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Assessment and management of sexual dysfunction in the context of depression

Pratap R. Chokka and Jeffrey R. Hankey

Abstract: Sexual dysfunction (SD) is pervasive and underreported, and its effects on quality of life are underestimated. Due in part to its bidirectional relationship with depression, SD can be difficult to diagnose; it is also a common side effect of many antidepressants, leading to treatment noncompliance. While physicians often count on patients to spontaneously report SD, treatment is optimized when the clinician instead performs a thorough assessment of sexual functioning before and during drug therapy using a standardized questionnaire such as the Arizona Sexual Experiences Scale (ASEX). Separating the effects of the disorder from those of medications is challenging; we present a concise, evidence-based schematic to assist physicians in minimizing treatment-emergent sexual dysfunction (TESD) while treating depression. Vascular, hormonal, neurogenic, and pharmacological factors should be considered when a patient presents with SD. We also recommend that physicians obtain patient information about baseline and historical sexual functioning before prescribing a drug that may lead to SD and follow up accordingly. When the goal is to treat depression while attenuating the risk of sexual symptoms, physicians may wish to consider agomelatine, bupropion, desvenlafaxine, moclobemide, trazodone, vilazodone, and vortioxetine.

Keywords: sexual dysfunction, depression, antidepressants

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Correspondence to:
Jeffrey R. Hankey
Chokka Center for Integrative Health, Researcher; 201–2603 Hewes Way NW, Edmonton, AB, T6L 6W6, Canada
jrhankey@chokkacenter.com

Pratap R. Chokka
Jeffrey R. Hankey
Chokka Center for Integrative Health, Edmonton, AB, Canada

Etiology and general assessment

Sexual dysfunction (SD) is a persistent, distressing change in any of the stages of the sexual response cycle.[1] These stages are traditionally thought to include desire, arousal, orgasm, and resolution, though the *Diagnostic and Statistical Manual of Mental Disorders* (5th Edition) (DSM-5) has combined desire and arousal in women into one disorder, called female sexual interest/arousal disorder.[1–3] Many researchers recommend a biopsychosocial approach to assessing and managing sexual disorders, allowing clinicians to capture the ever-evolving, interactive blend of biological, psychological, relational, and contextual factors that contribute to SD.[3–6] Accordingly, a comprehensive, integrated model, one that considers individual, relational, medical, erotic, sexual skill, and situational dimensions, is most likely to succeed, particularly in the long term, in treating male and female SD.[7] However, the epidemiology of SD is difficult due to the wide variety of biopsychosocial determinants that may influence the degree of distress.[8] Compounding the problem, patients often hold unsophisticated views of their dysfunction and its impact on their lives,[4] and the media are frequent sources of misinformation about sexuality and the heterogeneity of so-called normal sexual function.[3] Mahan claims that patients' knowledge deficit around matters of sexuality and SD is commonly overlooked and easily treated.[1] However, routine assessment of patients' sexual histories and consultation of guidelines about SD are not a generalized practice in primary care.[9]

Confounding diagnosis and treatment of each, SD shares a well-established bidirectional relationship with major depressive disorder

Table 1. Recommended protocol for clinical assessment of sexual dysfunction.

Box A. Medical history[2,3,6]	Box B. Psychological factors[3,6]	Box C. Laboratory investigation[2]
• Past sexual dysfunction • Chronic medical conditions, e.g. ○ Hypertension ○ Diabetes mellitus ○ Brain/spinal cord injury • Cancer (past or present), including history of chemotherapy or radiation • Past surgical procedures, e.g. ○ Pelvic surgery ○ Prostatectomy • Current medications, e.g. ○ Antihypertensive medications ○ Propranolol ○ Spironolactone ○ Opioids • Alcohol/drug use • Menopause	• Depression • Social phobia • Anxiety • Obsessive-compulsive disorder • Attention-deficit/hyperactivity disorder • Distraction • Performance anxiety • Body image • Sexual trauma/abuse • Relationship issues/divorce • Sexual skills	Suggestive blood work: HSDD: • fasting glucose • lipids • testosterone & free testosterone • luteinizing hormone ED: • testosterone & free testosterone • prolactin • glucose • lipids • urinalysis • blood count (anaemia) • TSH • serum creatinine • PSA

ED, erectile dysfunction; HSDD, hypoactive sexual desire disorder; PSA, prostate-specific antigen; TSH, thyroid-stimulating hormone.

