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Opioid Substitution Therapy and Sexual Dysfunction

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About the Reviewer

Dr Adrian Gray

Adrian graduated from Otago Medical School in 1975. Since 1999 he has worked for the Auckland Regional Community Alcohol and Drug Service and is a Fellow of the Australasian Chapter of Addiction Medicine.

In recent years his work has been mainly in Opioid Substitution Therapy. The recent increase in long term opioid prescribing since the introduction of slow-release oral preparations, (the 'opioid epidemic") has necessarily focused more attention on the physiological effects of consuming opioids over many years. The long term impact on the endocrine system, in particular, the hypothalamo-pituitary-gonadal axis, has probably not previously been accorded the attention it deserves.

This article presents an overview of sexual dysfunction associated with opioid substitution therapy (OST) with a focus on buprenorphine and methadone. This review is sponsored by Indivior Pty Ltd.

Methadone maintenance therapy (MMT) is established as an effective substitution intervention for opioid dependence.[1] However, sexual dysfunction is an important tolerability issue associated with MMT,[2-4] especially as it may lead some individuals to abandon MMT. Sexual dysfunction reported with methadone use includes:[5,6]

- Hypoactive sexual desire disorder.
- Erectile dysfunction (ED).
- Orgasm dysfunction.

Sexual dysfunction has been correlated with loss of quality of life (QOL) in opioid-dependent individuals, especially in the social relationships domain.[6,7] Sexual dysfunction leading to loss of sexual intimacy can result in premature MMT discontinuation under pressure from a partner or methadone dose reduction.[6]

Patterns of sexual dysfunction with OST

Estimates of the prevalence of impaired sexual function associated with MMT vary between studies (mainly due to differing ethnic populations and study methodologies); however, a 2014 meta-analysis of 16 cross-sectional studies determined a 52% prevalence of sexual dysfunction among users of methadone.[8]

Buprenorphine, which has lower misuse and diversion potential than methadone and carries less social stigma,[9-12] was introduced as an alternative OST agent. Buprenorphine and methadone are probably equally effective as OST agents.[13]

Clinical studies of the prevalence of sexual dysfunction with buprenorphine maintenance therapy compared with MMT have produced variable findings, probably mainly due to their small sample sizes. However, the 2014 meta-analysis found that the pooled prevalence of sexual dysfunction in patients using buprenorphine (24%) was nearly half that of patients using methadone (52%).[8] Additionally, pooled data from four comparative studies identified a 4-fold ($p<0.0049$) lower combined odds ratio of sexual dysfunction with buprenorphine than with methadone.

Buprenorphine and sexual dysfunction

Cross-sectional studies have demonstrated lower frequencies of sexual dysfunction in users of buprenorphine compared with methadone.[6,14-17] In a recent cross-sectional study that investigated sexual dysfunction and QOL in men receiving OST, Yee et al. found that MMT patients with a sexual partner scored significantly lower in the QOL domains of sexual desire ($p<0.012$) and overall satisfaction ($p=0.043$) compared with buprenorphine-treated patients.[6] They also found that improved erectile function and intercourse satisfaction while using buprenorphine was significantly associated with improvements in all domains of QOL measured and that increased sexual desire was significantly associated with improvements in the psychological and social relationship domains (**Table 1**).

	WHOQOL domain							
	Physical health		Psychological Health		Social relationships		Environment	
Mal-IIEF-15 domain	**MMT**	**BMT**	**MMT**	**BMT**	**MMT**	**BMT**	**MMT**	**BMT**
Erectile function	0.175	0.363*	0.222*	0.367*	0.162	0.367*	0.186	0.351*
Orgasmic function	0.161	0.268	0.211*	0.305	0.195*	0.278	0.215*	0.324
Sexual desire	0.075	0.086	0.111	0.444**	0.19	0.5**	0.112	0.283
Intercourse satisfaction	0.141	0.433**	0.277**	0.531**	0.206*	0.590**	0.207*	0.455**
Overall satisfaction	0.166	0.274	0.309**	0.241	0.262**	0.292	0.186	0.151

