ORIGINAL ARTICLE

Concomitant Drug Use in Patients on Methadone Maintenance Therapy

MARJAN EMJIK[1], DANYAL ZARIF [2], SHAHRAD TAJODDINI[3], AMIR BANIASAD[4], BITA DADPOUR[1,*]

[1]Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Iranian Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran
[3] Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[4] Division of Addiction, Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Background: Methadone maintenance therapy (MMT) is considered as an efficient and effective treatment in management of high risk opioids addiction; although, concomitant use of other drugs may interfere with treatment course and outcome in MMT cases. This study aimed at evaluating patterns of drug use along with methadone based on self reported and urine analysis data in two MMT clinics.
Methods: 135 patients on MMT recruited for this cross-sectional study which was conducted from March to September 2014. Data were obtained of MMT clinic of Imam Reza (p) hospital, Mashhad, Iran. After completing a written informed consent, a questionnaire including demographic information, duration of MMT, methadone dose, concomitant medication and other related information was fulfilled. Data were analyzed by SPSS software version 16.
Results: Mean (SD) age of patients was 42.8 (12.2). All patients were taking medication along with methadone. The most prevalent drug classes were antidepressants (32%) and benzodiazepines (BNZD) (25%). The next three drug groups were analgesics, GI and cardiovascular drugs respectively. Antidepressant and benzodiazepine use was more prevalent in patients who were on MMT for at least 7 months compared with shorter courses. Antidepressant use was more common in patients on maximum dose of 30 mg/day methadone while BNZD use was more frequent in patients on doses higher than 30 mg/d.
Conclusion: Psychiatric drug use is common in opioid addicted cases. BNZD and antidepressant drugs were two most consumed drugs in cases on MMT based on our study. Psychiatric drug consumption was more common in patients on higher length of methadone use. Dosage of methadone may affect kind of concomitant drug use. Physicians should be aware of interactions between psychiatric medications and opioids.

Key Words: Concomitant Drug Use; Opioid; Psychotropic Drugs; MMT

How to cite this article: Emjik M, Zarif D, Tajoddini S, Baniasad A, Dadpour B. Concomitant Drug Use in Patients on Methadone Maintenance Therapy. *Asia Pac J Med Toxicol* 2017;6:42-6.

INTRODUCTION

Opioid dependence is considered as a substantial problem worldwide. It has been recognized as a major health, economic and social problem in current decade (1, 2).

Based on epidemiological investigations, some kind of substance dependence disorder is estimated to be found in 1,200,000-3,300,000 of Iranian adults. opioid dependency has higher rate than other substance dependencies in Iran; due to some factors such as cultural acceptance as well as the neighborhood to main narcotics producers like Afghanistan (3).

Methadone is the main drug used to control the high risk opioid dependency. Main factor in treatment effectiveness is remaining on treatment for period of time that is long enough. It is important to evaluate factors that can affect treatment programs (2).

Previous investigations revealed that many of cases on methadone program consume other drugs or substances simultaneously. It is a challenging point that what kind of drugs are used and why they use them; also, is there any interference of drug use on outcome of methadone maintenance treatment?

An investigation on urine samples of 82 patients on methadone or buprenorphine-naloxone treatment by liquid chromatography/ mass spectrometry screening method found that about 46% of samples were positive for abused substances; benzodiazepines, amphetamines and cannabinoids were the most common detected substances (4).

While some studies show that opioid maintenance treatment with methadone (MMT) suppress high risk abuse of some other opioids such as heroin, some other investigations reported that abuse of other drugs and substances such as ephedrine increases within MMT (5,6).

On the other view, hyperprolactinemia and hypogonadism is expected to be a side effect of methadone

*Correspondence to: Bita Dadpour; MD. Division of Addiction, Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 513 852 5315, Email: DadpourB@mums.ac.ir
Received 21 January 2017, Accepted 30 May 2017

as an opioid and low serum level of testosterone might be followed by inappropriate sexual performance and finally lead to depression; depression could deteriorate sexual dysfunction vice versa (7-9). Continuous treatment with methadone may cause patients to search for specific medications to treat problems caused by regular intake of this medication.

Methadone may be a starting point for taking other medications. In a one-year prospective study, lifetime BZD abuse among cases on methadone program had a prevalence of 66.3% compared to 50.8% for current abuse. Importantly, the authors pointed that methadone treatment maybe even as a trigger for onset or exacerbating of BZD misuse (10).

