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Rosa Damascena oil improved sexual function and testosterone in male patients with opium use disorder under methadone maintenance therapy–results from a double-blind, randomized, placebo-controlled clinical trial

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ABSTRACT

Background: Some patients with opioid use disorder (OUD) are treated with methadone maintenance therapy (MMT). However, as with opioids, methadone has major side-effects; sexual dysfunction is a particularly distressing such effect. Rosa Damascena oil has been shown to reduce subjective sexual dysfunction in patients with major depressive disorders, but its influence on testosterone has not so far been tested. The aim of the present study was to investigate the influence of Rosa Damascena oil on sexual dysfunction and testosterone levels among male patients with OUD and undergoing MMT.

Methods: A total of 50 male patients (mean age: 40 years) diagnosed with OUD and receiving MMT were randomly assigned either to the Rosa Damascena oil (drops) or a placebo condition. At baseline, and four and eight weeks later, patients completed questionnaires covering sexual and erectile function. Blood samples to assess testosterone levels were taken at baseline and eight weeks later on completion of the study.

Results: Over time sexual dysfunction decreased, and testosterone increased in the Rosa Damascena oil, but not in the placebo condition. Sexual dysfunction scores and testosterone levels were not consistently related.

Conclusions: Results from this double-blind, randomized, and placebo-controlled clinical trial showed that Rosa Damascena oil improved sexual function and testosterone levels among males with OUD and undergoing MMT.

1. Introduction

Drug abuse is a serious health concern worldwide and this also holds true for Iran: Amin-Esmaeili et al. (2016) have shown that, in Iran, the prevalence of 12-month use disorders following the DSM-5 criteria was 2.44%, the highest prevalence rates being for opioid use disorders and more specifically opium. The prototypical drug abuser was male, previously married, of low socio-economic status, and with unmet treatment needs. Amin-Esmaeili et al. (2016) also found that self-help groups were the most common type of service used, followed by obtaining medication from pharmacies directly and outpatient treatment services. However, we also note that the 12-month prevalence rate in Iran for drug use disorder was lower than the equivalent rate of 3.9% in the USA (Grant et al., 2016).

Amin-Esmaeili et al. (2016) further reported that patients with OUD used various types of opioids including opium/opium dross (82.3%), the condensed extract of smoked opium ashes ('shireh'; 27.8%), methadone (not prescribed by a physician; 16.6%), heroin (16.1%) and morphine (2.6%); note that multiple responses were possible.

Maintenance substitution therapy with methadone is the standard treatment for OUD (Strain et al., 1999). However, methadone maintenance therapy (MMT) also has side effects. While Peles et al. (2016) found a risk of increased weight gain, Yee et al. (2014) showed in their meta-analysis that of the many adverse events reported, sexual dysfunction was one of the most common side effects, and that the risk of sexual dysfunction among MMT patients was higher than for

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those treated with buprenorphine. In a similar vein, Teoh et al. (2017) reported severe impairments in erectile function among male patients on MMT. More specifically, they assessed the psychological functioning and erectile dysfunction of 147 male outpatients undergoing MMT. The prevalence of erectile dysfunction among these patients was 67%, with 26.1% having mild erectile dysfunction, 30.4% having mild-to-moderate erectile dysfunction, 26.3% having moderate erectile dysfunction, and 17.2% having severe erectile dysfunction. These prevalence rates are in line with the range of 50% to 90% reported elsewhere (Hallinan et al., 2008; Quaglio et al., 2008; Tatari et al., 2010; Yee et al., 2016). Some patients, in addition to erectile dysfunction, have been found to experience orgasm dysfunction, lack of intercourse satisfaction, lack of sexual desire, and lack of overall sexual satisfaction (Zhang et al., 2014).

However, questions arise as to why sexual function, albeit not life-threatening, might be of special concern. Among humans, sexual activity and sexual intimacy serves at least four distinct goals: (1) exploring one's partner's values; (2) reproduction; (3) pair-bonding and pair stabilization (Sela et al., 2015) and (4) joy (Buss, 2015; Meston and Buss, 2007; Miller, 2000) and quality of life (Clayton et al., 2014; Miller, 2000). The sexual activity of couples usually signifies exclusivity, intimacy, and bond-reinforcing behavior (Sela et al., 2015). While typically private, the sexual activity and sexual intercourse of heterosexual couples can occur under many different conditions: (1) before and after the female's fertile phase (ovulation), (2) during pregnancy and (3) during the female's post-menopausal stage, thus indicating that, for heterosexual couples, sexual intercourse must serve needs beyond mere reproduction. Given the exclusivity of sexual activity and its importance to bonding and bonding quality, it is not surprising that its impairment is regarded as distressing and disturbing both for the individual and for couple-related quality of life. Accordingly, research has shown that sexual satisfaction and overall satisfaction are closely linked (Contreras et al., 2016; Fisher et al., 2015; Rosen et al., 2016).

Research on the treatment of methadone-induced sexual dysfunction is not straightforward, and indeed thus far there has been very little research on this issue. Tatari et al. (2010) investigated 55 opioid-addicted individuals undergoing MMT, who also reported erectile dysfunction. After six weeks of treatment with trazodone[1] at 100 mg daily dosages, erectile dysfunction had improved over baseline. The same research group (Tatari et al., 2013) followed up 57 male opioid-addicted individuals. Of these, 93% reported erectile dysfunction and completed a six-week treatment with bupropion. At post-test, methadone-induced erectile dysfunction had declined significantly.

