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REVIEW

The Impact of Buprenorphine Maintenance Therapy on Male Sexual Function in Opioid-Dependent Individuals: A Systematic Review and Meta-Analysis

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Abstract

Purpose of review Sexual dysfunction (SD) is a common complication of opioid use disorder (OUD), and its treatment. Methadone maintenance therapy (MMT), as a cornerstone of OUD treatment, is frequently associated with SD. Buprenorphine maintenance therapy (BMT), due to its distinct pharmacology, may offer an alternative with a potentially lower risk of SD. This study aimed to synthesize the evidence on the effects of BMT on male sexual function in opioid-dependent individuals.

Recent Findings Following PRISMA guidelines, a systematic search was conducted in PubMed, ProQuest, Web of Science, Scopus, and the Cochrane Library. This review identified 12 eligible studies for qualitative synthesis, mostly comparing BMT and MMT. Pooled data from seven studies employing the International Index of Erectile Function (IIEF) demonstrated that, compared to MMT, BMT was associated with significantly better scores in erectile function (SMD = 0.360, $p < 0.001$), orgasmic function (SMD = 0.22, $p = 0.046$), sexual desire (SMD = 0.70, $p < 0.001$), and intercourse satisfaction (SMD = 0.41, $p = 0.001$). The total IIEF score was also significantly higher for BMT (SMD: 0.807, $p < 0.0001$). However, no significant difference was found in the overall satisfaction. Meta-regression indicated that most IIEF scores were independent of buprenorphine dose, methadone dose, or treatment duration.

Summary The current evidence indicates that BMT is superior to MMT in preserving male sexual function, particularly desire and erectile function. These findings support the consideration of BMT as a preferred maintenance treatment for patients prioritizing sexual health and underscore the importance of routine sexual health screening in clinical management.

Keywords Buprenorphine · Methadone · Sexual dysfunction · Male · Opioid agonist treatment

Introduction

Opioid use disorder (OUD) represents a considerable global public health issue, impacting approximately 40.5 million individuals globally [1]. Opioid dependence adversely impacts several aspects of life, including physical health, psychological well-being, social functioning, and sexual health [2]. Among these, sexual dysfunction (SD) is a frequently reported complication associated with both opioid use and opioid agonist treatment (OAT) [3, 4].

Sexual function plays a vital role in overall human well-being, greatly affecting quality of life and relationship satisfaction [5, 6]. Moreover, its impairment can negatively impact self-esteem, interpersonal relationships, and treatment adherence, potentially leading to relapse.

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Heroin and various opioids interfere with the hypothalamic-pituitary-gonadal (HPG) axis, leading to hormonal imbalances resulting in reduced testosterone levels, elevated prolactin levels, and changes in luteinizing hormone (LH) secretion [7]. These hormonal dysregulations frequently present as decreased libido, erectile dysfunction, delayed ejaculation, and lower sexual satisfaction. Additionally, opioid-dependent individuals frequently become involved with high-risk sexual behaviors, which are potentially stimulated by sexual dissatisfaction or dysfunction, ultimately increasing their vulnerability to sexually transmitted infections, including HIV [8–10].

Methadone maintenance therapy (MMT), a fundamental approach to OUD treatment for decades, has been frequently associated with a high prevalence of SD. Studies report that up to 70–90% of men on MMT experience various forms of SD, often attributed to methadone's considerable suppression of testosterone [11]. However, the introduction of buprenorphine—a partial μ-opioid receptor agonist and κ-opioid receptor antagonist—has provided an alternative with a favorable safety profile and lower abuse potential than full agonists [12].

Its distinctive pharmacological characteristics may lead to a less prevalent suppression of the HPG axis, thereby alleviating sexual side effects [13]. Despite its growing clinical use, the impact of BMT on male sexual function remains a topic of ongoing research. Current studies yield contradictory findings; some suggest enhanced sexual outcomes compared to methadone, whereas others indicate no significant differences. Moreover, factors such as depression, partner status, concomitant substance use, and psychosocial context further complicate this association. This systematic review and meta-analysis aim to synthesize the available evidence for the effects of BMT on male sexual function in opioid-dependent individuals. By comparing BMT with other common treatments—including methadone, naltrexone, and opium tincture—we seek to clarify buprenorphine's role in preserving sexual health and improving overall treatment outcomes.

Methods and Materials

Study Design

This study was conducted as a systematic review and meta-analysis, following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The review protocol has been designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The protocol of the study was registered in the interventional prospective register of systematic reviews (PROSPRO) database (registration number: 1138860).

Search Strategy

A systematic literature search was conducted in electronic databases, including PubMed, ProQuest, Web of Science, Scopus, and the Cochrane Library, from inception until May 2025.

We combined Medical Subject Heading (MeSH) terms and text words to generate a search query that included three components and all their MeSH terms: "Male Sexual Dysfunction" and Buprenorphine. Furthermore, detailed individual search strategies were developed for each of the databases (Appendix Table S1). Bibliographies of eligible articles were searched to find cross-references and further relevant reports.

Study Selection

Studies retrieved from electronic database searches were imported to the EndNote Reference Manager (EndNote Software; V-20.4.1) to manage the studies and remove the duplicates.

Titles and abstracts of all retrieval articles were independently reviewed by two investigators (A.B., M.K.) to select relevant articles to screen full text. Any disagreements were resolved through discussion, and if necessary, the third researcher was consulted to make the final decision (R.M.).

Next, the full text of potentially eligible articles was independently assessed against the eligibility criteria by two investigators (A.B., M.K.). Again, in case of disagreement, the consensus was reached on inclusion or exclusion by discussion, and if necessary, the third researcher was consulted (R.M.). The inclusion criteria were applied as follows: (1) All interventional, longitudinal, and observational studies (2) were published in English (3) in which adult male individuals with OUD undergoing BMT were compared with (4) those who used Methadone Maintenance Therapy (MMT), opium tincture, or no treatment (heroin), and (5) they reported quantitative data on sexual dysfunction (e.g., prevalence, mean ± SD scores on validated scales like the International Index of Erectile Function (IIEF; including the Malay version, Mal-IIEF-15), and the Arizona Sexual Experience Scale (ASEX). Case reports, abstracts, letters, narratives, or systematic reviews were excluded.

Additionally, studies conducted on specific comorbid populations using buprenorphine not generalizable to the general BMT population, studies with overlapping data or duplicate publications, and studies where the full text was unavailable or where necessary outcome data could not be extracted or calculated were excluded.

Data Extraction

Data from included studies was extracted independently by two reviewers (A.B., M.K.) using a standardized, piloted data extraction form. The extracted information will include:

- General study characteristics: first author, publication year, country, study design.
- Population characteristics in the BMT and comparison groups: sample size, mean age.
- Intervention details in the BMT and comparison groups: mean dosage, mean duration of treatment.
- Comparison group details: type of control (e.g., methadone, no treatment).
- Outcome data: mean scores and standard deviations (SD) for sexual function questionnaires (IIEF, ASEX).
- Assessment tools: specific questionnaire used (e.g., IIEF-5, ASEX).

