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Geriatric Disorders (K Zdanys, Section Editor)

Treatment Approaches to Sexual Dysfunction in Late Life

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Abstract

Purpose of review This review provides an overview of the latest treatment options for sexual dysfunction in the elderly, specifically the DSM-5 male and female sexual disorders, medication-induced sexual dysfunction, and inappropriate sexual behaviors in dementia. Despite the increasing prevalence of sexual dysfunction with age, various factors including ageism, misconceptions about sexual behavior in the elderly, and discomfort discussing these issues can lead to under-recognition and under-treatment. This review highlights the importance of sexual health at any age and the available pharmacologic and non-pharmacologic treatments for these conditions.
Recent findings Research is robust for some disorders, like erectile dysfunction, but overall lacking for most disorders of sexual function in the elderly. Few FDA-approved treatments exist, but multiple treatments have been studied with varying results. A thorough evaluation of biological, psychological, and social factors should be completed prior to treatment. Psychiatrists should keep in mind that these conditions may be influenced by psychological factors, secondary to psychiatric illness, worsened or improved with psychotropic medications, and may be responsive to psychotherapy. Inappropriate sexual behaviors in dementia that are unresponsive to behavioral interventions may also respond to a number of psychotropic medications.
Summary Sexual dysfunction in the elderly remains understudied. However, several pharmacological and non-pharmacological options are available that may be of benefit.

Introduction

Sexual functioning is an important aspect of one's overall health, and psychiatrists should be comfortable discussing it with their patients. This is particularly true in older adults, the majority of whom, up to 86%, remain sexually active [1]. This is despite a normal age-related decline in both genders with sexual activity declining from 73 to 53% to 26% among adult ages 57 to 64, 65 to 74, and 75 to 85, respectively [2•]. Older adults are at higher risk for sexual dysfunction given changes in sex steroids [3], development or exacerbation of chronic medical conditions [4•], and polypharmacy [5]. Psychosocial challenges that can impact sexual health are also common in this population [6].

From a biological perspective, age-related declines in estrogen and testosterone lead to changes in sexual functioning. Among women, these include atrophy, decreased lubrication and sensitivity of urogenital tissues, reduced vital energy, hot flashes, and fatigue [3]. The DSM-5 describes three sexual function disorders in women: female orgasmic disorder, female sexual interest/arousal disorder, and genitopelvic pain/penetration disorder [7]. These disorders are frequently clustered together under the term "female sexual dysfunction" (FSD) [8•]. Multiple medical conditions may impact sexual function in women some of which include arthritis, coronary artery disease, diabetes, hypertension, hypothyroidism, malignancies, neuromuscular disorders, and gynecological conditions [9•].

Among men, age-associated changes in sexual function include changes in erectile functioning, decreased ejaculatory volume, and an increased refractory period. The DSM-5 includes four primary sexual dysfunctions in men: erectile dysfunction, delayed and premature ejaculation, and hypoactive sexual desire disorder [7]. Multiple epidemiological studies have shown an increasing prevalence of erectile dysfunction (ED) with age and an association with comorbidities common in the elderly including cardiovascular disease, diabetes, obesity, hormone deficiencies or imbalances, hypertension, and polypharmacy [10–14]. Depression and other psychological factors may also contribute to erectile dysfunction, as may medications, substance abuse, neurological disease, or surgical procedures like prostatectomy. However, studies have also shown that the increase in ED after age 60 occurs independent of these common comorbidities [15]. The other male sexual disorders are understudied in late life.

Dementia is associated with a variety of changes in sexual behavior [16] that may include persistent, disinhibited, sexual behaviors directed at oneself or others [17•, 18]. These are often difficult to diagnose and treat [19] and may be even more distressing for caregivers than other behavioral disturbances associated with dementia [20].

As adults live longer lives, they may face additional psychosocial challenges in establishing or maintaining sexual relationships. The mental or physical decline of a partner or loss of a partner altogether may lead to changes in sexual activity [21]. Many older adults live in long-term care facilities where restrictions may be placed on sexual activity due to ageist attitudes or out of concern for a resident's capacity to consent to sexual activity [22]. Concern for sexually transmitted infections has been reported as a reason for lack of sexual activity among some older adults [2•]. All of this occurs in the context of an ageist society where youth is associated with vitality and sexuality, while older adults are seen as irrelevant, debilitated, or burdensome [23].

