

Advantages and Disadvantages of Methadone among Children and Adults: A Systematic Review and Meta-Analysis

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Abstract

Background: Today, an increasing trend to methadone as an alternative maintenance treatment for opiate dependence in adults is observed; children for both intentional and accidental reasons are exposed to serious and fetal effects of methadone. We aimed to investigate effects of methadone on children and sexual functioning among adults in Iranian population.

Materials and Methods: An extensive search was done in databases of Medline, EMBASE, Scopus, Cochrane, and Web of Science until August 2018. Two independent researchers screened articles, and categorized them based on the evaluated outcomes and overall effect size was presented. After excluding the duplicated, irrelevant and low-quality articles, eligible ones were enrolled in the meta-analysis. Finally, pooled effect size was presented as standardized mean difference (SMD) or pooled prevalence with 95% confidence interval (95% CI).

Results: Methadone was found to be more effective than morphine on neonatal abstinence syndrome. The first four most common symptoms of methadone poisoning were loss of consciousness (81%), sleepiness (72%), meiotic pupils (76%), vomiting (56%), and Apnea (48%). The overall prevalence rate of sexual disorders and erectile dysfunction was 66.3% and 77.5%, respectively. The subjects in methadone group were over 2.5-fold more likely to use condom during intercourse ($p < 0.001$). The methadone therapy could lead to a significant reduction in orgasm functioning ($p < 0.001$), and a significant improvement in libido ($p = 0.001$). The methadone maintenance treatment (MMT) significantly resulted in decreased orgasm function and improved libido in males.

Conclusion: Evidence suggests a positive impact of methadone maintenance treatment on risky sexual behaviors. Regarding the methadone poisoning effect on children, people should be informed by health care providers about serious and fetal effects on children.

Key Words: Children, Iran, Methadone, Meta-Analysis, Poisoning, Sexual functioning.

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1- INTRODUCTION

Methadone is a derivative of Diphenylheptanes (*Hepta-amines*), which have been effective as clinical analgesics. The mechanism of its effect is that, it restrains transmission of impulse pain by connecting with Opioid receptors at the spinal cord. Methadone can be used orally, intravenously, and subcutaneously, which is well absorbed through the digestive system and its blood level is more than oral morphine (1). In studying the history of methadone maintenance treatment, methadone was first used in 1964 in New York as an alternative treatment of Heroin.

Methadone treatment also started in Europe in the late 1960s in response to the expanding use of heroin. Then, Sweden as a pioneer in 1967, and the Netherlands and the United Kingdom in 1968 officially instituted methadone treatment. But the official start of treatment with methadone was delayed in some countries, such as Belgium until 1967. In 2002, nearly 21,556 patients in the United States were under methadone treatment, and in 2004 nearly 47 countries began this program and 500,000 patients participated around the world (2). In Iran, in 2005 this drug was presented in the health system of the country, and now more than 3,000 centers in the country are offering this drug to patients based on the country's treatment protocol. Since 2009, methadone has been used only in preservative treatment (3). Addiction is a physical and mental disorder affecting all dimensions of life, including health, family and social activities (4). Reportedly, 86% of opium abusers were suffering from sexual problems, which is needed to be addressed by health providers (5). Long-term drug taking could decrease sexual satisfaction (6), as unrestrained sexual activities are common among addicts because of social exclusion. High-risk sexual behaviors are frequently seen in people with substance abuse. Additionally, a part of infectious

diseases transmission, such as HIV/AIDS, is related to risky and unprotected sexual behavior (7). Moliter et al. assessed the relationship between methamphetamine use and unsafe sexual behavior on 57 consumers and concluded that methamphetamine users often experience sexual activity with multiple partners, predisposing them to unprotected sex (8). Another study in Taiwan compared 85 high-risk sexual behaviors in male adolescents consuming methamphetamine versus 170 controls. The results showed that methamphetamine users were willing to have frequent sexual pairing with multiple partners (9). There are various methods for drug dependence treatments, among which the methadone maintenance treatment (MMT) is considered to be a major approach (10). Lollis et al. investigated the effect of MMT in decreasing risky sexual behavior. Out of 123 participants receiving methadone, 62 (50%) were reported to have fewer sexual partner and higher tendency to use condoms compared to the control group. The methadone users also stated more positive belief towards the efficacy of condoms to prevent the HIV/AIDS (11). Approximately 18.3 to 94% of patients under methadone treatment have been estimated to experience sexual problems (5). Treatment with methadone is associated with advantages and disadvantages. The MMT leads to sexual dysfunction (11). Treatment with methadone made this drug available to other family members. Due to favorable taste of methadone, it is attractive for children. As a result, methadone poisoning can occur in children (13). Unsafe maintenance of this substance, especially in the form of syrup in soda bottle, water, containers of other drugs, colors and appearance which are mistaken for water causes many complications and the high mortality rate of this poisoning in children. Therefore, due to the significant increase in use of methadone at home in the form of

addiction quitting programs and treatment of maintenance with methadone in recent years, and because this poisoning is new in children and the low number of studies in this area, as well as the increase of poisoning in recent years, this study was conducted to investigate effects of methadone on children and sexual functioning in adults in Iranian population.

