

A New Protocol of Methamphetamine Dependence Treatment with Taper-Up-Off Treatment of Opium Tincture, a New Hope to Cure the Methamphetamine Addiction

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Abstract

Methamphetamine is a neurotoxic drug and highly addictive stimulant, which causes a significant psychological dependence in use disorder and potential brain damage even in the first use disorder. Despite decades of research, no approved pharmacotherapy is available for methamphetamine (METH) use disorder, and behavioral therapies are faced with a great lack of long-term recovery and a high rate of relapse. Opium tincture is air-dried Papaver somniferum latex, formulated for oral administration. The present study aimed to evaluate the effectiveness of the new protocol for taper up-off method of opium tincture used for treatment of methamphetamine addiction in Iran, for more than 10 years.

In the present study, the effectiveness of the Opium tincture taper-up-off treatment method for methamphetamine dependence called "Dezhakam step time (DST) for methamphetamine" was assessed. We used data collected via the "Congress 60" a non-governmental organization in Iran, dedicated to addiction treatment with the DST method, from Jan 2018 until December 2020. We evaluated the treatment safety, success, and relapse rate in methamphetamine dependents treated in the "Congress 60" organization with the DST for methamphetamine method. All subjects were tested using Urine drug monitoring for both opioid and methamphetamine use after the treatment period and during the next two years as a follow-up. Findings revealed 89 percent of successful treatments for methamphetamine dependence and only 11 percent of substance abuse relapses in two years follow up. Also, less than one percent of the subjects that finished the treatment program abused opioids in two years follow up.

Findings suggest the safety and effectiveness of the Opium tincture taper-up-off method in the treatment of methamphetamine dependence. The findings of the study may help to a better understanding of a safe potential novel method for methamphetamine dependence treatment and its effects on psychological dependence on psychostimulants.

Key Words: Taper-Up-Off Treatment, Opium Tincture, Methamphetamine, Congress 60

1. Introduction

Methamphetamine is a synthetic stimulant with high psychological dependence which affects numerous pathways in different organs, especially both dopamine transmission and dopamine reuptake mechanisms [1]. While the specific molecular pathways of methamphetamine effects remain obscure, basal efflux that leads to dysregulation of dopamine release and dopamine-related behaviors is a proven effect of Methamphetamine abuse [2].

Addiction is a severe psychiatric disease that is responsible for

about 13% of deaths worldwide [3]. While methamphetamine is widely abused across the world, methamphetamine accounts for less than ten percent of total withdrawal treatment presentations [4]. In addition, withdrawal treatment accounts for about 13% of methamphetamine treatment accessed, and treatment completion is less than 50% which is the lowest rate of all drugs [5]. These huge failure in methamphetamine withdrawal treatment could be related to the lack of knowledge about the nature of methamphetamine dependence and the needs of methamphetamine users [6].

Previous established treatment for methamphetamine use disorders is effective only for reduction and cessation of use and harm reduction [7]. Given the recent increase in methamphetamine use worldwide, lack of effective treatment for methamphetamine-dependent individuals is a great global health concern [8]. At present, few limited options exist for psychosocial interventions of individuals seeking treatment for methamphetamine use disorder. While twelve-Step programs, like Narcotics Anonymous, is almost only intervention available for individuals with methamphetamine use there is a huge lack of evidence to support the efficacy of these programs [9]. While Mirtazapine and methylphenidate have modest effect for reduction of methamphetamine use, light and heavy methamphetamine users seem to respond differently to pharmacotherapy that shows heterogeneity of the nature of the methamphetamine dependence in response to pharmaceuticals [10]. Bupropion is an opium based aminoketone class medicine which has been approved both as an antidepressant and as a smoking cessation drug [11]. Studies' results regarding Bupropion efficacy to achieve methamphetamine abstinence in dependent seem to be controversial. Some studies suggest that Bupropion and placebo groups did not differ significantly in the percentage achieving abstinence in short time treatment periods [12]. Other data indicate that bupropion was effective for increasing the number of weeks of abstinence in male subjects with low or moderate level of methamphetamine use [13].

Opium tincture (OT) or Laudanum is a hydroalcoholic preparation of opium with Morphine as the main ingredient that "C17H19NO3" is its chemical formula. Opium tincture has been used for treating of chronic pains, diarrhoea etc. Using OT for treatment of opioid dependence as maintenance treatment was previously used in several countries but a successful protocol for gradual dose reduction combined that can lead to total abstentions of opium was missing [14]. In 1998, Dezhakam and colleagues in a NGO called congress 60 started a new taper off method using opium tincture for treatment of opium addiction which has been called Dezhakam step time (DST) [15].