Beliefs about the aging process and sexual activity in the elderly may discourage patients and providers from addressing these issues [8•]. When presented with a sexual concern, the psychiatrist should consider potential biological, psychological, and social contributors from the patient history. Other pertinent factors to consider are a history of sexual abuse, relationship conflict, substance use, cultural background, and personality traits [24]. Age-appropriate changes should be distinguished from pathological changes. A thorough evaluation of sexual dysfunction should be done in coordination with the patient's primary care physician and include a complete physical examination, medication inventory, and relevant laboratory studies (e.g., complete blood count, electrolytes, hormone levels) [21]. In this review, we outline treatment considerations for sexual dysfunction in late life: male and female sexual dysfunction, medication-related sexual dysfunction, and inappropriate sexual behaviors in dementia.

Male sexual dysfunction

Erectile dysfunction

Introduction: When surveyed about the cause of decreased sexual activity in patients over 70, male respondents cited erectile dysfunction as the most common reason [25]. In a recent epidemiological study in Australia, the prevalence of ED was found to be 67.3% in patients over 65 and 68.3% in patients over 80 [14]. Underlying physiological mechanisms most likely include atherosclerosis of the penile arteries, changes in smooth muscle density and the composition of the extracellular matrix proteins, modulation of alpha-adrenergic receptors leading to impaired adrenergic stimulation of smooth muscle contraction, and endothelial dysfunction [13, 26–31]. Treatment of erectile dysfunction in the elderly includes both pharmacologic and non-pharmacologic options. Not surprisingly, most studies regarding the treatment of erectile dysfunction include men over 65.

Treatment

Pharmacologic

Phosphodiesterase-5 (PDE5) inhibitors: This medication class constitutes the first line treatment for erectile dysfunction [32]. The available PDE5 inhibitors in the USA are sildenafil, tadalafil, vardenafil, and avanafil. Effectiveness has been demonstrated in multiple etiologies of ED.

Trials of sildenafil, the first of its class, have shown improvement in erectile functioning in 77 to 84% of men [33]. Though very similar in structure to sildenafil, vardenafil may have a slightly faster onset of action than sildenafil and has been shown in meta-analyses to be slightly more efficacious [34]. However, vardenafil may increase QTc, unlike sildenafil. Both sildenafil and vardenafil should be taken approximately 1 h prior to sexual activity but can be effective within a window of 30 min and can remain effective for 4 to 6 h. Tadalafil is longer acting and can be taken up to 30 h prior to intercourse. It has been shown to be safe and effective across all age groups with 81% of patients reporting improved erectile function [35]. It may also have greater efficacy than other PDE5 inhibitors [34].

The newest PDE5 inhibitor, avanafil, is considered a second-generation PDE5 inhibitor given its selectivity for PDE5, which was hypothesized to lead to a more preferable side effect profile. Avanafil may be effective within 15 min of administration and provides a similar improvement in erectile function to other PDE5 inhibitors [36]. However, meta-analysis has not borne out a lower risk of side effects and has shown avanafil to lag behind in efficacy measures [34].

The most common side effects of this class of medications include headache, flushing, hypotension, epistaxis, and dyspepsia. Rarely, PDE5 inhibitors have been associated with sudden vision or hearing loss that can be temporary or permanent. As a class, PDE5 inhibitors are contraindicated in patients taking nitrates because of the risk of sudden hypotension. Use is also contraindicated in those with severe cardiovascular disease or a high risk of MI during sexual activity. Alpha-blockers are not contraindicated but should not be administered within 4 h of PDE5 inhibitors [10, 37•].

A 2015 study comparing men age 51–87 with ED treated with PDE5 inhibitors to those without ED and those with untreated ED showed that, despite reporting greater sexual activity and a greater frequency of sexual intercourse, those receiving PDE5 inhibitors continued to be as dissatisfied with their sexual functioning and overall sexual health as those with untreated ED [38]. Therefore, a disconnect may exist between restoration of function and improvement in sexual satisfaction. This should be addressed with patients, particularly in psychiatric settings, as adjunctive psychosexual counseling may help bridge this gap [38, 39, 40•].

