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Diversity of Providing Services to Patients Suffering from Addiction Disorders is a Harm Reduction Thought, but...

Nader Charkhgard [1,*], Aida Afghani [2], Shahram Naderi [3], Shima Zahirian Moghadam [4] and Peyman Rad [5]

[1]Department of Neurosciences and Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Neuroscience and Addiction Studies, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3]Tehran University of Medical Sciences, Tehran, Iran
[4]Medical Council of Iran, Tehran, Iran
[5]Aja University of Medical Sciences, Tehran, Iran

[*]*Corresponding author*: Department of Neurosciences and Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran. Email: ncharkhgard@alumnus.tums.ac.ir

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Abstract

The diversity of the portfolio of pharmaceutical and non-pharmacological services is an undeniable necessity; however, we must remember that the thinking of harm reduction should govern this process. If we only pay attention to the variety of drugs and their different forms, eventually the noble goal of harm reduction will suffer. In an article that Pedersen et al. prepared about the slow-release form of buprenorphine, there are structural and content problems that will be addressed in this article. This article criticizes the rapid change in the provision of harm reduction services and discusses the impact of structural changes in the provision of services and the location of service provision.

Keywords: Harm Reduction, Opioid, Treatment

1. Background

Addiction is a global phenomenon, and with the industrialization of human societies, the world has faced an increase in patients suffering from addiction disorders. A total of 16 million individuals worldwide suffer from opioid use disorder (1). Opium users in Iran in 2015 were about 2 million 5 hundred thousand individuals (2). Substance use and high-risk behaviors and groups at risk, such as sex workers, have a direct relationship; as a result, drug use disorders are one of the risk factors for diseases such as human immunodeficiency virus (HIV).

Researchers believe that substance use affects many aspects of the personal and social lives of patients and those around them (3). The evidence and studies show that the patterns of drug use are changing; for example, the use of cannabis in Iran is increasing sharply (4). Despite the change in consumption patterns in different societies, opioid consumption is still one of the main problems and challenges of the judicial and health systems, even in societies where opioids are not the main disease pattern (5, 6). Due to the huge influence of opioids on the judicial and healthcare systems, the effort to treat patients suffering from the use of opioids and the supply of new treatment methods is still of great importance (7). Moreover, despite the effectiveness of maintenance treatments in harm reduction, the concern of providing new solutions and changing pharmaceutical forms is considered an important challenge for researchers and even policymakers (6, 8).

In addition to all the problems it causes for the patient, addiction creates a social stigma for the patient and his/her family. The treatment system should always behave in such a way that the patient and his/her family are not exposed to this social stigma and, as much as possible, as a defensive factor, prevent the leakage of patient information. Reassuring the patient and his/her family will lead to the formation of a correct therapeutic relationship between the treatment system and the patients, and the result will be an increase in the effectiveness of the provided services (pharmacological and non-pharmacological) (9, 10).

Methadone is a liposoluble drug with a fundamental nature. When it is administered orally, it experiences rapid and nearly complete absorption. It is a lipophilic

substance that is extensively distributed among various tissues, including the brain, intestines, kidneys, liver, muscles, and lungs. Detection of methadone in the plasma can be accomplished 30 minutes after oral dosage, with a peak plasma concentration reached at approximately 2.5 hours for oral solution and 3 hours for tablets. The bioavailability of methadone is high, ranging from 67% to 95%. As an opioid agonist, it exhibits a long half-life of approximately 24 hours; however, there is significant variability among individuals, ranging from 8 to 90 hours. These pharmacokinetic properties result in the accumulation of methadone in tissues following repeated doses, thereby increasing the risk of overdose.

Methadone is metabolized in the liver and excreted by the kidneys. Normally, methadone and its metabolites are excreted in the urine (20 - 50%) and feces (10 - 45%). However, in cases of kidney failure, there is an increased excretion of both metabolic products and methadone itself in the feces to the extent that the entire drug can be eliminated. Consequently, methadone can be regarded as safe for patients with kidney failure who are undergoing dialysis. Although methadone can be detected in breast milk, the concentrations are theoretically harmless to infants. Furthermore, methadone can pass through the placental barrier; nevertheless, this route of administration can lead to withdrawal syndrome in neonates.