2- MATERIALS AND METHODS

2-1. Data Sources

This systematic review and meta-analysis study was conducted on the articles published in national and international databases. The articles were independently searched by two independent persons on national (Irandoc, Magiran, Medlib, SID, and Barakatks), and international databases (Medline [via PubMed], EMBASE, Web of Science, Scopus and Cochran Central Register of

Controlled Trials) without any time limit since inception to August 2018. In addition, a manual search was conducted in Google motor engine, Google Scholar, and bibliography of related articles and reviews. The search keywords were: (Methadone Maintenance Program OR Opiate Replacement Therapy OR Neonatal Abstinence Syndrome OR Neonatal Withdrawal Syndrome OR Sexual) AND (Unsafe Sex OR Sexual Risk Behavior OR Substance Abuse Risk OR Behavior OR Condom Use OR Poisoning OR Children OR Toxicity OR Management OR Therapy OR Therapeutics OR Treatment) AND (Iranian OR Iranian). The search query in Medline (via PubMed) is shown in **Table.1**. We performed a hand-search on the list of references in the chosen articles to detect further researches. In addition, some of the editorial boards of national journals were contacted for finding gray literature.

Table-1: Search strategy for Medline (via PubMed).

((("methadone"[MeSH Terms] OR "methadone"[All Fields]) AND ("maintenance"[MeSH Terms] OR "maintenance"[All Fields]) AND program[All Fields]) OR ("opiate substitution treatment"[MeSH Terms] OR ("opiate"[All Fields] AND "substitution"[All Fields] AND "treatment"[All Fields]) OR "opiate substitution treatment"[All Fields] OR ("opiate"[All Fields] AND "replacement"[All Fields] AND "therapy"[All Fields]) OR "opiate replacement therapy"[All Fields]) OR ("neonatal abstinence syndrome"[MeSH Terms] OR ("neonatal"[All Fields] AND "abstinence"[All Fields] AND "syndrome"[All Fields]) OR "neonatal abstinence syndrome"[All Fields]) OR ("neonatal abstinence syndrome"[MeSH Terms] OR ("neonatal"[All Fields] AND "abstinence"[All Fields] AND "syndrome"[All Fields]) OR "neonatal abstinence syndrome"[All Fields] OR ("neonatal"[All Fields] AND "withdrawal"[All Fields] AND "syndrome"[All Fields]) OR "neonatal withdrawal syndrome"[All Fields]) OR ("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All Fields] AND ("unsafe sex"[MeSH Terms] OR ("unsafe"[All Fields] AND "sex"[All Fields]) OR "unsafe sex"[All Fields]) OR ("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All Fields] AND ("risk behavior"[All Fields] OR "risk-taking"[MeSH Terms] OR "risk-taking"[All Fields] OR ("risk"[All Fields] AND "behavior"[All Fields]) OR "risk behavior"[All Fields])) OR ("substance-related disorders"[MeSH Terms] OR ("substance-related"[All Fields] AND "disorders"[All Fields]) OR "substance-related disorders"[All Fields] OR ("substance"[All Fields] AND "abuse"[All Fields]) OR "substance abuse"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) OR ("behaviour"[All Fields] OR "behavior"[MeSH Terms] OR "behavior"[All Fields]) OR ("condoms"[MeSH Terms] OR "condoms"[All Fields] OR "condom"[All Fields]) OR ("poisoning"[Subheading] OR "poisoning"[All Fields] OR "poisoning"[MeSH Terms]) OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) OR ("toxicity"[Subheading] OR "toxicity"[All Fields]) OR ("organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]) OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND Iranian[All Fields] OR Iranian[All Fields].

2-2. Inclusion and exclusion criteria

All Persian and English studies reporting the efficacy of methadone therapy on risky sexual behavior or sexual function or methadone poisoning in children in Iran were included in the study. No time and language limitations were applied. The articles in languages other than English and Persian were excluded.

2-3. Data Extraction

After searching and eliminating some reports and duplicates, two independent authors read the titles and abstracts, and then relevant studies were selected. Any disagreement was solved by discussion among research team. Data related to the first author of article, year of study, sample size, age, and marital status, etc. were recorded.

2-4. Quality assessment of studies

Quality of studies was assessed using STROBE checklist for observational (non-randomized) studies included 22 items (20). Some items are: objectives, study design, setting, bias, statistical methods, main outcome, limitations, interpretation and generalizability. This checklist assessed methodological quality. Total STROBE score ranged from 0-22. Quality of systematic reviews studies was assessed using AMSTAR (A Measurement Tool to Assess Systematic Reviews) (21-24).

