Methadone and Buprenorphine for the Treatment of Opiate Addiction

Mahbobeh Firouzkouhi Moghaddam [a] | **Tayebeh Rakhshani** [b,*] | **Fariba Kadkhodaie** [a] | **Mostafa Rashki** [c]

[a] *Research Center for Health of Adolescents and Children, Zahedan University of Medical Sciences, Zahedan, Iran.*
[b] *Nutrition Research Center, School of Health, Shiraz University of Medical Science, Shiraz, Iran.*
[c] *Department of Public Health, Mashhad University of Medical Sciences, Mashhad, Iran.*

*Corresponding author: Tayebeh Rakhshani
Nutrition Research Center, School of Health, Shiraz University of Medical Science, Shiraz, Iran, 734411639.
Tell: +98-9196250473.
E-mail address: healthacademic2014@gmail.com

A R T I C L E   I N F O

A B S T R A C T

Background: The rate of drug dependence and abuse is a growing problem in the Iran, number of opioid – dependent people is estimated at a total of 2000.000-4000.000 individuals. The aim of this study was a Comparison of Methadone and Buprenorphine in the Treatment of Opiate Addiction referring to a treatment clinic of Baharan psychiatric hospital in Zahedan city.

Methods: In a cross sectional study, 152 patients with opioid dependence were assigned into two treatment groups i.e. Methadone and Buprenorphine. Data were collected from patients using a questionnaire COWS. ANOVA and repeated measures regressions were used to evaluate the significant differences on using drug (methadone and Buprenorphine), time, and drug-by-time interaction terms.

Results: Patients on MMT and BMT differed in terms of Age started addiction (P = 0.0001); education level (P = 0.0001); and income (P = 0.0001), and no differed in term of sex (P = 0.8). There was no significant difference between the two groups taking buprenorphine and methadone (P = 0.87).

Conclusion: In conclusion, our study indicated, Buprenorphine and methadone are both proven to be effective treatment options.

1. Introduction

Iran is a neighbor of Afghanistan (the major drug producer in Asia) and has the largest number of addicts in the world compared to its population. The number of opioid –dependent people in Iran is estimated at a total of 2000.000-4000.000 individuals [1, 2].

In Iran, addiction growth is three times as much as population growth. While the annual population growth is about 2.1 percent, addiction grows 8% a year. Thus, the number of addicts grows more than three times as much as the population growth annually [2]. In recent years, the rate of using psychoactive drugs, especially opiates, has increased in Iran and with the rapid growth of using drugs, a change in patterns of abuse from traditional (opium, heroin and cannabis) tochemical and industrial can also be seen [3,4]. Therefore, the young people's use of chemical and industrial drugs (psychedelic drugs, crack, crystal, glass, ecstasy, etc.) has increased [5].

The consumption of crystal and glass has replaced that of opium and heroin and they have become more common among young Iranians [6]. Reduction of the users' age, the change in consumption patterns, the diversity of drugs, affordable price as well as easy transportation of them, and the increasing tendency among users of crystal and glass have made a lot of problems for the society and families [5].

Given the growing incidence of addiction and drug abuse and dependence on them, it seems necessary to have effective treatments in order to treat and prevent the excessive use of drugs but it should be noted that the treatment is difficult, complex and multi-factorial [7,8].

Presently, three medications are accepted with the United States (US) Food and Drug Administration (FDA) for treating opioid dependence. Classified by their underlying mechanisms, these medications contain agonist (methadone), partial agonist (buprenorphine), and antagonist (naltrexone) agents [9].

Methadone

Methadone has been using in the treatment of drug addiction for years. This medication first entered the market in 1939 and it has been clinically shown that methadone reduces the dose of drug addiction by limiting side effects and, unlike other psychoactive drugs, taking methadone dose is without resistance. In other words, once the first dose of methadone is taken, addiction withdrawal symptoms will be gone and there will be no need to increase the dose in later uses [10,11]. In Methadone Detoxification method, methadone replaces the morphine which is joined to the receptors of cell surfaces. As a result, the morphine in the surface of body cells is gradually released into the blood and is replaced by methadone. The release morphine is analyzed by passing through the liver cycle and enters the intestine through the bile and goes out of the body by feces. Some morphine passes through the kidneys and is removed by urine [12].

