Gender Differences on Methadone Maintenance Treatment Outcome among Patients with Opioid use Disorder: A Systematic Review

Mohemmad Redzuan Mohemmad Rizal1,2, Amer Hayat Khan1, Sabariah Noor Harun1, Zaiton Saleh2

1Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia, 2Health District Pontian, Ministry of Health, Johor, Malaysia

Objectives: The objective of this study was to review the significant differences of MMT outcomes related to drug use behavior, health status, and social behavioral functioning between genders. Materials and Methods: A search of publication was conducted in PubMed/MEDLINE, Embase, CINAHL, PsycINFO, and Scopus database. Two reviewers independently screened the titles, abstracts, and keyword use for the search. Inclusion of studies was based on randomized controlled trials (RCTs) or observational studies that report the difference of opioid addiction treatment outcomes between genders. Any conflict between the two reviewers was resolved through discussion and consensus. The systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO with a registration number CRD42019116261. Results: A total of 25 studies were evaluated as part of qualitative synthesis. The review resulted in three main themes, which are (1) improving well-being and methadone-related outcome (five subthemes), (2) impact on social and behavioral (four subthemes), and (3) illicit drug use pattern–related behavior (four subthemes). Conclusion: This review will highlight how men and women differ in methadone treatment outcomes for further application and improvement in the clinical setting.

Keywords: Gender difference, methadone treatment outcome, systematic review

INTRODUCTION

Opioid abuse leading worldwide death. A significant increase is observed in rates of opioid use and the risk of its addiction. This risk of addiction includes medical, psychiatric comorbidity, infection, use of polysubstance, and criminal behavior.[1] The increasing pattern of opioid abuse and illicit substance use will approximately double from 2.8 million, which is annual average in 2002–2006, to 5.7 million in the year 2020.[2] Women are typically of younger age, married, unemployed, and have earlier onset age of heroin use.[3] Whereas for men, it is usually for pleasure and recreational purpose, and they have slower disease progression than women.[4] Moreover, women have shown late treatment entry compared to men, less frequent utilization of substance abuse treatment, and more psychological and medical problems at treatment admission compared to men.[5] This shows that the gender difference between men and women is not the same in methadone maintenance therapy (MMT), which requires attention in treatment strategies.

There were studies on factors associated with gender differences in MMT outcome including drug use pattern, opioid use, psychiatric comorbidity, prescription opioid use, smoking outcomes, and quality of life.

Address for correspondence: Mohemmad Redzuan Mohemmad Rizal, Pharmacist, Department of Clinical Pharmacy, School of Pharmaceutical Sciences, University Science Malaysia, Penang 11800, Malaysia. E-mail: evan_world89@yahoo.com

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However, the difference of MMT outcomes between genders reported in previous studies is inconclusive and needs to be compared. Besides, there were studies that investigated gender differences in terms of MMT remission, adverse events, health status, retention rate, criminal activity, social relation, and mortality, nevertheless they showed inconsistent result. Thus, a systematic review was performed to determine the significant differences of MMT outcomes related to drug use behavior, health status, and social behavioral functioning between genders.

**STUDY DESIGN**

**Literature search strategy**

Data for this review were identified by structured review of publications listed in PubMed/MEDLINE, Embase, CINAHL, PsycINFO, and Scopus database. Keywords used to find database studies were as follows: “drug addicts’ treatment,” “opioid addiction,” “opiate substitution treatment,” “methadone maintenance treatment,” “sex differences/characteristic,” “gender differences methadone outcome,” “male,” “female,” “men,” and “women. No language barrier and time constraints were applied. The search was limited to publications in English language that were published after January 1988 to January 2018. Additional publications were identified by reviewing study reference lists and consulting expert review.

**Inclusion and exclusion criteria**

Inclusion of studies was based on randomized controlled trials (RCTs) or observational studies that described/reported the differences of opioid addiction therapy outcomes between genders. Systematic reviews or studies that investigated patient subpopulations or studies that involved the use of methadone for other than opioid addiction, such as for chronic pain treatment, were also excluded. Studies that involved population that may be influenced by their environment, which lead to a high potential for confounding and bias in the outcome, were also excluded. Weak and irrelevant articles, such as patient on a substitute opioid treatment other than methadone (naltrexone and buprenorphine/naloxone) or using methadone other than maintenance treatment, were excluded.