(MDD). Depression is associated with a 50–70% increased risk of SD, while SD increases the risk of depression by 130–200%.[10,11] In one study, 67% of depressed men and 75% of depressed women reported SD, in particular, decreased interest in sex, prior to antidepressant treatment, and depressed patients' quality of life was further diminished in those with SD.[12] Additionally, regardless of treatment, a positive outcome for MDD has a significant impact on global sexual functioning, suggesting that antidepressants can enhance sexual function in depressed patients affected by illness-related SD.[13,14] Further complicating diagnosis of SD in depressed patients, treatment-emergent sexual dysfunction (TESD), including both the worsening of pre-existing dysfunction and the development of new dysfunction in previously untroubled patients,[15] is a common side effect of many antidepressants, often resulting in noncompliant or discontinued drug treatment.[13] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the most serious malefactors, possibly due to the inhibitory effect of serotonin on dopamine release in hypothalamic and mesolimbic areas.[16] For this reason, SSRIs are generally seen as the most efficacious treatment option for premature ejaculation, particularly citalopram, fluoxetine, paroxetine, and sertraline.[2,17]

In addition to MDD, additional risk factors for SD include older age, lower education level, chronic medical conditions such as type I diabetes and hypogonadism, sexually transmitted infections, excessive alcohol use, menopause, physical disfigurement, past sexual abuse, social phobia, performance anxiety, and relationship problems[11,18] (see Table 1). The prevalence of SD in depressed patients is underestimated in primary care, as physicians often believe that patients will spontaneously report the dysfunction.[11] Different assessment methods (spontaneous report *versus* direct inquiry) can produce vastly different prevalence estimates; in one study, incidence of men's SD was 60% when asked directly compared with 20% when dependent on spontaneous report.[19]

Standardized scales of sexual functioning include the Arizona Sexual Experiences Scale (ASEX), Changes in Sexual Functioning Questionnaire, Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ), and Sex Effects Scale.[11] We like the ASEX scale, as it has established reliability and validity, is concise, and is easy to administer in a clinical setting.[11,15,20–23] Differentiating the effects of MDD from those of the antidepressant can be quite challenging in clinical practice; busy clinicians often omit the important step of assessing baseline sexual functioning prior to drug administration, leaving them

Table 2. Treating MDD while managing SD: Summary of antidepressants and augmentation agents (with lowest effective dose for adults with MDD).

Category A (Improves sexual functioning)	• Sildenafil[2,5*†] • Tadalafil[2,5* †] • Vardenafil[2,5*†] • Flibanserin[26,34,36,37*α] • Bupropion[11,42–44] (100 mg × 2)[74]
Category B (No significant effect on sexual functioning)	• Agomelatine[45–48,75] (25 mg)[65] • Desvenlafaxine[49–51] (50 mg)[51] • Moclobemide[52,53,76] (450 mg)[53] • Trazodone[54–58] (150 mg)[77] • Vilazodone[11,59,60,78] (20 mg)[79] • Vortioxetine[11,61,62,80] (20 mg)[81]
Category C (Significant negative effect on sexual functioning)	• Citalopram[14,42] (20 mg)[82] • Clomipramine[11,33] (100 mg)[83] • Escitalopram[13,14,42,84] (10 mg)[85] • Fluoxetine[14,42] (10 mg)[86] • Imipramine[14,33] (50 mg)[87] • Paroxetine[14,42,84] (20 mg)[88] • Phenelzine[14] (15 mg)[89] • Sertraline[14,43] (50 mg)[90] • Venlafaxine[14,46] (75 mg)[49]
Category D (Inconclusive)	• Duloxetine[13,91,92] (60 mg)[93] • Levomilnacipram[64,65] (40 mg)[65] • Mirtazapine[68–71,94] (15 mg)[95]

*Not an antidepressant.
†Recommended for use with male patients only.
αPrescribed for premenopausal female patients only; not directed to treat SD due to depression or antidepressants.
MDD, major depressive disorder; SD, sexual dysfunction.

to conduct this evaluation post hoc when a patient presents with TESD.[19] A timely and thorough assessment of SD is necessary to establish if such symptoms pre-date the treatment, if they are secondary to comorbid conditions, or if they are a direct result of treatment with antidepressants.[6,18] Moreover, clinicians are advised not to rely on spontaneous report of sexual symptoms, as this method is likely to generate a vast underestimate of the prevalence of TESD.[11] Instead, we recommend that primary care providers establish the importance of sexual functioning for the patient and proceed with standardized assessment accordingly, with evaluation administered before and during treatment.