Buprenorphine

Buprenorphine (Buprexin) with the chemical formula $C_{29}H_{41}NO_4$ is a semi-synthetic opioid derived from the baine which is itself obtained from Papaversomniferu. Buprenorphine (Buprexin) is a partial agonist. This means that, although Buprenorphine (Buprexin) is an opioid and consequently can cause the common complications of drugs and side effects such as respiratory depression and inebriety, its maximum effect is less than that of full agonists such as heroin and methadone. In low doses, Buprenorphine provides sufficient agonistic effects to enable the people addicted to drugs to stop drug abuse without withdrawal symptoms. Agonist effects of Buprenorphine increases linearly with the increase of medication dose, until a plateau (pan) is reached. Then, a further increase in dosage will not increase the effects. This is known as the ceiling effect. So, Buprenorphine has lower potential for the risk of drug abuse, drug addiction and side effects compared to full agonist drugs. In fact, Buprenorphine can block the effects of full agonists and thereby, cause extreme symptoms of withdrawal in a patient taking drugs. This is in fact the result of the high tendency of Buprenorphine (Buprexin) for opiate receptors. Buprenorphine has higher tendency to join opiate receptors compared to other opiates. This leads to overcoming other opiates and wining the competition for joining these receptors [13].

Treatment with using methadone has been the most treatment modality, and there is extensive evidence of its effectiveness [14,15]. Studies have also shown the effectiveness of buprenorphine as a maintenance medication [16]. Several comparisons of buprenorphine and methadone have been made, but buprenorphine in flexible doses was found to be less effective in retaining patients [17]. Finally buprenorphine and methadone both are effective treatments for treatment of Opiate Addiction.

According to what was said and taking into account the fact that today the use of glass and crystal has increased and they have devastating effects on the lives of individuals as well as society, the need for the treatment of this type of addiction and choosing the best and most effective method to treat them is felt. Since buprenorphine and methadone are used to treat the addiction to drugs, this study is an attempt to examine the influence of these two medications on the process of treating the people addicted to glass and crystal.

In general, it can be said that in addition to comparing the effects of these two medications on the treatment of those addicted to glass and crystal, this study is going to answer the following question: What is the effect of Buprenorphine and methadone on the treatment of the patients addicted to both glass and crystal referring to drug rehabilitation center of Baharan Psychiatric Hospital in Zahedan city?

Objective: A Comparison of Methadone and Buprenorphine in the Treatment of Opiate Addiction referring to the a treatment clinic of Baharan psychiatric hospital in Zahedan city.

2. Materials and Methods

2.1. Design and Setting

Between 20 April to 22 July 2016, a cross-sectional study was conducted at a treatment clinic of Baharan psychiatric hospital in Zahedan city in the east of Iran (an area with problematic abuse problem). All 152 abusers referring to the treatment clinic of Baharan were recruited in the study. After providing informed consent, participants were interviewed by questioners.

2.2. Participants

Participants were a combination of glass and crystal-dependent clients who were regular users (n = 152). The inclusion criteria for this study was a combination of glass and crystal as drug of choice, patients had to enter in METH or BUP maintenance treatment during the 4 weeks of 2016. Current opioid physical dependence (i.e., withdrawal symptoms), and no current abuse of oral opioid analgesics, were aged 18 years or older; lived within commuting, distance of the clinic; appeared mentally competent to give informed consent; and signed informed consent. The exclusion criteria included major mental illness (e.g., schizophrenia), significant medical problem (e.g., history of seizure or hypertension).

