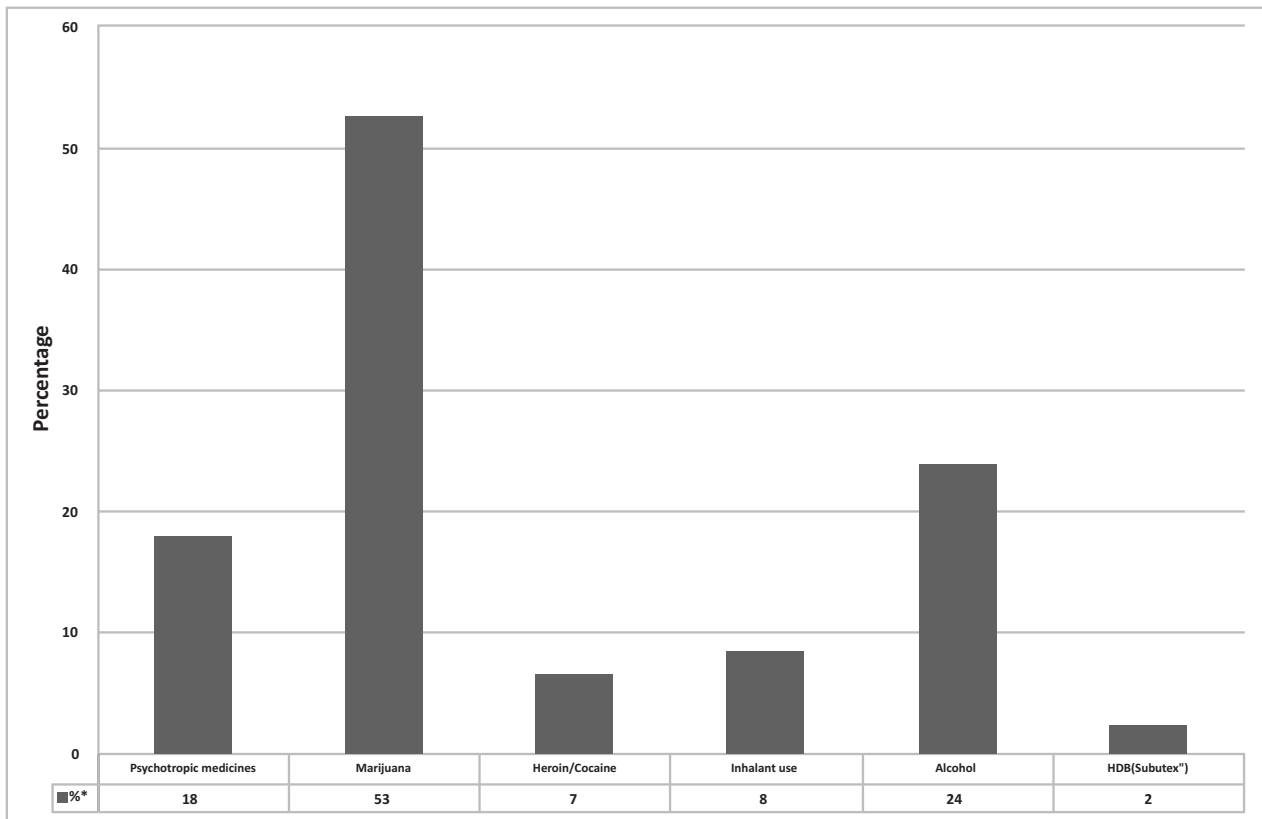


Figure 1. Substance used as the first recreational substance

Note: Initiation of substance use may start with one, two or more concomitant consumptions. Marijuana is the most popular substance to be used at the first time, followed by alcohol and psychotropic medicines that include tranquilizers and sedatives. Smaller proportions of the subjects used inhalants such as sniffing glue, and even less used heroin or cocaine as their first substance. HDB came last as the first ever consumed substance for recreational purposes.

terms of multiples of eighth (1/8) of a tablet. In fact, this is how the patients referred to their consumption: one tablet was typically cut in 8, sold and consumed in such portions. For the sake of clarity and consistency, the dosage of daily intake was directly calculated from the medical records then reported in milligrams, considering that a tablet contains 8mg of HDB as it is the most common form of diverted HDB in the country (Skhiri et al., 2014). The mean dosage of daily intake was 6.5 ± 3.8 mg per day. The mean number of daily intakes was 3.7 ± 2 times a day and the mean duration of HDB long-term use was evaluated to 7.5 ± 3.7 years.

