Review Article

Sexual Dysfunction in Patients with Alcohol and Opioid Dependence

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ABSTRACT

There are limited numbers of studies which have evaluated the sexual dysfunction (SD) in patients with alcohol and opioids dependence. This article reviews the existing literature. Electronic searches were carried out using the PubMed, Google Scholar, and ScienceDirect to locate the relevant literature. Subjects addicted to heroin or on methadone maintenance treatment (MMT) or buprenorphine maintenance treatment (BMT) show higher rates of SD in comparison to the general population. SD rates have ranged 34-85% for heroin addicts, 14-81% for MMT, 36-83% for BMT, and 90% for naltrexone maintenance. The rates of SD in alcohol-dependent population have ranged 40-95.2%, with rates being consistently much higher in alcohol-dependent population than in the healthy controls or social drinkers. The common SDs reported have been erectile dysfunction followed by premature ejaculation, retarded ejaculation and decreased sexual desire among men, and dyspareunia and vaginal dryness among women. This review suggests that long-term use of alcohol and opioids are associated with SD in almost all domains of sexual functioning. There is a need to increase the awareness of clinicians about this association as many times SD in patients with substance abuse lead to poor treatment compliance and relapse. Further, there is a need to carry out more number of studies to understand the relationship in a better way.

Key words: *Alcohol, opioids, sexual dysfunction*

INTRODUCTION

Sexual dysfunction (SD) is quite common in the community population. Large epidemiological community survey from the United States report >40% of women and 30% of men as suffering from some form of SD, with low sexual desire in women (22%) and premature ejaculation in men (21%) being the most common.[1] These figures are not very different from those of 34% women and 15% men from eight European countries reporting low sexual desire.[2]

Substance abuse is widely prevalent in the community. World Health Report in 2002 reported that 8.9% of the total burden of disease worldwide in 2000 came from the use of psychoactive substances.[3]

People may use alcohol and other substances to tackle sexual performance anxiety, enhance sexual performance, or overcome SD. A World Health Organization cross-cultural study for alcohol and high-risk sexual behavior across eight countries reported that 12% males in the general population consumed alcohol prior to first sexual intercourse due to perceived positive effect of alcohol to improve sexual pleasure.[4] Furthermore, alcohol was commonly used prior to intercourse with commercial sex worker.[4] However,

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in the long run, substance abuse impacts on sexual functioning negatively and may lead to the onset of sexual disorders.[5] Opioids have also been used as aphrodisiac and to delay ejaculation.[6] However, there is evidence that in the long run, substance abuse including for tobacco smoking impacts on sexual functioning negatively and may lead to the onset of SD or disorders,[5,7] Recovering substance abusers may face continuation or recurrence of SD, while the therapists may be perplexed about addressing the addiction and sexual problems of their clients.[8]

However, very few studies have systematically evaluated the relationship of SD and substances such as alcohol and opioids. This review aims to summarize the available literature on the effect of alcohol and opioids on the reproductive system and the prevalence of SD in males/dependent on alcohol and opioids.

For this review, an Internet search was carried out using the search engines of PubMed, Google Scholar, and ScienceDirect to locate the relevant literature. The keywords used in various combinations were: Alcohol, opioids, sexual function/dysfunction, alcohol dependence, opioid dependence, methadone, buprenorphine, heroin, erectile dysfunction (ED), premature ejaculation, libido, and reproductive hormones etc. Abstract of all the articles was screened, and the relevant articles were selected with a specific focus being effect of alcohol/opioid on the sexual hormones and prevalence of SD in patients with alcohol/opioid dependence. Full text articles were evaluated, and the relevant data were extracted. Cross references from these full-text articles also provided few more relevant articles.

PHYSIOLOGICAL SEXUAL FUNCTIONING: HOW IS IT INFLUENCED BY OPIOIDS AND ALCOHOL?