Women

Female SD is a common problem with a significant impact on well-being,[8] with women most often citing difficulties with arousal.[11,16] As few as one-third of women with distressing SD seek help, as many feel the issue is embarrassing or unworthy of treatment.[3] Drawing on evidence that the distinction between desire and arousal phases may be superficial, the DSM-5 has combined desire and arousal into one disorder, called female sexual interest/arousal disorder (SIAD).[3,24] This decision is not without controversy, as some researchers dispute whether there is sufficient evidence for the amalgamation[25] and others cite clinicians who find the new criteria excessively restrictive.[26] Nonetheless, 8–14% of women in the United States suffer from what the DSM-IV refers to as hypoactive sexual desire disorder (HSDD), characterized by distress due to decreased interest in sex, with effects on quality of life that continue to be underestimated.[26]

While lab testing for low desire in women is rarely useful, physicians can look for key biological factors, including hypertension, diabetes mellitus and their treatments, and psychological factors, including past sexual trauma/abuse, personality disorders, anxiety, distraction, and body image issues.[3,6] Furthermore, depressive symptoms and some antidepressants are known to associate with SD in men and women (see Table 2). In a study of women coping with SSRI-related TESD, it was reported that many of the

women's healthcare professionals neglected to inform them of the potential sexual side effects of their antidepressants.[27] This led to distress and confusion, as the women were left to wonder whether their problem was normal. Having their concerns validated played a key role in helping them to cope; however, some clinicians did not accept their sexual side effects as a legitimate issue. Additionally, for some of the women, TESD contributed to significant relationship problems; many patients coped by passively or proactively avoiding sex and several chose not to communicate the problem with their partners for fear of reprisal.[27]

Psychological interventions are thought to have two main advantages over pharmacological agents: there are no known negative side effects and they engender a broader approach, beyond simply reducing target symptoms.[28] Such interventions have been effective in reducing symptoms and improving sexual satisfaction, compared with wait-list controls, in female patients with orgasmic disorders and hypoactive desire.[28,29] Additionally, sex therapy and cognitive-behavioural therapy (CBT), alone and in conjunction, may bring about significant improvements in sexual function.[3,6] Sex therapy traditionally aims to improve a couple's erotic experiences while diminishing anxiety and self-consciousness[3]; sensate focus, which works to shift an individual's or couple's preoccupation from performance to sensations, is the cornerstone of sex therapy, particularly for addressing SIAD related to a woman's low self-esteem, poor self-image, or the internalization of negative messages about female sexuality, as well as anorgasmia related to performance anxiety.[6] CBT often includes sex therapy components but places more emphasis on modifying thoughts and beliefs that interfere with sexual pleasure and intimacy, leading to reduced anxiety, which, combined with behavioural strategies, can improve the patient's quality of sex life.[3,30] Notably, researchers have found evidence that CBT for women with HSDD works best when it includes her partner, if applicable.[29] Mindfulness therapy has been useful in treating arousal problems in women, including those who have suffered past sexual assault,[31] and mindfulness-based cognitive-behavioural sex therapy has been found to improve desire, arousal, lubrication, satisfaction, and overall functioning in otherwise healthy women who sought treatment for low sexual desire and arousal.[32] Finally, evidence suggests exercise before sexual activity may increase sexual desire.[33]