Quality and Risk of Bias Assessment

The methodological quality of included studies was assessed independently by two reviewers (A.B., N.E.), and any disagreements were resolved through consensus. For non-randomized observational studies (cohort, case-control, cross-sectional), the Newcastle-Ottawa Scale (NOS) was employed [15]. NOS employs a star-based rating system to evaluate eight criteria across three categories: selection (up to 4 stars), comparability (up to 2 stars), and outcome (up to 3 stars). (Appendix Table S2).

The following score conversions are applied to align with the Agency for Healthcare Research and Quality (AHRQ) categories—good, fair, and poor:

- Good quality: Studies must receive 3–4 stars in selection, 1–2 stars in comparability, and 2–3 stars in outcome.
- Fair quality: Studies are rated with 2 stars in selection, 1–2 stars in comparability, and 2–3 stars in outcome.
- Poor quality: Studies that score 0–1 star in selection, or 0 stars in comparability, or 0–1 star in outcome fall into this category.

Outcome Measured

The primary outcomes of our study include IIEF and its 5 domains (Erectile Function, Desire, Orgasm Function, Intercourse Satisfaction, and Overall Satisfaction) and the Five-Item IIEF (Total score). Although IIEF and Five-Item IIEF have similar functions, there are still differences in significance and scoring methods; therefore, we conducted meta-analyses on them separately to avoid bias. In order to more accurately understand the effect of BMT on each domain of IIEF, we conducted a meta-analysis on the 5 domains of IIEF.

Qualitative Data Synthesis and Statistical Analysis

Data synthesis involved both a qualitative narrative summary and a quantitative meta-analysis. For the qualitative synthesis, findings were summarized narratively to describe patterns of sexual dysfunction across studies and subgroups. When sufficient data were available and studies were clinically homogeneous, all statistical analyses and meta-analyses were performed using Comprehensive Meta-Analyses (CMA) V2 software (Biostat, NJ), and the significance level was set at $P<0.05$. The pooled prevalence of sexual dysfunction and pooled effect estimates (including Standard Mean Differences for questionnaire scores compared to controls) were calculated using random-effects models.

Heterogeneity was assessed using the I^2 statistic, with values exceeding 50% indicating substantial heterogeneity that warranted a random-effects model. Additionally, heterogeneity between studies was evaluated using Cochran's Q test (with statistical significance set at $p<0.1$) and quantified using the I^2 statistic (where $I^2 \geq 50\%$ indicated significant heterogeneity). A random-effects model was applied to do meta-analysis.

Planned subgroup analyses were conducted to determine potential sources of heterogeneity based on buprenorphine dosage, methadone dosage, BMT duration, mean age of each group, and prevalence of depression. Sensitivity analysis was performed using the leave-one-out method, systematically excluding individual studies and repeating the analysis to assess each study's influence on the overall effect size. Meta-regression employing the unrestricted maximum likelihood method was performed to examine associations between effect sizes and several variables: buprenorphine daily dose, methadone daily dose, BMT duration, and scores across IIEF domains.

Potential publication bias was evaluated through visual inspection of funnel plot asymmetry and statistical assessments using Begg's rank correlation and Egger's weighted regression tests. The Duval & Tweedie 'trim and fill' method and the 'fail-safe N' method were utilized to adjust for potential publication bias in the analysis.

Results

Study Selection

The systematic literature search of electronic databases (PubMed, Cochrane Library, ProQuest, Web of Science, and Scopus) yielded a total of 385 records. After removing

113 duplicate records, 272 unique articles remained for title and abstract screening. Following this initial screening, 244 articles were excluded for not meeting the inclusion criteria. The full texts of the remaining 27 articles were assessed for eligibility. Of these, 16 studies were excluded for the following reasons: the outcome of interest was not evaluated [9, 16–23], there was a lack of a relevant comparison group [10], or the study design was a review [24–26] or abstract [27]. One additional article was identified through a manual search of the reference lists [28]. Ultimately, 12 studies [28–39] met al.l eligibility criteria and were included in the qualitative synthesis. A meta-analysis was performed on a subset of these studies that provided comparable outcome data. The study selection process is detailed in the PRISMA flow diagram (Fig. 1).

Study Characteristics

The baseline characteristics of the 12 included studies are summarized in Table 1. The studies published between 2004 and 2025, were conducted in various countries, including Germany, the United Kingdom, Italy, Australia, Iran, India, Malaysia, and Slovenia. There were 11 cross-sectional studies and one randomized clinical trial [28]. The sample sizes in the BMT groups ranged from 17 to 116 participants.

All studies enrolled male participants with opioid use disorder. The most frequent comparison group was MMT, which was employed in 11 studies. Other comparisons included heroin use (active addiction), opium tincture, and sustained-release morphine.

The mean daily dose of buprenorphine varied across studies, ranging from 2.43 mg to 12.29 mg. The mean treatment duration for BMT, where reported, also showed considerable variation. Sexual dysfunction was assessed using several validated instruments, including the International Index of Erectile Function (IIEF, including the Malay version Mal-IIEF-15), the Arizona Sexual Experience Scale (ASEX), and other specialized questionnaires.

Quality and Risk of Bias Assessment

The methodological quality of the included non-randomized studies was assessed using the Newcastle-Ottawa Scale. The NOS scores ranged from 6 to 10 out of a possible 10 points. Based on these scores, nine studies were rated as high quality (Good quality and low risk of bias), one studies were of moderate quality (Fair quality and moderate risk of bias), and two studies were considered low quality (Poor quality and high risk of bias) (Appendix Figure S1). The primary areas leading to a lower score were related to the comparability and sample size justification. The detailed results of the quality assessment are presented in Fig. 2, Appendix Table S2.

Qualitative Synthesis

Based on a systematic review of the existing evidence, although the impact of maintenance treatment with opioid agonists on men's sexual function was complex, there is a consistent pattern indicating that BMT was associated with a more favorable sexual side effect profile compared to