Endogenous opioids play an important role in the physiological sexual functioning. They act at specific opioid receptors, and contribute to control the release of gonadotropin-releasing hormone and thus, the sex hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both FSH and LH are secreted by the anterior pituitary and act directly on the testes to stimulate the somatic cells that contribute to spermatogenesis. While FSH stimulates the proliferation of Sertoli cells during puberty, the LH regulates the synthesis of testosterone in the adult testes.[9] Morphine administration suppresses LH release and reduces the levels of testosterone and estradiol, which effects testicular function.[10,11] This is corroborated by an array of evidence. Opioid abuse is linked to the development of hypogonadism, decreased libido, ED, and infertility.[12-14] Opioid antagonists like naltrexone can improve symptoms of hypogonadism and erectile function without increasing testosterone or LH levels, suggesting regulation at the central rather than the peripheral level.[15] Opioids also exert a negative influence on adrenal androgen production. The adrenal hormones dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenedione are weakly androgenic, and they are precursors of testosterone. Serum DHEAS levels are used to determine adrenal function in general and adrenal androgen production in particular. Daily use of opioids decreases adrenal androgen production as measured by DHEAS levels.[16]

Studies on endocrine and other biological effects of alcohol report that long-term use of alcohol leads to inhibition of hypothalamic-pituitary-adrenal axis and reduces the release of gonadotropins from the pituitary. Chronic alcohol abuse has been recorded to cause testicular atrophy, inhibition of testosterone production, and inhibition of spermatogenesis, apart from its direct oxidative toxicity.[17,18]

Animal studies have shown that acute and chronic alcohol exposure affects sex hormones in terms of profound testosterone suppression accompanied by lower or normal LH and FSH levels, when actually elevated levels of these are expected.[19,20] Human studies have shown lower levels of hypothalamic LH-releasing hormone and pituitary LH in adults[21,22] and inhibition of testosterone secretion by the testes[23] by alcohol.

Testicular opioids are messenger molecules similar to morphine within the testes, which suppress testosterone synthesis. An opioid, beta-endorphin has been shown to increase with acute and chronic alcohol consumption and may be a link between alcohol use and testicular damage.[24] Increased level of testicular opioids has been implicated to increase the rate of apoptosis.[25,26] Apoptosis at gonadal level may result in the death of both Leydig and seminiferous cells, which are involved in sperm cell formation and maturation; thus, leading to low testosterone levels and diminished sperm production. Another mechanism postulated for alcohol's harmful effect on testosterone production is the reduced level of nitric oxide (NO) that acts as a local vasodilator.[27] Oxidation of alcohol, part of alcohol metabolism, generates oxidants that can contribute to cell damage and play a role in alcohol-induced tissue damage in the testes. An imbalance between oxidants and antioxidants can create oxidative stress. Alcohol consumption may induce oxidative damage either by enhancing the production of toxic free radicals or by decreasing the levels of antioxidants. Certain oxidants

produced by alcohol metabolism are known as reactive oxygen species (ROS). These include anion superoxide, hydrogen peroxide, hydroxyl radicals, and nitrogen reactive species like NO. The metabolism of alcohol and acetaldehyde, which is the principle product of alcohol metabolism, produces highly toxic ROSs. Increased oxidative stress is a well-accepted mechanism of alcohol-induced tissue injury, particularly in the liver,[28,29] heart, and central nervous system, and this also occurs in the testes.[30] There is some suggestion that acetaldehyde is more toxic than alcohol to the production of testosterone, altering the process of testosterone production by inhibiting protein kinase C, a key enzyme in testosterone synthesis.[31] There is research to show that men with chronic alcoholism and hypogonadism actually eliminate alcohol more rapidly, building up less acetaldehyde. Because the build-up of acetaldehyde in the body is nauseating, enhanced clearance of these by-products could lead to reduced gastrointestinal side-effects from drinking (e.g., abdominal discomfort and vomiting) in men with low testosterone levels. This may increase the risk of developing a drinking problem, because a person who does not experience the negative gastrointestinal side-effects of drinking will be more likely to continue to drink, often in larger amounts.[32] Lipid rich testicular membranes being prone to oxidative injury it is reasonable to consider that lipid peroxidation (i.e., damage to the cell membranes) may contribute to the gonadal dysfunction that occurs as a result of chronic alcohol use. Other explanations for alcohol-related gonadal suppression invoke the metabolic cascade of alcohol to toxins lok acetoacetate to salsolinol and others.[33] In alcohol fed animals and chronic alcoholics, when testosterone levels decrease the expected increase in LH levels is not seen. This inability of the pituitary gland to respond appropriately to testosterone decline implies that alcohol has a central effect on the interaction between the nervous system and the endocrine system.[19,20] Studies in alcohol-fed rats have established that the decrease in LH levels results from impairment in both LH production and LH secretion[22] and alcohol's deleterious effects on LH function appear to be both qualitative as well as quantitative. Secretion of FSH also appears to be reduced by alcohol; though, alcohol does not appear to affect FSH synthesis.