**Data screening**

Two reviewers independently screened the titles and abstracts and recruited the original studies, which fulfill the inclusion criteria. Any conflict between the two reviewers was resolved through discussion, and consensus was developed. Author of the article was contacted directly if data clarification was needed.

**Preferred reporting items for systematic reviews and meta-analyses**

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] [Figure 1]. The systematic review was registered in “International prospective register of systematic reviews (PROSPERO)” with a registration number CRD42019116261.

**Data analytical strategy**

The two reviewers independently assessed the risk of bias by using Newcastle–Ottawa Scale (NOS) for observational studies, and the Cochrane Collaboration tool for assessing the risk of bias in RCTs. Risk of bias was measured on a scale of 0 (high risk of bias) to 3 (low risk of bias), and specific description with example was provided. Items regarding selecting participant and ascertainment of outcome were retained, whereas other items relating to the comparability of groups and adequate follow-up for Cohort and case–control studies were removed as these were not directly applicable to this review. There were categories introduced to emphasize on confounding effect and statistical analysis to minimize bias on methodology. Besides, seven domains on Cochrane’s tool to assess risk of bias in RCTs were used, that is, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was evaluated and assessed on a per study or a per domain basis accordingly based on high or low risk of bias.

![Data extraction of article by using Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines](image-url)
RESULTS

The identification of articles through the searching and information strategy revealed a total of 1747 articles. Examination of these records through abstract and full-text review against the inclusion criteria resulted in a total of 25 studies. Therefore, a total of 25 studies were evaluated as part of qualitative synthesis. The review consists of three main themes: improving well-being and methadone-related outcome (five subthemes), impact on social and behavior (four subthemes), and illicit drug use pattern–related behavior (four subthemes) [Table 1].

DISCUSSION

From this review will be focused on generate ideas during methadone intervention and enhance healthcare, especially among opioid use disorders. Opioid addiction is a crucial concern with limited treatment community. Gender difference, especially men or women, are difference in their susceptibility to opioid addiction and response to methadone treatment.

Improving well-being and methadone-related outcome

The effectiveness of methadone treatment helps by improving well-being outcome toward patient in many aspects, such as psychological status, health status, reduce mortality, adverse drug reaction, and methadone-related dose issues. Concerning the psychological status of the patient, both women and men are different in their mental and psychological aspect. However, in terms of psychological status, women showed greater medical, family-social, and psychiatric illness compare to men. [7-9]

Besides, a significant difference between men and women is found in family support, the proposition than women tend to be more concerned with interpersonal issues than men. [10,11] Women tend to have conflict with family members and felt greater need for treatment for family problems compared to men. [11] Men showed likely to have lifetime diagnose cannabis and alcohol compare to women. Besides, women are likely to have lifetime diagnoses of major depression, bipolar, generalize anxiety, and simple phobia. [10]

Physical and health status is main concern towards opioid use disorder during methadone treatment. Women have overall poorer health status, more chronic health problems, and poorer functioning particularly related to mental health. [8,12] The older age and physical limitation are a greater risk factor for developing chronic illness and comorbidities. Although death from methadone have been reported over the past 30 years, and methadone treatment is likely to reduce mortality risk among men, concurrent opioid and methamphetamine/cocaine use increase the mortality risk among women. [13-15] This is the reason that most of the death related to methadone is due to the respiratory depression and more likely if it is used in combination with other illicit drugs, which include opioid and alcohol.

While, methadone related dose in the differences physiological function between men and women showed no significance differences between gender. [8]

Impact on social and behavioral function

Methadone treatment gives a positive impact on social and behavioral function toward the patient by reducing opiate use. By reducing opiates use related behavior. This resulted on decreasing negative behavior such as committed crimes to obtain money for purchase illegal drugs. There are three studies showed that methadone effectiveness in reducing negative behavior and crime related drug use. [8,20,21]

As a response to this, women show more engaging weekly and daily illegal activities, and they had committed more serious crimes in the past year compared to men. [8] Women were significantly more likely than men to have arrested for prostitution and forgery, whereas men compared to women were arrested for burglary. Arrest for theft significantly decreased for women but remained constant for men. Besides, methadone helps to reduce expenditure on drug-injecting behavior and high-risk behavior, involving the sharing of syringes and needles. There are three studies, which reported that women differ from men in their patterns of obtaining drugs, drug use, and in equipment-sharing behavior. [17-19] Besides, Women showed have a higher risk to be infected with human immunodeficiency virus (HIV) because of unprotected sex by partner and injection practices. [18,19] The difference is in their unsafe sexual intercourse, drug injection, and prison.