Intra-cavernosal drug injection: Considered a second line treatment of ED, intra-cavernosal injections of prostaglandin E1 (alprostadil), papaverine, phentolamine, or vasoactive intestinal peptide can provide rapid, on-demand erection. Success rates range from 70 to 90%. Possible side effects include priapism, pain, and penile fibrosis [37•].

Urethral suppository therapy: Prostaglandin E1 therapy is also available as an intraurethral suppository that has been shown to improve erectile dysfunction in up to 69% of men [41]. Side effects are similar to those of intra-cavernosal injection but can also include hypotension, syncope, and urethral discomfort [37•].

Testosterone replacement therapy: It remains standard practice to include assays of testosterone levels in the workup of ED, but hypogonadism is a relatively rare cause of erectile dysfunction, estimated to account for 1 to 35% of cases, with more recent, larger studies finding a clustering around 5% [42]. In those with hypogonadism, an average of 65% of men experienced improved or restored erectile function with testosterone supplementation [43]. However, only limited and inconsistent evidence exists to suggest a benefit of testosterone replacement therapy in eugonadal men with erectile dysfunction and its use is not recommended for this purpose [32, 37•, 44, 45]. Testosterone replacement therapy, even in hypogonadal men, may involve risks including cardiovascular adverse events, prostate cancer, erythrocytosis, acne, breast swelling and tenderness, reduced testicular size, and sleep apnea, but this remains an area of controversy and there is no clear consensus in literature [44, 46–50]. Two recent studies prompted the FDA to require warnings about the possible increased risk of myocardial infarction and stroke with testosterone treatment [51•, 52•, 53]. Testosterone replacement in older hypogonadal individuals may be less efficacious and potentially of higher risk as compared to younger men [54•].

Non-pharmacologic

Lifestyle changes: Weight loss, smoking cessation, and the modification of other cardiovascular risk factors like hypertension, hyperlipidemia, and diabetes have been associated with improved sexual function. [55–58]. However, these changes may need to occur in midlife because modification in older adults may be too late to restore normal function [55]. Bacon et al. correlated smoking, alcohol consumption, and television viewing time with increased erectile dysfunction in men age 53 to 90. Conversely, physical activity and maintenance of a normal BMI were associated with retention of normal erectile function [59].

Psychotherapy: ED with a psychological etiology is more common in men under 40 but possible at any age. Psychogenic ED is more common in patients who continue to have normal nocturnal erections or the ability to masturbate, but there is not always a clear correlation between normal nocturnal erections

and the ability to achieve an erection during sex [10]. Psychotherapy may be indicated depending on the underlying psychological factors at play. Studies have demonstrated a positive response to individual or group therapy for the treatment of ED and specifically for the combination of psychotherapy and sildenafil over sildenafil alone [39, 60–62].

Vacuum constriction devices: These devices consist of a tube placed over the penis that produces negative pressure drawing blood into the penis to cause engorgement and erection. A constricting cuff is applied at the base of the penis to maintain turgidity for up to 30 min. Vacuum constriction devices are generally safe in most patients and provide a completely non-pharmacologic option for those who wish to avoid medication or surgery, those who require medications contraindicated with phosphodiesterase inhibitors, or those who have had an incomplete response to other pharmacological treatments [10]. Caution should be advised for patients with bleeding disorders or those on anticoagulants. Patients should also be advised that the erection produced is non-physiologic and will be cool and possibly cyanotic. An erection sufficient to achieve intercourse has been demonstrated in up to 93% of patients using this method, but dropout rates range from 20 to 54% [63]. Side effects may include numbness, pain, delayed ejaculation, bending of the penis, petechiae, and a sense that this method is non-spontaneous and the result unnatural [37•, 63].

Penile prosthesis: Implantable penile prostheses are an option for patients who have failed phosphodiesterase or injectable therapies. Inflatable prostheses consist of thin tubes implanted into the shaft of the penis, a pump inserted in the scrotum, and a fluid-filled reservoir in the abdomen. A 2016 study comparing treatment outcomes for tadalafil, intra-cavernosal injections, or implantable penile prosthesis found that patients who underwent prosthesis implantation (and their partners) reported greater improvement in function and greater satisfaction [64]. Side effects of penile prosthesis can include scarring, penile shortening, and recurrent infections [10].