SEXUAL DYSFUNCTION ASSOCIATED WITH OPIOIDS AND ALCOHOL

Prevalence of sexual dysfunction in patients with opioid dependence

We identified 24 studies [Table 1] that specifically evaluated prevalence of SD in opioid-dependent patients taking illicit opioids like heroin or opioid substitution therapy like methadone maintenance treatment (MMT) or buprenorphine maintenance treatment (BMT); a few studies included those receiving opioid antagonist naltrexone.

Heroin addiction or MMT or BMT subjects show higher rates of SD in comparison to the general population.[38,41,42,49,52,53] SD rates have ranged 34-85% for heroin addicts,[41,45,46,52] 14-81% for MMT,[35,39,45,51,52,55,56] 36-83% for BMT,[42,43,45,56] and 90% for naltrexone maintenance.[45,56]

Most of the quoted studies did not evaluate SD comprehensively; some focused only on premature ejaculation[34,47] or ED,[41,49,52,55] some evaluated only the frequency of sexual intercourse and masturbatory activity,[38,53] and some did not use a standardized instrument for assessment of SD.[34,35,38,53] Studies that assessed more than one functioning domain suggest the most common dysfunction to be any of the following: ED,[45,49,50,52,55] premature ejaculation,[47,56] orgasmic dysfunction,[51,52,54] and low libido.[38,49,53] However, dysfunction across all the domains has been reported more often.[37,39,52-54,56]

Prevalence of sexual dysfunction in patients with alcohol dependence

In clinical population, the relationship between alcohol and SD has been studied from the following point of view: Prevalence and correlates of SD in patients seeking treatment for alcohol problems, prevalence of alcohol use/abuse/dependence in patients seeking treatment for SD, and effect of alcohol on various mechanisms involved in proper sexual functioning.

In one of the first observations, Lemere and Smith[59] reported the prevalence of SD in alcohol-dependent population to be 8%, the dysfunction persisting in 50% patients even into long-term abstinence from alcohol. They postulated the persistent SD to the neurogenic damage caused by alcohol. The research since then is summarized in Table 2. With sample sizes of 18-816 covering men, women, or both, the rates of SD have ranged 40-95.2%, with rates being consistently much higher in alcohol-dependent population than in the healthy controls or social drinkers. The common SDs reported have been ED followed by premature ejaculation, retarded ejaculation and decreased sexual desire among men, and dyspareunia and vaginal dryness among women. Association between long-term and high amount of alcohol consumption and SD has been widely reported[60,61] and men with SD are frequently noted to be chronic alcohol dependent.[78] A review of clinical and experimental studies concluded that in male alcoholics, the greater quantity, frequency, and duration of drinking are associated with ED, inhibited