Less than 1% of the patients used HDB via the sub-lingual route. Almost 70% started HDB intake through intravenous

route and more than a quarter (26%) started HDB consumption through the intranasal route or “sniffing”. At the time of admission to the clinic, the majority of the sample (96%) was self-administrating HDB through intravenous syringe use, in opposition to 4% who have not transitioned from sniffing yet.

Treatment and treatment outcome

The mean length of stay at the center was 16.8 ± 8.3 days. About 47% of the medical records indicated that the patient had undergone at least another previous withdrawal management therapy.

Statistical Analysis

The chi-square test revealed that incarceration recidivism ($p < 0.05$), alcohol

dependence (or alcoholism) ($p < 0.01$) and migration ($p < 0.01$) were associated with the daily dosage of HDB. In addition, duration of HDB consumption was significantly related to marital status ($p < 0.01$), past heroin dependence ($p < 0.01$) and alcohol dependence (Table 2). A correlation was established between the place of living and the self-reported causes of HDB use ($p < 0,05$).

Kendall non-parametric test showed that the daily dosage was positively correlated to the number of daily intakes ($r = 0.33$, $p < 0.01$) and to the long-term HDB intake ($r = 0.18$, $p < 0.01$). A positive correlation between the early onset of substance use and the early onset of substance injection was also found but not significant ($r = 0.08$, $p = 0.2$). Finally, another positive correlation was revealed between the age of the subject and HDB consumption duration ($r = 0.39$, $p < 0.01$).

DISCUSSION

Through the analysis and discussion of the results and identification of the unmet needs of patients at the rehabilitation center, this study aims at providing

evidence-based alternatives and solutions to prevent HDB use and mitigate its consequences in Tunisia.

The results showed that the majority of HDB users seeking help at the center are young adult men, single, unemployed, and with low educational level. Although the center did not use any selection criteria and accepted patients from all over the country, the majority of the sample came from urban areas. These findings are similar to other reports that have stated that trafficking of this substance occurs in low-income urban settings among groups of young unemployed men with history of criminal cases (Skhiri et al., 2014). Other research studies have consistently portrayed comparable aspects of people who inject drugs in Tunisia, as well (Becheikh et al., 2008; Belarbi, Ben Ammar, Moula, Bouasker, & Ghachem, 2013; Robbana, Moula, Guermani, Bouasker, & Ghachem, 2013). The social stigma around IDU has amplified through its consistent portrayal in relation to criminality in major published studies and official reports. Consequently, other groups such as adolescents and women with substance use disorders become harder to reach and include in

Table 2. Consumption of high-dosage buprenorphine

	A+	A-	χ^2	P	H+	H-	χ^2	P	E+	E-	χ^2	P	I>2	I<1	χ^2	P	Single	Married	χ^2	p
Daily dosage of HDB	21.56%	71.27%	52.2	3.47E-05	32.34%	67.66%	15.77	0.07184	39.52%	60.48%	22.79	0.006675	44.31%	25.75%	121.36	0.01541	73.05%	20.36%	16.35	0.9459
Duration of HDB consumption			56.15	0.009793			32.21	0.01415			23.86	0.1231			142.18	0.6629			77.56	0.009654

$p < 0.01$

Note: A+ Reported alcohol addiction ; A- No reported alcohol addiction; H+ Reported heroin addiction; H- No reported heroin addiction; E+ Have emigrated; E- Have never emigrated; I>2 Have been incarcerated more than once; I<1 Have been incarcerated once or never.

research studies as they fear stigma or other social or legal consequences.