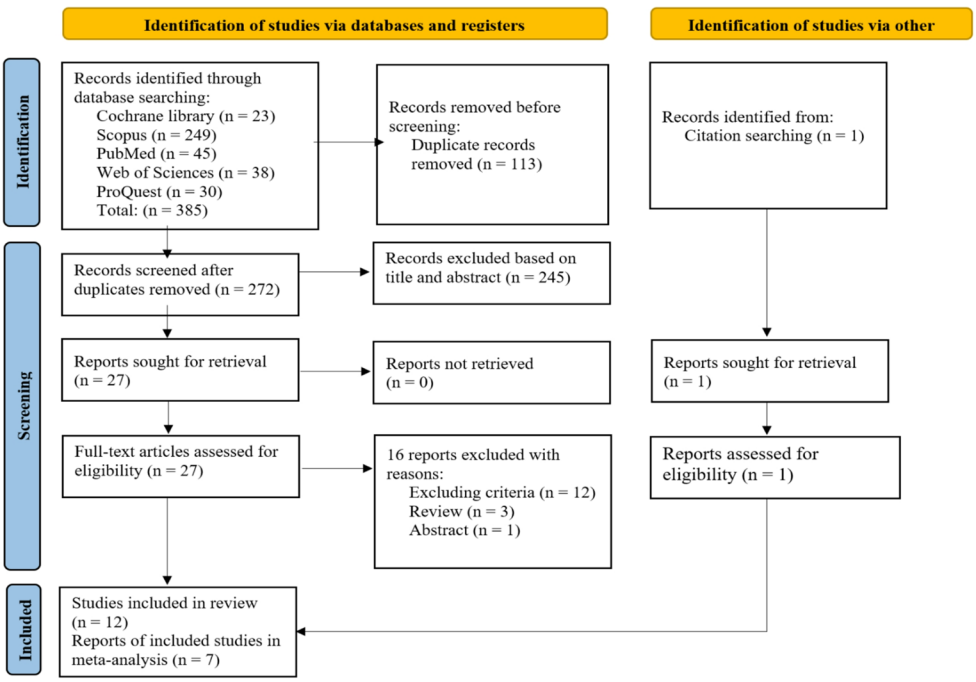

Fig. 1 PRISMA flow diagram demonstrating study selection

Table 1 Baseline characteristics of the studies

Author (year)	Country	Comparison group	Buprenorphine group(*n*)	Comparison group(*n*)	Mean age(B), Year	Mean age(C), Year	Daily dose(B), mg	Daily dose(C), mg	Duration of BMT	Criteria for definition of SD (Questionnaire)	Quality (NOS Score)
Bliesener (2005) [30]	Germany	Methadone	17	37	34.7	37.5	11.2	88.4	-	Self-rating sexual function questionnaire	6
Al-Gommer (2007) [32]	United Kingdom	Methadone, heroin	28	33	25.5	29	6.45	56	7.4	Loyola University Clinic-special history sheet for men	9
Quaglio (2008) [31]	Italy	Methadone	116	85	31	30.4	6	40	11.5	Mal-IIEF-15	10
Hallinan (2008) [33]	Australia	Methadone	19	84	35	38.3	10.2	106	26 m	Mal-IIEF-15	9
Tafreshian (2014) [34]	Iran	Methadone	56	102	33	39	8	64	92	IIEF	6
Yee (2016) [35]	Malaysia	Methadone	67	171	43.43	43.01	4.06	77.08	50.03	Mal-IIEF-15	10
Yee (2018) [36]	Malaysia	Methadone	31	76	41.87	43.3	2.43	75.92	63.94	Mal-IIEF-15	9
Yee (2019) [37]	Malaysia	Methadone	31	95	41.6	43.51	2.44	74.53	64.47	Mal-IIEF-15, SDI-2BM,	10
Kheradmand (2019) [28]	Iran	Methadone, Tincture	28	28 in each group	38.78	37.03	-	-	-	ASEX	10
Bahadori (2022) [38]	Iran	Methadone, Tincture	24	116	46.80	48.31	3.33 mi	18.15	9.75 m	IIEF	8
Sen (2023) [29]	India	heroin	49	63	37.1	31.7	12.29	-	36.8	NSSS-S, SQoL-M, Mal-IIEF-15, IPE	6
Segrec (2025) [39]	Slovenia	Methadone, SR morphine	60	60 in each group	34.7	34.6	40	77.5	-	IIEF 9	9

ASEX: Arizona Sexual Experience Scale, B: Buprenorphine, BMT: Buprenorphine Maintenance Therapy, C: Comparison, IIEF: International Index of Erectile Function, IPE: Index for Premature Ejaculation, Mal-IIEF-15: Malay version of International Index of Erectile Function 15, NOS: Newcastle-Ottawa Scale, NSSS-S: the New Sexual Satisfaction Scale-Short form, SD: Sexual Dysfunction, SDI-2: Sexual Desire Inventory-2, SEAR: Self-esteem and Relationship Questionnaire, SQoL-M: the Sexual Quality of Life Questionnaire-Male

MMT. The prevalence of SD in both treatment groups was significant, but it has been consistently reported to be higher in patients undergoing MMT. Research indicates that the prevalence and severity of SD in the MMT group are significantly elevated; for example, the incidence of ED has been recorded as high as 78% [29], accompanied by a decrease in libido of up to 83% [30]. Conversely, these statistics are markedly lower in the BMT group (ED: 12.5% to 39% [29, 31, 34]; decrease in libido: 8.9% to 23% [30, 34]). This pattern is also supported by better scores for BMT patients on standardized questionnaires.

Factors influencing sexual dysfunction extend beyond the type of agonist used. Total plasma testosterone levels in MMT patients are considerably lower than those in BMT patients [33, 35–37]. Additionally, psychological factors such as depression [31, 33] and the lack of a stable sexual partner [31, 36] have been identified as significant predictors of sexual dysfunction. In addition, higher doses of methadone and a longer duration of therapy have been correlated to more sexual side effects in MMT [34]. However, the evidence was not entirely uniform. Several studies, following the adjustment for confounding factors, found no statistically significant differences between the two groups [28, 31, 33, 38]. These findings suggest that in certain populations, psychosocial factors and concurrent issues like depression may play a more important role than the type of medication in sexual health.

Quantitative Synthesis (Meta-Analysis)

A meta-analysis was conducted to compare the mean scores of the IIEF domains between the BMT and MMT groups. Forest plots summarizing the random-effect meta-analysis of studies assessing BMT's effects on male sexual function using the IIEF questionnaire are illustrated in Fig. 3. A total of seven studies reported the IIEF score. We analyzed the IIEF total Score and its five domains separately

