

# Buprenorphine for Opiate Dependence: Clinic Based Therapy in Israel

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## ABSTRACT

**Background:** Opioid dependency is characterized by repeated use of an opioid drug despite physical dependence, behavioral impairments and social dysfunction. Therapeutic approaches for the treatment of opioid dependence are total abstinence and opioid agonist maintenance treatment (OAMT). Opiate agonist maintenance therapy is administered using opioid replacement pharmacological agents, i.e., methadone or buprenorphine. Methadone acts as a full opiate agonist while buprenorphine acts as a partial agonist. Strict supervision is necessary when dispensing methadone, because overdose can be fatal. Buprenorphine associates with opioid receptors slowly but with high affinity, and dissociation from the receptor site is (pseudo) irreversible. It is safer than opioid full agonists such as methadone.

**Methods:** We probed the therapeutic efficacy of buprenorphine using a retrospective evaluation of numerical data in the first private buprenorphine clinic in Israel. Data was collected for all patients attending the clinic in December 2012. Our indicator for treatment success is retention in the program.

**Results:** During the years 2005-2012, 1,399 individuals approached the clinic; 1,224 (87.5%) of them attended the clinic at least twice; treatment adherence in this group was 66.5% at the end of one year.

**Conclusions:** The success rates of patients who are treated with buprenorphine and are able to eventually return to their families and re-enter the workforce is encouraging. Thus, the community based minimal intervention treatment model using buprenorphine for the treatment of opiate dependence is a viable treatment option in the war against opiate abuse.

## BACKGROUND

Opioid dependency is characterized by repeated use of an opioid drug despite physical dependence, behavioral impairments and social dysfunction. It is also associated with severe social consequences such as delinquency and prostitution and often precipitates the spreading of fatal infectious diseases such as HCV, HIV, HBV (1, 2).

The two main therapeutic approaches for the treatment of opioid dependence are total abstinence and opioid agonist maintenance treatment (OAMT). The latter treats addiction as a chronic disease that requires ongoing pharmacotherapy focused on harm reduction (3). As with any chronic illness, the goal of the treatment is to stabilize patients and reduce harm, thereby increasing life expectancy and quality of life (4).

Opiate agonist maintenance therapy is administered using one of two available opioid replacement pharmacological agents, methadone or buprenorphine. Methadone acts as a full opiate agonist and buprenorphine acts as a partial agonist. Since the mid-1960s, methadone maintenance has proven successful for the treatment of opioid dependence (1, 5). It decreases drug use, reduces medical comorbidity, decreases transmission of human immunodeficiency virus, reduces mortality and improves social functioning.

Strict supervision is necessary when dispensing methadone because overdose can be fatal (2). Israeli methadone treatment centers implement strict rules and regulations. The medication is dispensed in daily doses, during five visits to the treatment center per week. Buprenorphine acts as a partial agonist at the opioid  $\mu$  receptor, which mediates analgesia, respiratory depression and reduced gastrointestinal motility. Buprenorphine associates with opioid receptors slowly but with high affinity, and dissociation from the receptor site is (pseudo) irreversible. The half-life of buprenorphine is 24-60 hours (6).

It is safer than opioid full agonists such as methadone (7). Buprenorphine is also used as an opioid replacement therapy during pregnancy, causing fewer neonatal abstinence syndrome symptoms than methadone (8).

Buprenorphine was approved for opioid dependence in France in 1995, and is currently approved for such use in many countries (9). The U.S. Federal government approved the use of buprenorphine for treating opioid dependent patients in 2000 (6,10).

The safety profile of this medication has enabled significant reduction in the supervision required for pharmacological treatment of opioid addiction. Thus, opioid addiction can be treated in community based settings without requiring referral to specialized opioid treatment programs (OTPs), and daily clinic visits are no longer necessary.

Buprenorphine is available as buprenorphine pills intended for sublingual use, or Suboxone pills which combine buprenorphine and naloxone. This formulation has the advantage that the medication cannot be misused by crushing and injecting since the naloxone has high bioavailability when taken by this route. This combination pill has become the accepted standard of treatment; however it was only introduced recently to the Israeli market and therefore was not used in the time period of this study. The estimated number of opioid dependent patients in Israel as per the Knesset protocol of 2011 is 15,000 (11). The Israel Ministry of Health approved methadone use in 1975 (12). An estimated 4,500 patients are currently treated with methadone in Israel. Until recently the waiting list for methadone treatment in some clinics was over a year-long.

In 2005 the Israel Ministry of Health approved the use of buprenorphine for opioid dependence treatment purposes (13). Publicly funded buprenorphine clinics are scarce. In 2011 only 613 patients received buprenorphine treatment in public clinics in Israel. During that same year the estimated number of private clinic buprenorphine patients was approximately double (personal communication - Ministry of Health sources).