2.3. Measures

Data were collected from patients who received methadone and buprenorphine treatment during a 20 April to 22 July 2016 using a Clinical Opiate Withdrawal Scale (COWS) questionnaire. It is a clinician-administered, pen and paper instrument that rates eleven common opiate withdrawal signs or symptoms. The summed score of the eleven items can be used to assess a patient's level of opiate withdrawal and to make inferences about their level of physical dependence on opioids. Since development of the first opiate withdrawal scale in the mid-1930s, many different opioid withdrawal scales have been used in clinical and research settings. (PDF formatted versions of the COWS are also available from the websites of the American Society of Addiction Medicine, the California Society of Addiction Medicine, the UCLA Integrated Substance Abuse Programs, and Alcohol MD.com) [18].

2.4. Statistical Analysis

Statistical analysis were performed using SPSS for Windows (version 16.0, 2007; SPSS Inc., Chicago, IL, USA).

Mean scores and standard deviations were calculated for each time point in the methadone and challenge sessions. ANOVA for repeated measures regressions were used to evaluate the significant differences on using drug (methadone and buprenorphine), time, and drug-by-time interaction terms.

2.5. Ethical Considerations

The protocol of the study was approved by the Institutional Review Board of Zahedan University of Medical Sciences in Zahedan, Iran. Interviews were conducted individually and participants were assured of the confidentiality of interviews. An identification code was included on each questionnaire. Participants were ensured that non-participation in the study would not affect their.

3. Results and Discussion

3.1. Demographic Characteristics

152 participants who had entered for treatment participated in the study. 50% (n = 76) of the patients were on Methadone maintenance treatment (MMT), and the remaining 50% (n = 76) were on Buprenorphine maintenance treatment (BMT). The mean age of the participants were 27.01 years (range: $\geq$ 25 years). 82.9% were men and 15.1 % were female. 77.6 % were under diploma of education. Table 1 showed the baseline characterizes. Patients on MMT and BMT differed in terms of Age started addiction ($P = 0.0001$); education level ($P = 0.0001$); and income ($P = 0.0001$), and no differed in term of sex ($P = 0.8$).

The mean symptoms for those who took buprenorphine were 29.24 when starting the treatment and they were 4.33 at the end of the fourth week. The difference between the

beginning and end of the treatment were 24.908 units. Also the mean symptoms for those who took methadone were 27.25 when starting the treatment and they were 8.76 at the end of the fourth week. The difference between the beginning and end of the treatment were 18.487 units. The symptoms for the entire people changed from 28.24 to 6.55.

To determine the efficacy of buprenorphine and methadone in the treatment of drug addicts, both to crystal and glass, the ANOVA test (analysis of variance) with frequent measures was used. Given that $P < 0.05$, it might be concluded that completing the treatment course had a significant effect on the patients' symptoms; i.e. the average symptoms of the patients were significantly different within the 7-step test. Furthermore, the interactive effects of medication and time were also significant ($P < 0.05$).

To determine the difference between the symptoms over time, the Bonferroni procedure was used. The results showed that the symptoms had no significant difference only within the first and the fourth weeks ($P = 0.9$), but there was a significant difference within the other weeks ($P \leq 0.05$).

Table 3 shows the effect of the independent variable of the consumed medication on the dependent variable of time. Given the significant level of average symptoms within the seven-stage treatment, there was no significant difference between the two groups taking buprenorphine and methadone ($P = 0.87$).

Addiction can occur in every one and is often the outcome of taking additional than the prescribed opiate dose or obtain opiates illegally so that the users can experience desired effects such as analgesia or euphoria. As a result of the analgesia and euphoric effects, there is a high addiction possible for many persons, which is why opiate addiction and dependence is such a widespread problem [19]. As a distinct aspect of Iran's drug culture, co-use of a combination of glass and crystal is a newly emerged health problem in Iran, especially among young people. Considering this problem necessitates that effective treatment is developed to treat addiction thus the current study was conducted to determine the responses to BUP and METH in combination of glass and crystal dependent patients, in the 4 weeks of a maintenance treatment period in 2016. The study findings showed that participants were commonly young, and with low level of education, that these Findings are in contrast with an American study [20].