The reasons why methadone may lead to sexual dysfunction remain somewhat unclear, though it may be that methadone as a long-lasting and slow-acting opioid-agonist stimulates the opioid-receptors in the CNS, affecting both the tubero-infundibular and hypothalamic-pituitary-gonadal axes. As a result, prolactin levels increase and the release of gonadotropin-releasing hormone decreases, leading to a down-regulation of sex hormones such as testosterone (de la Rosa and Hennessey, 1996). At a behavioral level, sexual assertiveness and sexual drive decrease (Bawor et al., 2015; de la Rosa and Hennessey, 1996; O'Rourke and Wosnitzer, 2016; Smith and Elliott, 2012; Yee et al., 2016; Yee et al., 2014). In this regard, Bawor et al. (2015) showed in their systematic review and meta-analysis that all opioids suppressed testosterone levels of male opioid users, while such testosterone suppression was not observed among female opioid users. Recently, Gerra et al. (2016) queried whether a purely physiological explanation is sufficient. They assessed 40 patients with opioid-addiction and receiving MMT, and 40 healthy controls. The assessment covered both physiological and psychological variables. Results showed that erectile dysfunction was predicted by methadone dosages, while this was not the case for sexual dysfunction. While sexual dysfunction was associated with the hypothalamus-pituitary-gonadal axis (HPGA)-function and prolactin (PRL) pituitary release, HPAG function and pituitary release was also associated with psychiatric symptoms and childhood neglect scores. Gerra et al. (2016) concluded that the associations between sexual dysfunction, psychological issues and MMT are interlinked, and that an exclusively patho-pharmacological explanation might not be sufficient. Given that MMT leads to the down-regulation of sexual function, both physiologically and psychologically, the aim of the present study was to investigate whether and to what extent Rosa Damascena oil might influence sexual dysfunction. Specifically, we wished to see whether there would be any change in testosterone levels from baseline to the end of the study eight weeks later.

From previous studies we learn that MMT leads to testosterone suppression, sexual dysfunction and erectile dysfunction, that drugs such as trazodone and bupropion might reduce erectile dysfunction, but that there are few if any randomized clinical trials with drugs to reduce not only erectile dysfunction but also sexual dysfunction. Further, drugs such as bupropion and trazodone have side effects that may weaken patients' adherence. To address the current gaps in research, the aim of the present study was therefore to investigating the influence of Rosa Damascena oil on sexual dysfunction among male patients with OUD and undergoing MMT. We also asked to what extent Rosa Damascena oil might affect testosterone levels.

As regards the role of Rosa Damascena oil in ameliorating sexual dysfunction, in two previous double-blind, randomized and placebo-controlled studies, Rosa Damascena oil had a favorable impact on male and female patients with major depressive disorders and with selective-serotonin-reuptake-inhibitors, or SSRI-induced, sexual dysfunction. However, while the influence of Rosa Damascena oil on male SSRI-induced sexual dysfunction in major depressive disorders was moderate to high, its influence on female SSRI-induced sexual dysfunction was small. As detailed in Farnia et al. (2015a,b), in the context of more traditional treatments based on phytopharmaca, Rosa Damascena oil deserves particular attention because, within the long history of Persian medicine, Rosa Damascena (and its oil) is well known for its positive effects on mood, on a broad range of illnesses and diseases and, most importantly, on sexual dysfunction (Boskabady et al., 2011). Rosa Damascena is a hybrid rose species predominantly grown in Iran, Turkey, and Bulgaria to produce rose oil and rose water for use in perfume and in the cosmetic and food industries. The cultivation and consumption of Rosa Damascena in Iran has a long history (Chevallier, 1996). It is believed that the crude distillation of roses for the oil originated in Persia in the late 7th century AD and spread to the provinces of the Ottoman Empire in the 14th century. Iran was the main producer of rose oil until the 16th century and exported it to destinations around the world (Babaei et al., 2007; Rusanov et al., 2005). The extract has also been found to have medicinal properties. It has been shown to have antimicrobial activity. It also has been reported to protect neurons against amyloid-β-toxicity, a major pathological component of Alzheimer's disease, and to protect rats against seizures (Awale et al., 2011; Basim and Basim, 2003; Ramezani et al., 2008; Shokouhinejad et al., 2010). The active components of Rosa damascena are not known. Rosa Damascena oil is composed of a large number of volatile organic compounds including various terpenes, such as citronellol, heneicosane, and disiloxane (Basim and Basim, 2003; Chevallier, 1996). The marc, material left after rose oil is extracted, has significant polyphenol content, including quercetin, myricetin, kaempferol, and gallic acid, though the predominant molecules have been suggested to be glycosides of quercetin and kaempferol (Kumar et al., 2008). With the exception of the previous studies (Farnia et al., 2015a,b) of the effects of Rosa Damascena oil on sexual dysfunction in patients with major depressive disorders and SSRI-induced sexual dysfunction, we currently lack evidence based on double-blind, randomized, and placebo-controlled clinical trials. This holds particularly true for

[1] Trazodone is a SARI, a serotonine-antagonist-reuptake-inhibitor, acting above all on the 5-HT2A-receptor; trazodone is proven for its effectiveness in treating erectile dysfunction (Fink et al., 2003).