About 70% of the patients had a criminal record with drug-related felonies in more than 50% of them. Findings also indicated long periods of custody and frequent recidivism. High incarceration rates have also been reported by Dakhliya et al. and Robbana et al. in their studies on smaller samples of patients with HDB dependence admitted in public hospitals (Dakhliya Boukhari & Zalila, 2010; Robbana et al., 2013). Nevertheless, HDB was depicted in the literature to be considered by people who inject drugs as a “*safer*” substance to use in order to avoid criminal convictions, since it is not detectable through forensic investigations (Skhiri et al., 2014). The high rates of drug-related felonies in the survey sample may be related to the use of other substances in concomitance with HDB or in the past at the initiation of recreational substance use.

A study conducted in Singapore, stated that 80% of people who injected HDB served a prison sentence (Winslow, Ng, Mythily, Song, & Yiong, 2006). Both Singapore and Tunisia have strong legislation governing substance use. In Tunisia, non-medical consumption of opioids and other drugs is criminalized (Narcotics Law n° 92-52, 18th May 1992) and treatments of opioid addiction are not available in prisons. Apart from hindering the work of harm reduction programs, such strong laws doubled with strict moral social norms constrain people who inject drugs and dissuade them from coming forward to seek medical care and social assistance. Furthermore, HDB consumption was correlated to migration among the study sample. Both Becheikh et al. in 2008, and Robbana et al. in 2013,

also reported in their respective studies high rates of illegal migration to European countries, among a subgroup of people who inject HDB with a history of heroin addiction. The subgroup of HDB users who have lived in European countries have first encountered HDB during a prescribed OMT to treat their heroine dependence. Illegal use of HDB later on in life, and in places where OMT is not a legally available therapeutic option, is an attempt to self-manage a long-term opioid dependence.

The circumstances and rationales of HDB use in Tunisia, where it is illegally sold in the black market, are different from other countries where it can be legally procured within an OMT framework. In fact, the self-reported causes of HDB initiation were correlated to the place of living. In Italy, younger opioid consumers were reported to be more likely to divert HDB (Moratti, Kashanpour, Lombardelli, & Maisto, 2010), while in Sweden a study showed that buprenorphine was typically used at a later stage or at a severe level of opioid dependence (Johnson & Richert, 2015) as an attempt to self-treat withdrawal or to manage pain (Cicero, Ellis, Surratt, & Kurtz, 2014). These studies occurred in countries where HDB is legally available, which is not the case in Tunisia where HDB is not perceived as a medication but rather as an illegal, recreational, and dependence-producing substance. HDB has never been introduced as a treatment option in any sanitary structures; and Tunisian healthcare professionals have not been trained to prescribe it. Therefore, even though the rationales behind the illicit use of HDB in Europe and in Tunisia can be similar, the patterns of self-administration and dependence stages are different.

The initiation of injection of a dependence-producing substance among people who already use it through other routes, is a complex phenomenon involving a wide range of biological, socioeconomic and psychological factors such as peer-pressure (Goldsamt, Harocopos, Kobra, Jost, & Clatts, 2010). Ability to use less of an opioid or tolerance to different modes of administration can also, lead to initiating intravenous intake. The correlation found between the daily dosage of HDB and the number of daily intakes demonstrates the biological tolerance phenomenon that is particular to opioids and leads the user to increase the dosage or resort to a quicker intake route, in order to obtain the same effect of the substance. In fact, nearly all patients transitioned to injecting the substance per intravenous, after starting with intranasal administration. Peer-pressure, affluence and availability of HDB despite its illegal characteristic, were self-reported reasons for the initiation of injection of the substance. HDB is indeed considered to be a widely available and cheaper opioid than other illegal opioids on the black market (Skhiri et al., 2014).

On another note, 98% of the sample reported concomitant consumption of one or multiple other recreational, dependence-producing substances next to HDB. In a 2012 survey conducted by the Center for Urgent Medical Assistance of Tunis, 92% of HDB users co-administered other substances at the same time which the authors labeled as *poly-consumption* (Ben Salah & Hamouda, 2013). The most common psychotropic compounds used with HDB being benzodiazepines and alcohol, these associations may become very dangerous and may lead to fatalities (Häkkinen, Launiainen, Vuori, & Ojanperä, 2012).