1.1. Dezhakam Step Time (DST) Method For Opium Addiction

Opium and opioid compounds are the most prevalent class of addictive substances worldwide which affect the nervous system as well as euphoric and pain relief effects. Opioid compounds dependence can cause compulsive behavior and constant craving to use opioid drugs [3]. In the last two decades a nongovernmental organization in the Islamic Republic of Iran called "congress 60", established a treatment for opium addiction using taper off of opium tincture associated with a package of comprehensive psychological treatments, group classes, social caring, and harm reduction methods for patients and their family members. Opium addicts once opium dependents became members of "congress 60" and start the treatment, they do not take any medication besides opium tincture (OT). Opium dependents that are under Dezhakam step time (DST) in "congress 60" are called passengers. During the twelve months, opium dependents will reduce the dosage

of OT use step by step that each step takes 21 days. During the DST treatment, passengers will participate in classes and group training and events of congress 60 such as sports training, passing the courses about the reason of human tendency to addiction, and cognitive-behavioral therapies for some cases. Expected time for DST method for passengers with opium addiction is twelve months and it is supposed that the passengers leave opium abuse completely after this period of time. Since 1998, about 50000 Iranian individuals with opium dependence were successfully finished the 12 months of treatments with DST method in congress 60 and cut the opium abuse until now. Five years follow-up of persons who cut the opium abuse with DST method for opium addiction, showed a very low relapse [16].

1.2. Dezhakam Step Time (DST) Method For Methamphetamine Addiction

Successfulness of DST method for treatment of opium addiction in one hand, and potential efficacy of Bupropion as an opioid based medication to increasing the period of abstinence in methamphetamine-dependent patients on the other hand, raised a question about the possibility of using DST method and opium tincture for treatment of methamphetamine addiction [17]. There were two major issues regarding using DST method/ opium tincture for methamphetamine addiction treatment, first how to replace the methamphetamine with opium tincture and second how to avoid abuse or dependence of opium tincture or other opium based compounds after the treatment period. For these reasons the designed protocol for "DST for methamphetamine" was including two level, taper up and taper off. Both level would take 12 months and separated in 21 days periods. In taper up period methamphetamine dependent subject cut the methamphetamine abuse and start taking opium tincture orally. The opium tincture dosage increase in each 21 days step until reach the maximum dosage after twelve months or 17th steps. Then taper off period would be start and during next 12 months the opium tincture dosage will be reduced in each 21 days step until complete termination of usage. Given all together whole period of protocol for "DST for methamphetamine" will take 24 months or two years of time. No methamphetamine abuse is allowed during the 24 months of treatment and it is expected that after the treatment, treated individuals will terminate the methamphetamine abuse completely and also do not abuse opium tincture or any other opioid based compound.

The present study is the report of the effectiveness of the new method for methamphetamine addiction treatment with taper up-off treatment of opium tincture, by evaluating of two clinical parameters, successfulness of treatment and relapse rate.

2. Material and Methods

2.1. Subjects Recruitments for Cohort Study

Two years follow-up of 3972 methamphetamine dependents who registered for Dezhakam step time (DST) for methamphetamine with taper up-off of opium tincture in 61 out of 100 branches of congress 60 around Iran reported in present study. Individuals with

any sever psychological or somatic disorders have been excluded from the study. None of the subjects had a current or history of any severe medical condition, neurological disorder, and history of head trauma with loss of consciousness, and any other drug abuse history rather than methamphetamine. Efficacy to achieve methamphetamine abstinence tested with Methamphetamine use monitoring in all subjects that finished the treatment right after the

treatment and two years later for follow- up test. All subjects have explained about the aim of the study and next, written informed consent has been provided based on Helsinki Declaration ethical principles Medical research involving human subjects. The studies' proposal and all processes of study have been approved by the central ethical committee of Islamic Azad University. Clinical and demographic data of participants were presented in table 1.