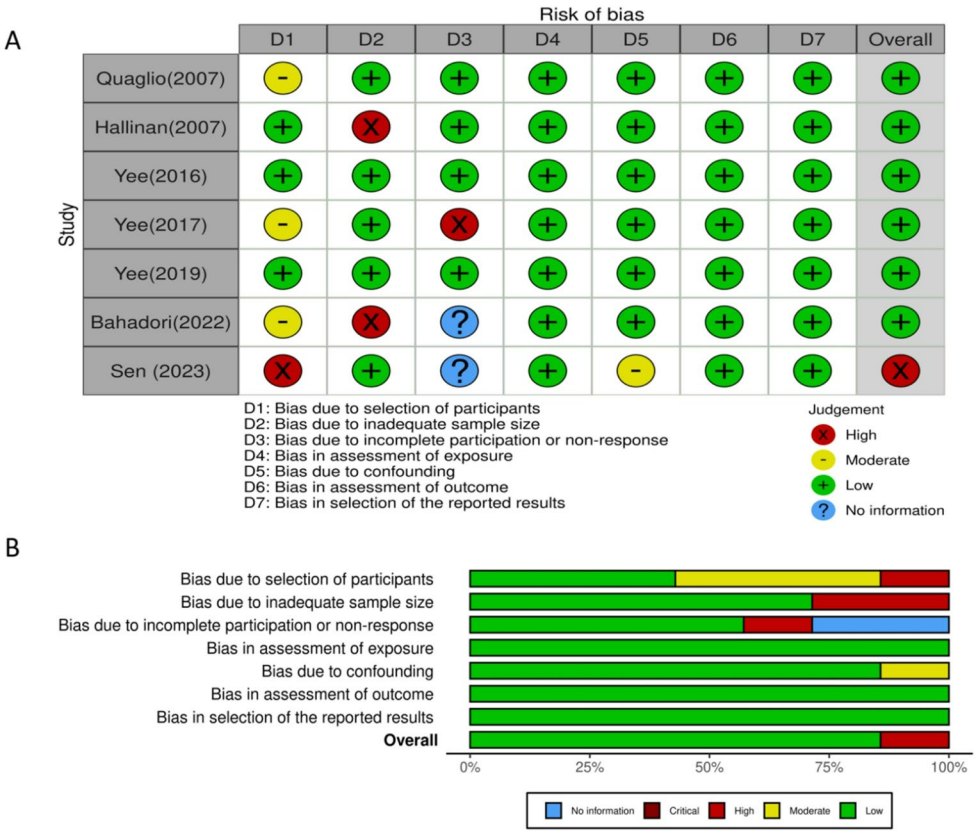

Fig. 2 Risk of bias assessment for the studies included in the meta-analysis using the Newcastle-Ottawa Scale. Traffic light plot (**A**), Summary plot (**B**)

to comprehensively understand the effect of BMT on male sexual function.

The pooled results from six studies, using a random-effects model, demonstrated a statistically significant higher mean erectile function score in the BMT group compared to the MMT group (SMD = 0.360, 95% CI: 0.18 to 0.53, $p < 0.001$) with no significant heterogeneity among the studies (Q = 6.11, $I^2 = 18.18\%$, $p = 0.296$). This suggests better erectile function in patients receiving buprenorphine (Fig. 3A).

Analysis of the orgasmic function domain from five studies also favored BMT over MMT. The pooled mean difference was 0.226 (95% CI: 004 to 0.449, $p = 0.046$, $I^2 = 24.42\%$), indicating superior orgasmic function in the BMT group (Fig. 3B). The meta-analysis of the data from five studies showed significant effect of BMT on the sexual desire score (SMD: 0.707; 95% CI: 0.512 to 0.902; $P < 0.001$, I^2: 0.00) (Fig. 3C).

Regarding intercourse satisfaction, meta-analysis of five studies indicated that treatment with buprenorphine led to a significantly higher score (SMD = 0.411, 95% CI: 0.174 to 0.648, $p = 0.001$) with moderate heterogeneity (Q = 5.90, $I^2 = 32.24\%$, $p = 0.206$). However, no significant difference was found in the overall satisfaction score between the two groups (SMD = 0.016, 95% CI: −0.045 to 0.398, $p = 0.940$, $I^2 = 77.71\%$).

Four cross-sectional studies, with a total of 448 participants, reported the total IIEF score. The random-effects model meta-analysis showed that the total IIEF score was significantly higher in BMT patients than in MMT patients (SMD = 0.807, 95% CI: 0.531 to 1.083, $p < 0.0001$). No significant heterogeneity was found (Q = 6.11, $I^2 = 18.18\%$, $p = 0.296$).

Subgroup and Sensitivity Analyses

Planned subgroup analyses were performed to explore potential sources of heterogeneity by categorizing age in BMT group, age in MMT group, buprenorphine dose, methadone dose, BMT duration, and the depression prevalence for each IIEF domain separately. As presented in Table 2, stratification by BMT duration (< 50 month vs. ≥ 50 month) revealed a more pronounced favorable effect of BMT on overall satisfaction score in the longer duration subgroup, and the difference between subgroups was statistically significant (p-value for subgroup difference = 0.037). Similarly, analysis based on depression prevalence consistently favored BMT over MMT for the overall satisfaction score in the subgroup with a lower prevalence of depression ($p = 0.037$); in this subgroup, heterogeneity was either decreased or entirely removed. The results of the subgroup

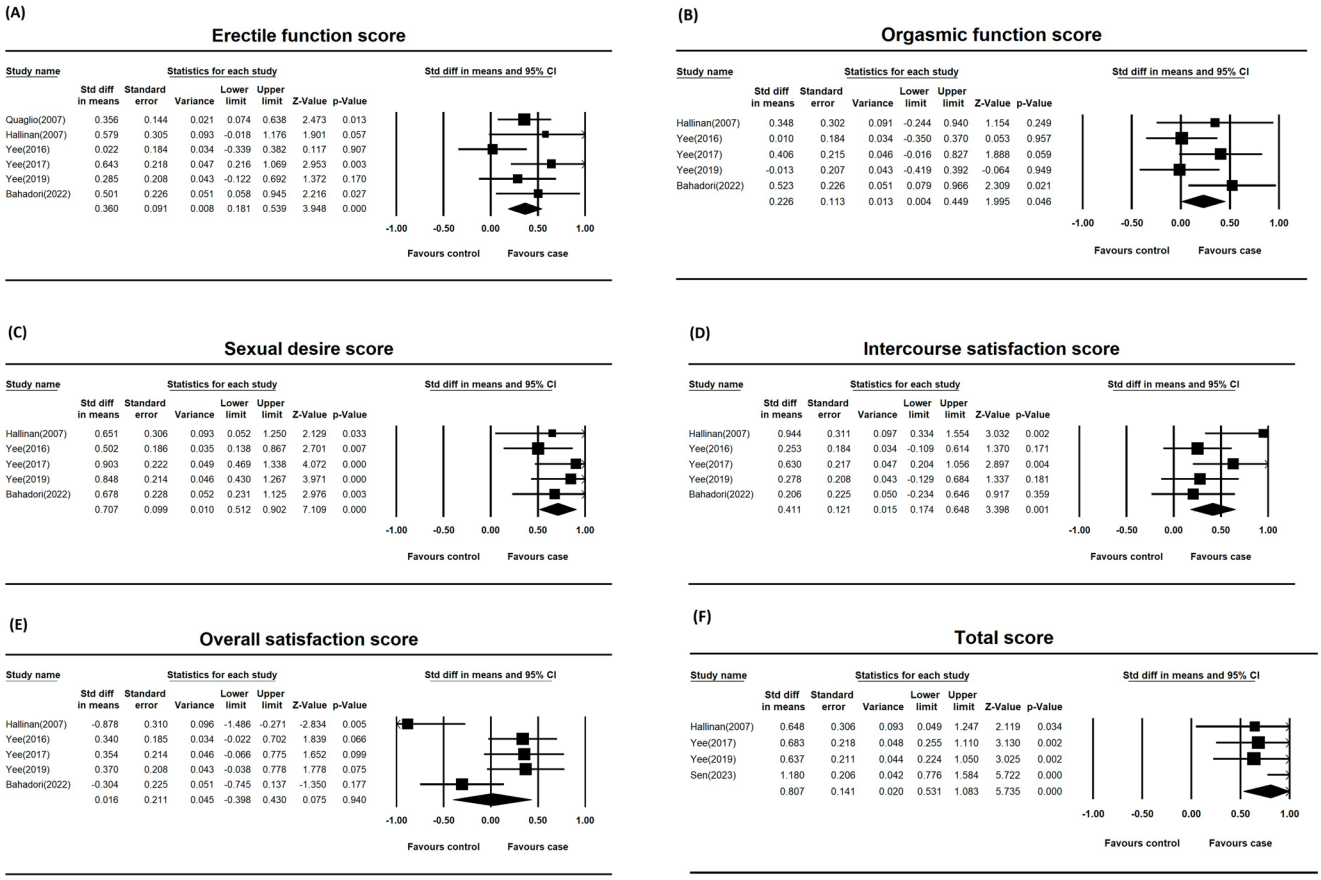

Fig. 3 Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of BMT on IIEF domains score. Erectile function Score (**A**), Orgasmic function score (**B**), Sexual desire score (**C**), Intercourse satisfaction score (**D**), overall satisfaction score (**E**), Total score (**F**)

analyses for the remaining factors in the other domains were non-significant.