Anxiolytic medications, sought for their tranquilizing effects, also have a major diversion and dependence potential. Poly-consumption challenges the therapeutic management as it is complex to tackle numerous addictions simultaneously. The length of the treatment at Thyna center for dependence was approximately two weeks, indicating a high drop-out rate and poor health outcomes. Derbel et al. evaluated the outcomes of the medical management of patients admitted at Thyna center and concluded that the symptomatic care of the withdrawal symptoms had limited and poor outcomes (Derbel, Ghorbel, Akrouf, & Zahaf, 2016). Alternatively, maintenance therapy can be a beneficial tool to optimize treatment outcomes.

In addition, high rates hepatitis C and HIV-hepatitis C double infections were registered, illustrating the role of HDB injection and high-risk behaviors as risk factors behind the expansion of HIV and hepatitis among people who inject drugs in Tunisia (Belarbi et al., 2013). In a hospital-based study, 78% of HIV-positive inpatients had history of substance injection (Kilani et al., 2007). Numerous preventive public health interventions in Tunisia, such as the unlimited selling of sterile syringes over the counter in community pharmacies, are strategic to face the expansion of blood-borne infections but remain insufficient. Modern health policies are needed to democratize the harm-reduction facilities and improve their accessibility.

Providing affordable and safe HDB was established as an effective strategy to limit its diversion (Lofwall & Walsh, 2014). Policies that facilitate access to therapeutic options for opioid users were proven to be better solutions than constrained substance use policies. Relaxed legislation and OMT treatment options have been proved

to have positive outcomes and were associated with not only an improved quality of life, but also with a better social rehabilitation of the people who inject drugs and with positive effects on their families and social networks as well (Bart, 2012). In France, the marketing of HDB as a treatment for opioid dependence, proved to bring major public health benefits (Fats-eas & Auriacombe, 2007). Sun. et al meta-analysis looked at the OMT experience in China and concluded that it is an effective tool for the successful rehabilitation of opioids' users (Sun et al., 2015). In the light of this available evidence about the importance of OMT, implementation of modern and patient-centered therapeutic options coupled with responsive and Human Rights-based drug policies in Tunisia, will help to lower the high incarceration rates and poor treatment outcomes depicted in the results. Tailored long-term replacement and maintenance medication treatment with simultaneous psychotherapy are effective to prevent relapses, lower blood-borne infection risks, promote social reinsertion and improve general quality of life (Carrieri et al., 2006). Introducing OMT in Tunisia will help reduce the illegal use of HDB and its consequences on a broader scale.

OMT medications (HDB and Methadone) were enlisted on the WHO list of essential medicines since 2005 (Herget, 2005). Yet, in 2018 they are not legally accessible to the patients who need them in Tunisia. Introducing OMT could prove to be a multi-fold scheme that will encompass various sectors. However, successful experiences from other middle-income countries have been extensively documented and evidence-based guidelines are available. To carry-out OMT in Tunisia, training and technical support to health-

care providers and social workers will be necessary to equip them with the necessary tools.

CONCLUSION

Opioid diverted use has been largely documented in North Africa and particularly in Tunisia under the umbrella of HIV prevention programs. However, all reports align with this survey showcasing a homogenous group of single and unemployed men with criminal records with substance use disorders, seldom portraying out-of-reach groups such as women and adolescents who inject drugs. Despite the alarming expansion of substance use disorders and its public health repercussions since the 2011 uprising, therapeutic and preventive solutions are still limited in Tunisia. The social factors surrounding HDB dependence are yet to be explored. Evidence-based policies such as OMT are paramount to improve the current situation, rehabilitate the alarming growing number of HDB users, and reverse the trends. Advocacy for introducing OMT in Tunisia should be supported as a Human Rights-based approach and an efficient alternative to the existing withdrawal management therapy.