Pharmacological interventions include flibanserin, a nonhormonal oral treatment used to treat HSDD in premenopausal women, which is thought to impede sexual inhibition effects while promoting dopaminergic sexual excitement effe cts.[26,34–36] Compared with placebo, flibanserin has shown only small positive effects on sexual desire, though it has a severe drug interaction with alcohol (hypotension and syncope) and is therefore only available through a restricted Risk Evaluation and Management Strategy program, in which prescribers and pharmacies must be certified to prescribe and dispense flibanserin to pati ents.[26,34,36,37] Moreover, flibanserin is not indicated for women whose low sexual desire can be attributed to a coexisting medical or psychiatric condition (including depression), the effects of medication or substance abuse (TESD), or relationship problems.[26,34] Accordingly, treating depression- or antidepressant-related SD with flibanserin would require off-label prescriptions, for which safety and efficacy data are not available. Instead, the antidepressant and smoking cessation aid bupropion has been shown to increase desire in non-depressed women and treat SSRI-induced SD in women with MDD,[3] and the topical (intravaginal) use of dehydroepiandrosterone (DHEA) has shown promise in treating multiple domains of SD, including low libido.[8] In addition, testosterone therapy is a long-standing off-label treatment for decreased libido, particularly for postmenopausal women, though its long-term effects have not been well studied.[2,3]

Men

Men with TESD most frequently report problems with desire and ejaculation.[11,16] There are several barriers to the treatment of SD in men, including their own lack of knowledge about normal sexual functioning, a dearth of available resources and treatment options, and fear of embarrassment.[38] HSDD in men is an area lacking substantial research, though there is evidence that various drugs can contribute to decreased libido, including antihypertensive medications, propranolol, spironolactone, opioids, recreational drugs, and alcohol.[2] Blood screening, including fasting glucose, lipids, testosterone, and luteinizing hormone levels, can aid in diagnosis, in order to identify any underlying disease processes that may contribute to SD.[2] Some men with diminished libido and low testosterone levels have seen improvements with testosterone supplementation.[2,17] Reduced libido is a common side effect of

some antidepressants as well[11,16] (see Table 2). It is important to consider that a single factor may be responsible for SD, but often a comprehensive assessment will identify multiple contributing factors (e.g. low testosterone compounded by performance anxiety).[6]

Erectile dysfunction (ED) is often underreported due to low health literacy, cultural taboos and social stigma, and ethnic differences; fewer than half of men with ED seek medical treatment.[2] Psychogenic factors are common culprits, with one study identifying two models of psychogenic causes: the behaviour-based model, according to which depressed men's neurotic thoughts and behaviours negatively affect arousal, leading to reduced libido and sexual pleasure; and the biological model, where the stress of depression affects the hypothalamic–pituitary–adrenal (HPA) axis.[2] If psychogenic and treatment-emergent causes are ruled out, a laboratory analysis of testosterone and free testosterone, prolactin, luteinizing hormone, glucose, lipids, urinalysis, blood count, thyroid-stimulating hormone (TSH), serum creatinine, and prostate-specific antigen (PSA) is recommended[2] (see Table 1). ED can have vascular, hormonal, neurogenic, and psychogenic causes, with diabetes being a common factor[2]; furthermore, ED may not only be caused by cardiovascular factors but may in fact be a warning sign of future cardiovascular disease.[6] Certain disease states, particularly diabetes, endocrine disease, cardiovascular disease, and some neurological disorders such as multiple sclerosis, epilepsy, Parkinson's disease, and brain or spinal cord injury, can impair sexual functioning in different ways, by restricting blood flow to the genitals, impairing nerve impulses needed for arousal, or by lowering hormone levels associated with sexual desire.[6] Accordingly, a comprehensive exam is necessary to determine predisposing, precipitating, and maintaining biomedical and psychosocial factors, as well as an account of specific symptoms of dysfunction.[6]

Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, and vardenafil) are the first line of pharmacotherapy in the treatment of ED.[2,5] These medications have high rates of efficacy and safety, even in patients who are difficult to treat, such as those with diabetes mellitus.[17] Indeed, studies have shown sildenafil to be 76% effective in treating ED in depressed men.[5] Medications, however, only treat vascular and hormonal contributors to ED. Cognitive therapy addresses psychological components, focusing on distorted beliefs, attitudes, and thought patterns, such as all-or-nothing thinking, overgeneralizing, and catastrophizing; indeed, psychotherapy and medications appear to exhibit a synergistic effect, working better together than either one alone.[1,5] In addition, lifestyle interventions, including improved diet, exercise, smoking cessation, and reduced alcohol intake, have been shown to benefit men with ED.[2] Finally, there is limited evidence to suggest that some forms of complementary and alternative medicine may reduce ED, namely saffron,[39] yohimbine,[5,40,41] and red ginseng.[40,41]