Male hypoactive sexual desire disorder

Introduction: Male hypoactive sexual desire disorder (HSDD) is characterized by a persistently or recurrently decreased or absent desire for sexual activity lasting for at least 6 months and causing distress to the patient. It has not been extensively studied in the elderly.

Among adults ages 57 to 84 in the USA, 28% of men surveyed reported decreased or absent interest in sex with 65% of those reporting this problem expressing distress because of it [2•]. Acknowledging that sexual activity declines with age, attention should be paid to a patient's dissatisfaction or sex-related distress in order to consider a diagnosis of male HSDD. Epidemiological studies seeking to better characterize this disorder and the men who suffer from it show no statistically significant differences in age, serum testosterone, depressive symptomatology, erectile function, concomitant illness, or medication use between men with and without hypoactive sexual desire disorder. The only appreciable differences are self-reported measures of interest in sex, sex-related distress, and frequency of sexual activity [65].

The DSM-5 distinguishes subcategories of lifelong versus acquired and generalized versus situational HSDD in men. The DSM also recommends that the full workup of HSDD and treatment take into account factors related to

one's partner, the relationship, individual vulnerabilities like a history of abuse, substance use, or psychiatric comorbidity, cultural and religious factors and comorbid medical illness [7].

Treatment

Treatment: There is a lack of evidence regarding treatment of HSDD, particularly in elderly men. Most available evidence focuses on addressing possible contributing factors like depression, medication use, anxiety, relational conflicts, and the management of risk factors associated with a decline in sexual health in general like cardiovascular disease, inactivity, and obesity. Treatment of underlying psychiatric illness or psychological factors may improve symptoms though the use of antidepressants can further decrease libido. Sex therapy, including couples therapy or individual therapy and incorporating cognitive-behavioral, psychodynamic, or mindfulness-based interventions, is sometimes used but has limited evidence [66].

A recent trial of DHEA for hypoactive sexual desire in postmenopausal men and women showed an increase in sexual desire and satisfaction in women thought secondary to increased testosterone levels, but no significant response in men [67].

O'Carroll and Bancroft examined the use of testosterone in eugonadal men with ED or low sexual interest and found that supplementation of testosterone increased sexual desire but had no effect on erectile function [68]. A more recent study showed that biweekly intramuscular testosterone injections in eugonadal men significantly increased ejaculatory frequency and correlated with non-significant but marked increases in desire, masturbation, sexual experiences with a partner, and nocturnal erections. Testosterone had no effect on erectile function, sexual satisfaction, or mood [69]. Other studies have demonstrated a moderate improvement in libido with testosterone supplementation, but the response is more robust in hypogonadal men [45].

Delayed/premature ejaculation

Introduction: Sometimes understood as two ends of a spectrum of ejaculatory dysfunction, delayed and premature ejaculation are understudied in elderly men. Premature ejaculation is a more common complaint among younger men but does persist into late adulthood, and delayed ejaculation can become more common with age. Defined by the American Urological Association as ejaculation that occurs sooner than desired and causes distress, premature ejaculation is estimated to affect 21% of men ages 18 to 59 [70]. There is a primary, lifelong form as well as an acquired form. Delayed ejaculation is more rare, estimated to affect 3% of men, and is defined as a marked delay, infrequency, or absence of ejaculation in 75 to 100% of partnered sexual encounters [7, 54•].

Treatment

Pharmacologic

Pharmacologic: Multiple studies have investigated SSRIs for the treatment of premature ejaculation, and many agents have been found effective [71–79].

Significant differences between SSRIs likely exist with paroxetine causing the greatest delay in ejaculation followed by fluoxetine and then sertraline [76]. The rapidly acting SSRI dapoxetine is the only FDA-approved medication for on-demand use in PE [80]. Recent evidence has suggested that combination therapy with SSRIs and PDE-5 inhibitors may be more efficacious than either alone [81]. Topical treatments such as prilocaine-lidocaine sprays and creams may also improve symptoms [82, 83]. Medications have thus far shown little efficacy for delayed ejaculation and there are no FDA-approved medications though bupropion and cabergoline are the most commonly tried [84].