Methadone is an opioid agonist acting by binding to μ, κ, and δ opioid receptors (MOR, KOR, and DOR, respectively). Methadone's pharmacodynamic properties, such as analgesia, respiratory depression, dependence, and tolerance, are primarily triggered by MOR activation. An experimental study has shown that methadone is an opioid less sensitive to tolerance. Chronic opioid therapy might also produce opioid-induced hyperalgesia (OIH), which sensitizes patients or triggers acute pain episodes (11).

Buprenorphine, a derivative of the alkaloid thebaine found in the poppy plant, is a semi-synthetic opioid. Initially, it was created as one of several compounds derived from oripavine. During its early stages of development, it was observed that buprenorphine did not exhibit typical mu-opioid agonist behavior. Instead, it displayed the ability to both produce mu opioid action and block mu opioid effects, which led to its initial characterization as an opioid agonist-antagonist. Currently, it is understood that buprenorphine acts as a partial opioid agonist at the mu receptor, an antagonist at the kappa opioid receptor, and a partial agonist at the nociceptin/orphanin opioid-like receptor. The clinical relevance of buprenorphine's kappa antagonist and/or nociceptin/orphanin partial agonist activity remains uncertain, although there has been speculation on this matter. For instance, it has been hypothesized that buprenorphine, with its kappa antagonist actions, might produce euphoria as a secondary effect, potentially acting as an antidepressant to enhance mood (12). The duration of time until the highest concentration of a substance in the blood is reached after it is administered under the tongue can vary, ranging from 40 minutes to 3.5 hours.

Buprenorphine has a large distribution throughout the body and is strongly bound to proteins (96%). The amount of time it takes for half of the buprenorphine to be eliminated from the body is long, and there is a significant difference in reported values (with the average values ranging from 3 to 44 hours). The majority of a dose of buprenorphine is removed from the body through the feces, with approximately 10 - 30% being excreted in urine. Buprenorphine can pass through the placenta during pregnancy and enter breast milk. The dosage of buprenorphine does not need to be adjusted significantly for patients with impaired kidney function. It seems that the way buprenorphine and benzodiazepines interact is more likely to be a result of their combined effects (additive or synergistic) rather than their effects on the body's processes (pharmacokinetic). The correlation between the concentration of buprenorphine in the blood and the response to treatment for opioid dependence has not been thoroughly researched (13).

Methadone and buprenorphine are the two main drugs that have played a major role in the treatment and control of opioid use; however, the treatment method and different styles of drug delivery are still controversial issues. Sometimes, this scientific challenge turns into a controversy, and the question of this controversy is methadone or buprenorphine. This article examined the effects and effectiveness of methadone and buprenorphine and evaluated different methods of providing services to patients.

In a valuable article, Pedersen et al. pointed out the cost-effectiveness of the long-acting form of buprenorphine (14). The tremendous impact and great transformation of buprenorphine in the treatment of opiate addiction disorders cannot be ignored (15). However, there is no consensus regarding the cost-effectiveness of this form of agonist drug, and it might divert the goals of harm reduction from the right path.

The new approaches to harm reduction need to take into account the risk factors involved in addictive disorders, and along with that, the privacy of the patient and his/her family should also be considered. It is recognized that addiction and related disorders today are influenced by multifactorial factors. Environmental,

biological, genetic, hormonal (16), migration (17), and family factors all affect this disease (18).

However, apart from these approaches, sometimes there are questions and challenges for the continuation of harm reduction processes, and some of these challenges are even in areas, such as the continuation of treatment and the manner of this process. This article briefly examines some of the following questions:

1.1. Methadone (Full Agonist) or Buprenorphine (Partial Agonist), Which is More Effective?

Numerous studies have been conducted in this regard, and sometimes contradictory results have been obtained. Nevertheless, in a general view, to compare these two drugs, it must be acknowledged that in low doses of methadone and buprenorphine, the rate of persistence in treatment and non-slippage of patients treated with methadone is higher. However, in high doses of these two drugs, the same results of long-term treatment and non-slippage have been reported, and since it is practically not possible to keep patients treated with agonist drugs at a high fixed dose, it seems that methadone is effective in keeping the patient in the treatment process. Moreover, avoiding the use of drugs is significantly preferable (19).

Methadone is the first drug that has been approved for the treatment of opiate addiction and has been used since 1960 (20). Although methadone has a higher risk of overdose, in patients who take this drug under the supervision of a doctor, this risk is reduced. It decreases significantly, and most of the overdose cases are related to consumption outside the treatment network and not receiving the medicine from the doctor. In patients under medical supervision and treatment, the risk of overdose is very small (21). Even studies show that patients' access to the treatment system (centers that provide treatment and drug distribution services) reduces their mortality (22), and if compared to the risk of overdose and overdose of opiates, the risk of overdose in methadone can be ignored. Methadone has high safety in studies and laboratories to the extent that it is considered the treatment of choice for opioid addiction in pregnant women and is not a contraindication for breastfeeding (23, 24).