Public buprenorphine clinics are generally adjacent to methadone clinics and therefore employ similar administration regimens. Strict supervision of buprenorphine administration is not medically justified, and is counterproductive because it impedes return to normal social functioning owing to the required five visits to the treatment center each week. Private community based buprenorphine clinics were initiated in Israel in 2004 and introduced a new concept of treatment. The aim of the clinic was to make buprenorphine treatment more

accessible. For the purpose of this paper, successful treatment is defined as treatment retention that is indicative of the patient being free of illegal opiate use, adherence to follow care including urine tests and willingness to engage in more intensive care when abuse of psychoactive substances is revealed.

#### **WORKING MODEL OF THE HEBETIM CLINIC**

The Hebetim clinic is the first private buprenorphine clinic in Israel, founded in 2004. The clinic is open four days a week from 4:00 p.m. to 7:00 pm. The clinic's branches are located in office buildings in city centers. Clinic visits focus on interventions including psycho-education, stabilization and rehabilitation.

- Patients are received on a drop-in basis, during treatment hours.
- A psychiatrist makes an initial assessment that takes approximately 30 minutes.
- Treatment is initiated based on clinical assessment and a urine sample test.
- The patient's urine is tested for opiates/ cocaine/ benzodiazepines/ buprenorphine.
- Positive results of opiates and cocaine are followed by weekly instead of monthly prescriptions and recurrent motivational discussions with the psychiatrist or counselor, until stabilization is achieved or referral to public treatment facility.
- Patients receive dosages of 2-24 mg per day. The dose is determined by self report of amount of previous drug use. The most common dose is 16 mg/d.
- Patients are instructed how to begin therapy at home with "remote supervision" if necessary. (Most new patients who seek treatment have already begun using buprenorphine that they purchased "on the street").
- We are aware of the fact that buprenorphine diversion exists, and that there is demand for it. We address this issue in our clinic by monitoring of urine for buprenorphine traces as a prerequisite for the next prescription. We also believe that the fact that there is such a demand for buprenorphine raises the question as to whether accessibility to this drug is sufficient.
- Two counselors who are rehabilitated buprenorphine patients mentor clinic patients during treatment including outside of clinic hours.
- During the first month patients visit the clinic once a week after which the frequency of visits is reduced to once a month. A full psychosocial evaluation is performed after the first month of treatment.
- All medical treatments aside from buprenorphine

are referred to appropriate medical facilities. When necessary, psychiatrists recommend which treatments or examinations the patients require.

- The clinic's administrative director assists patients in communication with authorities such as the social security office.
- The patients pay 1,150 NIS in advance for the first three months of the clinic services, and subsequently 250 NIS per month. The cost of buprenorphine is 1,200 NIS per month for the average dose of 16 mg/d.

## METHODS

We probed the therapeutic efficacy of buprenorphine using a retrospective evaluation of numerical data in a naturalistic environment in the Hebetim clinic. We evaluated treatment success as the rate of retention in active treatment.

Data were collected for all patients who approached the clinic at any time between January 2005 and December 31, 2012. Our main indicator of treatment success is retention in the program, which implies being free of illegal opioid use. Status of illegal opioid use was determined by self report and random urine tests for non-buprenorphine opiates. Our experience shows that it is rare for patients who are using buprenorphine to concurrently use illegal opiates, since buprenorphine occupies the  $\mu$ -opiate receptor with higher affinity than other opiates which renders other opiates ineffective.

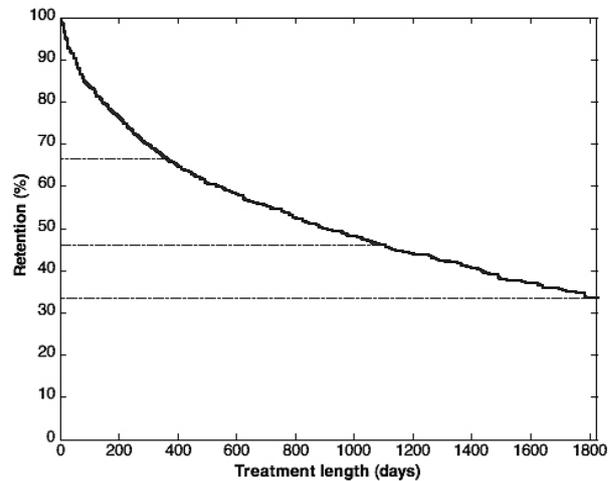
Retention was calculated from first to last visit in clinic. Patients who did not visit the clinic for two months were considered as dropouts from treatment. Patients whose last visit to the clinic was less than two months prior the end of the data collection were defined as right censored, since we do not know when their true last visit to the clinic occurred – it may either have been at the last registered visit or at any time after this visit. For the retention rate calculations, patients who were right censored prior to the defined time points were excluded from the analysis at that time point. This methodology was applied to the calculation of retention rate at the three specified time points (one year, three years or five years) as well as for each time point in the Kaplan Meier curve.