AUTHOR NOTE

This study was conducted as part of Pharm D. thesis project by the first author, Hager Ben Mosbah, who conducted data collection, data analysis and writing of the manuscript. Asma Ghorbel supervised and assisted in the data collection and data analysis and participated in the writing. Abderrazek Hedhili oriented and supervised the research process. All

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REFERENCES

- Bart, G. (2012). Maintenance medication for opiate addiction: the foundation of recovery. *Journal of Addictive Diseases, 31*(3), 207–225. <https://doi.org/10.1080/10550887.2012.694598>
- Becheikh, D., Ghachem, R., Zalila, H., & Boussetta, A. (2008). Mésusage de buprénorphine haut dosage : Un phénomène émergent en Tunisie. *Alcoolologie et addictologie, 30*(1), 25–28.
- Belarbi, A., Ben Ammar, H., Moula, O., Bouasker, A., & Ghachem, R. (2013). 1823 – Addiction to high dose buprenorphine and sexually transmitted diseases in tunisia. *European Psychiatry, 28*, 1. [https://doi.org/10.1016/S0924-9338\(13\)76788-9](https://doi.org/10.1016/S0924-9338(13)76788-9)
- Belarbi, A., Robbanna, L., Moula, O., Nasri, A., Bouasker, A., & Ghachem, R. (2014). EPA-1783 – Comparative study of the addiction to high dose buprenorphine before and after the tunisian revolution. *European Psychiatry, 29, Supplement 1*, 1. [https://doi.org/10.1016/S0924-9338\(14\)78906-0](https://doi.org/10.1016/S0924-9338(14)78906-0)
- Ben Salah, N., & Hamouda, C. (2013, December). *Cadre légal tunisien de lutte contre les stupéfiants*. Presented at the Troisième colloque international francophone sur le traitement de la dépendance aux opioïdes, Geneva. Retrieved from http://www.tdo3.ch/pdf/presentation/Symposiums/T7-2/T7-2_Ben_Salah&Hamonda.pdf
- Bénéficiaires principaux Sida. (n.d.). Retrieved April 17, 2016, from <http://www.ccmtunisie.org.tn/index.php/fr/beneficiaires/beneficiaires-principaux-sida>
- Carrieri, M. P., Amass, L., Lucas, G. M., Vlahov, D., Wodak, A., & Woody, G. E. (2006). Buprenorphine use: the international experience. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 43 Suppl 4*, S197-215. <https://doi.org/10.1086/508184>
- Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). Factors contributing to the rise of buprenorphine misuse: 2008–2013. *Drug and Alcohol Dependence, 142*, 98–104. <https://doi.org/10.1016/j.drugalcdep.2014.06.005>
- Dakhliya Boukhari, N., & Zalila, H. (2010, December). *Toxicomanes à la « BHD » ou Subutex : Profil sociodémographique*. Presented at the La 23ème Journée Nationale de Psychiatrie. Retrieved from <http://www.psyttunisienne.org/>
- Degenhardt, L., Whiteford, H. A., Ferrari, A. J., Baxter, A. J., Charlson, F. J., Hall, W. D., ... Vos, T. (2013). Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet (London, England), 382*(9904), 1564–1574. [https://doi.org/10.1016/S0140-6736\(13\)61530-5](https://doi.org/10.1016/S0140-6736(13)61530-5)