Non-pharmacologic

Non-pharmacologic: Behavioral and psychosocial interventions for ejaculatory disorders have shown promise. Education on sensuality, movement of the body, speed of sexual activity, muscular tension and breathing, and squeeze and stop/start techniques have improved symptoms of premature ejaculation [85]. Based on early research findings of Masters and Johnson [86], graduated behavioral exercises to prolong latency time as well as psychotherapy to address issues of self-esteem, performance anxiety, avoidance, and interpersonal conflict are recommended [87]. The body of evidence on these interventions as a whole, particularly when used without adjunctive pharmacotherapy, is variable [88, 89].

Female sexual dysfunction

Introduction: Limited literature exists regarding the treatment of sexual disorders in women. Even less information specifically addresses the treatment of sexual dysfunction in women over the age of 65 and additional research specific to elderly women is needed. Much of the information below is extrapolated from studies examining post-menopausal women, typically with a mean age in the mid-50s. Beliefs about sexual dysfunction being a natural part of the aging process may discourage patients and providers from addressing these issues during routine clinic visits [8•]. Elderly women reporting sexual dysfunction should have a thorough medical work-up including hormonal assessment, consideration of pelvic floor weakness, and review of alcohol and illicit substance use prior to pharmacological intervention [24]. Psychiatrists may want to consider referring patients to primary care providers, gynecologists, or urogynecologists for additional work-up and management depending on the specific concern.

Treatment

Pharmacologic

Hormonal Treatments: Sexual excitement may involve hormones such as oxytocin, norepinephrine, and dopamine while the traditional sex steroids (estrogens, progestins, and androgens) exert activating and organizational effects [8•]. Estrogen replacement therapy, sometimes in combination with progestin, has been shown to provide some improvement in sexual function in

postmenopausal women, particularly in pain syndromes [90]. Systemic use of dehydroepiandosterone (DHEA) is not recommended due to concerns about safety and efficacy [91], but some studies suggest that intravaginal use of DHEA may improve dyspareunia and low libido in postmenopausal women [92]. Estradiol patches were not shown to be more effective than placebo in one study of post-menopausal women (ages 60–80) with orgasm dysfunction [93]. However, a randomized controlled trial of conjugated estrogens combined with medroxyprogesterone acetate in postmenopausal women did show increased orgasm frequency [94]. Ospemifene, an estrogen receptor modulator, is approved by the FDA for treatment of postmenopausal dyspareunia at a dose of 60 mg by mouth once daily [95].

Testosterone (300 μg/day) supplementation was associated with a moderate improvement in orgasm in one randomized control trial of postmenopausal women [96], while another study of testosterone gel showed improvement in orgasm, arousal, and sexual interest, but with a ten-fold increase in the serum testosterone level [97]. Combined treatment with estradiol implants and testosterone may be more effective than estradiol alone in postmenopausal women receiving treatment every 3 months for 2 years [98]. Providers should be aware that estrogens may carry significant risks for elderly women including carcinogenic potential in breast and endometrial tissue and cognitive impairment [99].

Non-hormonal Treatments: Psychotropic medications including bupropion, buspirone, and trazodone have been prescribed off label for women with hypoactive sexual desire [8•]. No evidence exists to support using these medications to treat decreased sexual desire in women over 65. Flibanserin is a 5-HT_{1a} agonist and 5-HT_{2A} antagonist that was initially developed as an antidepressant and has been approved for the treatment of hypoactive sexual desire disorder in premenopausal women [8•, 100]. Placebo-controlled trials of this medication in postmenopausal women showed initial promise but the study was underpowered and ultimately terminated early by the study sponsor [100]. Primary adverse events reported with flibanserin included insomnia, somnolence, and dizziness [100]. Phosphodiesterase inhibitors such as sildenafil have been shown to lack efficacy as a treatment for female sexual dysfunction [8•, 101].