The results of leave-one-out method sensitivity analysis are presented in Appendix Figure S2. The estimated effect of BMT on the orgasmic function score was sensitive to the exclusion of the studies conducted by Yee et al. and Bahadori et al. (Appendix Figure S2B). In contrast, the effect size for sexual desire score was robust in the leave-one out sensitivity analysis (Appendix Figure S2C). For the other outcomes, the removal of any single study did not substantially influence the results; the direction and statistical significance of the pooled effect estimate for the IIEF total score and other domain scores remained unchanged. This indicates that the overall findings were not unduly influenced by any individual study.

Meta-Regression

A univariable meta-regression analysis was performed to evaluate the association between IIEF domain scores and potential moderator variables (Table 3). The results suggested that the pooled estimate of erectile function score was independent of the buprenorphine daily dose (slope: 0.01; 95% CI: −0.077 to 0.098; $P=0.817$), methadone daily dose (slope: −0.0008; 95% CI: −0.006 to 0.006; $P=0.845$), and the duration of BMT (slope: −0.001; 95% CI: −0.010 to 0.007; $P=0.750$) (Figure S3).

Regarding the overall satisfaction score, the coefficient for the buprenorphine dose was negative and statistically significant, indicating that an increase in the buprenorphine dose was associated with a decrease in the overall satisfaction score. Furthermore, the meta-regression revealed a positive association between BMT duration and the overall satisfaction score. For the remaining IIEF domains, the results showed no significant associations with these moderators, as presented in Figures S4-S7.

Publication Bias

Visual inspection of the funnel plot for the comparison of IIEF scores between BMT and MMT revealed a roughly symmetrical distribution (Fig. 4). However, as this method is not recommended when fewer than 10 studies are included in a meta-analysis, we supplemented the assessment by

Table 2 Results of subgroup analysis of included studies

IIEF domains	Moderators	subgroups	SMD (95% CI)	*P* value*	I^2%	*P*-value Heterogeneity
Erectile function	**Buprenorphine dose**	<3 mg (2 studies)	0.458 (0.108–0.808)	0.010	29.28	0.234
		>3 mg (4 studies)	0.320 (0.092–0.548)	0.006	26.09	0.255
	Methadone dose	<75 mg (3 studies)	0.369 (0.164–0.574)	<0.001	0.00	0.773
		>75 mg (3 studies)	0.386 (−0.049−0.820)	0.082	63.95	0.062
	BMT duration	<50 month (3 studies)	0.423 (0.202–0.644)	<0.001	0.00	0.741
		>50 month (3 studies)	0.302 (−0.051−0.655)	0.094	57.93	0.093
	Age (BMT group)	<42 year (4studies)	0.422 (0.229–0.615)	<0.001	0.00	0.585
		>42 year (2 studies)	0.243 (−0.226−0.712)	0.309	63.08	0.100
	Age (MMT group)	<43 year (3 studies)	0.275 (−0.006−0.557)	0.055	37.75	0.201
		>43 year (3 studies)	0.469 (0.224–0.715)	<0.001	0.00	0.486
	Depression	<10% (2 studies)	0.458 (0.108–0.808)	0.010	29.28	0.234
		>10% (2 studies)	0.243 (−0.226−0.712)	0.309	63.08	0.100
Orgasmic function	**Buprenorphine dose**	<4 mg (3 studies)	0.296 (−0.027−0.619)	0.072	42.76	0.174
		>4 mg (2 studies)	0.101 (−0.206−0.409)	0.519	0.00	0.338
	Methadone dose	<75 mg (2 studies)	0.247 (−0.278−0.778)	0.357	67.24	0.081
		>75 mg (3 studies)	0.212 (−0.052−0.477)	0.116	10.12	0.329
	BMT duration	<50 month (2 studies)	0.460 (0.105–0.815)	0.011	0.00	0.644
		>50 month (3 studies)	0.121 (−0.135−0.377)	0.355	21.28	0.281
	Age (BMT group)	<42 year (3 studies)	0.222 (−0.054−0.498)	0.115	9.00	0.333
		>42 year (2 studies)	0.249 (−0.252−0.751)	0.330	67.67	0.079
	Age (MMT group)	<43 year (2 studies)	0.101 (−0.206−0.409)	0.519	0.00	0.338
		>43 year (3 studies)	0.296 (−0.027−0.619)	0.072	42.76	0.174
	Depression	<10% (2 studies)	0.192 (−0.218−0.603)	0.359	49.28	0.160
		>10% (2 studies)	0.249 (−0.252−0.751)	0.330	67.67	0.079
Sexual desire	**Buprenorphine dose**	<3 mg (2 studies)	0.875 (0.573–1.176)	<0.001	0.00	0.858
		>3 mg (3 studies)	0.587 (0.331–842.331)	<0.001	0.00	0.814
	Methadone dose	<75 mg (2 studies)	0.769 (0.463–1.074)	<0.001	0.00	0.586
		>75 mg (3 studies)	0.665 (0.412–0.918)	<0.001	0.00	0.383
	BMT duration	<50 month (2 studies)	0.668 (0.310–1.026)	<0.001	0.00	0.943
		>50 month (3 studies)	0.729 (0.473–0.984)	<0.001	17.08	0.299
	Age (BMT group)	<42 year (3 studies)	0.829 (0.560–1.099)	<0.001	0.00	0.794
		>42 year (2 studies)	0.573 (0.290–0.855)	<0.001	0.00	0.550
	Age (MMT group)	<43 year (2 studies)	0.542 (0.231–0.854)	0.001	0.00	0.678
		>43 year (3 studies)	0.813 (0.563–1.063)	<0.001	0.00	0.762
	Depression	<10% (2 studies)	0.875 (0.573–1.176)	<0.001	0.00	0.858
		>10% (2 studies)	0.573 (0.052–1.250)	<0.001	0.00	0.550
Intercourse satisfaction	**Buprenorphine dose**	<3 mg (2 studies)	0.448 (0.103–0.793)	0.011	27.20	0.241
		>3 mg (3 studies)	0.407 (0.017–0.797)	0.041	53.80	0.115
	Methadone dose	<75 mg (2 studies)	0.245 (−0.054−0.543)	0.109	0.00	0.815
		>75 mg (3 studies)	0.553 (0.174–0.932)	0.004	52.30	0.123
	BMT duration	<50 month (2 studies)	0.544 (−0.177−1.264)	0.139	72.95	0.054
		>50 month (3 studies)	0.369 (0.139–0.599)	0.002	1.60	0.362
	Age (BMT group)	<42 year (3 studies)	0.568 (0.211–0.924)	0.002	42.10	0.178
		>42 year (2 studies)	0.234 (−0.045−0.513)	0.101	0.00	0.872
	Age (MMT group)	<43 year (2 studies)	0.553 (−0.119−1.225)	0.107	72.62	0.056
		>43 year (3 studies)	0.372 (0.117–0.626)	0.004	7.44	0.339
	Depression	<10% (2 studies)	0.448 (0.103–0.739)	0.011	27.20	0.241
		>10% (2 studies)	0.234 (−0.045−0.513)	0.101	0.00	0.872