## RESULTS

During the years 2005-2012, 1,399 individuals approached the clinic; 1,224 of them attended the clinic at least twice (87.5%), treatment retention rates for these patients were

calculated as described in the Methods section. One year retention rate was 66.5%, three years retention rate was 46.1% and five years retention rate was 33.5%. The Kaplan Meier curve for retention in treatment is presented in Figure 1.

**Figure 1.** Kaplan Meier curve showing retention rate for all durations up to five years in patients who attended the clinic at least twice during the years 2005-2012. Horizontal dashed lines indicate treatment retention at one, three and five years.



## DISCUSSION

This retrospective evaluation presents findings from a naturalistic environment that allowed us to probe the therapeutic efficacy of buprenorphine. The clinic offers buprenorphine as the main focus of therapy in a community based opiate rehabilitation treatment clinic.

Our findings of 66.5 % treatment adherence at one year of treatment and 46.1% at three years of treatment are comparable to similar treatments models - Alford et al. (14) reported a 49 % treatment retention at one year in collaborative care of opioid-addicted patients in primary care using buprenorphine.

One year retention rates at methadone clinics in Israel are currently estimated at 75% (15).

Considering the devastating effects of opiate addiction on patients and their families, the increasing success rates of patients who are successfully treated with buprenorphine and are able to eventually return to their families and re-enter the workforce is encouraging.

Thus, the community based minimal intervention treatment model using buprenorphine for the treatment of opiate dependence is a viable treatment option in the war against opiate abuse.

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**References**

1. O'Connor PG. Methods of detoxification and their role in treating patients with opioid dependence. *JAMA* 2005;294:961-963.
2. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Sys Rev* 2008;(2):CD002207.
3. Torrens M, Fonseca F, Castillo C, Domingo-Salvany A. Methadone maintenance treatment in Spain: The success of a harm reduction approach. *Bull World Health Organ* 2013;91:136-41.
4. Van den Brink W, Haasen C. Evidenced-based treatment of opioid-dependent patients. *Can J Psychiatry* 2006 ;51:635-646.
5. Maremmani I, Pacini M, Pani PP, Popovic D, Romano A, Maremmani AG, Deltito J, Perugi G. Use of street methadone in Italian heroin addicts presenting for opioid agonist treatment. *J Addict Dis* 2009;28:382-388.
6. Drug Addiction Treatment Act of 2000 (DATA) <http://buprenorphine.samhsa.gov/fulllaw.html> . Accessed 22.5.13.
7. Working Party, National Medicines Information Centre, St. James's Hospital. Report to the National Advisory Committee on Drugs on "Use of Buprenorphine as an intervention in the treatment of Opiate Dependence Syndrome" St. James's Hospital, Dublin 8, 22nd March, 2002. Available at: <http://www.drugsandalcohol.ie/5253/1/1221-0964.pdf> Accessed May 1, 2013.
8. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363:2320-2231.
9. Hamza H, Bryson EO. Buprenorphine maintenance therapy in opioid-addicted health care professionals returning to clinical practice: A hidden controversy. *Mayo Clin Proc* 2012;87:260-267.
10. FDA. Subutex and Suboxone approved to treat opiate dependence T02-38, October 8, 2002, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191521.htm>. Accessed 20.5.13.
11. Nathan G. Treatment of addiction to hard drugs and alcohol in Israel. Research and Information Dept. Knesset, 20.12.2013, <http://www.knesset.gov.il/mmm/data/pdf/m03064.pdf> [Hebrew] Accessed 22.5.13.
12. Inter-office committee for the comprehensive treatment of drugs. Comprehensive blueprint for dealing with the problems of drug abuse in the State of Israel (Mann Committee Report), 1983, Jerusalem.
13. Israel Ministry of Health, Department of Treatment of Addictions. Procedures for buprenorphine (Subutex) treatment in approved facilities, Procedure no. 40.009, 2.4.2005.
14. Alford DP, LaBelle CT, Kretsch N, Bergeron A, Winter M, Botticelli M, Samet JH. Collaborative care of opioid-addicted patients in primary care using buprenorphine: Five-year experience. *Arch Intern Med* 2011;171:425-431.
15. Peles E, Schreiber S, Adelson M. 15-year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. *Drug Alcohol Depend* 2010;107:141-148.