Table 1: Studies evaluating SD in males receiving/taking opioids

Author	Opioid	Scale	Conclusion
Mintz *et al*.[34]	136 heroin addicts (45 on MMT)		PE was a common complaint when subjects were drug free, but unclear if this finding represents true baseline levels or subtle abstinence reactions Heroin and methadone both increased the frequency of erectile failure and delayed ejaculation, though the effects of heroin were substantially more dramatic
Hanbury *et al*.[35]	50 men on MMT		Seventeen subjects (33%) reported SD, occurring in 50% within 1-month after initiating methadone therapy Inadequate sexual function on heroin, was reported in 12 (71%) of those experiencing similar difficulties on methadone Persons with altered sexual function while on the street heroin represent a high-risk group for developing inadequate sexual function upon initiation of methadone maintenance
Spring *et al*.[36]	25 men on MMT	Derogatis sexual functioning inventory	SD was more in those receiving higher doses of methadone
Teusch *et al*.[37]	37 men on MMT, 45 men with schizophrenia on antipsychotics, 50 neurotic patients without treatment and 41 normal controls	Sex differentiated semi-str-uctured questionnaire on sexual function	Three clinical groups and controls differed significantly in sexual interest, emotional arousal, physiological arousal (erectile function/vaginal lubrication), performance (ejaculatory function/dyspareunia/vaginism), and orgasm satisfaction All the patients on MMT and nearly all the patients with schizophrenia suffered from dysfunctions in at least one domain Reduced sexual interest, emotional arousal, and orgasm satisfaction were reported more frequently by the patients on MMT than by the neurotic men There was no correlation between SD and methadone dosage
Palha and Esteves[38]	101 heroin addicts		Significant decrease in weekly sexual intercourse and masturbatory activity in 101 heroin male addicts compared to healthy controls
Brown *et al*.[39]	92 men on MMT		14% reported some SD Dysfunction (erectile or libido or global dysfunction) increased with increasing age Methadone dose showed a significant direct correlation with increased orgasmic dysfunction, both before and after adjusting for duration of treatment None of the SD subscales or global dysfunction was associated with plasma testosterone or plasma prolactin levels
Bliesener *et al*.[40]	17 men on BMT 37 men on MMT and 51 controls	SFQ BDI	BMT cases had a significantly higher testosterone level and a significantly lower frequency of SD compared with MMT patients The testosterone level of BMT cases did not differ from that of healthy controls
Wu *et al*.[41]	276 heroin users and 196 healthy controls	IIEF-5	44.2% were reported to have ED with an odds ratio for ED of 4.8 compared to the nonaddict controls
Hallinan *et al*.[42]	84 men on MMT and 19 men on BMT	IIEF-5, BDI, hormone assays	Among partnered men on MMT, 53% had ED compared to 24% of reference groups On multiple regression, depression, older age, and lower total testosterone were associated with lower IIEF and EF domain
Quaglio *et al*.[43]	201 males 84 on MMT and 115 on BMT	IIEF-15, Zung depression rating scale	58% reported no ED, 24% reported mild to moderate ED, and 18% severe ED BMT cases had less ED than MMT cases Subjects living with a partner had less ED than others More depressed subjects had more ED. Heterosexual patients reported less ED than homo/bi-sexual patients and partner's use of heroin was associated with more ED
Bang-Ping[44]	701 subjects using illicit drugs, most commonly heroin, amphetamine, and MDMA ("ecstasy"); 196 control subjects	IIEF-15	ED was reported in 36.4% of the abusers The odds ratio of having ED (compared with the controls) in mono-users of heroin, amphetamine, and MDMA was 4.8 ($P < 0.05$), 3.2 ($P < 0.05$), and 1.4 ($P > 0.05$), respectively Decreased sexual desire was reported by 38.6% of abusers of illicit drugs, more often seen in the heroin mono-users (46.7%); enhanced sexual desire was reported by 18.4%, more often by amphetamine mono-users (22.6%) Increased and decreased ejaculation latency affected by illicit drugs was reported in 49.9% and 14.3% of the abusers, respectively, showing no significant difference among the mono-users of three different drugs Mean IIEF sexual desire domain score of the abusers was lower than that of the control, even for those who reported to have enhanced sexual desire
Tufani and Afshari[45]	34 patients using illicit opioids, 51 on MMT and 16 on BMT	IIEF-5	68% of illicit opioid users, 60% of those on MMT, and 36% of those on BMT had ED ED was significantly more severe in MMT cases in comparison to BMT subjects Orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction were not significantly different among these groups
Cioe *et al*.[46]	57 men using illicit opioids	IIEF-5, hormonal assay	34% reported ED Low total testosterone was detected in 17% of those reporting ED, but total testosterone was not significantly associated with ED Older age was significantly associated with ED
Chekuri *et al*.[47]	65 men on MMT	IIEF	58.5% cases reported "lifetime" history of PE 30.76% reported "current" history of PE 16.9% reported that PE preceded opiate misuse 63.2% felt that heroin helped their PE and 18.4% felt that heroin worsened it 36.8% felt that methadone helped PE, while 26.3% felt methadone worsened PE

(Continued)

Table 1: (*Continued*)