Compared to methadone, buprenorphine has a lower risk of causing respiratory depression and overdose (25). Other forms of buprenorphine (implantable implants and slow-release injectable form) theoretically increase treatment adherence; however, significant and valuable studies have not been conducted in this field. When comparing the abuse of methadone and buprenorphine, it should be remembered that the abuse of buprenorphine outside of therapeutic uses is much more than methadone (25), and it is abused in injectable and intranasal (intranasal) forms (26). The main concern of France, as one of the pioneers in the use of buprenorphine in the treatment of opiate-using patients, is still the abuse of buprenorphine and its non-medicinal forms (27, 28).

1.2. Drug Supply (Buprenorphine, Methadone, or Other Narcotics) in the Pharmacy?

Global experiences indicate the weight of the bottom of the scale in favor of the supply of narcotic drugs (agonist or partial agonist) in medical centers (29). Because methadone and buprenorphine are considered narcotic drugs by nature, they should be offered in controlled environments and after the patient's visit, and it might be necessary to change the dose in a patient visit with a fixed dose of several years (30), which requires the presence of a therapist in the place of supply; therefore, most of the countries that have taken agonistic treatments and harm reduction approaches do not supply these drugs in pharmacies (31). It is possible that the supply of medicine in a place other than medical centers, in addition to problems for drug-using patients, might cause the spread of drug addiction among other individuals in society who are not familiar with them. Similar to this issue happened in America after the introduction of oxycodone in pharmacies (32); individuals say that they started using narcotics with the experience of oxycodone, and it turned narcotics into the first substance consumed in America after many years (33). In addition, the provision of narcotic drugs in the pharmacy removes individuals from the cycle of non-pharmacological interventions to a great extent.

1.3. Slow-Release Forms of Buprenorphine?

There are two major formulations and forms for the slow-release form of buprenorphine:

- Subcutaneous implants

This form should be placed under the skin through a small skin incision and removed from the skin after 6 months through another incision. The duration of using this type of medicine is two periods of 6 months, after which the patient should be shifted to the sublingual style of medicine, and even in some cases, the patient might need a sublingual dose while using the implant. In some studies, the problems of this type of treatment (e.g., local pain, bleeding, and itching) have caused a quarter of patients not to want to continue the treatment.

- Injectable form

It is used in different forms that last between 1 week and 6 months. As the pioneer of this type of treatment, the French Pharmaceutical Agency has, up to now, remained silent on the distribution and treatment of patients and has not commented. In the use of injectable drug forms, patients drop out after several injections.

Another drawback of slow-release forms is their long-term effect on the patient's body, and if the patient needs to receive opioids (in emergency situations such as myocardial infarction), many problems and even life-threatening problems occur. Numerous researchers and therapists emphasize the use of this form in completely controlled conditions, such as patients hospitalized in Biaristan or patients living in centers, such as prisons, and they do not consider this form of medicine suitable for general distribution in society (34). This same and constant dose of the drug causes an increase in the dose of the drug in patients with a low dose and discomfort in patients who need higher doses. Regarding complications and problems and adherence to treatment in injectable forms, few studies have been conducted, and it is difficult to comment on them.

With the expansion of harm reduction approaches, today's world needs a change in its harm reduction thinking (35), and the type of medicine, especially the long-acting types, can be a kind of deprivation of human rights for patients and endangering their physical conditions.