Non-pharmacologic

Non-pharmacologic: Prior to pharmacological interventions, patients may benefit from education, normalization, and even psychotherapy [9•, 21]. Encouraging techniques such as self-stimulation, foreplay, and sensate focus may help expand the definition of fulfilling sexuality activity beyond intercourse alone [21]. Providers may also want to consider referral to sex therapy [9•]. Other non-pharmacological options include the Eros-Clitoral Therapy Device, which creates a vacuum over the clitoris to increase blood flow and is FDA-approved for treatment of female orgasmic disorder [24]. Zestra, a botanical massage oil, was shown to increase desire and arousal in one placebo-controlled trial that enrolled women up to age 65 [102]. Patients and providers should be aware that the lack of FDA-approved treatments for female sexual dysfunction means there are a variety of products available on the market with limited data regarding efficacy and safety [8•].

Table 1. Common medications with potential to induce male or female sexual dysfunction

Psychotropics	Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants First and second generation antipsychotics Mood stabilizers Benzodiazepines
Anti-hypertensives	Beta blockers Alpha blockers Calcium channel blockers Diuretics
Anti-Parkinson's agents	Carbidopa/Levidopa Dopamine agonists
Anti-androgens	GnRH agonists 5 alpha reductase inhibitors
Drugs of abuse	Alcohol Opioids Marijuana Nicotine Cocaine Amphetamines
Other	Anti-histamines Hormonal therapies Immunomodulators (interferon) Cytotoxic agents/chemotherapy

Medication/substance-induced sexual dysfunction

Introduction: Multiple medications can induce sexual dysfunction. Common culprits include antidepressants, antipsychotics, antihypertensives, alcohol, opiates, and other drugs of abuse. See Table 1 for a more comprehensive list. Evidence also suggests that even after controlling for other risk factors, the prevalence of sexual dysfunction increases due to polypharmacy alone [103].

While some patients may initially report increased sexual desire or pleasure when using recreational drugs, evidence suggests that prolonged, repetitive substance use can impair one or more of the three stages of the human sexual response cycle (desire, arousal, and orgasm). Prolonged, regular use of alcohol has been associated with impairments in arousal and orgasm for women as well as desire, arousal, and orgasm for men. Cocaine can impair desire, arousal, and orgasm in both men and women; and amphetamines have been associated with erectile dysfunction in men and delayed orgasm in both men and women [104]. Little evidence exists to draw clear conclusions about the impact of prolonged marijuana use on sexual function, but some studies suggest a

negative effect on female orgasm [104]. Benzodiazepines have been associated with anorgasmia in one study [105•]. Finally, smoking has been strongly associated with an increased risk for erectile dysfunction in men and, while not directly studied in women, may also impair female arousal due to decreased peripheral blood flow. Effects may be reversible with smoking cessation [104]. Unfortunately, little evidence exists to make more specific statements about the pattern, amount, or duration of use required for these adverse effects to manifest.

With respect to the management of psychotropic agents in the setting of sexual dysfunction, many trials and meta-analyses have examined the relationship between sexual dysfunction, depression, and antidepressant use. Given that mood disorders can themselves lead to sexual dysfunction, the treatment of these conditions with agents that may then worsen sexual function complicates treatment decisions. More complicated still is the fact that sexual dysfunction can lead to or exacerbate depression while treatment of ED alone has been shown to improve depressive symptoms [106, 107].

Complicated interactions of multiple neurotransmitters are required for normal function of the human sexual response cycle. Desire, arousal, and orgasm depend in large part upon appropriate modulation of dopamine, testosterone, estrogen, prolactin, serotonin, acetylcholine, norepinephrine, and nitric oxide, among others [108•]. The main mechanism underlying sexual dysfunction due to antidepressants, including TCAs, SSRIs, and SNRIs, is likely activation of 5HT2 receptors and inhibition of 5HT3 receptors as well as the inhibition of dopamine activity by increased levels of serotonin [105•, 109, 110].

Men and women who develop sexual side effects on antidepressants will most frequently experience delayed or absent orgasm or ejaculation, but multiple subgroups of sexual dysfunction are possible. Both men and women can experience decreased desire and reduced sexual satisfaction. For men, erectile dysfunction or painful erections are also possible, and women may experience impaired lubrication, vaginismus, or dyspareunia [111•]. These side effects generally emerge within 1 to 2 weeks of treatment, usually before antidepressant effects occur [105•]. Estimates of the incidence of sexual dysfunction due antidepressants have generally ranged between 30 and 60% but vary widely by specific agent [108•]. Head-to-head comparisons of antidepressants have attempted to characterize these differences [105•, 111•, 112]. Of note, most of the studies included in these analyses were completed in a general adult population and rarely included patients over age 60.