Table 2 (continued)

IIEF domains	Moderators	subgroups	SMD (95% CI)	*P* value*	I^2%	*P*-value Heterogeneity
Overall satisfaction	**Buprenorphine dose**	<3 mg (2 studies)	0.362 (0.070–0.655)	0.015	0.00	0.958
		>3 mg (3 studies)	−0.246 (−0.918−0.426)	0.472	84.35	0.002
	Methadone dose	<75 mg (2 studies)	0.039 (−0.622−0.699)	0.909	79.30	0.028
		>75 mg (3 studies)	−0.020 (−0.684−0.645)	0.954	84.57	0.002
	BMT duration	<50 month (2 studies)	−0.551 (−1.109−0.006)	0.053	55.57	0.134
		>50 month (3 studies)	0.353 (0.126–0.581)	0.002	0.00	0.994
	Age (BMT group)	<42 year (3 studies)	−0.015 (−0.707−0.677)	0.966	84.62	0.001
		>42 year (2 studies)	0.031 (−0.599−0.661)	0.923	79.53	0.027
	Age (MMT group)	<43 year (2 studies)	−0.244 (−1.436−0.949)	0.689	91.22	0.001
		>43 year (3 studies)	0.0146 (−0.280−0.572)	0.501	67.13	0.048
	Depression	<10% (2 studies)	0.362 (0.070–0.655)	0.015	0.00	0.958
		>10% (2 studies)	0.031 (−0.599−0.661)	0.923	79.53	0.027

IIEF; International Index of Erectile Function, CI; Confidence Interval, BMT; Buprenorphine Maintenance Therapy

*Significant difference at the 0.05 level

Table 3 Meta-regression estimates of effect size moderated by Buprenorphine dose, Methadone dose and BMT duration

IIEF domains	Moderators	No. of studies	No. of subjects	Meta-regression slope	95% CI	*P*-value
Erectile function	Buprenorphine dose	6	915	0.010	−0.077−0.098	0.817
	Methadone dose	6	915	−0.0008	−0.008−0.006	0.845
	BMT duration	6	915	−0.001	−0.010−0.007	0.750
Orgasmic function	Buprenorphine dose	5	714	0.013	−0.087−0.113	0.800
	Methadone dose	5	714	−0.004	−0.012−0.004	0.333
	BMT duration	5	714	−0.006	−0.016−0.003	0.190
Sexual desire	Buprenorphine dose	5	714	−0.028	−0.114−0.057	0.517
	Methadone dose	5	714	0.000	−0.007−0.007	0.999
	BMT duration	5	714	0.003	−0.006−0.012	0.513
Intercourse satisfaction	Buprenorphine dose	5	714	0.067	−0.024−0.159	0.148
	Methadone dose	5	714	0.005	−0.002−0.014	0.163
	BMT duration	5	714	0.0004	−0.012−0.013	0.951
Overall satisfaction	Buprenorphine dose	5	714	−0.147	−0.259-(−0.035)	0.009
	Methadone dose	5	714	−0.001	−0.017−0.015	0.879
	BMT duration	5	714	0.017	0.004–0.029	0.010*

IIEF; International Index of Erectile Function, CI; Confidence Interval, BMT; Buprenorphine Maintenance Therapy

*Significant difference at the 0.05 level

performing Begg's and Egger's tests. Detailed results of these tests are provided in Appendix Table S2. Egger's linear regression test did not provide statistical evidence of significant publication bias.

The corrected effect sizes were 0.283 (95% CI: 0.181 to 0.385) for erectile function and 0.337 (95% CI: 0.070 to 0.604) for intercourse satisfaction. Begg's rank correlation test also showed no significant indication of publication bias, except for overall satisfaction (Kendall's Tau = −0.9, z = 2.204, p-value = 0.027). The 'fail-safe N' test indicated that 26, 3, 61, 19, and 47 studies would be required to bring the effect size for erectile function, orgasmic function, sexual desire, intercourse satisfaction, and total IIEF score down to a non-significant ($p > 0.05$) value respectively (Table S2). Finally, the overall assessment does not strongly support the presence of substantial publication bias across the analyzed outcomes. All included studies received ethical approval, and no conflicts of interest were reported by the authors.

Discussion

This systematic review and meta-analysis assessed the impacts of BMT in comparison to MMT, on the sexual function of opioid-dependent males. The findings demonstrate a more favorable profile for buprenorphine compared to methadone in various aspects of male sexual function, especially in terms of sexual desire and satisfaction during intercourse. The narrative synthesis corroborates that the majority of the included studies indicated a reduced prevalence or diminished severity of SD in patients undergoing