Author	Opioid	Scale	Conclusion
Wong *et al*.[48]	65 women (47 opioid users and 18 nonopioid analgesic controls) and 32 men (26 opioid users and six controls)	Hormonal assays	81% men and 67.4% women who were opioid users had SD There was no significant difference in the incidence of SD (decreased desire, ED or both) between opioid users and nonopioid analgesic users Prolactin levels were significantly increased in opioid user men compared with controls Other hormones showed no differences between groups Increased prolactin was present in the opioid users regardless of whether ED or desire was normal or abnormal
Zhang *et al*.[49]	612 men on MMT	IIEF-5	88.6% were dissatisfied with their current sexual function The number of those suffering from hypo-sexuality and ED significantly increased at post-MMT than at pre-MMT ($P < 0.01$) Both the dose of methadone and the age of subjects were negatively correlated with IIEF scores No correlation was found between the duration of MMT and IIEF scores
Chen *et al*.[50]	74 male heroin addicts enrolled in 4 MMT clinics	IIEF-5, Zung depression rating scale, Zung self-rating anxiety scale	ED was reported in 75.7% at the baseline; and 88.7%, 80.8%, and 80.9% reported SD at 1-, 2-, and 3-month follow-ups
Babakhanian *et al*.[51]	30 patients on MMT	IIEF-15, Zung depression rating scale	On admission 8% reported no SD, 69% reported mild to moderate SD, and 23% reported severe SD Post-MMT program, the rate of mild to moderate SD decreased to 61% and that of severe SD reduced to 20% In comparison with admission, the mean IIEF-15 score showed moderate improvement The mean score for intercourse satisfaction showed complete improvement whereas slight improvements were noted in the mean score for sexual desire, overall satisfaction The mean score for orgasmic function on IIEF did not show any improvement
Trajanovska *et al*.[52]	20 men on MMT and 20 men on heroin	IIEF-15, CLIA for measuring prolactin levels	More patients on street heroin had SD compared to those on MMT Comparison of SD in different domains showed that SD in the domain of (85% vs. 55%), orgasm function (85% vs. 65%), sexual desire (80% vs. 55%) and overall satisfaction (85% vs. 65%) was more common in those using street heroin; however, these differences were significant only for the domains of and orgasm function Prolactin levels were elevated in 55% of men who were on street heroin compared to only 15% in MMT group
Xia *et al*.[53]	27 MMT patients (13 men and 14 women)		All participants reported some kind of SD Commonly perceived sexual problems were libido inhibition and decreased sexual pleasure Methadone was thought to have a stronger inhibition effect on sexual desire than heroin SD was associated with poor quality of sexual life, negative impact on intimate relationships; drop out from treatment and use of illicit opioids
Vallejo-Medina and Sierra[54]	53 heroin addicts among total 549 drug abusers	CSFQ 14	Heroin affected all the four dimensions of sexual functioning: Pleasure, desire, arousal and orgasm Orgasm was the most affected dimension. followed by pleasure, desire, and arousal Abstinence of substance for 2 weeks did not lead to improvement in sexual functioning
Jaafar *et al*.[55]	108 opioid addicts on MMT	IIEF-15, BDI	The rate of ED was 68.5% (mild ED, 36.1%; mild to moderate ED, 22.2%; severe ED, 3.7%) Older age, concurrent illicit heroin use and having an older partner were significantly associated with ED
Ramdurg *et al*.[56]	30 men on naltrexone and 30 men on BMT	BMFSI	83% of the men on BMT and 90% on naltrexone reported at least one of the SD symptoms Commonly reported dysfunctions were PE (83% in BMT and 87% in naltrexone), ED (43% in BMT and 67% in naltrexone), and loss/reduction in sexual desire (33% in BMT and 47% in naltrexone)
Mattoo *et al*.[57]	50 men with opioid or alcohol dependence, matched healthy controls	ASEX, IIEF-15	SD was present in 24% as per ASEX and 28% as per IIEF criteria; comparative figures in matched healthy controls were 0% and 7%, respectively. While the dysfunction was moderate to severe in one half of the patients, it was mild in the other half of the patients as also in all of the dysfunctional controls
Cioe *et al*.[58]	111 men using heroin	IIEF-5, hormonal assay	44.1% of the cohort had ED; among those identified as sexually, 26.1% had ED
Vallejo-Medina and Sierra[54]	53 heroin dependent men	CSFQ	All the four dimensions, i.e., pleasure, desire, arousal, and orgasm are affected. The most commonly affected domain included orgasm, followed by pleasure and desire

MMT – Methadone maintenance treatment; PE – Premature ejaculation; BMT – Buprenorphine maintenance treatment; ED – Erectile dysfunction; IIEF – International index of erectile function; MDMA – 3,4-methylenedioxymethamphetamine; CSFQ – Changes in sexual functioning questionnaire; BMFSI – Brief male sexual functioning inventory; BDI – Beck depression inventory; CLIA – Chemiluminescent immunometric assay; SD – Sexual dysfunction; SFQ – Sexual function questionnaire

libido, and retarded ejaculation.[79] A major limitation of these data has been the lack of standard instruments to assess SD; only four recent studies using International Index of Erectile Function (IIEF), of which two used full form of IIEF to assess SD.

