

# Erectile Dysfunction and Methadone Maintenance Therapy

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## ABSTRAK

Gangguan fungsi ereksi adalah salah satu kesan sampingan metadon yang paling lazim. Gangguan ini menjejaskan lebih daripada separuh populasi pesakit metadon dari segi fungsi seksual mereka. Masalah ini dikaitkan dengan penurunan kualiti hidup yang ketara. Gangguan fungsi ereksi boleh menyebabkan masalah yang lebih besar jika tidak dirawat kerana pesakit mungkin memilih untuk menggunakan rawatan sendiri yang berbahaya seperti menyalahgunakan methamphetamine. Penggunaan dadah untuk mengatasi kesan sampingan metadon boleh menyebabkan gangguan penggunaan dadah ganda yang dapat mengganggu rawatan ketagihan dadah. Untuk mengatasi masalah ini, pengamal dan pesakit memainkan peranan yang penting dalam pengurusan gangguan fungsi ereksi. Kesedaran pesakit mengenai gangguan fungsi ereksi dan impaknya serta intervensi aktif oleh doktor untuk mengesan gangguan fungsi ereksi, adalah penting untuk meningkatkan tingkat pengesanan dan pengurusan gangguan fungsi ereksi. Saringan gangguan fungsi ereksi yang kerap dan faktor risikonya akan membantu mengenalpasti pesakit yang menderita gangguan fungsi ereksi. Pelbagai pilihan rawatan seperti rawatan bupropion, trazodone dan banyak lagi tersedia untuk merawat gangguan fungsi ereksi yang akan diterokai lebih lanjut dalam kajian ini.

*Kata kunci:* gangguan fungsi ereksi, kebergantungan opiat, metadon

## ABSTRACT

Erectile dysfunction is one of the most common side effects of methadone affecting

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more than half of methadone patient population. The problem is associated with prominent reduced quality of life. Erectile dysfunction may perpetuate greater problem if left untreated as patients may opt to use harmful self-treatment such as abusing methamphetamine. This illicit drug use to overcome the side-effects of methadone may lead to polysubstance use disorder that further compromise addiction therapy. To overcome this issue, both practitioners and patients play a major role in the management of erectile dysfunction. Patient awareness regarding erectile dysfunction and its impact as well as doctor's active intervention to detect erectile dysfunction, are essential to improve the detection rate and management of erectile dysfunction. Frequent screening of erectile dysfunction and its risk factors will help with the identification of patients suffering from erectile dysfunction. Multiple treatments options such as bupropion, trazodone and many more are available to treat erectile dysfunction which will be further explored in this review.

Keywords: erectile dysfunction, methadone, opioid-related disorder

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## INTRODUCTION

Methadone has been widely used for the treatment of opioid use disorder. It has been proven to be effective in reducing heroin use, craving, criminality and transmission of infectious diseases (Joseph et al. 2000). However, methadone treatment also causes significant side effects related to opioid such as sexual dysfunction (SD), sleep disorder and weight gain (Parvaresh et al. 2015).

Erectile dysfunction (ED) is one common adverse effects of opioids, including methadone. Zhao et al. (2017) in a meta-analysis study reported nearly two-fold increased risk of ED in opioid-dependent patients. The risk of ED was 82% greater in patient on methadone maintenance treatment (MMT) than those who were not on MMT (Zhao et al. 2017). ED in MMT population deserve significant attention as it is associated

with lower quality of life (Teoh et al. 2017) particularly in patients with more severe ED (Lugoboni et al. 2017; Cheng et al. 2017).

Moreover, ED in MMT patients might facilitate the use of illicit drugs such as methamphetamine. Wang et al. (2015) found the use of methamphetamine in MMT patients was significantly associated with a longer and higher dose of methadone. Radfar et al. 2016 reported that SD as one of the reasons that motivate the use of this methamphetamine to self-treat the side effects of MMT (Radfar et al. 2016).