Footnotes

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References

1. Azadfard M, Huecker MR, Leaming JM. Opioid addiction. *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC; 2023.
2. Noorbala AA, Saljoughian A, Bagheri Yazdi SA, Faghihzadeh E, Farahzadi MH, Kamali K, et al. Evaluation of drug and alcohol abuse in people aged 15 years and older in Iran. *Iran J Public Health*. 2020;**49**(10):1940–6. [PubMed ID: 33346232]. [PubMed Central ID: PMC7719666]. https://doi.org/10.18502/ijph.v49i10.4697.
3. Zareie B, Rasouli MA, Gouya MM, Akbarpour S, Hadavandsiri F, Rezaei E, et al. Drug use patterns and related factors among female sex workers in Iran in 2019-2020: results from Integrated Bio-Behavioral Surveillance-III (IBBS-III). *Arch Public Health*. 2023;**81**(1):120. [PubMed ID: 37391840]. [PubMed Central ID: PMC10311839]. https://doi.org/10.1186/s13690-023-01143-x.
4. Rostam-Abadi Y, Gholami J, Amin-Esmaeili M, Baheshmat S, Hamzehzadeh M, Rafiemanesh H, et al. Evidence for an increase in cannabis use in Iran - A systematic review and trend analysis. *PLoS One*. 2021;**16**(8). e0256563. [PubMed ID: 34460847]. [PubMed Central ID: PMC8404985]. https://doi.org/10.1371/journal.pone.0256563.
5. Whelan PJ, Remski K. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *J Neurosci Rural Pract*. 2012;**3**(1):45–50. [PubMed ID: 22346191]. [PubMed Central ID: PMC3271614]. https://doi.org/10.4103/0976-3147.91934.
6. Kim EJ, Hwang EJ, Yoo YM, Kim KH. Prevention, diagnosis, and treatment of opioid use disorder under the supervision of opioid stewardship programs: it's time to act now. *Korean J Pain*. 2022;**35**(4):361–82. [PubMed ID: 36175336]. [PubMed Central ID: PMC9530691]. https://doi.org/10.3344/kjp.2022.35.4.361.
7. Das A, Sharma A, Kothari N, Goyal S. Are we ready to manage an opioid epidemic in the intensive care unit? *Anaesthesiol Intensive Ther*. 2022;**54**(3):271–8. [PubMed ID: 36062420]. [PubMed Central ID: PMC10156511]. https://doi.org/10.5114/ait.2022.118881.
8. Tabanelli R, Brogi S, Calderone V. Targeting opioid receptors in addiction and drug withdrawal: Where are we going? *Int J Mol Sci*. 2023;**24**(13). [PubMed ID: 37446064]. [PubMed Central ID: PMC10341731]. https://doi.org/10.3390/ijms241310888.
9. Vanyukov MM. Stigmata that are desired: contradictions in addiction. *Addict Res Theory*. 2023:1–10. https://doi.org/10.1080/16066359.2023.2238603.
10. Liahaugen Flensburg O, Richert T, Väfors Fritz M. Parents of adult children with drug addiction dealing with shame and courtesy stigma. *Drugs: Educ Prev Policy*. 2022;**30**(6):563–72. https://doi.org/10.1080/09687637.2022.2099249.
11. Barbosa Neto JO, Garcia MA, Garcia JBS. Revisiting methadone: Pharmacokinetics, pharmacodynamics and clinical indication. *Revista Dor*. 2015;**16**(1). https://doi.org/10.5935/1806-0013.20150012.
12. Walsh SL, Middleton LS. Buprenorphine pharmacodynamics and pharmacokinetics. *Handbook of Methadone Prescribing and Buprenorphine Therapy*. Springer; 2013. p. 163–81. https://doi.org/10.1007/978-1-4614-6974-2_12.
13. Elkader A, Sproule B. Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet*. 2005;**44**(7):661–80. [PubMed ID: 15966752]. https://doi.org/10.2165/00003088-200544070-00001.
14. Pedersen MH, Dano A, Gibbons C, Jensen R. Administration and patient-incurred costs associated with opioid agonist treatment in Norway. *Curr Med Res Opin*. 2022;**38**(11):1959–65. [PubMed ID: 36172758]. https://doi.org/10.1080/03007995.2022.2129230.
15. Cawley J, Dragone D. Harm reduction: When does it improve health, and when does it backfire? *Natl Bur Econ Res*. 2023:1–38. https://doi.org/10.3386/w30926.
16. Charkhgard N, Zahmatkesh M, Vousooghi N, Farahmandfar M, Torkaman-Boutorabi A. Effect of testosterone on the extinction period of morphine-induced CPP in male rats. *Arch Neurosci*. 2022;**9**(2). https://doi.org/10.5812/ans-127059.
17. Saleh EA, Klapprott F, Heinz A, Kluge U. Challenges in substance use treatment as perceived by professionals and Arabic-speaking refugees in Germany. *Subst Abuse Treat Prev Policy*. 2023;**18**(1):69. [PubMed ID: 37978534]. [PubMed Central ID: PMC10656940]. https://doi.org/10.1186/s13011-023-00576-5.
18. Medina-Martinez J, Alino M, Vazquez-Martinez A, Villanueva-Blasco VJ, Cano-Lopez I. Risk and protective factors associated with drug use in healthcare professionals: A systematic review. *J Psychoactive Drugs*. 2023:1–15. [PubMed ID: 37341709]. https://doi.org/10.1080/02791072.2023.2227173.

19. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;**2014**(2). CD002207. [PubMed ID: 24500948]. [PubMed Central ID: PMC10617756]. https://doi.org/10.1002/14651858.CD002207.pub4.
20. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *JAMA*. 1965;**193**:646–50. [PubMed ID: 14321530]. https://doi.org/10.1001/jama.1965.03090080008002.
21. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;**357**:j1550. [PubMed ID: 28446428]. [PubMed Central ID: PMC5421454]. https://doi.org/10.1136/bmj.j1550.
22. Corace K, Thavorn K, Suschinsky K, Willows M, Leece P, Kahan M, et al. Rapid access addiction medicine clinics for people with problematic opioid use. *JAMA Netw Open*. 2023;**6**(11). e2344528. [PubMed ID: 37991762]. [PubMed Central ID: PMC10665968]. https://doi.org/10.1001/jamanetworkopen.2023.44528.
23. Bethesda. Methadone. *Drugs and Lactation Database (LactMed®)*. National Institute of Child Health and Human Development; 2006.
24. Facher L. *Top US addiction researcher calls for broad deregulation of methadone*. STAT; 2022. Available from: https://www.statnews.com/2022/11/16/nora-volkow-nida-broad-deregulation-methadone/.
25. Zamani N, Buckley NA, Hassanian-Moghaddam H. Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial. *Crit Care*. 2020;**24**(1):44. [PubMed ID: 32033582]. [PubMed Central ID: PMC7006192]. https://doi.org/10.1186/s13054-020-2740-y.
26. Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. *J Addict Med*. 2014;**8**(5):315–26. [PubMed ID: 25221984]. [PubMed Central ID: PMC4177012]. https://doi.org/10.1097/ADM.0000000000000045.
27. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol*. 1998;**22**(6):430–4. [PubMed ID: 9788517]. https://doi.org/10.1093/jat/22.6.430.
28. Mariottini C, Kriikku P, Ojanpera I. Investigation of buprenorphine-related deaths using urinary metabolite concentrations. *Drug Test Anal*. 2022;**14**(10):1696–702. [PubMed ID: 35834288]. [PubMed Central ID: PMC9796430]. https://doi.org/10.1002/dta.3347.
29. Busch AB, Kennedy-Hendricks A, Schilling C, Stuart EA, Hollander M, Meiselbach MK, et al. Measurement approaches to estimating methadone continuity in opioid use disorder care. *Med Care*. 2023;**61**(5):314–20. [PubMed ID: 36917776]. [PubMed Central ID: PMC10377507]. https://doi.org/10.1097/MLR.0000000000001838.
30. Furst JA, Mynarski NJ, McCall KL, Piper BJ. Pronounced regional disparities in united states methadone distribution. *Ann Pharmacother*. 2022;**56**(3):271–9. [PubMed ID: 34184584]. https://doi.org/10.1177/10600280211028262.
31. Wong NS, Lee SS, Lin H. Assessing the spatial distribution of methadone clinic clients and their access to treatment. *Harm Reduct J*. 2010;**7**:14. [PubMed ID: 20602756]. [PubMed Central ID: PMC2908587]. https://doi.org/10.1186/1477-7517-7-14.
32. Janssen A, Zhang X. Retail pharmacies and drug diversion during the opioid epidemic. *Am Econ Rev*. 2023;**113**(1):1–33. https://doi.org/10.1257/aer.20210357.
33. Sim Y. The effect of opioids on crime: Evidence from the introduction of OxyContin. *Int Rev Law Econ*. 2023;**74**. https://doi.org/10.1016/j.irle.2023.106136.
34. Chappuy M, Trojak B, Nubukpo P, Bachellier J, Bendimerad P, Brousse G, et al. Prolonged-release buprenorphine formulations: Perspectives for clinical practice. *Therapie*. 2020;**75**(5):397–406. [PubMed ID: 32499082]. https://doi.org/10.1016/j.therap.2020.05.007.
35. Naderi S, Charkhgard N, Rad P, Jafari S, Niknejad S. Changing harm reduction approaches is not a choice; it is necessary to survive. *Int J High Risk Behav Addict*. 2023;**12**(3). https://doi.org/10.5812/ijhrba-139609.