One consistent correlate that emerges in these studies is advancing age; other correlates include age of onset for alcohol use, duration of chronic alcoholism, presence of liver disease, cigarette use, education level, and unemployment.

Table 2: Prevalence of SD in patients with alcohol dependence

Authors	Sample size and characteristics	Measure used to assess SD	Prevalence of SD
Stankvshve *et al*.[62]	373 patients aged 20-50 years Time of assessment: Not known	None stated	51% each reported hypoactive sexual desire and impotence
Akhtar[63]	45 inpatients alcoholics Time of assessment: 1-month after admission	None stated	53% reported hypoactive sexual desire and 31% had impotence, 6.6% had premature ejaculation, and 17.8% had retarded ejaculation
Whalley[64]	50 hospitalized alcoholic men with a matched sample from the general population Time of assessment: 6 days after admission	None stated	54% of alcoholics had SD compared to 28% in healthy controls
Van Thiel and Lester[65]	Time of assessment: Not known	None stated	61% of patients dependent on alcohol reported SD, the most common being erectile dysfunction followed by reduced sexual desire
Jensen[66]	*n*=100, outpatients taking disulfiram Time of assessment: After initiation of pharmacoprophylaxis	None stated	57% reported hypoactive sexual desire and 23.8% had impotence, 15.9% had premature ejaculation, and 25.4% had retarded ejaculation
Vijayasenan[67]	97 in-patients in a facility for alcoholics Time of assessment: Not known	None stated	Two-third had SD 58% of chronic alcohol consumers experienced lack of sexual desire, 16% experienced erectile disorder, 4% experienced premature ejaculation, and 22% experienced retarded ejaculation problem
Mandell and Miller[68]	44 alcoholic men Time of assessment: 47% abstinent and 53% taking alcohol	None stated	59% experienced ED during periods of heavy drinking and 84% reported some SD related to alcohol abuse
Jensen[69]	*n*=60, both male and females addicts compared to age and gender matched controls Time of assessment: Between 4 and 8 weeks after starting disulfiram treatment	None stated	63% of the men reported SD-mainly erectile and libido disorders-compared to 10% in the control group
Jensen and Gluud[70]	18 young men (<56 years) alcoholic cirrhosis with a steady female partners Time of assessment: Outpatients; other details not specified	None stated	61% claimed to have SD, with erectile dysfunction and/or reduced sexual desire being the most common symptoms
Fahrner[60]	101 men taking inpatient treatment for alcohol dependence Time of assessment: Not known	None stated	75% had erectile dysfunction, loss of libido, and premature or delayed ejaculation
O'Farrell *et al*.[61]	26 married couples with an alcoholic husband compared with 26 maritally conflicted and 26 nonconflicted couples without alcohol-related problems Time of assessment: Not specified	None stated	Male alcoholics and their wives experienced less sexual satisfaction and had more SD-specifically husbands' diminished sexual interest, impotence and premature ejaculation, and wives' painful intercourse-than nonconflicted couples. However, impotence was the only aspect on which alcoholics reported more difficulties than did martially conflicted couples
Wylie *et al*.[71]	40 alcoholics, both genders Time of assessment: Outpatients – other details not specified	GRISS	40% reported SD
Paparriropoulos *et al*.[72]	101, men taking inpatient treatment for alcohol dependence Time of assessment: 4-6 weeks after detoxification as inpatients and at 6 months	IIEF	62% had SD
Grinshpoon *et al*.[73]	54 men Time of assessment: 1-month after detoxification	IIEF-15, Q-LES-Q, GHQ-12	85.5% had ED, 70.3% had decreased libido, 61.3% had PME or delay in ejaculation, 25% had weak or absent orgasm, and 5.5% had a lack of pleasure or pain
Dişsiz and Oskay[74]	233 men with DSM-IV alcohol dependence Time of assessment: Not specified	IIEF-15	70.3% of participants had a mild, and 4.4% had moderate erectile dysfunction
Lee *et al*.[75]	816 sexually active men consuming ≥3 standard drinks/week	Self-report questionnaire	Increased incidence of ED in current drinkers and tobacco smokers
Krupnov *et al*.[76]	80 alcohol dependent men and 40 controls Time of assessment: Not specified	None stated	Endocrine and vasculogenic form of ED in alcohol dependent group
Vallejo-Medina and Sierra[54]	109 alcohol dependent men	CSFQ	All the four dimensions, i.e., pleasure, desire, arousal and orgasm are affected. The most commonly affected domain included orgasm, followed by pleasure and desire Among the various substances, i.e., alcohol, heroine, speedball, alcohol were the substance which led to a maximum dysfunction in the arousal
Pandey *et al*.[77]	50 alcohol dependent patients and matched controls Time of assessment: Not specified	None stated	68% of the patient reported one or another SD