In current study, we aimed at evaluating pattern of concomitant drug use with methadone in MMT cases that were provided from a large methadone maintenance clinic in Mashhad, Iran.

METHODS

135 patients on MMT recruited for this cross-sectional study, which was conducted from March to September 2014. Data were obtained of MMT clinic of Imam Reza (p) hospital, Mashhad University of medical sciences, Mashhad, Iran. All cases completed a written informed consent. A questionnaire was compiled and discussed with the researcher's three supervisors, professional toxicologists working in poisoning department in Imam Reza(p) Hospital, Mashhad University of Medical Sciences, and a statistician. Changes suggested by these persons were implemented. The questionnaire was prepared in a very simple expression so that participants could easily understand the concept. Demographic information, duration of MMT, methadone dose, concomitant medication and other related information were assessed. Patients were asked to name the main drug and other medications that they used concomitantly with methadone. The major reason they first began to use main and other medications were also recorded. This study was approved by ethics committee of Mashahd University of Medical Sciences (MUMS), Iran.

Statistical analysis

Data were represented as frequency distributions and simple percentages. Chi-square test was performed for discrete variables. Also Independent-samples t-test, ANOVA and Fisher's Exact Test were used to find the significant differences. P value<0.05 was considered as significant. Data were analyzed by SPSS software version 16. Qualitative urine toxicology test was requested for cases who consented.

RESULTS

Mean (± SD) age of patients was 42.8(±12.2) years. All patients were taking medication along with methadone. 23 patients (17%) used three drugs, 24 patients (17.7%) used two drugs and 36 patients (26.6%) used only one drug during methadone maintenance therapy.

The most prevalent drug class was antidepressants (32%) with fluoxetine and amitriptyline at the top of list respectively. The second drug group was benzodiazepines (BNZD) (25%) with higher prevalence of alprazolam followed by clonazepam and lorazepam. The next three drug groups were analgesics, GI and cardiovascular drugs respectively (23%, 16%, and 16%) (Table 1).

Antidepressant and benzodiazepine use was more prevalent in patients who were on MMT for at least 7 months compared to shorter courses. Antidepressant use was more common in patients with maximum dose of 30 mg/day methadone while BNZD use was more frequent in patients with doses higher than 30mg/day (Table 2, Table 3).

Urine sample for toxicology test was taken from 71 cases. Positive test for BNZD and Antidepressant were reported in 10 and 21 cases respectively. Twelve cases had positive test of phenothiazine and 8 cases had positive test of morphine;

Table 1. Frequency of concomitant drug use based on specific drug group

Drug group	N (%)	Type	N (%)
Antidepressants	32 (23.7)	Fluoxetin	24 (75)
		antidepressant	2 (6.3)
		Amitriptiline	5 (15.6)
		Bupropion	1 (3.1)
Benzodiazepines	25 (18.5)	Alprazolam	16 (64)
		Clonazepam	4 (16)
		Lorazepame	4 (16)
		Diazepam	1 (4)
Analgesics(NSAIDs, Anticonvulsants, Muscular relaxants)	23 (17.0)	A.S.A/A.C.A	4 (17.4)
		Gabapenthine	9 (39.1)
		Indomethacin	1 (4.3)
		Gelofen/Ibuprofen	5 (21.7)
		Carbamazepine	2 (8.7)
		Metocarbamol	1 (4.3)
		Non identified Analgesic drug	1 (4.3)

Table 1. Continued

Drug group	N (%)	Type	N (%)
G.I Drugs	16 (11.9)	Ranitidine	9 (56.3)
		Magnesium hydroxide	2 (12.5)
		Lactulose	
		Non identified GI drug	
		Omeprazole	1 (6.3)
		C-lax	
		Panthoprazole	
Cardiovascular Drugs	16 (11.9)	Anti hypertension	6 (37.5)
		Lipid lowering drugs	3 (18.8)
		Atenolol	1 (6.3)
		TNG	
		Warfarin	
		Non identified cardiovascular drug	
		Atorvastatin	
		Triamteren-H	
		Simvastatin	
miscellaneous	17 (12.6)	Clonidine	2 (11.8)
Other Drugs			1 (5.9)

Table 2. Comparison of frequency (%) of drug use in different period of MMT

period of MMT	0-2 month	3-6 month	7 and more month	P value
Number (%)	25 (18.5)	81 (60.0)	29 (21.5)	-
Mean ±SD age (year)	40.0 ± 12.4	42.9 ± 12.4	44.9 ± 11.6	0.330
Antidepressants consumers	5 (20.0)	19 (23.5)	8 (27.6)	0.805
Benzodiazepines consumers	4 (16.0)	14 (17.3)	7 (24.1)	0.672
Analgesics consumers	5 (20.0)	12 (14.8)	6 (20.7)	0.700
G.I drugs consumers	3 (12.0)	11 (13.6)	2(6.9)	0.633
Cardiovascular drugs consumers	2 (8.0)	7 (8.6)	7 (24.1)	0.069
Miscellaneous drug consumers	2 (8.0)	11 (13.6)	4 (13.8)	0.745

therapeutic levels for acetaminophen and salicylate of serum were detected in11 and 9 cases respectively.