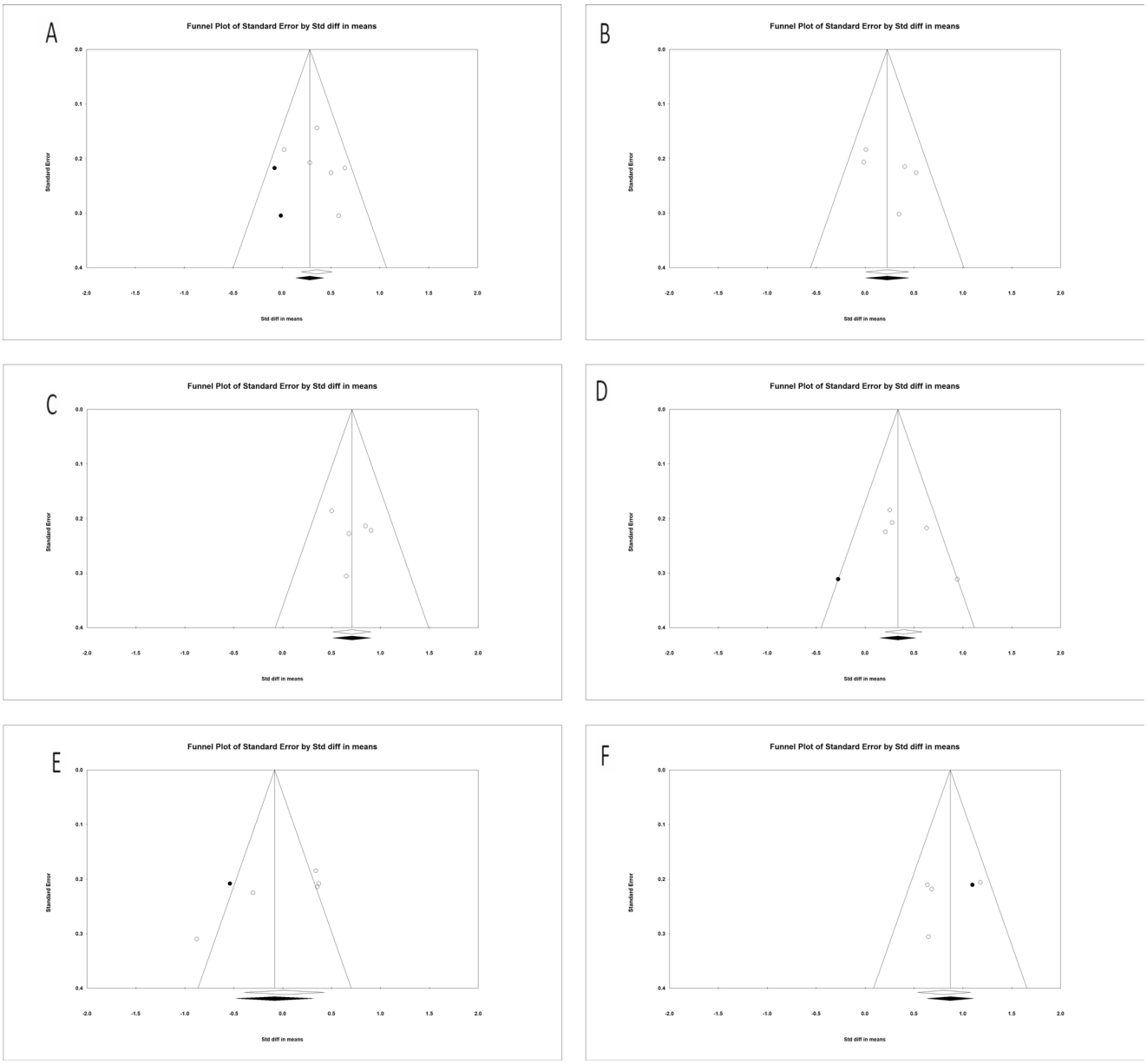

Fig. 4 Funnel plots detailing publication bias in the studies selected for analysis of BMT effects on male sexual function.The trim and fill method was used to impute for potentially missing studies. Open circles represent observed published studies; closed circles represent imputed unpublished studies. Erectile function Score (**A**), Orgasmic function score (**B**), Sexual desire score (**C**), Intercourse satisfaction score (**D**), overall satisfaction score (**E**), Total score (**F**)

BMT in comparison to those receiving MMT. A meta-analysis of data from seven studies showed mixed but mostly positive results for BMT in the IIEF domains. There was a statistically significant advantage in sexual desire. However, no statistical difference between BMT and MMT groups regarding overall satisfaction scores was found. Meta-regression analysis confirmed that the pooled estimate of the IIEF scores was independent of potential moderating variables such as buprenorphine daily dose, methadone daily dose, and BMT duration.

The current results align with a considerable body of evidence suggesting the superiority of buprenorphine over methadone in alleviating sexual side effects, largely attributable to their unique pharmacological effects on the HPG axis. A significant explanatory factor is the varying impact on testosterone levels. Methadone, a complete mu-opioid receptor agonist, is known to cause testosterone deficiency and hypogonadism by inhibiting the production of hypothalamic gonadotropin-releasing hormone (GnRH) and possibly directly suppressing testicular testosterone secretion [40, 41]. Opioids inhibit the HPG axis by decreasing the

levels of GnRH mRNA, which lowers the amount of GnRH released from the hypothalamus. They also make the pituitary less responsive to GnRH, leading to decreased LH and, to a lesser extent, follicle-stimulating hormone (FSH) secretion, which subsequently reduces testosterone production in men, resulting in hypogonadism [7, 42]. Another idea is that long-term stimulation of mu-opioid receptors changes dopaminergic pathways, which lowers dopamine secretion [43]. This leads to disinhibition of prolactin release and the subsequent inhibition of GnRH.

Although acute administration of buprenorphine exerts a biphasic effect on prolactin secretion – low doses increase prolactin, whereas high doses decrease it – [44] the effects of chronic buprenorphine use on prolactin are variable, with studies showing reduced, similar, or higher levels compared to healthy controls [13, 45]. These findings highlight that while both medications can induce hyperprolactinemia and disrupt the HPG axis, buprenorphine's partial mu-opioid agonist and kappa-opioid properties result in less pronounced suppression of GnRH and better preservation of LH pulsatility. The kappa -antagonist activity may additionally offset HPG axis inhibition, contributing to the more favorable endocrine profile.

The clinical significance of buprenorphine's prolactin effects differs from that of methadone. Multiple regression analyses demonstrate that lower total testosterone—rather than prolactin—is one of the primary factors associated with lower erectile function scores [36]. This suggests that the superior sexual function outcomes with buprenorphine would be primarily mediated through better preservation of testosterone rather than differences in prolactin. Bliesener et al. showed that BMT patients had much higher total and free testosterone levels than MMT patients, with levels comparable to healthy controls, and they also reported a lower frequency of sexual dysfunction [30]. Yee et al. supported these findings, observing markedly lower total testosterone plasma levels in the MMT group, which were associated with reduced sexual desire scores [36].

Smith and Elliot suggested that opioids exert their effects at multiple locations within the HPG axis, leading to an endocrine dysfunction termed opioid-associated androgen deficiency (OPIAD), which is marked by decreased pituitary hormone levels and subsequent hypogonadism due to reduced testosterone [46]. Heidari et al. reported that buprenorphine has a lower risk of OPIAD than methadone, attributed to its kappa-opiate receptor antagonist activity potentially offsetting HPG axis inhibition [47]

Another thing to consider is how different the usual doses are for the two drugs. The average dose for MMT groups was much higher than for BMT groups when using morphine milligram equivalent conversion factors (30 for sublingual buprenorphine and 12 for methadone at doses > 80 mg/day) [48]. This difference in dosing, which has been observed across several comparative studies, may help explain why the HPG axis has different effects [33, 36]. Buprenorphine is a partial agonist, which means that higher doses don't always have stronger effects, and it is often administered in flexible doses. On the other hand, methadone, which is a full agonist, can cause more pain relief and euphoria at higher doses, which could lead to requests for higher doses.

Furthermore, methadone is generally reserved for severe opioid dependence owing to its enhanced retention and suppression of illicit use, whereas buprenorphine is employed for mild to moderate dependence. Consequently, the observed hypogonadism may indicate the underlying severity and duration of opioid use preceding substitution therapy [49].