Antidepressants and augmentation agents

SD is a common symptom of both MDD and some antidepressants. In the context of treating depression while minimizing SD, we have categorized widely available antidepressants and augmentation agents according to their sexual side effect profiles (Table 2). To facilitate a thorough, evidence-based review of medications, we searched *EBSCO Discovery Service*, containing journal articles from over 70 different databases including *MEDLINE* and *ScienceDirect*, for articles from 1993 to 2017 using the terms 'antidepressant' and 'sexual dysfunction', and followed up with searches for particular medications (e.g. 'agomelatine and sexual dysfunction'). Category A medications are those that can be taken safely with antidepressants, including SSRIs, and have been shown to improve sexual symptoms. PDE5 inhibitors are augmentation agents for treating ED in men,[2,5] flibanserin is indicated for improving sexual functioning in women, but only those whose SD is not depression- or antidepressant-related,[26,34] and bupropion can be used as an augmentation agent in men and women and is an effective antidepressant in its own right.[11,42–44]

Category B medications are effective antidepressants that have been shown to exhibit little or no negative effect on sexual functioning compared with placebo. Agomelatine trials have shown high rates of MDD remission, a superior side effect profile compared with paroxetine and venlafaxine, and similar rates of sexual side effects to placebo, at both 25 mg and 50 mg doses.[45–48] The effects of desvenlafaxine on sexual functioning at both 50 mg and 100 mg are similar to placebo, while antidepressant efficacy is significantly better than placebo.[49–51] The selective reversible monoamine oxidase (MAO)-A inhibitor, moclobemide,

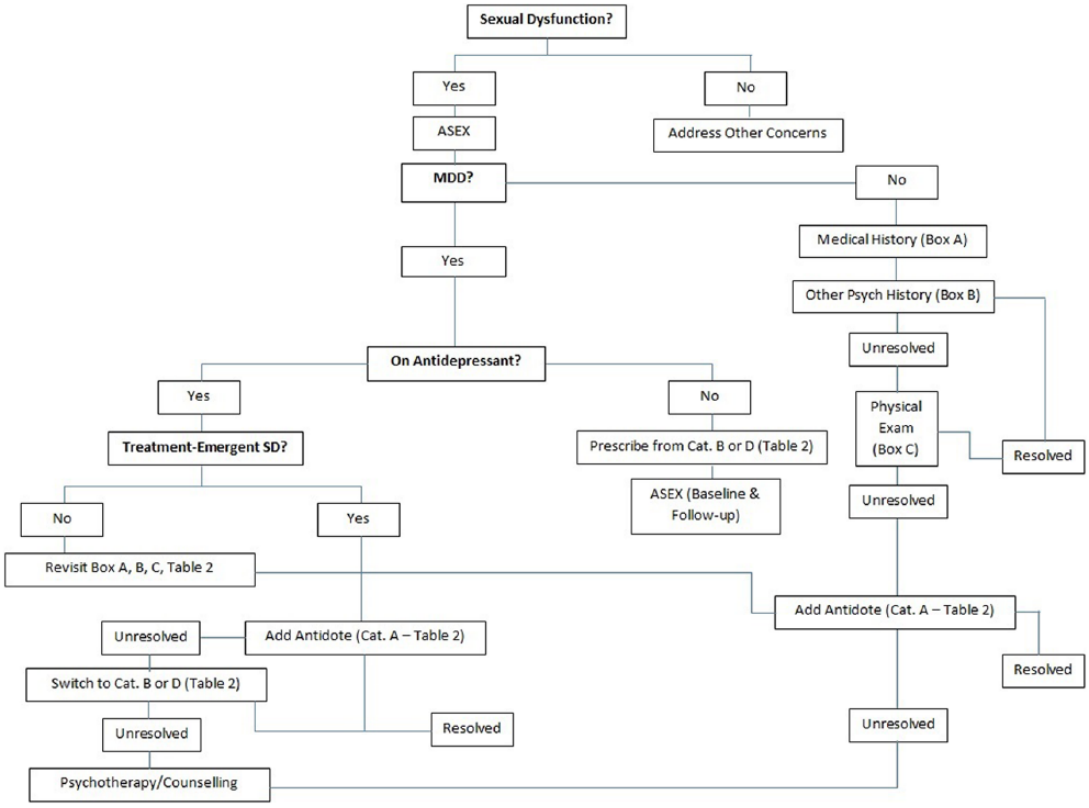

Figure 1. Diagnostic for patients presenting with sexual dysfunction.
ASEX, Arizona Sexual Experiences Scale; MDD, major depressive disorder; SD, sexual dysfunction