- Derbel, I., Ghorbel, A., Akrouf, F. M., & Zahaf, A. (2016). Opiate withdrawal syndrome in buprenorphine abusers admitted to a rehabilitation center in Tunisia. *African Health Sciences, 16*(4), 1067–1077. <https://doi.org/10.4314/ahs.v16i4.24>
- Dewing, S., Plüddemann, A., Myers, B. J., & Parry, C. D. H. (2006). Review of injection drug use in six African countries: Egypt, Kenya, Mauritius, Nigeria, South Africa and Tanzania. *Drugs: Education, Prevention and Policy, 13*(2), 121–137. <https://doi.org/10.1080/09687630500480228>
- Fatseas, M., & Auriacombe, M. (2007). Why buprenorphine is so successful in treating opiate addiction in France. *Current Psychiatry Reports, 9*(5), 358–364.
- Goldsamt, L. A., Harocopos, A., Kobrak, P., Jost, J. J., & Clatts, M. C. (2010). Circumstances, pedagogy and rationales for injection initiation among new drug injectors. *Journal of Community Health, 35*(3), 258–267. <https://doi.org/10.1007/s10900-010-9231-z>
- Häkkinen, M., Launiainen, T., Vuori, E., & Ojanperä, I. (2012). Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning. *European Journal of Clinical Pharmacology, 68*(3), 301–309. <https://doi.org/10.1007/s00228-011-1122-4>
- Herget, G. (2005). Methadone and buprenorphine added to the WHO list of essential medicines. *HIV/AIDS Policy & Law Review, 10*(3), 23–24.
- Horton, R., & Das, P. (2010). Rescuing people with HIV who use drugs. *The Lancet, 376*(9737), 207–208. [https://doi.org/10.1016/S0140-6736\(10\)61025-2](https://doi.org/10.1016/S0140-6736(10)61025-2)
- Johnson, B., & Richert, T. (2015). Diversion of methadone and buprenorphine by patients in opioid substitution treatment in Sweden: prevalence estimates and risk factors. *The International Journal on Drug Policy, 26*(2), 183–190. <https://doi.org/10.1016/j.drugpo.2014.10.003>
- Khanna, I. K., & Pillarisetti, S. (2015). Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. *Journal of Pain Research, 8*, 859–870. <https://doi.org/10.2147/JPR.S85951>
- Kilani, B., Ammari, L., Marrakchi, C., Leitaief, A., Chakroun, M., Ben Jemaa, M., ... Ben Chaabène, T. (2007). Seroepidemiology of HCV-HIV coinfection in Tunisia. *La Tunisie Médicale, 85*(2), 121–123.
- Lofwall, M. R., & Walsh, S. L. (2014). A Review of Buprenorphine Diversion and Misuse: The Current Evidence Base and Experiences from Around the World. *Journal of Addiction Medicine, 8*(5), 315–326. <https://doi.org/10.1097/ADM.0000000000000045>
- Moratti, E., Kashanpour, H., Lombardelli, T., & Maisto, M. (2010). Intravenous misuse of buprenorphine: characteristics and extent among patients undergoing drug maintenance therapy. *Clinical Drug Investigation, 30 Suppl 1*, 3–11. <https://doi.org/10.2165/11536020-000000000-00000>
- Mumtaz, G. R., Weiss, H. A., Thomas, S. L., Riome, S., Setayesh, H., Riedner, G., ... Abu-Raddad, L. J. (2014). HIV among people who inject drugs in the Middle East and North Africa: systematic review and data synthesis. *PLoS Medicine, 11*(6), e1001663. <https://doi.org/10.1371/journal.pmed.1001663>
- People who inject drugs, HIV and AIDS. (2015, July 20). Retrieved May 24,

2018, from <https://www.avert.org/professionals/hiv-social-issues/key-affected-populations/people-inject-drugs>

- Rahimi Movaghar, A., Amin Esmaeili, M., Aaraj, E., & Hermez, J. (2012). *Assessment of Situation and Response of Drug Use and Its Harms in the Middle East and North Africa*. Middle East and North Africa Harm Reduction Association (MENAHRRA). Retrieved from <http://menahra.org/images/pdf/Menahra.pdf>
- Robbana, L., Moula, O., Guermani, M., Bouasker, A., & Ghachem, R. (2013). 1795 – Course of dependent patients with buprenorphine high dosage: about 32 cases. *European Psychiatry*, 28, Supplement 1, 1. [https://doi.org/10.1016/S0924-9338\(13\)76766-X](https://doi.org/10.1016/S0924-9338(13)76766-X)
- Skhiri, H. A., Zalila, H., Zid, T., & Boukassoula, H. (2014). *Tunisia - Drug*

- situation and Policy*. Co-operation Group to Combat Drug Abuse and Illicit trafficking in Drugs. Retrieved from <https://www.coe.int/T/DG3/Pompidou/Source/Images/country%20profiles%20flags/profiles/CP%20Tunisia%20English%20V2.pdf>
- Sun, H.-M., Li, X.-Y., Chow, E. P. F., Li, T., Xian, Y., Lu, Y.-H., ... Zhang, L. (2015). Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: a systematic review and meta-analysis. *BMJ Open*, 5(1), e005997. <https://doi.org/10.1136/bmjopen-2014-005997>
- Winslow, M., Ng, W.-L., Mythily, S., Song, G., & Yiong, H.-C. (2006). Socio-demographic profile and help-seeking behaviour of buprenorphine abusers in Singapore. *Annals of the Academy of Medicine, Singapore*, 35(7), 451–456.