2-5. Statistical Analysis

A comprehensive meta-analysis version 2.00 (Bio stat, Englewood, NJ, USA) was used to analysis the data, and Fix effect model to calculate the effect size using Cochran Q test ($p < 0.05$ as statistically significant) and I^2 index.

3- RESULTS

Process of selecting the studies which were included in systematic review and meta-analysis is shown in **Figure.1**. Five studies were included in unsafe sex systematic review, four studies were included in methadone poisoning in children systematic review and two meta-analysis. **Table.2** shows main characteristic of subjects and results of risky behaviors, sexual function and methadone poisoning. STROB scores for nine studies are shown in **Table.2**. **Table.3** shows methodological quality assessment of systematic review studies using the AMSTAR rating (*Please see the table.3 at the end of paper*).

A systematic review published recently assessed the therapeutic approaches with methadone on neonatal abstinence syndrome (11). Two studies included in systematic review compared the effect methadone with morphine on neonatal abstinence syndrome. In first study, 14% decline was observed in stay (days) in hospital ($p=0.046$) with shorter treatment duration in methadone group than morphine ($p=0.02$).

In the second study, treatment duration was shorter in infants treated with methadone in comparison to morphine ($p=0.008$), and they conclude that methadone was found to be more effective than morphine. However, authors conclude based on current finding, that it is not possible to determine a certain conclusion because of low quality, small size and short-term treatment (11).

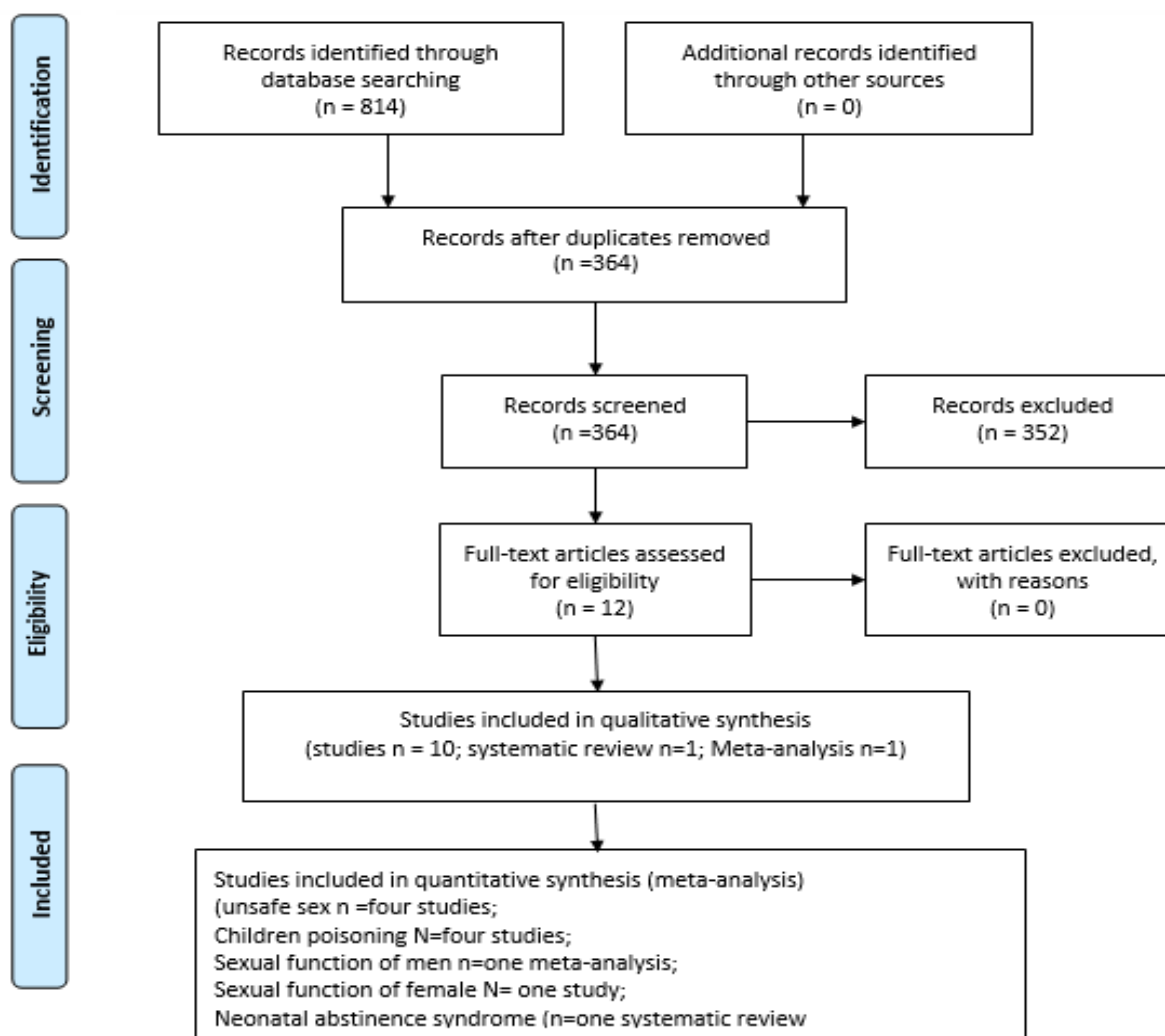


Fig.2: PRISMA flowchart of present study.