Because a limited number of cases consented to give urine sample, an evaluation on urine test result was not possible as we did not find any relationship between any positive tests and dose and duration of methadone consumption; likewise, we can't determine many drugs by urine qualitative test in our setting.

DISCUSSION

While methadone maintenance program effectively treats many problems of opioid dependence, several factors may interfere with treatment benefits and adherence. Concomitant drug and substance use is a major problem in cases on MMT. Consumption of psychoactive substances is reported in most of opioid addicts (11). Previous investigations point that addict patients have difficulties with identify, accept, and withstand negative emotions. Then, rapid ways turn to a main solution to manage problems. They self-medicate with illegal substances. Based on this theory, substance abuse is considered as a way to get rid of negative emotions for example anxiety or depression (3).

Several studies showed relationship between substance dependence and some other psychiatric disorders like depression and anxiety syndromes. Although, the main and accurated etiology for this relationship remains unknown (3).

In current study we found that all of included cases concomitantly consumed a kind of medication along with methadone. About 42% of our cases used antidepressants and benzodiazepines as two more common drugs.

Table 3. Comparison of frequency (%) of specific drug consumption in two groups of methadone dose

variable	Dose of Methadone		*P* -value
	≤30	>30	
Number (%)	117 (86.7)	18 (13.3)	-
Mean ±SD age (year)	43.0 ± 12.0	41.1±14.0	0.523
Number(%) of Antidepressant consumers	31 (26.5)	1 (5.6)	0.072
Number(%) of Benzodiazepine consumer	21 (17.9)	4 (22.2)	0.745
Number(%) of Analgesic consumers	19 (16.2)	4 (22.2)	0.510
Number(%) of G.I drug consumers	15 (12.8)	1 (5.6)	0.695
Number(%) of Cardiovascular drug consumers	16 (13.7)	0 (0)	0.128
Number(%) of Miscellaneous drug consumers	16 (13.7)	1 (5.6)	0.468

In a study on 375 cases on MMT, 48% of patients reported symptoms of sleeping problem or anxiety before turn to opioid use and 61.5% stated these problems before admission to MMT (11).

Based on an investigation, BZD users were more likely to have anxiety problems before entering the methadone program and also before use of opioids compared to those cases on MMT who never consumed BZD. The main reason for BZD use without prescription was curiosity, relieving anxiety or tension and feeling of well-being respectively. Noticeably, half of all cases who self-reported BZD use, did not consume BZD before they entered into MMT program and resumption of BNZ use or increased consumption were reported in 61% of previous BZD consumers after initiating methadone program (10). Based on this study, it seems that methadone use may increase need to BZD consumption.

18.5 % of patients in our study consumed benzodiazepines. BNZD use was more frequent in patients on daily doses higher than 30 mg. alprazolam, clonazepam and lorazepam were the most common used drugs in this class.

Depression and mood disorders have been considered as most frequent co-morbid disorders with addiction based on DSM-IV classification; So, frequency of Major Depression is 50 to 60 percent in addict patients and this number is nearly 10 for Minor Depression (1). Based on another study, the incidence of lifetime and current depression among opioid addict patients range between 19% –74.3% and 10%–30% respectively. Studies on MMT cases found that depression was more common in people with some other psychological disorders (12). Although some investigations reported 28 to 40% prevalence of major depression in cases that entered an MMT clinic, some others stated that patients who had just been admitted to methadone treatment were not found to suffer depression (12-14).

Peles et al in a cross sectional study on 90 MMT patients found that cases with depression received high doses of methadone, although not been controlled in multivariate analyses for other variables. As to findings of another study, a psychiatric disorder, BZD abuse, sleep disorders and chronic pain have been reported to be associated with consumption of higher doses of methadone (12, 15).