Despite the high prevalence of ED and its unfavorable effects on MMT patients, the management of this issue is still inadequate. Both patients and practitioners factors contributes to the lack of ED management. The attitude of patients regarding ED problem would determine their health-seeking behaviour. In the general population,

the rate of ED consultation with the doctors varies, ranging from 10.5-25% (Giuliano et al. 2002; Ab Rahman et al. 2011). The reasons for patients' refusal to refer their ED issue for medical attention include the perception of ED as a normal ageing consequence or due to other medical problem (Ab Rahman et al. 2011). In MMT population, only 18.5% of patients sought for medical treatment. The main barriers for seeking medical treatment in this specific population are the perception that ED is not a serious condition and hesitancy (Ramli et al. 2019). In terms of practitioners aspect, engagement of practitioners in sexual-related topic and proper documentation are crucial. A Global Study of Sexual Attitudes and Behaviors (GSSAB) demonstrated that 15% or less of men had ever been asked regarding their sexual problem in the past three years across all regions in the world (Moreira Jr et al. 2005). In total, 48% of men in GSSAB highlighted doctors should routinely inquire patients regarding their sexual function. Moreover, Read et al. (1997) had reported the absent of SD-related notes in 25 people with the most severe SD. These data show the lack of interest or awareness of doctors regarding the sexual health-related topic.

Awareness and knowledges of both patients and practitioners regarding ED and its available treatment options are important so that, ED can be managed efficiently in this specific population. This review aims to increase knowledge and awareness of medical practitioners involve in methadone facilities service with focus on the ED and methadone, prevalence,

pathophysiology, risk factors, screening tools and current treatment options available. We propose an algorithm for ED management in the MMT population.

## **Erectile Dysfunction**

ED is defined as 'the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse' (NIH 1993). The prevalence of ED in the general population varies, ranging from 18.4% to 69.5% (Ab Rahman et al. 2011; Rosen et al. 2004; Selvin et al. 2007). The physiology of erection lies on both neurogenic and vasculogenic factors. Erection needs smooth muscle relaxation of both corpus cavernosa and penile arteries. Relaxation of these structures is regulated by both local and systemic factors and leads to the filling of intracavernosal structures and blood engorgement with subsequent erection (Andersson & Wagner 1995). Interruption of any factors related to this hemodynamic process would result in ED.

There are various factors that can increase the risk of ED, one of which is age. Increasing age is associated with higher risk of ED as well as its severity as demonstrated in multiple studies (Akkus et al. 2002; Selvin et al. 2007). Certain diseases are also related to increased risk of ED such as diabetes, hypertension, heart disease and dyslipidemia (Akkus et al. 2002; Rosen et al. 2004; Selvin et al. 2007; Wei et al. 1994). Wei et al. (1994) found that person with higher total cholesterol, higher low-density lipoprotein or lower high-density lipoprotein has higher

risk of ED. Psychogenic causes such as depression and anxiety are another risk factors for ED (Akkus et al. 2002; Rosen et al. 2004). Sedentary lifestyle such as lack of exercise can also contribute to ED (Selvin et al. 2007).

## **Methadone**

Methadone has similar pharmacological properties to morphine and is categorized into the  $\mu$  opioid receptor (MOR) agonist (Schumacher et al. 2015; Yaksh & Wallace 2017). The affinity of methadone is more prominent towards  $\mu$  receptor whilst affinity towards  $\kappa$  and  $\delta$  receptors is low (Kristensen et al. 1994). Moreover, methadone has the capability of inhibiting NMDA and monoaminergic reuptake transporters (Schumacher et al. 2015).

Methadone is well absorbed orally and the peak concentration is achieved in 2.5-4 hours (Lugo et al. 2005; Yaksh & Wallace 2017). The bioavailability ranged between 60-70% and could be affected by pH, gastric motility as well as gut perfusion (Lugo et al. 2005). Methadone is widely distributed particularly in certain tissue such as brain (Lugo et al. 2005). The half-life of methadone ranges from 15-40 hours (Yaksh & Wallace 2017). Methadone is highly protein-bound with the major portion being bound to alpha-1-acid glycoprotein (Lugo et al. 2005). Methadone is metabolized by the liver into two major inactive metabolites, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP) by CYP3A4 and

CYP2B6 (Lugo et al. 2005; Schumacher et al. 2015). Both renal and faeces are the route of methadone elimination.