Despite the general consensus favoring BMT, some recent studies employing various methodologies reported no significant differences. Bahadori et al. utilized the IIEF and found no significant difference in sexual function among patients administered buprenorphine, methadone, or opium tincture [38]. Kheradmand et al. similarly reported no notable difference in overall sexual dysfunction assessed via the Arizona Sexual Experience Scale (ASEX) among MMT, BMT, and opium tincture groups over a three-month period [28]. These inconsistencies underscore the complex, multifactorial etiology of SD in this population, influenced by factors beyond pharmacology, including sample size, treatment duration, concurrent substance use, psychiatric comorbidities, and assessment tools.

A meta-analysis conducted by Yee et al. delineated nine factors associated with sexual dysfunction in opioid users, including age, hormonal levels, duration of therapy, methadone dosage, medical and psychiatric conditions, concurrent substance use, familial status, and treatment modality (MMT versus BMT) [50]. Interestingly, some studies find an association between methadone use and sexual dysfunction regardless of testosterone levels and hypogonadism, suggesting contributions from factors such as childhood adversities and comorbid psychiatric symptoms. A randomized controlled trial demonstrated that bupropion, a dopamine reuptake inhibitor, enhanced both testosterone levels and sexual function in patients undergoing MMT compared to a placebo after six weeks [51]. This indicates a potential adjunctive intervention to mitigate MMT-related sexual dysfunction, potentially enhancing adherence and retention, as sexual dysfunction is associated with early dropout from MMT.

It is critical to acknowledge that while BMT demonstrates a more favorable profile compared to MMT, both maintenance therapies are associated with a substantial burden of sexual dysfunction relative to healthy individuals. The prevalence of SD in patients receiving opioid agonist

therapy remains clinically significant, with studies reporting that up to 83% of men undergoing BMT experience at least one domain of sexual dysfunction [30, 34]. Ramdurg et al. found substantial rates of erectile dysfunction and decreased libido among men receiving buprenorphine, although these were less pronounced than in those receiving full opioid agonists [52]. This underscores an important clinical reality that buprenorphine does not eliminate the risk of sexual side effects but rather reduces its severity and prevalence compared to methadone.

Nevertheless, the persistence of sexual dysfunction in a substantial proportion of BMT patients underscores the multifactorial nature of this complication, involving contributions from psychiatric comorbidities (particularly depression), psychosocial factors (lack of stable partner, socioeconomic disadvantage), and the residual endocrine effects of chronic opioid exposure. Therefore, routine sexual health screening remains essential for all patients receiving opioid agonist therapy, regardless of the specific medication used.

The findings have serious implications for clinical practice. The high prevalence of SD among patients on OAT, especially MMT, necessitates routine sexual health screening. Patients often avoid reporting these concerns due to embarrassment, and clinicians may neglect them, representing a major missed opportunity to improve treatment adherence and quality of life.

Given the evidence supporting BMT for sexual desire and intercourse satisfaction, buprenorphine should be considered the preferred maintenance treatment for patients concerned about sexual side effects or those experiencing SD on methadone. Future comprehensive longitudinal studies are essential to confirm these findings, elucidate exact mechanisms, and develop evidence-based management guidelines for opioid-induced SD. Switching from MMT to BMT or methadone dose reduction should be considered when SD is identified.

Limitations and Future Research Directions

The current systematic review and meta-analysis, along with the foundational studies reviewed, highlight several limitations that future research must address. A prevalent limitation among included studies is the cross-sectional design, which relies heavily on self-report and patient memory, leading to potential recall and response biases. This design limits the ability to establish causal attribution between the medication and SD. It is worth pointing out that for the subgroup analysis, due to the limited studies, few studies have been pooled in each subgroup. Additionally, many studies suffered from small and unequal sample sizes (e.g., the BMT group often had fewer participants than the MMT group). Crucially, hormonal assays (total testosterone, LH, FSH) were omitted from several studies due to logistical or financial constraints. While the meta-analysis found no correlation between dose and IIEF scores, longitudinal studies incorporating hormonal levels are still needed to fully explore the dose-response relationship for BMT in causing testosterone depletion, particularly since some authors suggest that higher than conventional BMT doses might suppress testosterone levels.

Future research must focus on conducting longitudinal cohort studies with higher and equal sample sizes, carefully controlling for major confounders such as psychiatric disorders, psychosocial context, and concomitant substance use. It is vital that such studies incorporate a detailed endocrinologic evaluation, including testosterone, LH, and FSH measurements, to fully explore the underlying biological correlates and pathophysiology of opioid-induced SD. Lastly, prospective clinical trials are necessary to confirm the therapeutic benefit of switching patients from MMT to BMT (or dose reduction strategies) specifically to alleviate SD.

Conclusion

The systematic review and meta-analysis confirmed that BMT appears to offer a distinct advantage over MMT in preserving key domains of male sexual function, particularly sexual desire and intercourse satisfaction. This clinical difference is likely rooted in the less pronounced HPG axis suppression associated with buprenorphine's partial agonist/antagonist pharmacological profile compared to methadone, a full mu-opioid agonist.

The persistence of sexual dysfunction in patients receiving OST represents a clinically significant obstacle to treatment success, adherence, and overall quality of life. Therefore, these findings highlight the necessity for clinicians to integrate sexual health screening into routine care and to apply the knowledge of BMT's comparatively lower propensity for sexual side effects during the shared decision-making process for initiating or modifying opioid maintenance treatment.

Key References

- Yee A, Loh HS, Hisham Hashim HMB, Ng CG. Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine

maintenance treatment: a meta-analysis study. Int J Impot Res. 2014;26(5):161–6.

  - An important early meta-analysis that established the foundational evidence for the comparative risk of sexual dysfunction between MMT and BMT. This study delineated nine factors associated with sexual dysfunction in opioid users, including age, hormonal levels, duration of therapy, methadone dosage, medical and psychiatric conditions, concurrent substance use, familial status, and treatment modality (MMT versus BMT).

- Bahadori Z, Safaie N, Mirmohammadkhani M. Comparison of psychiatric disorders in addicted patients treated with buprenorphine, methadone, and opium tincture in Iran. Middle East Curr Psychiatry. 2022;29(1):60.

  - A recent study that expands the comparative framework by including a non-synthetic opioid treatment (opium tincture). Its importance is two-fold: it confirms a lower prevalence of comorbid psychiatric disorders in patients treated with buprenorphine compared to methadone, and it highlights the broader biopsychosocial context in which sexual dysfunction occurs. This underscores that BMT's potential benefits for sexual health may be linked to its favorable psychiatric side-effect profile.

- Yee A, Loh HS, Loh HH, Riahi S, Ng CG, Sulaiman AH. A comparison of sexual desire in opiate-dependent men receiving methadone and buprenorphine maintenance treatment. Ann Gen Psychiatry. 2019;18(1):25.

  - A direct, comparative study specifically assessing sexual desire, a core domain of sexual function. Its importance lies in demonstrating a significant and clinically relevant advantage for buprenorphine over methadone in this critical area, providing key evidence for the differential side-effect profile of these medications.

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Declarations

Ethical approval All authors read and approved the final manuscript.

Human and Animal Right and Informed Consent No human or animal subjects by the authors were used in this study.

Competing interests The authors declare no competing interests.

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