Table-2: Methodological quality assessment of systematic reviews using the AMSTAR (21-24).

Authors, Year, (Reference)	1	2	3	4	5	6	7	8	9	10	11
et al.,Babakhanian 2012, (6)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ghazanfarpour et al., 2019, (11)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

- 1 Was an ‘a priori’ design provided?
- 2 Was there duplicate study selection and data extraction?
- 3 Was a comprehensive literature search performed?
- 5 Was a list of studies (included and excluded) provided?
- 4 Was the status of publication (i.e. grey literature) used as an inclusion criterion?
- 6 Were the characteristics of the included studies provided?
- 7 Was the scientific quality of the included studies assessed and documented?
- 8 Was the scientific quality of the included studies used appropriately in formulating conclusions?
- 9 Were the methods used to combine the findings of the studies appropriate?
- 10 Was the likelihood of publication bias assessed?
- 11 Was the conflict of interest stated?

3-1. Prevalence of methadone poisoning in children

The first four most common symptoms of methadone poisoning in children were reported in review. According to three

studies (25-27), prevalence of meiotic pupils was 76% (95% Confidence Interval (CI): 35% to 74%: heterogeneity; I^2 : 83%; **Figure.2**).

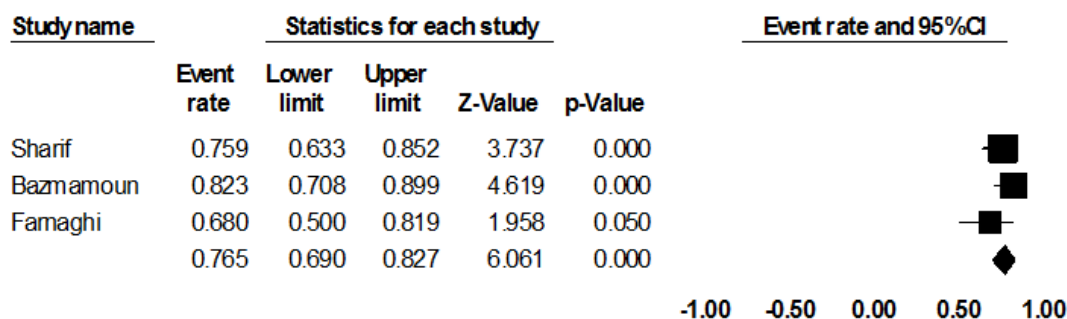
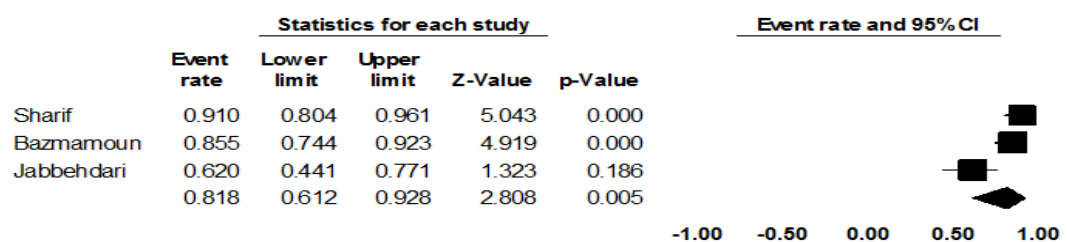


Fig.2: The prevalence of meiotic pupils in methadone poisoning on children. The horizontal lines denote the 95% confidence interval; ■, point estimate (size of the square corresponds to its weight); ◆, combined overall prevalence.

According to three studies (26-28), prevalence of loss of consciousness was

81% (95%CI: 61% to 92%: heterogeneity; I^2 : 81%; **Figure.3**).



Meta Analysis

Fig.3: The prevalence of Loss of consciousness in methadone poisoning on children. The horizontal lines denote the 95% confidence interval; ■, point estimate (size of the square corresponds to its weight); ◆, combined overall prevalence.