Methadone is indicated for the treatment of opioid use disorder. It is suitable to be used as replacement therapy for other opioids such as morphine due to its characteristics such as longer half-life and availability in oral form with acceptable bioavailability. The use of methadone as replacement therapy for opioids had demonstrated favourable outcome in multiple studies. In a meta-analysis study, methadone was shown to retain patients in MMT programme as well as reduce illicit heroin use as compared to non-opioids replacement therapy (Mattick et al. 2009). Another meta-analysis study demonstrated the effectiveness of MMT for reduction of illicit drug use, criminal-related to drug and HIV risk behaviors (Marsch 1998). Despite the proven evidence of methadone effectiveness, methadone is associated with many adverse effects. In this review article, we focus on methadone induced ED.

## **Prevalence of Erectile Dysfunction in Methadone Maintenance Treatment Patients**

The prevalence of ED among MMT patients varies, ranging from 53-87.4% (Hallinan et al. 2008; Nik Jaafar et al. 2013; Teoh et al. 2017; Zhang et al. 2014). Nik Jaafar et al. (2013) found that mild ED was the most prevalent group in MMT patient with prevalence of 36.1%. Teoh et al. (2017) reported the most prevalent group was mild-moderate ED (30.4%). Hallinan et al.

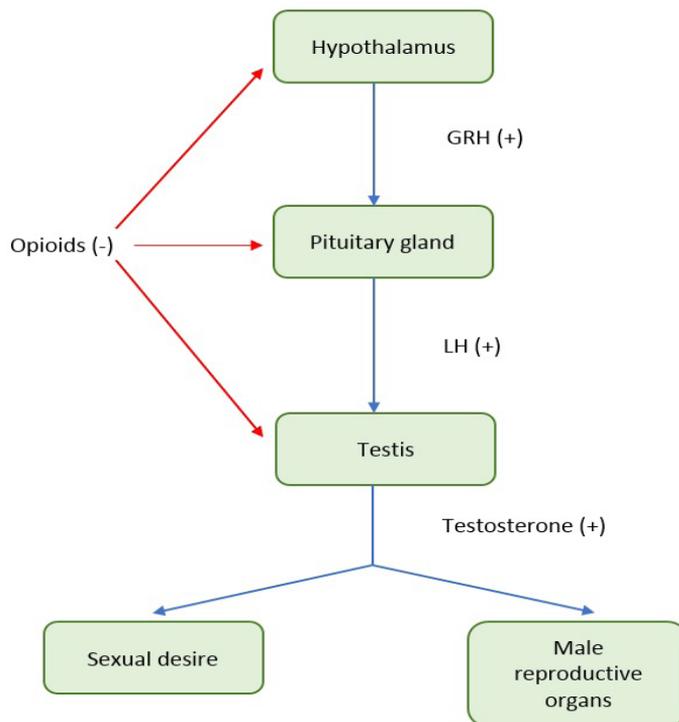


Figure 1: Pathophysiology of opioid-induced sexual dysfunction. Red line indicate the inhibition of opioid on organs. The consequence of opioid inhibition on these organs is low levels of testosterone. Low levels of testosterone may have negative impact on sexual desire and lead to structural and functional alteration of male secondary sexual organ such as seminal vesicles. GRH: gonadotropin-releasing hormone, LH: Luteinizing hormone.

(2008) reported higher prevalence in men with partners above 40s in comparison to under 40s (65% vs 45,5%). Cheng et al. (2017) reported a higher prevalence of patients above 40 in both no-mild ED group (79.6%) and moderate-severe ED group (80%).

### Pathophysiology of Methadone-Induced Erectile Dysfunction

Reduction of serum testosterone level is one of the possible mechanisms for ED in the opioid user which include methadone patients and this might be related to the effect of methadone on hypothalamic-pituitary-gonadal (HPG)

axis (Figure 1). Singh et al. (1982) had demonstrated the gonadotropins-releasing hormone (GnRH) from hypothalamus was inhibited following administration of methadone due to blockade of dopamine pathway resulting in pronounced decreased in testosterone levels in the blood, 15 minutes post methadone administration.

A study conducted in rats showed pronounced effects of methadone on serum testosterone levels and secondary male sex organs (Cicero et al. 1976). This study showed significant reduction in serum testosterone levels and weight of seminal vesicles

and prostate glands. The effects can be explained by the action of opioids on hypothalamus or pituitary gland, resulting in decreased level of luteinizing hormones (LH) and leading to a secondary reduction of testosterone level (Cicero et al. 1976).