One of the most important aspect of opiate addiction treatment is the capability to keep patients in the treatment plan long enough to create a successful outcome. Decide the suitable treatment for a person with opioid addiction is a matter of physician discretion, taking into consideration the relevant medical standards and the characteristics of the individual patient [21].Requiring people to stop taking their addiction medications is counter-productive and increases the risk of relapse [22]. Because tolerance to opioids fades rapidly, one episode of opioid misuse after detoxification can result in life-threatening or deadly overdose [23]. Methadone is a very powerful medication. Incorrect prescription or misuse of it can be harmful or even fatal.

Table 1: Demographic characteristics of the participants (n = 152)

Variable		MMT%	BMT%	χ2, Z,t	*P* value
Sex	Female	78.1	90.8	0.23	0.8
	Male	21.9	9.2		
Age started addiction	≤ 25 years	22.4	29.7	71.2	0.0001
	25-35years	38.2	45.9		
	35-50 year	35.5	21.6		
	≥ 50 year	3.9	2.7		
Duration of addiction	≤ 5 years	36.8	26.3	44.9	0.0001
	5-10 years	32.9	36.8		
	10-15 year	10.5	13.2		
	15-20 year	10.5	9.2		
	≥ 50 year	9.2	14.5		
Education level	Diploma & under Diploma	73.3	90	151.1	0.0001
	Bachelor	18.7	7.1		
	PhD	8	2.9		
Income	≤15000000 Rills	43.1	32.9	47.2	0.0001
	15000000 - 25000000Rils	15.3	67.1		
	≥ 25000000Rils	41.7	0		

Table 2: Table of ANOVA for the impact of the independent variable of time and its interaction with the type of medication on the symptoms of the disease

Source		Type of sum of square	df	Mean square	f	*P* value
Time	Sphericity Assumed	59846.930	6	9974.488	462.613	< 0.001
	Greenhouse-Geisser	59846.930	3.090	19364.915	462.613	< 0.001
	Huynh-Feldt	59846.930	3.184	18796.410	462.613	< 0.001
	Lower-bound	59846.930	1.000	59846.930	462.613	< 0.001
Time Group	Sphericity Assumed	1532.295	6	255.383	11.845	< 0.001
	Greenhouse-Geisser	1532.295	3.090	495.811	11.845	< 0.001
	Huynh-Feldt	1532.295	3.184	481.255	11.845	< 0.001
	Lower-bound	1532.295	1.000	1532.295	11.845	0.001
Error(time)	Sphericity Assumed	19405.060	900	21.561		
	Greenhouse-Geisser	19405.060	463.572	41.860		
	Huynh-Feldt	19405.060	477.593	40.631		
	Lower-bound	19405.060	150.000	129.367		

Table 3: Results of the F test for the effect of the medication type independent variable on the symptoms

Source	Type of sum of square	df	Mean square	f	*P* value
Intercept	159372.635	1	159372.635	1110.289	< 0.001
Group	3.850	1	3.850	0.027	0.87
Error	21531.229	150	143.542		

Taking sufficient dose of Methadone can not only preserve security in a period of time, but also make the most effective response in patients. However, based on the complexity and function of methadone and the individual differences between patients, patient responses vary greatly.

Taking the doses of methadone should be determined based on the individuals' physical-psychological factors without limitations. Also, one should be careful to take to prevent the occurrence of adverse effects. But according to the results of a study conducted by Schottenfeld et al. (1997), higher daily BUP and MET maintenance doses versus lower doses appear to be more effective for reducing illicit opioid use [24].The results of our study indicated that methadone and buprenorphine were both effective in treating opioid dependence, both producing clinically and statistically significant reductions in illicit opioid use.

Numerous studies have shown that MET reduces illicit abuse, disease rates, and criminal activity among opioid addicted persons [25, 26]. Further, methadone maintenance therapy for opioid addiction has been shown to decrease the mortality and morbidity associated with illicit abuse. Also our study showed the effect of buprenorphine in treating opioid dependence that this funding is agreement with previous studies [27-31].

BUP is an option with an efficacy similar to MT, somewhat more expensive, but safer, with a better interaction profile, less stigmatized and with the possibility of being distributed by pharmacists once patients are released, which might enhance social reintegration. Due to all this, and especially because it features in the Social Security drug provision, it should be available for patients who request it and for whom healthcare professionals consider it more suitable regarding the patient's individual characteristics, as it currently occurs outside prisons [32].