According to two studies (25, 26), prevalence of apnea was 48% (95% CI:

38% to 58%: heterogeneity; I^2 : 22 %; **Figure.4).**

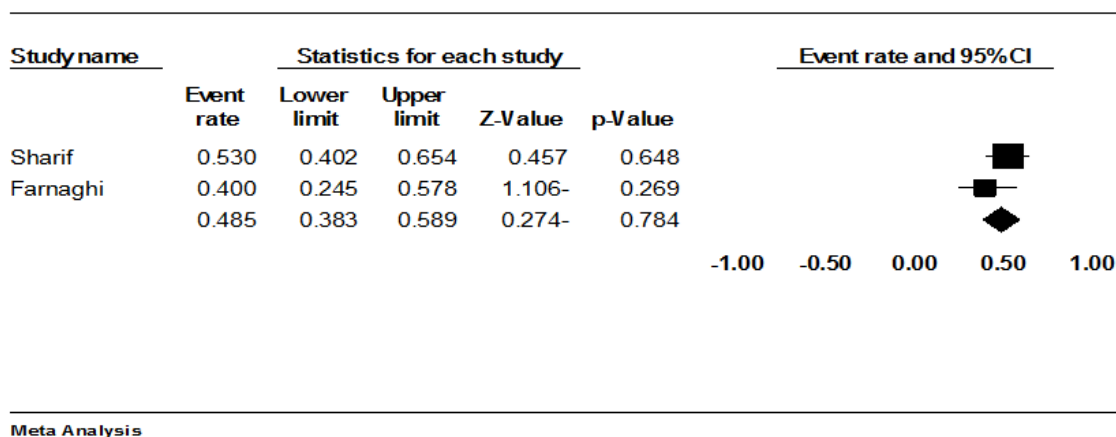


Fig.4: The prevalence of apnea in methadone poisoning on children. The horizontal lines denote the 95% confidence interval; ■, point estimate (size of the square corresponds to its weight); ♦, combined overall prevalence.

Three studies (25-27) reported prevalence of vomiting. Prevalence of vomiting was

56% (95% confidence interval: 35% to 74%: heterogeneity; I^2 : 83%; **Figure.5).**

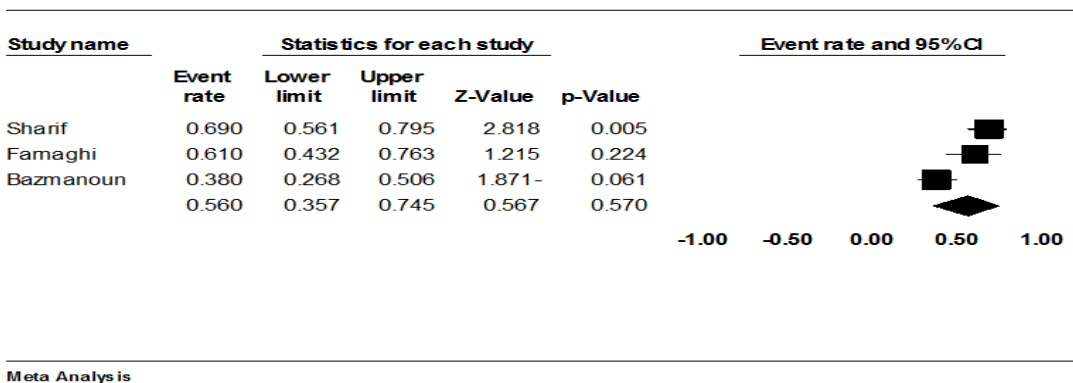


Fig.5: The prevalence of vomiting in methadone poisoning on children. The horizontal lines denote the 95% confidence interval; ■ point estimate (size of the square corresponds to its weight); ♦, combined overall prevalence.

Three studies (25-27) reported prevalence of sleepiness. Prevalence was 72% (95%

CI: 32% to 93%: heterogeneity; I^2 : 93%; **Figure.6**).

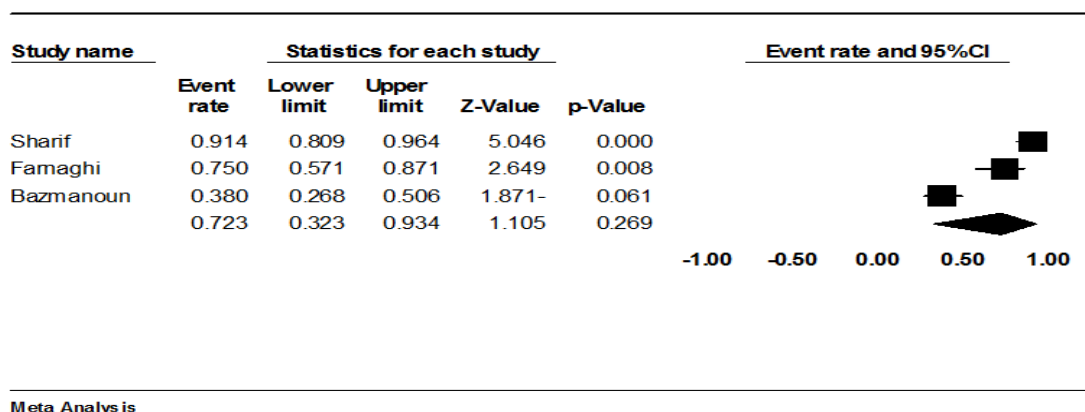


Fig.6: The prevalence of sleepiness in methadone poisoning on children. The horizontal lines denote the 95% confidence interval; ■, point estimate (size of the square corresponds to its weight); ♦, combined overall prevalence.