Ghowsi & Yousofvand (2015) found similar finding in term of testosterone level. They found significantly lower testosterone level in morphine as well as morphine+methadone treated group compared to the control group. However, LH level was not significantly lowered in morphine+methadone group compared to control group. Similarly, follicle-stimulating hormone (FSH) level was found not to be significantly different. In terms of the effect on secondary sexual organs, only seminal vesicles fluid volume was noted to be significantly reduced in morphine+methadone group. Moreover, Adams et al. (1993) reported that opioid has direct suppressive effects on testosterone secretion via opioid receptors found in the testes.

The reduction of plasma testosterone level might lead to ED. Gerra et al. (2016) had demonstrated a significant association between lower testosterone level with higher SD. Bawor et al. (2015) found significantly lower testosterone levels in men on MMT and negative association between methadone dose and testosterone level in a case-control study. A meta-analysis study on randomised controlled trial found a significant effect of low testosterone levels on diminished libido (Bolona et al. 2007). This indicates lower testosterone level leads to SD by decreasing libido. Figure 1 illustrates

the pathophysiology of methadone-induced ED.

### **Risk Factors of Methadone-Induced Erectile Dysfunction**

Multiple factors are associated with ED in this population. One of the common risk factors is age. Zhang et al. (2014) found significant association between age and SD in heroin-dependent patients after initiation of MMT in three domains; ED, inability to orgasm and lack of sexual desire. Nik Jaafar et al. (2013) and Cioe et al. (2010) demonstrated age was the only significant risk factor for ED among MMT patients. On contrary, Cheng et al. (2017) showed no considerable age difference between no-to-mild ED group and moderate-severe ED group.

Depression is another risk factor for ED in MMT patients. Quaglio et al. (2008) showed MMT patients had a significantly higher risk of depression compared to buprenorphine maintenance therapy (BMT) group with the odds ratio (OR) of 1.06 (95% CI=1.03-1.09). Teoh et al. (2017) demonstrated that depression was significantly associated with ED with the OR of 3.98 (95% CI=1.52-10.40). Lugoboni et al. (2017) found depression was significantly associated with ED with the OR of 2.25 (CI=1.43-3.53). Depression was also found to be substantially correlated with severity of ED (Lugoboni et al. 2017). Another study found no significant association between depression and ED (Nik Jaafar et al. 2013).

The dose and duration of methadone treatments are the other risk factors associated with ED in MMT patients.

The results from various studies yielded either positive or negative significant association as well as no significant correlation. Some studies demonstrated higher methadone dose is associated with worse SD. A meta-analysis study conducted found a significant positive association between methadone dose and ED in MMT patients compared to BMT group (Yee et al. 2014). Similarly, Cheng et al. (2017) found a significant association between higher methadone dose and increased severity of ED. On the other hand, some studies showed a positive impact of MMT on sexual function. Babakhanian et al. (2012) found a significant improvement of erectile function domain score after 6 months MMT. Zhang et al. (2014) reported pronounced improvement in all domains of IIEF-15 after MMT. The improvement in sexual function in both studies above compare before and after MMT treatment in heroin-dependent patients that conclude SD is worse with heroin than methadone. Other studies found no significant association between dose of methadone treatment and ED (Brown et al. 2005; Nik Jaafar et al. 2013).

Abnormal hormone level is also associated with ED. Hallinan et al. (2009) found significantly lower total testosterone, free testosterone and LH level in MMT patients compared to age-matched reference group as well as BMT group. FSH and prolactin levels were not significantly lower compared to other groups. Similarly, Gerra et al. (2016) found that lower testosterone level was significantly associated with higher SD and no significant

association found between prolactin level and SD. On the contrary, Cioe et al. (2010) showed no significant difference in total testosterone level between ED and non-ED group in BMT group.

## Screening for Erectile Dysfunction

International index of erectile function (IIEF) is one of the commonest diagnostic tools for ED. IIEF has been validated in multiple languages and is available in full or simplified version. IIEF discriminate between ED and non-ED as well as classify the severity of ED. The cut-off point in each version might be similar or different, depending on the version. IIEF is introduced by Rosen et al. (1997) and consists of 15 items which include five domains (sexual desire, erectile function, orgasmic function, intercourse satisfaction and overall satisfaction). The internal consistencies (Cronbach's alpha) for each of five domains and overall score were  $\geq 0.73$  and  $\geq 0.91$ , respectively. The test-retest repeatability value were 0.64-0.84.