GROUP	Age (year)	Gender	Marital status	Duration of addiction before registration to Congress60 (year)
Cohort group	30.6±6.7	Male: 2912 Female: 1060	Married: 2186 Single: 1786	5.7±3.2

Table 1: Demographic data of participants

2.2. Methamphetamine use Monitoring and Self-Report Analysis

The urinary [d-MA-d0]: [l-MA-d3] provides a quantitative, continuous measure of illicit MA exposure. Immunoassay screening conducted with enzyme immunoassay (EIA) using DRIR Amphetamines EIA reagents (Diagnostic Reagents, Inc., Sunnyvale, CA.), with a cut-off concentration of 500 ng/mL. Then, combined gas chromatography (GC)-MS, using dl-MA-d9 for internal standard were used to measurement of d-MA-d0 and l-MA-d3 in urine samples. Based on the previous studies, the accuracy for the measurement of MA-d0 and MA-d3 in urine ranged from 100 to 109%, respectively, at the 5 ng/ml limit of quantitation, and higher [18]. Qualitative urinalysis is the golden standard for verification of abstinence or relapse of drug drugs misuse. Based on the previous studies, results in drugs with slow elimination, such as methamphetamine (MA), may contain false negative and a single episode of abuse can result in up to 5 days of positive urine drug screens [19]. Given that, any self-reports of misuse during last two years were considered as relapse as well. All Methamphetamine use monitoring were conducted based on previous studies [20,21].

2.3. Urine Drug Monitoring for Opium

To analysis of safety of the treatment method, urine drug monitoring conducted for all participants in two separate periods. First period of testing was after the termination of treatment period and second period was 12 months after the treatment as follow-up approach to measure the rate of any abuse of opium tincture or any other opium based drugs. Immunoassay and chromatography (GC-MS, gas chromatography–mass spectrometry) performed for each period. Opiate panel for opium alkaloids and/or their metabolites, including morphine and codeine had been tested. Participants gave

a minimum of 30 mL of urine collected in a private restroom. Validity testing of urine specimens including temperature (33-36 Celsius), specific gravity (1.002-1.03), pH (4.5-7), urine creatinine (20-400 mg/dL), and presence of adulterants were conducted. Specimen outside of the physiological range was exclusion criteria. The opiate test cut off line has set for 2000 ng/ml and any subject with higher opiate rate in first or second testing period in any of chromatography or immunoassay considered as opium abuser. Results checked with self-report of subjects as well. Urine opium monitoring conducted based on the standard protocols and previous studies [22].

2.4. Statistical Analysis

Kolmogorov-Smirnov test used to evaluation of normal distribution of continuous variables. One-way ANOVA analysis used for testing the relationship between the two independent variables. Descriptive data are expressed as mean ± SD (range) and the level of statistical significance was set at P < 0.01. Multiple comparison examinations evaluated with Bonferroni correction test. SPSS version 23 software used for statistical examinations.

3. Results

3.1. Evaluation of Successfulness and Relapse Rate

SPR-based immunoassay and the conventional gas chromatography-mass spectrometry method used for methamphetamine determination, and results showed 3375 individuals out of 3972 subjects were completed the DST period and cleared from methamphetamine abused. Also 369 out of 3375 individuals that were completed the DST period showed relapse during the period of two years follow up. Statistical data of immunoassay and chromatography of methamphetamine detection presented in table 2.

Testing period	Immunoassay subject with negative result Vs. subject with positive results	Chromatography subject with negative result Vs. subject with positive results
First time (day after treatment)	P : 0.002	P : 0.002
Second time (12 months after treatment)	P : 0.006	P : 0.007

Table 2: Urine drug monitoring data of subjects for methamphetamine

3.2. Evaluation of Opium Abuse Rate

Only 12 individuals out of 3375 subjects were self-reported the abuse of opium after the treatment. Self-reports were confirmed in immunoassay and chromatography. Statistical results of both

immunoassay and chromatography (GC-MS, gas chromatography–mass spectrometry) of the opiate panel for opium alkaloids and/or their metabolites in all period of analysis presented in table 3.

Testing period	Immunoassay subject with negative result Vs. subject with positive results	Chromatography subject with negative result Vs. subject with positive results
First time (day after treatment)	P : 0.0001	P : 0.0001
Second time (12 months after treatment)	P : 0.0001	P : 0.0001

Table 3: Urine Drug Monitoring Data of Subjects for Opium

4. Discussion

The DST method had been providing an effective steps each including 21 days period which has successfully led opium dependents to taper off and leave the opioid abuse with a low rate of relapse or craving behavior on opium. On the other hand DST method for opium addiction were known for better psychological and cognitive improvement compared to methods including sudden leave of opioid abuse. The main difference between DST methods for methamphetamine addiction versus opium addiction is that for opium addiction substantial decreases in drug use would lead to achieve complete abstinence but for methamphetamine addiction due to the nature of methamphetamine effect on reward system, methamphetamine abuse should be terminated and completely replaced with opium tincture. An effective DST method for methamphetamine addiction is based on successfulness in two phases. First phase is the replacement of methamphetamine psychological dependence with physiological and psychological dependence to opium tincture and cut the methamphetamine abuse; and the second phase is the safe reduction of the opium tincture dosage until complete termination of usage along with termination of psychological dependence and craving to any opium based compound. Findings of present study suggest that both phases reached their goals in most of the individuals.