3-2. The effect of MMT on sexual function

Only two studies (29, 30) investigated the effect of methadone on female sexual function. Kheradm et al. (16) conducted a cross-sectional study with a sample size of 13 women under MMT. They measured sexual functioning using Arizona sexual experience scale (ASEX) consisting of five items rated on the basis of a 6-point Likert scale, indicating greater scores as higher sexual dysfunction, the scores over 5 for each item and over 19 for total as sexual dysfunction. The maximum sexual dysfunction was seen in the item of orgasm satisfaction (3.62 ± 0.27), followed by the ease of orgasm (3.54 ± 0.35), psychological arousal (3.46 ± 0.35) and sexual drive (3.23 ± 0.17) and vaginal lubrication (2.92 ± 0.26) (16). Parvaresh et al. conducted a cross-sectional study involving 19 women under methadone maintenance, and found no significant difference between pre- and post-treatments of sexual function (17).

A meta-analysis assessed the effect of MMT on sexual disorders in opium-dependent Iranian men. The MMT significantly leads to a decrease in orgasm

function (mean difference [MD] = -0.01; 95%CI= -0.75-0.74; heterogeneity $I^2=93\%$; $p<0.001$; random effect; three studies, $n=279$) and an improvement in libido (MD=0.16; 95%CI=0.68-0.99; $I^2=94.5\%$; $p=0.001$; random effect; three studies, $n=279$). No significant publication bias was found in the reviewed cross-sectional studies assessing the effect of methadone on libido and orgasm. In this meta-analysis, the overall prevalence rate of sexual disorder was 66.3% (95%CI=27.1-105.5; $I^2=99.4\%$; $p<0.001$; random effect model; four studies), and the rate of erectile dysfunction was 77.5% (95%CI=61.9-93.1; $I^2=95.5\%$; $p<0.001$; random effect model; three studies) (31).

3-3. Relationship between methadone and unprotected sex

Two studies (32, 33) assessing the relationship between methadone and unprotected sexual contact (without condom) provided sufficient information to be included in the meta-analysis. The subjects in methadone group were over two and half times more likely to use condom during intercourse (odds ratio [OR] =2.77, $p<0.001$; 95%CI =4.21 to 4.79; $I^2=0\%$, $p=0.83$; **Figure.7**).

In a study of Dolan et al., some subjects had the unsafe sex in return for drugs (10%, n=40), money (15%, n=40) and strangers (10%, n=40); while none of the subjects underlined such behaviors during six-month follow-up (33). Alavian et al., performed a study with a sample size of

259 people. The participants after receiving methadone reported a significant reduction in unsafe monthly homosexuality and heterosexuality. However, they also reported significantly greater sexual contacts with their spouse per month (34).

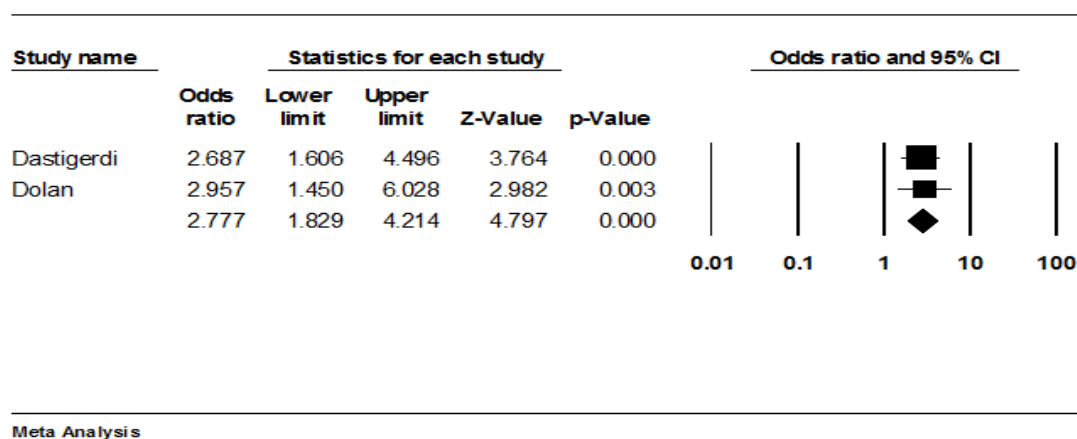


Fig.7: Odds ratio of methadone therapy effect on unsafe sex. The horizontal lines denote the 95% confidence interval; ■, point estimate (size of the square corresponds to its weight); ♦, combined overall prevalence.