ED – Erectile dysfunction; IIEF – International index of erectile function; CSFQ 14 – Changes in sexual functioning questionnaire; DSM-IV – Diagnostic and statistical manual-IV; GHQ – General health questionnaire; GRISS – Golombok–Rust inventory of sexual satisfaction; SD – Sexual dysfunction; PME – premature ejaculation

However, some of the recent studies refute the link between SD and alcohol. One study which evaluated the effect of alcohol abuse, panic disorder, and depression on ED did not report any increase in the risk of ED with alcohol abuse.[80] Another study with HIV-positive men reported IIEF assessed ED to be related to nonalcohol drinking status.[81] A more recent population-based cross-sectional postal survey of men's health which assessed the association between usual alcohol consumption and IIEF assessed ED reported that compared to never-drinkers, the age-adjusted odds of having ED were lower among current, weekend, and binge drinkers and higher among ex-drinkers. Among current drinkers, the odds were the lowest for consumption of 1-20 standard drinks a week. After adjustment for cardiovascular disease or cigarette smoking, age-adjusted odds of ED were reduced by 25-30%.[82] A meta-analysis of population-based cross-sectional studies to assess association of alcohol consumption and ED yielded a protective association of alcohol on ED.[83] Studies on patients presenting with SD have reported a variable percentage of alcohol use. Fagan *et al*.[84] reported 29% of 145 consecutive patients with sexual problems to score on the probable alcoholism range on the Michigan Alcohol Screening Test, of which only six were diagnosed with alcoholism. Masters and Johnson[85] reported that in 35 out of 213 men with secondary impotence, the ED occurred as a direct result of acute alcohol intake; they did not detail out the chronicity of alcohol intake. One study from China reported alcohol as one of the important risk factors for low sexual function among urban women; the odds ratio of 2.67 was more than that for age, depression, low education level, chronic medical disease, and living apart from the partner.[86] Snyder and Karacan[87] measured nocturnal penile tumescence in 26 alcoholic men going through detoxification and found that their nocturnal erections were fewer, slower, and less rigid than in a nonalcoholic comparison group; they speculated peripheral neuropathology as the explanatory factor. Another double-blind study[88] reported significantly decreased frequency and duration of full erections in abstinent alcoholics on disulfiram. This finding is of particular importance due to the possible confounding effect of disulfiram on the reported frequency of sexual disorders.

Correlates of sexual dysfunction

Other studies have correlated ED with older age[4,9,13] and lower total testosterone.[4,20] Studies which have tried to establish a correlation between altered hormonal levels (testosterone, prolactin, and LH) and SD have in general come up with negative findings.[6,9,18,20] Some studies suggest that there is no correlation between methadone dose and SD[10,21,22] whereas others suggest that ED is higher in those taking higher doses of methadone.[5,18,23] Studies have also reported that higher methadone dose correlates negatively with ejaculation frequency[22] and positively with orgasmic dysfunction in men on MMT.[11] Other studies suggest that the rates of SD are affected by co-morbid depression[15] and number of psychological symptoms[23] whereas some studies suggest no correlation between SD and depression.[12,13,18]

A study in patients on MMT reported that those with altered sexual function while on street heroin represented a high-risk group for developing inadequate sexual function upon initiation of MMT.[35] Other studies have correlated ED with older age[42,46,55] and lower total testosterone.[42,48] Some others failed to establish a correlation between altered hormonal levels (testosterone, prolactin, LH) and SD.[46,48,50,52] While some studies suggest no correlation between methadone dose and SD[35,37,89] others suggest that ED is higher in those taking higher doses of methadone.[36,49,50] In contrast, some studies have also reported that higher methadone dose correlates negatively with ejaculation frequency[89] and positively with orgasmic dysfunction in men on MMT.[39] Other studies suggest that the rates of SD are affected by co-morbid depression[43] and number of psychological symptoms[36] whereas some studies suggest no correlation between SD and depression in patients with opioid dependence.[50,51,55]