showed similar antidepressant efficacy to SSRIs (fluoxetine, fluvoxamine, sertraline, and paroxetine) but about one-tenth the rate of SD (1.9% *versus* 21.6%) reported as adverse events[52]; it may even have a therapeutic effect in the treatment of ED.[53] There is limited evidence that trazodone may increase libido and ameliorate ED,[59,60] though a double-blind, placebo-controlled, randomized study found no difference between trazodone and placebo on sexual function in men with ED.[56] Most evidence points to trazodone as neither helping nor hindering sexual function[54,57,58] and accordingly we have grouped it in Category B. Vilazodone has demonstrated clinical efficacy compared with placebo in treating MDD without eliciting clinically significant SD at a dose of up to 40 mg.[59,60] Finally, vortioxetine demonstrated antidepressant treatment efficacy while sexual side effects were similar to placebo at doses of 5–20 mg.[11,61,62]

Category C includes those antidepressants that have been shown to elicit significantly higher TESD than placebo. With the exception of venlafaxine and phenelzine, an SNRI and irreversible MAO inhibitor, respectively, these medications are all tricyclics or SSRIs. Up to 70% of patients on SSRIs report TESD, while more than 90% of clomipramine-treated patients report orgasmic dysfunction.[42] There is evidence to suggest that citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine show the highest rates of TESD.[14,42]

Finally, Category D includes antidepressants for which the evidence around sexual functioning is inconclusive. Studies of TESD with duloxetine have showed mixed results; for instance, Jacobsen and colleagues found duloxetine was associated with significantly higher risk of worsening SD compared with placebo, while Montejo and colleagues found the probably of continued or emergent SD with duloxetine was associated primarily with the MDD response status of the patients.[62,63] Levomilnacipran is a recently approved SNRI for which little sexual side effect data are available. Preliminary data indicate the drug is associated with higher rates of ejaculation disorder and ED compared with placebo in men, with the latter showing dose dependence.[64,65] However, no TESD effects have been

shown in women. Numerous studies have shown potential efficacy of mirtazapine as an augmentation agent to ameliorate SSRI-associated TESD; however, these studies were open-label, retrospective, or naturalistic.[66–71] A randomized, placebo-controlled trial found no difference between mirtazapine and placebo in treating SSRI-associated TESD in premenopausal women,[72] while a meta-analysis suggested mirtazapine was less likely to induce TESD than SSRIs.[73] However, due to a paucity of conclusive randomized, controlled trials with mirtazapine,[73] we have included it in Category D; further research is needed to establish its potential as a Category A or B drug.

In the event of TESD, we recommend against drug holidays (e.g. going off medication on weekends) as these can elicit symptoms of medication withdrawal, the reemergence of depressive symptoms, or encourage treatment noncompliance.[11,18] Instead, physicians might consider switching medications, adding an augmentation agent or antidote, or lowering the dose, albeit with careful monitoring for reduced efficacy[11,15,18,33] (see Table 2 for lowest effective dose for treating adult MDD). Figure 1 contains a concise diagnostic tool for addressing SD in a clinical setting.

Conclusions

SD in men and women, particularly those with MDD, is common and difficult to diagnose. Due to patients' propensity to underreport SD and its potential negative effect on quality of life, we recommend that physicians obtain patient information about baseline and historical sexual functioning before prescribing a drug that may have sexual side effects and follow up accordingly. Vascular, hormonal, neurogenic, and other pharmacological factors should also be ruled out when a patient presents with SD, prior to the introduction of psychological or pharmacological interventions. When prescribing antidepressants for patients who consider sexual functioning important, we suggest clinicians first consider agomelatine, desvenlafaxine, moclobemide, trazodone, vilazodone, and vortioxetine, as these medications are least likely to impair sexual functioning. In some cases, lifestyle changes such as diet, exercise, and smoking cessation, as well as psychotherapy, including sex therapy, mindfulness therapy, and cognitive behavioural therapy, can also be useful.

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