4- DISCUSSION

In one hand, increasing trend to methadone as an alternative maintenance treatment for opiate dependence in children and adult was observed. In the other hand, children due to intentional and accidental reasons were exposed to serious and fetal effects of methadone. Therefore, it seems that it is important and necessity provide comprehensive information about advantages and its side effects on children. Opium poisoning and its derivatives are dangerous and lethal poisoning can lead to decreased consciousness and coma, apnea, respiratory suppression, and finally death. It is also a reason of deaths resulting from poisoning in children and unfortunately is one of the most common poisonings of children in our country, so that it forms about 10 percent of admissions that result from poisoning of children who come to Luqman Hakim Hospital which is the only

pediatric poisoning treatment center in Tehran. Methadone is a synthetic opioid and has a long lasting effect. Unfortunately, consumption and emergency room visits and deaths related to it have been increasing in the world in recent years. For example, hospital emergency room visits related to methadone increased 612 percent in Florida in the years 1997 to 2004. Following the prevalence of replacement treatment with methadone in Iran, this dangerous substance entered into households. This exposed children to accidental contact and its cases of poisoning and mortality increased. Increasing use of methadone on the one hand and lack of taking the necessary measures to prevent poisoning of this dangerous substance in the community on the other hand, has resulted in poisoning becoming a serious threat for children. Even in Canada, despite the distribution of

drugs in containers that children are not able to open, sticking warning labels on the drug container, the pharmacist explaining about keeping the drugs away from children, there have been poisoning cases and deaths resulting from methadone. Therefore, in Iran, the risk is more serious because, unfortunately, these measures are not considered (35). This is the first systematic review and meta-analysis to address several important issues: first, the relationship between MMT and risky sexual behaviors in Iran, second, the effect of methadone on sexual function of men and women, and third, the side effects of methadone on children.

According to our meta-analysis, the first four most common symptoms of methadone poisoning were loss of consciousness (81%), sleepiness (72%), meiotic pupils (76%), vomiting (56%), and Apnea (48%). Evidence shows that the use of methadone could have a positive impact on unsafe sex, significantly leading to decreased orgasm function and improved libido in male. However, it induced no change in female sexual function. The subjects in methadone group were more likely to use condom during intercourse and less likely to have the unsafe sex for drug or money, as well as experiencing unsafe sex with strangers, unsafe homosexuality and heterosexuality.

According to the results, the frequency of sexual contacts with the spouse was significantly elevated after the referral to the drug rehab center, due to a better attitude of voluntarily attending and promoted mental health, increased energy and improved mood. Returning to the family established more willing level towards emotional communication with the spouse. Sexual dysfunction refers to poor desire (i.e. libido), arousal (i.e. difficult vaginal lubrication and erection), and completion (i.e. orgasm and ejaculation) (36). Although, the MMT is considered as the first-line therapy for

those with drug abuse, one of the most common complications of treatment is sexual disorders. In a meta-analysis (2014) on 14 articles, the prevalence of sexual function among methadone users was reported to be 14% up to 96.5%. Pooled prevalence was 52% (95%CI=0.39-0.65) (37), meaning it was higher than the sexual function (62%). Based on a meta-analysis on seven studies, the prevalence of sexual dysfunction was 66% in Iranian methadone users (5), which was higher (52%) than that of our meta-analysis. Two possible explanations were reported for different prevalence rates, including varied study methods among countries. This meta-analysis showed 66.3% and 77.5% for the overall prevalence rate of sexual disorder and erectile dysfunction, respectively.

4-1. Study Limitations

There were several limitations in this systematic review and meta-analysis that are needed to be addressed, such as most importantly, poor methodology. First, almost all studies employed convenience sampling method instead of random one, which raised question about generalization of findings. Limited questions were observed in questionnaires in almost all studies. Validity and reliability of the tools were assessed as well. The second restriction was small number of studies and sample size. Third, almost all studies had no control group. The variables in all of the studies had no similar measurement method. Moreover, almost none of the studies reported the life style and number of sexual partners. The MMT has been shown to be effective for substance abuse in controlling high-risk sexual behaviors. Previous studies revealed that the opioid users may under-report their risky sexual behaviors due to the fear of stigmatization, which raised concerns about the validity of self-reported risky behaviors (38). Therefore, before implementing the MMT in nationwide scale, it is necessary to

compare its effectiveness with other intervention methods. The findings related to methadone meta-analysis may not be generalizing to other countries for several reasons: in Iran, methadone comes in one of either two routes, tablet or syrup. In Europe and America, methadone syrup contains one milligram per milliliter. Therefore, it is expected to be less severe poisoning in mentioned countries than Iran. Second, all studies conducted in Iran, prevalence of methadone poisoning may be underreported because being under this lower cut-off may reflect under-reporting due to fear of stigma and concern about legal issues such as children and parent addiction, self-care, etc.