Results of the current study showed that using buprenorphine and methadone to treat the addicts to both glass and crystal who referred to drug rehabilitation center of Baharan Psychiatric Hospital in Zahedan city had difference effects on the treatment process. The symptoms declined significantly in both groups in the end of the treatment period compared to the beginning of that, and the reduction was more for the users of buprenorphine than the users of methadone. This means despite more withdrawal symptoms at the start of treatment for users of buprenorphine, at the end of the period their symptoms were less than those of methadone users. There are several comparative studies confronting buprenorphine vs methadone, but their results are so metimes contradictory, for they include different doses, induction periods, etc. Originally, buprenorphine trials. Some studies comparing methadone and buprenorphine have not observed methadone to have superior retention compared to buprenorphine whereas others have found methadone to retain patients better [33, 34]. Where differences in retention have favored methadone, it is usually the case that the authors have attributed the poorer retention of buprenorphine maintained patients to one of two factors: slow induction onto buprenorphine or low maximum doses of that medication [35-37]. The difficulty to begin treatment with BUP in comparison with METH in high dependent patients and lower retention rate in BUP patients, as reported by Mattick et al. (2009), have suggested the need to induct patients more rapidly onto BUP than METH, and start treatment at a higher BUP dose, but also the opportunity to investigate other variables possibly influencing the effects of BUP in particular subsets of addicts was not excluded [17]. Finally we can say the decision between these two medications is a difficult one to make and many factors must be considered including their dosing schedule, side effects, risk of abuse and overdose, cost, and long term effects. Overall, both medications can be effective in reducing the rates of opiate addiction, but the choice of medication must be made as a collaborative effort between the provider and patient while considering all the above factors.

In short, both methadone and buprenorphine were appropriate for addiction treatment; nonetheless, one of the most important aspects of addiction withdrawal was the treatment success in preventing the disease returning. It is many years that Methadone has been known and used as a medication for treatment addiction. However, many studies showed that the use of buprenorphine was appropriate for addiction treatment. But choosing one of these medications depends on many factors such as age, sex, type of drug, duration of addiction and many other things. This study has several limitations including insufficient cooperation of some people in the distribution of questionnaires and collecting them, and the likelihood of false responses due to the fear of disclosure.

Compared with other drugs of abuse, opioid dependence benefits from a wider range of available pharmacological tools for treatment. In spite of this, the large majority of the 1 million heroin addicts and 2 to 3 million prescription opioid abusers are not receiving treatment, and those who enter often only seek detoxification, from which early relapse is the most common outcome. The most successful treatment is long-term maintenance on agonists such as methadone and buprenorphine, but a variety of obstacles, including government regulations, cost, availability, and stigma, combine to diminish their use. The death rate among heroin addicts is approximately 2% to 3% per year, significantly higher than among their age- and social-economically matched cohorts. In addition to dealing with the obstacles above, what is needed to decrease this are new approaches that deal with the brain changes produced by chronic dependence and could reverse the intracellular changes related to addiction and craving.

4. Conclusion

Opiate addiction is a serious and increasing global trouble and due to the immense impact of opiate addiction, all medical professionals require to be well-known with useful treatment options. It is important to recognize and utilize the most effective treatment options to prevent opiate overdoses and reduce the addiction rates. MT and buprenorphine are both adequate drugs for Treatment of Opiate Addiction. Much research has been conducted on these medications and both have verified to be useful, however each medication comes with its own risks and benefits.

The decision between these two medications is a difficult one to make and many factors must be considered including their dosing schedule, side effects, risk of abuse and overdose, cost, and long term effects. Overall, both medications can be effective in reducing the rates of opiate addiction, but the choice of medication must be made as a collaborative effort between the provider and patient while considering all the above factors. According to the results of the present study, improving the cognitive infrastructures of possible disorders for the risk of drug addictions, analyzing the effect of preserving treatments with Methadone and buprenorphine on the treatment of the addicts, creating the right knowledge and attitude toward health and disease among the public, and pushing towards behaviors that reduce the risk of addiction are suggested.