Near to 24% of cases in current study used antidepressant. fluoxetine and amitriptyline were two most frequent used drugs in this class. Antidepressant use was more prevalent in cases on maximum daily dose of methadone 30 mg. it is in contrast with finding of Peles et al. Antidepressant and benzodiazepine use was more common in cases who were on MMT for a longer time (at least 7 months) in comparison with who were on shorter courses based of our findings.

CONCLUSION

Psychiatric drug use is common in opioid addicted cases. BNZD and antidepressant drugs were two most consumed drugs in cases on MMT based on our study. Psychiatric drug consumption was more common in patients on higher length of methadone use. Dosage of methadone may affect kind of concomitant drug use. Physicians should be aware of interactions between psychiatric medications and opioids.

LIMITATIONS

We don't access to standard qualitative toxicological tests for many drugs. Likewise, quantitative assessment of many suspected drugs and substances that we thought to be used by patients is not possible in our setting because of limitations in related technical methods. The findings of our study were based on self-report data and same as other similar investigation it can be considered as the main limitation.

ACKNOWLEDGEMENT

We should appreciate all kind attempts of staffs in Methadone clinic.

Conflict of interest: None to be declared.
Funding and support: None.

REFERENCES

1. Momeni F, Moshtagh N, Pourshahbaz A. Effectiveness of cognitive-behavioral group therapy on craving, Depression& anxiety among the Opiate abusers under MMT. *Iran Rehab J* 2010; 8:19-23.
2. Yin W, Pang L, Cao X, McGoogan JM, Liu M, Zhang C et al. Factors associated with depression and anxiety among patients attending community-based methadone maintenance treatment in China. *Addiction* 2015;110:51-60.

3. Saedy M, Kooshki S, Jamali Firouzabadi M, Emamipour S, Rezaei Ardani A. Effectiveness of Acceptance-Commitment Therapy on Anxiety and Depression among Patients on Methadone Treatment: A Pilot Study. *Iran J Psychiatry Behav Sci* 2015; 9: e222.
4. Heikman P, Sundström M, Pelander A, Ojanperä I. New psychoactive substances as part of polydrug abuse within opioid maintenance treatment revealed by comprehensive high-resolution mass spectrometric urine drug screening. *Hum Psychopharmacol* 2016; 31:44-52.
5. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2004; (3):CD002207.
6. Li L, Sangthong R, Chongsuvivatwong V, McNeil E, Li J. Multiple substance use among heroin-dependent patients before and during attendance at methadone maintenance treatment program, Yunnan, China. *Drug Alcohol Depend* 2011; 116:246-9.
7. Amini Lari M, Parsa N, Marzban M, Shams M, Faramarzi H. Depression, testosterone concentration, sexual dysfunction and methadone use among men with hypogonadism and HIV infection. *AIDS Behav* 2012; 16: 2236-43
8. Déglon JJ, Martin JL, Imer RL. Methadone patients' sexual dysfunctions: Clinical and treatment issues. *Heroin Add Rel Clin Probl* 2004; 6:17-26.
9. Gerra G, Manfredini M, Somaini L, Maremmani I, Leonardi C, Donnini C. Sexual Dysfunction in Men Receiving Methadone Maintenance Treatment: Clinical History and Psychobiological Correlates. *Eur Addict Res* 2016; 22:163-75.
10. Chen KW, Berger CC, Forde DP, D'Adamo C, Weintraub E, Gandhi D. Benzodiazepine use and misuse among patients in a methadone program. *BMC psychiatry* 2011; 11:90.
11. Specka M, Bonnet U, Heilmann M, Schifano F, Scherbaum N. Longitudinal patterns of benzodiazepine consumption in a German cohort of methadone maintenance treatment patients. *Hum Psychopharmacol Clin Exp* 2011; 26:404-11.
12. Peles E, Schreiber S, Naumovsky Y, Adelson M. Depression in methadone maintenance treatment patients: rate and risk factors. *J Affect Disord* 2007; 99:213-20.
13. Ross J, Teesson M, Darke S, Lynskey M, Ali R, Ritter A et al. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). *Drug Alcohol Rev* 2005; 24:411-8.
14. Brienza RS, Stein MD, Chen M, Gogineni A, Sobota M, Maksad J et al. Depression among needle exchange program and methadone maintenance clients. *J Subst Abuse Treat* 2000; 18:331-7.
15. Peles E, Schreiber S, Gordon J, Adelson M. Significantly higher methadone dose for methadone maintenance treatment (MMT) patients with chronic pain. *Pain* 2005; 113:340-6.