IIEF is also available in a simplified version. IIEF-5 is one of the versions with high sensitivity (0.98) and specificity (0.88) at cut-off point of 21 (Rosen et al. 1999). The estimated area under receiver operating characteristics (ROC) curve was 0.97 and the estimated kappa coefficient was 0.85 (Rosen et al. 1999). Based on IIEF-5, ED is classified into no ED (score 22-25), mild (score 17-21), mild-moderate (score 12-16), moderate (score 8-11) and severe (score 5-7) (Rosen et al. 1999). The other versions

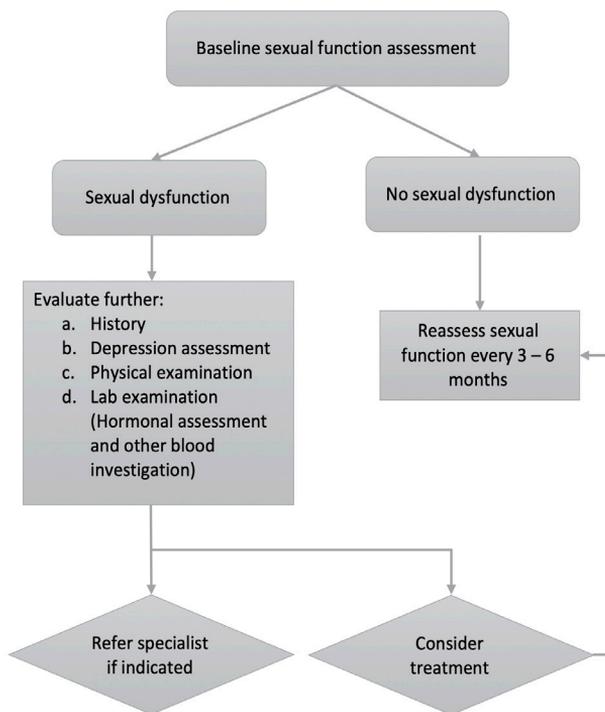


Figure 2: Algorithm for management of erectile dysfunction in methadone maintenance treatment patients

of IIEF-5 have a cut-off point of 17 such as Korean version and Malay version (Ahn et al. 2001; Lim et al. 2003).

Cappelleri et al. (1999) had produced another version of IIEF based on erectile function domains of IIEF-15. This questionnaire consists of six items and has a cut-off point of 25 with the sensitivity of 0.97 and specificity of 0.88. The weighted kappa of this instrument is 0.80. ED severity is classified as no ED (score 26-30), mild (22-25), mild to moderate (17-21), moderate (11-16) and severe (score 6-10).

### Management for Methadone-Induced Erectile Dysfunction

Algorithm for management of erectile dysfunction in methadone patients

All patients who are enrolled in MMT program should be screened for ED using a questionnaire such as IIEF. The propose algorithm is shown in Figure 2. Patient with ED should be further evaluated for current or history of illness or disease and other medications used concurrently. The history taking is important as certain diseases such as hepatitis (Kim et al. 2015), hypertension and diabetes are associated with higher risk of ED (Rosen et al. 2004). Medication such as antihypertensive (Blumentals et al. 2003) and antidepressant (Kupelian et al. 2013) are potential risk for ED. Patient sexual history with partner should be

obtained as partner sexual-related problem may impair sexual activity (Seen Heng et al. 2013). Depression assessment could be considered as depression is an independent risk factor in MMT patient with ED. The risk of ED in MMT patients is four times higher than those without depression (Teoh et al. 2017). Physical examination such as body mass index and blood pressure can be performed to screen for risk factors associated with ED. Blood investigations such as lipid profile (Wei et al.1994) and glucose level or glycemic index (Ugwu et al. 2016) should be carried out to determine the possible condition associated ED. Hormonal assessment such as testosterone level should be conducted to see any hormonal abnormalities as opioids including methadone is a known substance associated with testosterone suppression (Bawor et al. 2015). Underlying conditions such as hypertension, diabetes or depression should be treated accordingly and referral to the specialist should be considered for concurrent management of underlying disease and ED. Physician should carefully select the medication with less potential to cause ED. Pharmacotherapy such as bupropion (Tatari et al. 2013; Yee et al. 2018) and trazodone (Tatari et al. 2013) can be considered for management of ED in MMT patients. Partners with sexual problem should be advised to get assessment and treatment as improvement of partner may contribute to better sexual experience and less dysfunction (Seen Heng et al. 2013). Periodic assessment of ED is needed for patients with or without ED

to assess ED occurrence and response of ED treatment.