Authors' Contributions

M.F.M., and T.R., designed the study and wrote the manuscript; F.K., analyzed the data; M.R., editing the manuscript. All authors revised and approved the final manuscript.

Conflict of Interest

There is no conflict of interest.

References

1. AlamMehrjerdi Z, Abarashi Z, Mansoori S, Deylamizadeh A, SalehiFadardi J, Noroozi A, et al. Methamphetamine Use Among Iranian Heroin Kerack-Dependent Women: Implications for Treatment. *Int J High Risk Behav Addict*. 2013; 2(1): 15-21.

2. Sarami H, GHorbani M, Minoei M. Prevalence of Addiction in Iran Four Decades of Research. *Q J Res Addict*. 2013; 7(26): 29-52.

3. Nouri R, Sedighian A, Rafie H, Narengiha H, Sarrami , Baghestani A. Analysis of Trends in Abuse during the Past Two Decades [Research Project]. *Tehran: Soc Welf Rehabil Sci*; 2009.

4. United Nations Office on Drugs and Crime (UNODC). World Drug Report. *New York: UNODC*; 2013.

5. Doaaagoyan D, Habibzadeh A. Factors Affecting the Changing Patterns of abuse among Youth (Lighter Materials to Heavy Materials). *Quarterly knowledge Disciplinary*. 2012; 13(1): 106-33.

6. Jadidi M. A Review of Drug Dependence, Proceedings of the First International Conference of Applied Science to Improve Social Security. *Iran: Express Publications Gorgan Rahman;* 2008.

7. Rassool G. Addiction for Nurses. Chichester, West Sussex. London: *Wiley-Blackwell*; 2010.

8. Papadakis MA, McPhee SJ. Current Medical Diagnosis and Treatment. *New York: McGraw Hill*; 2014.

9. Tai B, Saxon AJ, Ling W. Medication-Assisted Therapy for Opioid Addiction. *J Food Drug Anal*. 2013; 21(4): S13-S 15.

10. Bart G. Maintenance Medication for Opiate Addiction: The Foundation of Recovery. *J Addict Dis*. 2012; 31(3): 207-25.

11. Crowley RA, Kirschner N. The Integration of Care for Mental Health, Substance Abuse, and Other Behavioral Health Conditions into Primary Care: Executive Summary of an American College of Physicians Position Paper. *Ann Intern Med*. 2015; 163(4): 298-9.

12. Peddicord AN, Bush C, Cruze C. A Comparison of Suboxone and Methadone in the Treatment of Opiate Addiction. *J Addict Res Ther*. 2015; 6: 248.

13. Mauger S, Fraser R, Gill K. Utilizing Buprenorphine–Naloxone to treat illicit and Prescription-opioid Dependence. *Neuropsychiatr Dis Treat*. 2014; 10: 587-98.

14. Clausen T, Anchersen K, Waal H. Mortality Prior to, During and after Opioid Maintenance Treatment (OMT): A National Prospective Cross-Registry Study. *Drug Alcohol Depend*. 2008; 94: 151–7.

15. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of Death During and after Opiate Substitution Treatment in Primary Care: Prospective Observational Study in UK General Practice Research Database. *BMJ*. 2010; 341: c5475.

16. Bell J, Byron G, Gibson A, Morris A. A Pilot Study of Buprenorphine-naloxone Combination Tablet (Suboxone) in Treatment of Opioid Dependence. *Drug Alcohol Review*. 2004; 23(3): 311–7.

17. Mattick RP, Breen C, Kimber J, Davoli M. Methadone Maintenance Therapy Versus no Opioid Replacement Therapy for Opioid Dependence. *Cochrane Database Syst Rev*. 2009; 3.

18. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003; 35(2): 253-9.

19. Papadakis MA, McPhee SJ. Current Medical Diagnosis and Treatment. *New York: McGraw Hill*; 2014.

20. Rawson RA, Marinelli-Casey P, Anglin MD, Dickow A, Frazier Y, Gallagher C, et al. A Multi-Site Comparison of Psychosocial Approaches for the Treatment of Methamphetamine Dependence. *Addict*. 2004; 99(6): 708-17.