While, for employment status showed that men were more likely to be employed compared to women for the past six months on methadone treatment. [8,20,21] Men are easily employed due to the job demand or sociocultural. [21]

Illicit drug use pattern–related behavior

The higher methadone dose may reflect patient with poly substance use, which led to poor sleep quality and chronic pain. [21,22] This may affect patient behavior, psychological, and physical health. [23,24] Patient taking methadone and other poly substance drugs may develop...
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| Table 1: Gender difference on methadone maintenance treatment |
|---------------------------------------------------------------|
| **Aspect** | **Treatment outcome** | **Definition** | **Measurement** | **Article studies** |
| Improving well-being and methadone-related outcome | Psychological status | Mental health and psychiatric disorder | Documented case mental health and psychiatric problems, case reported signs and symptom, and validated psychiatric assessment | Brown et al.[7] Chatham et al.[8] Steer et al.[9] Magura et al.[10] Icick et al.[11] Chatham et al.[8] Grella and Lovinger.[12] Jimenez-Treviño et al.[13] Schiff et al.[14] Evans et al.[15] Chatham et al.[8] |
| | Health status | Improvement/decrease health status | Physical examination/interview/intervention/number of warded | |
| | Mortality | Deceased-related illicit drug use/methadone | Number of deceased, deceased causes, and annual mortality rate per year | |
| Impact on social and behavioral function | Adverse drug reaction | Adverse reaction and side effect during treatment | Physical examination/interview/intervention/number of warded | Graziani and Nisticò.[16] |
| | Methadone-related dose | Average daily dose | Mean dose, milligram/day | |
| | Community relation and support | Relationship status with society and family | Case documented, marital status, friends and family status, and social interaction | Wells et al.[17] Camacho et al.[18] Rezaei et al.[19] Chatham et al.[8] Marsch.[20] Savage and Simpson.[21] Chatham et al.[8] Savage and Simpson.[21] |
| | Risk of sexual behavior | Put others at risk on HIV and other infectious disease | Sexual partners and incidence unprotected sex | |
| | Criminal behavior | Involvement in illegal activities, arrest, or incarcerations throughout treatment or follow-up | Interview/case documented and checklist | |
| | Employment | Status of employment and financial income | Interview/case documented | |
| Ilicit drug use pattern–related behavior | Polysubstance use | Use of at least two non-opioid substances during treatment | Interview/case documented and net reduction in proportion of drug abuse after specific duration | |
| | Response to treatment | Abstaining from illicit drug or opioid use during treatment | Documented case on opioid use during treatment, urine test, and questionnaire | |
| | Retention rate or duration | Proportion of participants completing treatment days | Period of treatment (in days) and proportion of patients retained in treatment for specific period | |
| | Remission status posttreatment | Abstinence from use of illicit drug and opioid use at follow up | Documented case on opioid use after treatment, urine test | Mulvaney et al.[27] Marsch.[20] Savage and Simpson.[21] Grella and Lovinger.[12] Levine et al.[24] Adelson et al.[28] |
several side effects including dizziness, drowsiness, constipation, nausea, and vomiting. Overdose may occur due to increased dosage and build up concentration in plasma of substance abuse overtime.

There are no differences between women and men in response to the treatment[23] and they have a similar retention rate during methadone treatment.[25,26] However, methadone client rarely refused to terminate drug abuse unless they refused to have their methadone dose raised or if they refused to address chronic drug abuse unless they refused to have their methadone treatment.甲

CONCLUSION
The systematic review performed will highlight the difference between men and women in methadone treatment outcome and will help us to understand methadone treatment. This review helps us to provide essential information to physicians and pharmacists during patient monitoring and to perform an intervention on methadone dose adjustment and management of sign and symptom withdrawal and intoxication effect.

Future review direction
This review suggests several recommendations for future studies. First, more studies are needed as it requires to have specific and standard systematic review method for guide research synthesis in the context of methadone treatment outcome, and second, further examination into sex differences in methadone treatment prognosis for individual's treatment is needed.

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Conflicts of interest
There are no conflicts of interest.
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