A longitudinal study evaluated the effect of short-term and long-term abstinence from alcohol, opioids, speedball, cocaine, and cocaine plus alcohol on SD; the authors recorded the SD to persist after 3 weeks as also 1-year despite continued abstinence from substance abuse.[54]

DISCUSSION

In substance dependence, SD is of high clinical relevance as it often leads to treatment nonadherence and sexual or marital disharmony. Yet, it is often neglected and unexplored in routine clinical care. This is also reflected by the limited research in this area. This review suggests that long-term use of alcohol and opioids are associated with SD in almost all domains of sexual functioning. Studies in patients with either heroin addiction or on MMT or BMT have demonstrated higher rates of SD than in the general population, the rates ranging 34-85% for heroin addicts, 14-81% for MMT, 36-83% for BMT, and 90% for naltrexone maintenance. In contrast, in case of alcohol dependence, the SD rates have varied from 51% to 58% for low sexual desire, 16-59% for erectile impotence, 4-15.9% for premature ejaculation, and 17.8-25.4% for retarded ejaculation. There is

evidence to suggest that endogenous opioids play a role in alcohol-related SD too.

However, the available studies suffer from many limitations. Some assessed SD by either spontaneous self-reporting (which might give lower rates) or by open questions (which may be interpreted differently by different patients). Some used inconsistent and nonvalidated measures of SD. Others took mixed groups of subjects (i.e., single and married subjects) or did not evaluate for contextual factors which could contribute to SD. Still others lacked consecutive or random samples and matched controls, or did not evaluate the impact of other opioids like dextropropoxyphene, codeine, etc. Furthermore, some studies did not try to distinguish the SD due to harmful effects of alcohol/opioid *per se* and SD due to other co-morbidities like use of other substances, effects of co-administered medications, the presence of a primary sexual disorder, presence of a medical condition affecting sexual function, psychosocial factors such as relationship conflict, presence of co-morbid psychiatric disorder, hepatocellular dysfunction, etc. Many co-morbid disorders are known to influence the prevalence of SD. Among the major predictors of ED observed in the Massachusetts Male Aging Study, diabetes mellitus, heart disease, hypertension, and decreased high-density lipoprotein levels were all associated with increased risk for ED. Medications for diabetes, hypertension, and cardiovascular disease also increase the risk of ED.[90] A prospective study[91] showed obesity and smoking to be additional risk factors for ED. In addition, there is a higher prevalence of ED among men who have undergone radiation or surgery for prostate cancer, or who have a lower spinal cord injury. Delayed or absent ejaculation may be associated with a variety of medical or surgical conditions (e.g., multiple sclerosis, spinal cord injury, surgical prostatectomy), or the use of anti-adrenergic or neuroleptic medications. A recent study that assessed the bio-psychosocial determinants of sexual desire in men concluded that cognitive factors (sexual beliefs and automatic thoughts during sexual activity) were the best predictors of sexual desire in men.[92] Various beliefs related to restrictive attitudes toward sexuality, erection concerns, and lack of erotic thoughts in a sexual context had a significant direct effect on reduced sexual desire. This set of cognitive-emotional factors also mediated the relationship between medical problems, age, and sexual desire. Another similar study[93] also highlighted the impact of early maladaptive schemas, helpless, and incompetence schemas impacting sexual function in men. A major limitation of existing research is that most of the studies have focused only on men, and the data for women are very limited.

Sexual side effects are not spontaneously reported by patients due to associated feelings of inadequacy; hence, direct inquiry is required. A careful enquiry can establish the patient's baseline levels of desire, arousal, and orgasmic function and determine whether a plausible chronological relationship exists between the onset of substance dependence and the beginning of SD. The most valuable asset is the patient's own history and description. SD is most obviously a side effect when it is reported as a new symptom after onset of substance dependence. In such a situation, clinicians should take measures to keep the patient abstinent and evaluate the SD longitudinally and treat it with appropriate measures.

There is thus, a need to study the multiple dimensions of association of substance abuse and SD. Future research should attempt to overcome the limitations of the existing literature. There is a need for studies with larger sample size using standardized instruments. These studies should attempt to evaluate the SDs in various phases of drug dependence, especially during the stable abstinence phase. Although studies have evaluated efficacy of various pharmacological agents in patients with SD, there is a need to evaluate these agents in patients with drug dependence using double-blind randomized control trials.

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