Addiction is a multifactorial complex behavioral with numerous involved parameters such as psychological, social, neurobiological, genetic and epigenetic issues [23]. Several physiological and psychological mechanisms were found associated to addiction which most of these pathways are strongly related to dopamine signaling and reward system [24]. Previous studies suggest that a single pharmacotherapeutic approach have a low chance for effectiveness for the different heterogeneous methamphetamine dependent population [25]. Several studies confirmed the similarities of neurobiological mechanisms involved in methamphetamine and opium in brain that could explain the effectiveness of replacement of methamphetamine with opium; but it seems that this replacement can only achieved by opium itself not opioid based compounds such as Bupropion [26]. Disappointing findings in different pharmacotherapeutic categories from antidepressant to cognitive enhancer and cholinesterase inhibitor could be associated to the

significant psychological dependence that methamphetamine can establish especially in heavy users. It seems that the long period of treatment and replacement of one dependence to another less addictive dependence are playing the key roles to achieving better treatment outcomes of DST for methamphetamine compared with other pharmacotherapy that has been used for methamphetamine addiction so far.

While standardizing procedures for methamphetamine addiction is controversial, comparison of DST method with other methods regarding sample size and relapse rate revealed in follow up results deserves further consideration to achieve clinically relevant conclusions. Findings suggest that DST as a package of psychological caring, group educations similar to cognitive behavioral therapy along with the opium tincture taper up-off could be a reliable treatment for methamphetamine addiction.

5. Conclusion

The present study was a two years follow-up of a new pharmacotherapy method for the treatment of methamphetamine addiction with opium tincture. We examined the successfulness rate, relapse rate and opium abuse rate of methamphetamine dependents during and after the treatment to evaluation of effectiveness and safety of treatment method. It seems that using opium tincture with DST method is a potential hope for a safe and successful method for dependence treatment and complete abstain of methamphetamine.

Declarations

Ethical statement: The studies' proposal and all processes of study have been approved by the central ethical committee of Islamic Azad University.

Conflict of Interest

The authors declare no competing interests.

References

1. Ares-Santos, S., Granado, N., & Moratalla, R. (2013). The role of dopamine receptors in the neurotoxicity of methamphetamine. *Journal of internal medicine*, 273(5), 437-