Table 1. Adjusted partial correlation coefficients between sexual function (Mal-IIEF-15) scores and quality of life (WHOQOL-BREF) scores for buprenorphine (BMT) and methadone maintenance therapy (MMT) in opioid-dependent patients with sexual partners.[6] Abbreviations: Mal-IIEF-15 = Malay version of the International Index of Erectile Function 15; WHOQOL-BREF = World Health Organization Quality of Life – Abbreviated version. Statistically significant correlation: *$p<0.05$; **$p<0.01$.

Sexual function changes with buprenorphine have also been assessed longitudinally. In a randomised, double-blind, placebo-controlled study, opioid-dependent men with ED who initiated and remained on buprenorphine maintenance therapy for 3 months achieved significant baseline improvements in erectile function ($p=0.001$) and sexual desire ($p=0.02$).[18] Contrastingly, a 3-month follow-up study in opioid-dependent men receiving MMT found that ED worsened over time after initiation of MMT.[4]

Mechanisms of sexual dysfunction

A lower likelihood of experiencing impaired sexual function during buprenorphine maintenance therapy than during MMT may be due to the differing opioid receptor binding profiles of buprenorphine and methadone.

Methadone is a full agonist at the μ (mu)-opioid receptor,[19] whereas buprenorphine is a mixed agonist-antagonist opioid acting as partial agonist at the μ-opioid receptor and full antagonist at the κ (kappa)-opioid receptor.[20] Stimulation of κ-opioid receptors has been demonstrated to suppress the gonadal axis,[21] and it has been proposed that the antagonism of buprenorphine at the κ-opioid receptor may counteract μ-opioid receptor-mediated suppression of the gonadal axis.[14]

Sexual dysfunction is, however, a complex phenomenon involving the interplay of hormonal, neurobiological, and psychosocial factors and can be attributed to physiological effects of medical disorders such as atherosclerosis and to an inhibitory role of some drugs in reduced sexual desire such as opioid-induced sedation.[22,23]

EXPERT'S CONCLUDING COMMENTS

It has become well recognised that opioids exert significant effects on the endocrine system with the most marked changes observed in the hypothalamic-pituitary-gonadal axis and to a lesser extent the hypothalamic-pituitary adrenal axis. This has been labelled opioid-induced androgen deficiency (OPIAD), and highlights the fact that greatest effect has been observed in the reduction of testosterone levels in males.[24] However, similar reductions (in oestradiol and testosterone) have been demonstrated in both pre- and post-menopausal women,[25] and surveys have demonstrated very high levels of sexual dysfunction in both men and women.

It is a simple matter to test early morning testosterone levels in men. The potential advantages of testosterone augmentation can be discussed and the contraindications reviewed.[26] For women, the interpretation of hormone levels is more complex and the benefit-to-risk ratio in post-menopausal women is complicated. A discussion with a gynaecologist with expertise in the subject should precede any decision to treat.

Alternatively, the potential benefits of converting to buprenorphine, with its reported reduced incidence of sexual dysfunction, may be discussed with the patient.

It is most important, however, to remember to enquire about sexual dysfunction in patients on long-term opioid treatment as they may be reluctant to raise the subject. If the impact on wellbeing is clear and hormone levels are reduced a trial of hormone replacement therapy could lead to a marked improvement.

TAKE-HOME MESSAGES

- Sexual dysfunction reduces QOL in patients on OST, which may contribute to treatment non-adherence.
- Current clinical evidence suggests that buprenorphine is less likely than methadone to cause sexual dysfunction in opioid-dependent individuals undergoing OST.
- The mechanism underlying a lower rate of sexual dysfunction with buprenorphine is unclear but may be due to simultaneous partial agonism at the μ-opioid receptor and full antagonism at the κ-opioid receptor.
- Buprenorphine can be considered an effective OST option for opioid-dependent individuals in whom sexual dysfunction is identified.

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