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EXPERT OPINION

Contemporary Considerations in the Pathophysiology of Low Sex Drive in Men

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DEFINITION

The term libido, which, in Latin, denotes "desire" or "lust", is firmly ensconced in the field of sexual medicine. Originally adopted from the language of psychoanalysis, it may be more usefully replaced by English usage going forward. While the terms sex drive and sexual desire (SD) have historically been used interchangeably, more recent studies have differentiated the 2 and more broadly use the contemporary term "hypoactive sexual desire disorder." Beginning with International Classification of Diseases 11, this term was further updated to hypoactive SD dysfunction (HSDD), which is characterized by "absence or marked reduction in desire or motivation to engage in sexual activity as manifested by any of the following: (1) reduced or absent spontaneous desire (sexual thoughts or fantasies); (2) reduced or absent responsive desire to erotic cues and stimulation; or (3) inability to sustain desire or interest in sexual activity once initiated."[1] Although this definition is preferred by the authors given its widespread recognition and contemporary use in scientific publications, differing terms are used throughout the article to maintain consistency with the original definitions used within the referenced publication.

SD, as a scientific concept, is undergoing significant maturation, as is evidenced by the updated International Classification of Diseases 11 diagnosis and coalescing upon commonly agreed upon terminology. However, there are several limitations with HSDD, including the lack of objective diagnostics and measures of therapeutic success. In this context of lack of formal consensus, in the authors' considered opinions, SD consists of 3 components: (1) biological (visceral) drive, the physiologic feeling of being sexually aroused, (2) psychological (intellectual) motivation, the idea that engaging in sexual activity will bring pleasure and satisfaction, and (3) cultural influences, with which we assign meaning to sexual activity or define what sexual behavior is acceptable.[2]

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Prevalence

The US National Health and Social Life Survey (1999) suggested that 14% of men had a lack of sexual interest, while the Global Study of Sexual Attitudes and Behaviors (2005) cited a similar prevalence of 13−20%.[3,4] Interestingly 77% of these men stated they were not happy with their life in the latter study. Furthermore, in this analysis, in 29,000 adults aged ≥40 years, low SD increased with age.

Neurobiological Influences

The central nervous system (CNS) is, arguably, the most influential driver for HSDD. Several distinct neuroactive chemicals including dopamine, serotonin, catecholamines (epinephrine/norepinephrine), testosterone, kisspeptin, histamine, melanocortin, opioids, and endocannabinoids, among others, have been linked to SD. Although the majority of these have agonistic effects on SD, serotonin and opioids most often reduce SD.[5,6] However, as with many body systems, neurochemical regulation depends not only on the specific substance but also on the presence and function of receptors. Centrally acting medications also may demonstrate varied and unpredictable responses on SD, even within similar therapeutic classes. This is likely due to the fact that medications that cross the blood brain barrier are nondiscriminating and are distributed to all regions of the CNS. Medications also exhibit unique receptor-binding profiles, which may lead to simultaneous agonist and antagonistic effects on SD. Interestingly, some have reported persistent sexual or other psychological effects after discontinuing CNS medications, although this remains controversial.[7]

Dopamine is one of the most important neurochemicals impacting SD. Among dopamine receptors, D4 and D5 are the primary targets that regulate SD.[8] D4 is distinct, as it is activated based on situational cues (visual and other sexual stimulation), while D5 is responsible for pre-ejaculatory intromission pleasure.[9] It is therefore not surprising that antipsychotics (which may block dopamine) are commonly linked to low SD.

Serotonin is another key chemical which has effects on SD. It is also important clinically, as a large number of people take selective serotonin reuptake inhibitors (SSRIs), which serve to increase the amount of serotonin present in the neuronal synapses. In contrast to dopamine, serotonin functions to reduce SD, and as such, SSRIs are responsible for low SD.[10] Among the receptor subtypes, 5-HT1a and 5-HT2 appear to most impact sexual function.[5,10] Therapies that impair only one of the 2

subtypes appear to have less of an impact on sexual function overall, including mirtazapine, nefazodone, buspirone, and buproprion.[11]

Epinephrine and norepinephrine serve to modulate SD. This is relevant clinically, as amphetamines are agonistic and used as a recreational drug or to treat various medical conditions. Amphetamines are particularly noteworthy because they increase norepinephrine and dopamine, increasing SD.[12]

Endocrine Influences

Hormones play a significant role in SD modulation. The 4 endocrine disorders that have most commonly been associated with low SD in men are hyperprolactinemia, low estradiol, thyroid dysfunction, and testosterone deficiency (TD).

While hyperprolactinemia is commonly associated with TD in men, hyperprolactinemia can occur without TD and can result in low SD.[13] Hyperprolactinemia is typically associated with reversible conditions such as hypothyroidism, renal failure, pituitary tumors, and certain medications.[14] Medications that have been associated with hyperprolactinemia include dopamine agonists, antipsychotics, antiemetics, proton pump inhibitors, and opiates.[14] Thus, by treating the underlying medical cause, prolactin levels will usually normalize, and men may notice an improvement in their SD.