- 453.
2. Hedges, D. M., O'Bray, J. D., Yorgason, J. T., Jang, E. Y., Weerasekara, V. K., Uys, J. D., ... & Steffensen, S. C. (2018). Methamphetamine induces dopamine release in the nucleus accumbens through a sigma receptor-mediated pathway. *Neuropsychopharmacology*, 43(6), 1405-1414.
 3. Koob, G. F. (2020). Neurobiology of opioid addiction: opponent process, hyperkatifeia, and negative reinforcement. *Biological psychiatry*, 87(1), 44-53.
 4. Madden, A., Lea, T., Bath, N., & Winstock, A. R. (2008). Satisfaction guaranteed? What clients on methadone and buprenorphine think about their treatment. *Drug and Alcohol Review*, 27(6), 671-678.
 5. Courtney, K. E., & Ray, L. A. (2014). Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and alcohol dependence*, 143, 11-21.
 6. Pennay, A. E., & Lee, N. K. (2009). Barriers to methamphetamine withdrawal treatment in Australia: findings from a survey of AOD service providers. *Drug and alcohol review*, 28(6), 636-640.
 7. Meade, C. S., Towe, S. L., Watt, M. H., Lion, R. R., Myers, B., Skinner, D., ... & Pieterse, D. (2015). Addiction and treatment experiences among active methamphetamine users recruited from a township community in Cape Town, South Africa: A mixed-methods study. *Drug and alcohol dependence*, 152, 79-86.
 8. Cumming, C., Troeung, L., Young, J. T., Keltly, E., & Preen, D. B. (2016). Barriers to accessing methamphetamine treatment: a systematic review and meta-analysis. *Drug and alcohol dependence*, 168, 263-273.
 9. Galanter, M., Dermatis, H., Post, S., & Santucci, C. (2013). Abstinence from drugs of abuse in community-based members of Narcotics Anonymous. *Journal of studies on alcohol and drugs*, 74(2), 349-352.
 10. Soares, E., & Pereira, F. C. (2019). Pharmacotherapeutic strategies for methamphetamine use disorder: mind the subgroups. *Expert Opinion on Pharmacotherapy*, 20(18), 2273-2293.
 11. Shoptaw, S., Heinzerling, K. G., Rotheram-Fuller, E., Steward, T., Wang, J., Swanson, A. N., ... & Ling, W. (2008). Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug and alcohol dependence*, 96(3), 222-232.
 12. Anderson, A. L., Li, S. H., Markova, D., Holmes, T. H., Chiang, N., Kahn, R., ... & Elkashef, A. M. (2015). Bupropion for the treatment of methamphetamine dependence in non-daily users: a randomized, double-blind, placebo-controlled trial. *Drug and alcohol dependence*, 150, 170-174.
 13. Elkashef, A., M., Rawson, R., A., Anderson, A., L., Li, S., H., Holmes, T., et al. (2008). Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology*, 33(5), 1162-1170.
 14. White, W. L. (2015). Congress 60: An addiction recovery community within the Islamic Republic of Iran. *Alcoholism Treatment Quarterly*, 33(3), 328-347.
 15. WHITE WL, LAUER T, PARRISH K. The Foundations of Resilient Recovery.
 16. Dezhakam, A., Dezhakam, H., & Haghightafard, A. (2022). Taper off treatment can improve executive functions and regulate expression of BDNF and 5HTTPLR genes in opium abusers after six months period.
 17. Li, L., Galloway, G. P., Verotta, D., Everhart, E. T., Baggott, M. J., Coyle, J. R., ... & Mendelson, J. (2011). A method to quantify illicit intake of drugs from urine: methamphetamine. *Journal of Pharmacology and Experimental Therapeutics*, 338(1), 31-36.
 18. Cao, F., Xu, J., Yan, S., Yuan, X., Yang, F., Hou, L., ... & Chen, H. (2018). A surface plasmon resonance-based inhibition immunoassay for forensic determination of methamphetamine in human serum. *Forensic Chemistry*, 8, 21-27.
 19. Huang, Z., & Zhang, S. (2003). Confirmation of amphetamine, methamphetamine, MDA and MDMA in urine samples using disk solid-phase extraction and gas chromatography-mass spectrometry after immunoassay screening. *Journal of chromatography B*, 792(2), 241-247.
 20. Ko, T. F., Chiou, R. Y., Shieh, S. S., & Sheu, S. C. (2008). Assessment of methamphetamine abuse patterns in southern Taiwan by immunoassay and quantification by gas chromatographic-mass spectrometric analysis of urine samples. *Journal of Food and Drug Analysis*, 16(5), 13.
 21. Raouf, M., Bettinger, J. J., & Fudin, J. (2018). A practical guide to urine drug monitoring. *Federal practitioner*, 35(4), 38.
 22. Goldman, D., Oroszi, G., & Ducci, F. (2006). The genetics of addictions: uncovering the genes. *Focus*, 6(3), 521-415.
 23. Le Foll, B., Gallo, A., Le Strat, Y., Lu, L., & Gorwood, P. (2009). Genetics of dopamine receptors and drug addiction: a comprehensive review. *Behavioural pharmacology*, 20(1), 1-17.
 24. Wang, J., Kelly, B. C., Liu, T., & Hao, W. (2016). Studying psychosocial barriers to drug treatment among Chinese methamphetamine users using a 3-step latent class analysis. *Journal of Substance Abuse Treatment*, 62, 89-95.
 25. Lee, Y. K., Park, S. W., Kim, Y. K., Kim, D. J., Jeong, J., Myrick, H., & Kim, Y. H. (2005). Effects of naltrexone on the ethanol-induced changes in the rat central dopaminergic system. *Alcohol and Alcoholism*, 40(4), 297-301.
 26. Trivedi, M. H., Walker, R., Ling, W., Dela Cruz, A., Sharma, G., Carmody, T., ... & Shoptaw, S. (2021). Bupropion and naltrexone in methamphetamine use disorder. *New England Journal of Medicine*, 384(2), 140-153.

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