21. Mee-Lee D, Shulman GD, Fishman MJ, Gastfriend DR, Miller MM, eds. The ASAM Criteria: Treatment Criteria for Addictive,

Substance-Related, and Co-Occurring Conditions. 3ʳᵈ ed. *Carson City*, *NV: The Change Companies*; 2013.

22. Day E, Strang J. Outpatient versus Inpatient Opioid Detoxification: A Randomized Controlled Trial. *J Subst AbuseTreat*. 2011; 40(1): 56-66.

23. Chalk M, Alanis-Hirsch K, Woodworth A, et al. FDA Approved Medications for the Treatment of Opiate Dependence: Literature Reviews on Effectiveness and Cost-Effectiveness. 2013. Available from: URL: http://www.asam.org/docs/advocacy/Implications-for-Opioid-Addiction-Treatment.

24. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs. Methadone Maintenance treatment for Concurrent Opioid Dependence and Cocaine Abuse. *Arch Gen Psychiatry*. 1997; 54(8): 713–20.

25. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among Regular or Dependent Users of Heroin and other Opioids: A Systematic Review and Meta-Analysis of Cohort Studies. *Addict*. 2011; 106(1): 32-51.

26. Mattick RP, Breen C, Kimber J, Davoli M. Methadone Maintenance Therapy Versus no Opioid Replacement Therapy for Opioid Dependence. *Cochrane Database Syst Rev*. 2009; 3.

27. Petitjean S, Stohler R, Deglon, JJ, Livoti S, Waldvogel D, Uehlinger C, et al. Double-blind Randomized Trial of Buprenorphine and Methadone in Opiate Dependence. *Drug Alcohol Depend*. 2001; 62(1): 97-104.

28. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A Comparison of Levomethadyl Acetate, Buprenorphine, and Methadone for Opioid Dependence. *N Engl J Med*. 2000; 343(2): 1290-97 .

29. Ling W, Amass L, Shoptaw S, Annon JJ, Hillhouse M, Babcock D, et al. A Multi-Center Randomized Trial of Buprenorphine-naloxone Versus Clonidine for Opioid Detoxification: Findings from the National Institute on Drug Abuse Clinical Trials Network. *Addict*. 2005; 100: 1090-100.

30. Pani PP, Maremmanim I, Pirastu R, Tagliamonte A, Gessa GL. Buprenorphine: A Controlled Clinical Trial in the Treatment of Opioid Dependence. *Drug Alcohol Depend*. 2000; 60(1): 39-50.

31. Marco A, Lopez-Burgos A, Garcia-Marcos L, Gallego C, Anton JJ, Errasti A. Is the Availability of Buprenorphine/naloxone Therapy for Opioid-Dependent Inmates a Necessity? *Rev Esp Sanid Penit*. 2013; 15: 105-13.

32. Johnson RE, Jaffe JH, Fudala PJ. A Controlledtrial of Buprenorphine Treatment for Opioid Dependence. *JAMA Clinical Challenge*.1992; 267(20): 2750-55.

33. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus Methadone in the Treatment of Opioid Dependent Cocaine Users. *Psychopharmacol*. 1994a; 116(4): 401–6.

34. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of Buprenorphine and Methadone in the Treatment of Opioid Dependence. *JAMA Psychiatry*. 1994b; 151: 1025-30.

35. Fischer G, Gombas W, Eder H, Jagsch R, Peternell A, Stuhlinger G, Pezawas L, Aschauer HN, Kasper S. Buprenorphine Versus Methadone Maintenance for the Treatment of Opioid Dependence. *Addict*. 1999; 94(9): 1337-47

36. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus Methadone Maintenance for Opioid Dependence. *J Nerv Ment Dis*. 1993; 181: 358-64.

37. Oliveto AH, Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Cocaine Use in Buprenorphine- vs. Methadone-Maintained. *Am J Addict*. 1994; 3: 43-8.