5- CONCLUSIONS

According to the results obtained from the present systematic review and meta-analysis, the treatment with methadone could have a positive impact on risky sexual behaviors. However, the findings should be interpreted cautiously due to poor quality of studied methodology. Given the active effect of methadone in reducing unsafe sex, further studies are required to ensure the accessibility and the adherence to MMT. With the prevalence of use of methadone in society, it is essential that families, doctors and health personnel of the country have adequate awareness of the dangerous side complications of methadone. Methadone can cause harmful and life-threatening complications in children that require proper and timely treatment. One important and significant issue about poisoning with methadone is the starting of delayed symptoms and the need for long-term treatment. Proper maintenance and keeping this dangerous material away from children should be taught to parents and giving sufficient advice to consumers by doctors is very useful.

6- CONFLICT OF INTEREST: None.

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Table-2: Main characteristic of subjects and results of risky behaviors, sexual function, Methadone poisoning and total STROB scores.

Author, Year, (Reference)	Type of study	Characteristics of subjects	Comparis on groups	Substance abuse (%)	Duration Methadon e therapy (month)	Average age, year	Sample size		Results	STROB Score Ranges (0 - 22)
							Before	After		
Dolan et al., 2012, (33)	Cohort	Married (55%), widowed (18%), divorced (14%), separated (9%). Three quarters of subjects are able to read and write	Before and after	Alcohol, n=10 (12.8), Cannabis, n=10 (12.8) Opium, n=54 (69.2) Heroin, n=68 (87.2), Stimulants, n=21 (26.9)	Six months follow-up	36 (±10.16)	40	40	Reports of condom use with regular partners increased 2 times at 6-month follow-up compared to base line. Unsafe sex for drug and for money showed a significant decrease compared to baseline. A significant reduce in sex with stranger compared to before treatment with methadone.	18
Dastjerdi et al., 2010 (32)	Cross-sectional	Married (89.2%) and Single (10.8%), 72.1% of subjects had high school education or less	Before and after	Heroin= 64.5%, Opium= 55%. Crack=9% Cannabis =14% Meth= 10.8% Alcohol=7.5% Addiction to more than one substance= 66%	Six months	Ranged (20-40)	93	93	30% reported unsafe sex before treatment with methadone while 14% reported unsafe sex at a 6-month follow-up.	16
Alavian et al., 2013, (34)	Cross-sectional	Gender: male 255 (98.4) and female 4 (1.6). Marital status: single 144(55.6), married68 (26.3), divorce 46(17.8)	Comparis on before and after	-----	12 months	33.1±7.58	259	259	Participants mentioned significantly reduced sexual intercourse frequency per month except spouse, unsafe homosexual contacts frequency per month and frequency of unsafe heterosexual contacts per month. Significantly having greater sexual contacts with spouse per months.	17

Kheradmand et al., 2015, (29)	Cross-sectional	Male: 185(93.4) Female: 13(6.6) Marital status: Single: 155(55.6), Married:155(78.3) Divorced: 15(7.6) and Single 28(14.1)	-	Heroin, n=108 (54.5), Opium, n=50 (25.3) Opium residue, n= 35(17.7) Crystalline, n= 5 (2.5)	Subjects under MMT for more than 6 months	41.2 ± 7.9 years	210	198	The most severe sexual problems were seen in item orgasm satisfaction 3.62±0.27, then followed by ease of orgasm 3.54±0.35, psychological arousal 3.46±0.35 and sexual drive 3.23±.17, and vaginal lubrication 2.92±0.26.	17
Parvaresh et al., 2015, (30)	Cross-sectional	Male n=180 (90.5%), Female n=19 (9.5%). Single n= 39 (19.6%), Married, n=158 (79.4%), Divorced, n= 2 (1.0%).	Comparison before and after	Heroin n= 9(4.5%), Methn=4(2.0%), Opium33 (16.6%), Crystal 1(0.5%), 13 (6.6%), 139 addiction to two or more substances (69.8%).	6 months	----	199	199	No significant difference between before and after treatment regarding sexual function.	17
Sharif and Nouri, 2015, (26)	Cross-sectional		-	-	-	5.2 ± 1.0	58		Prevalence of sleepiness (91%) Prevalence of vomiting (69%) Prevalence of apnea (53%) Prevalence of loss of consciousness (96%) Prevalence of meiotic pupils (75%).	18
Farnaghi et al., 2012, (25)	Cross-sectional		-	-	-	55 months	31		Prevalence of sleepiness (75%) Prevalence of vomiting (61%) Prevalence of apnea (48%) Prevalence of meiotic pupils (68%).	17
Bazmemoon et al. 2014, (27)	Cross-sectional		-	-	-		62		Prevalence of sleepiness (38%) Prevalence of vomiting (38%) Prevalence of loss of consciousness (85%) Prevalence of meiotic pupils (82%).	17
Jabbehdari et al., 2013, (28)	Cross-sectional	16 boys and 15 girls	-	-	-	55 months	31		Prevalence of loss of consciousness (81%).	17