Both hypothyroidism and hyperthyroidism have been reported to impair SD in men.[12] However, hypothyroidism's impact on male SD is mixed. The mechanisms by which hyperthyroidism affects SD include an associated elevation in SHBG levels (lower free testosterone levels) and hyperthyroidism's association with depression (31−69%) and anxiety (33−61%).[15]

Low testosterone (T) levels are associated with low SD, and T therapy (TTh) has been shown to improve SD in many men. A meta-analysis by Corona et al evaluated 14 studies with 2,298 hypogonadal men receiving TTh and found that TTh significantly improved SD in men with TD, although the effect was modest and variable.[16] Younger men with lower T levels tend to see greater improvements in low SD on TTh. Finally, the 2018 American Urological Association Testosterone Guidelines state that patients should be informed that TTh may result in improvements in SD.

Some data have demonstrated that estradiol (E) plays a role in men's SD. Animal data have demonstrated that aromatase knock out mice have a decreased sexual interest, intromission, and ejaculation.[17] Once these aromatase knock out mice were given estradiol, there was a significant improvement in all 3 of these sexual parameters. A study by Finkelstein et al found that it was actually E (not T) deficiency that was primarily accounted for the decline in SD in men.[18] This supported by other data which found on multivariate analysis that the best predictor of SD in men receiving TTh was actually higher E (not T) levels.[19] While these data are preliminary, one concern is that many men's health clinics across the country are using large amounts of aromatase inhibitors, which block the conversion of T to E, resulting in low E levels.

Psychosocial Influences

Psychosocial correlates of HSDD can be individual, historical, relational or cultural, or any combination of these. Individual factors include psychological problems, daily stress, worry about other sexual dysfunctions (including erectile dysfunction), fatigue, frequent masturbation, and overuse of pornography. Historical factors include sexual and physical trauma. Relationship-related factors include interpersonal conflict, sexual problems in the couple, and coping with infertility. Culture may also influence SD. Prevalence of low SD is highest in Southeast Asian countries and lowest in Southern and Northern Europe.[3] This is an understudied area, but research on Asian men suggests that they accept SD as an aspect of aging.[20] Men in cultures that idealize sexual prowess may experience diminished SD when they are unable to measure up to performance expectations.

Research on psychosocial interventions that improve low SD in men is limited. This may be, at least in part, due to the fact that low SD is a topic that has not been, until recently, a focus of interest in sexual health research. In addition, unlike studies of drug effectiveness, it is never possible to truly blind study participants in psychosocial interventions or provide sham control therapies. In clinical practice, patients have been taught to cultivate desire. Based on Basson's model of female sexual arousal, a subjective decision to engage in sexual activity can lead to stimulation; stimulation can lead to arousal, which promotes desire, increased arousal, and orgasm.[21] Men and couples can plan sexual encounters, replacing spontaneity with anticipation. The use of erotica, sex toys, or visual stimuli can enhance the encounter's appeal. Sensate focus exercises, developed by Masters and Johnson, may help reduce anxiety and aid in identifying new pleasurable sensations.[22] Conducted without demand for sexual activity, the exercises can reduce pressure on performance and ultimately expand the couple's sexual repertoire. While these approaches have been successful in clinical practice, they have yet to be tested empirically.

Interventions designed to increase women's SD can guide future research on interventions for men. Brotto et al used a mindfulness meditation-based cognitive behavioral approach to increase women's SD, arousal, and lubrication.[23] Bossio et al adapted this approach to treating men's situational ED, which led to improved ED and sexual satisfaction.[24] This promising approach might be considered in designing and testing interventions aimed at encouraging SD in men.

Medication Influences

The list of medications that have been at some point in time been linked to low sex drive is extensive. The medication list includes psychotropics (SSRI/SNRI agents, benzodiazepines, anti-psychotics), antihypertensives (spironolactone and centrally

acting agents such as clonidine), antiandrogens, 5-alpha reductase inhibitors, narcotics, and histamine type 2 (H2) antagonists, among others. However, literature directly supporting the link between many of these medications and SD is limited and weak. In particular, the literature makes it difficult to differentiate between low SD related to the medication itself vs the underlying psychopathology for which patients are being treated (depression, anxiety, psychosis). As with any medication-induced sexual problem, stopping, lowering the dose, or switching the medication to another agent within the same class might be useful in resolving low SD in such patients.

CONCLUSION

Assessment and treatment of HSDD in male patients require taking a multifactorial perspective. Educating men about all potential factors that may be affecting their SD is critical to their recognition that multiple approaches to treatment may need to be used. This approach fosters realistic expectations and will likely lead to more satisfactory outcomes.

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