#### Pharmacological intervention

There are multiple treatment modalities for the management of ED in MMT patients. Treatments include altering methadone dose, switching to buprenorphine, testosterone replacement therapy or treatment with bupropion, trazodone or rosa damascena oil.

Methadone dose may be reduced to deal with SD side effect. This approach is supported by a meta-analysis study that showed higher methadone dose is associated with a higher SD level (Yee et al. 2014). Cheng et al. (2017) also found a significant association between higher methadone dose and more severe ED. However, this approach might reduce the effectiveness of methadone treatment for opioid disorder and promote illicit drug use such as methamphetamine.

Buprenorphine may be considered as an alternative treatment for those patients with opioid use disorder on MMT who are suffering from ED. This recommendation is supported by a study that demonstrated buprenorphine group had lower SD in libido and potency aspects than methadone group (Bliesener et al. 2005). Another study found a significant difference in IIEF score in MMT group compared to BMT group that indicates more severe ED in the former group (Hallinan et al. 2008). Buprenorphine may be used as an alternative to methadone as it is effective in suppressing illicit opioid use and retaining patient in replacement therapy. The effectiveness

of buprenorphine is comparable to methadone when used as a fixed-dose with medium to high range dose (Mattick et al. 2014).

Testosterone replacement therapy may also benefit MMT patient with ED. Blick et al. (2012) showed significant improvement of sexual function in opioid users patients in 12 months treatment with 1% testosterone gel. This result was comparable to those non-opioid users with SD. The testosterone level was significantly increased after one-month treatment but not at 6 and 12 months probably due to less number of samples collected (n=6-9).

Another treatment option is bupropion. Bupropion is an antidepressant. Pharmacological properties of this medication lie on its ability to increase the level of dopamine and noradrenaline blockade effects centrally via multiple signaling pathway such as dopaminergic and nitric oxide signaling pathway (Dhir & Kulkarni 2007). A result from randomised, placebo-controlled trial found a significant improvement in several domains of IIEF-15 (erectile function, sexual desire) as well as in Sexual Desire Inventory-2 Malay Version (SDI-2-BM) (Yee et al. 2018). Salehi et al. (2015) also reported improvement in SD after eight weeks of treatment with bupropion but not for depression. Tatari et al. (2013) showed significant improvement of SD after 6-week treatment with 100 mg daily bupropion in MMT patient with ED.

Trazodone is an antidepressant that might have beneficial therapeutic effects for the treatment of ED in this population. Trazodone has the ability to

block both serotonin and noradrenaline that explains its therapeutic action as an antidepressant (Brogden et al. 1981). The antagonism of both alpha-1 and -2 adrenergic receptors might explain trazodone effects on erection (Krege et al. 2000). A meta-analysis study conducted showed a beneficial effect of trazodone in the treatment of psychogenic-related ED (Fink et al. 2003). However, data regarding the use of trazodone in MMT group with ED is limited. Tatari et al. (2010) had shown a significant improvement in MMT patients with ED treated with 100 mg daily trazodone after eight weeks of treatment. Further study may need to be done with a larger sample size to investigate the role of trazodone for methadone-induced ED treatment.

Rosa Damascena oil is an alternative treatment for ED in this population. This plant can be found predominantly in certain countries such as Iran and Turkey (Tabaei-Aghdai et al. 2007). Pharmacological effects of Rosa Damascena flowers include antioxidant, antibacterial, antidiabetic, hypnotics and many more (Boskabady et al. 2011). A double-blind randomised-controlled trial had proven the use of this for the treatment of ED. In this study, 2 ml of Rosa Damascena oil or placebo were administered via drop to the patients for eight weeks. Results showed a significant improvement of SD as well as testosterone level in Rosa treated group (Farnia et al. 2017).

## CONCLUSION

ED is a common side effect of

methadone treatment that needs to be addressed. Assessment with a simple tool such as IIEF-5 helps in ED detection. Practitioners who deal with MMT patients should actively screen for ED and provide appropriate management. Testosterone replacement therapy, bupropion, trazodone and Rosa Damascena oil treatment show promising results from randomized controlled trials.

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