Antipsychotics may also impair sexual function by a combination of effects that include alteration of dopaminergic, adrenergic, serotonergic, histaminergic, and cholinergic systems as well as hyperprolactinemia [113].

Treatment

Treatment: The psychiatrist addressing a patient's sexual dysfunction must work closely with primary care, urology, and other specialties to carefully examine medication burden and safely reduce or eliminate agents that may be contributing. This includes a thorough history of substance use including alcohol, opiates, stimulants, tobacco, benzodiazepines, and marijuana all of which can all impair sexual function as described above.

Several treatment strategies have been proposed for antidepressant-induced sexual dysfunction. Though less likely, tolerance to this side effect may develop and sexual function may return to normal after a period of time. Others include dose reduction, scheduling drug holidays to coincide with likely times of sexual activity, or dosing medications, especially those with shorter half lives, shortly after usual times of sexual activity [105•]. Should these interventions not be effective, switching to a medication less likely to induce sexual dysfunction may be beneficial. In a recent meta-analysis, sertraline, citalopram, fluoxetine, paroxetine, and venlafaxine were shown to have the highest rates of treatment emergent sexual dysfunction. Fluvoxamine, escitalopram, duloxetine, phenelzine, and imipramine showed rates higher than placebo but significantly less than the previous group. Finally, bupropion, mirtazapine, nefazodone, and moclobemide showed rates similar or inferior to placebo [112].

Some medications may be capable of reversing antidepressant-induced sexual dysfunction. Results have been mixed but there is weak evidence to support the use of bupropion, mirtazapine, and possibly buspirone for this purpose [111•, 114]. Treatment with PDE5 inhibitors has more robust evidence for improvement in treatment-emergent sexual dysfunction due to antidepressants [115]. Other options include amantadine, stimulants, yohimbine, ropinirole, bromocriptine, cryoheptadine, gingko biloba, saffron, and maca, but none of these interventions has shown positive results in randomized controlled trials [108•, 114].

Antipsychotics may cause dysfunction in all stages of the human sexual response cycle in up to 60% of patients [113]. Prolactin-sparing antipsychotics, like aripiprazole, quetiapine, and ziprasidone, may be less likely to induce sexual side effects. Though prolactin-sparing, clozapine appears as problematic as other antipsychotics likely to raise prolactin levels like risperidone, haloperidol, and thioridazine. Similar strategies, including dose reduction, switching agents, waiting for spontaneous improvement, or adding PDE5 inhibitors (for men), may be helpful [113].

Inappropriate sexual behaviors in dementia

Introduction: Inappropriate sexual behavior (ISB) occurs not infrequently in patients with dementia [17•]. There is limited evidence supporting various treatments (including lack of randomized controlled trials) and no practice guidelines exist for providers faced with this particularly challenging aspect of dementia care [16, 18, 19, 116].

Treatment

Pharmacologic

Antidepressants: If non-pharmacologic treatment fails, selective serotonin reuptake inhibitors (SSRIs) are often considered first-line treatment for ISB in dementia [19, 117] because of their known sexual side effects including decreased libido, orgasm, and arousal [20, 118]. Providers should appreciate that elderly patients are more likely to respond to lower doses of these medications,

even doses half that usually started in younger adults [116]. In one case report of a 55-year-old man with Alzheimer's disease, citalopram 40 mg daily was shown to be effective at reducing hypersexuality, with continued symptom relief up to a year after initiation of treatment [20]. A second case found citalopram 20 mg daily effective in decreasing compulsive behaviors and anxiety in an 85-year-old man with dementia and a subsequent obsessive interest in pornography [119]. A retrospective chart review found that in three out of seven patients with ISB citalopram reduced inappropriate behaviors [18]. Paroxetine has also been shown to curb public masturbation and inappropriate touching in a patient with frontotemporal dementia living in long-term care [120] as well as ISB in a 69-year-old man with alcoholic dementia [121]. Common potential side effects when using SSRIs include gastrointestinal disturbances, headache, and insomnia [16]. Alternative antidepressant options include trazodone, a mild serotonergic agent, and clomipramine, a tricyclic antidepressant [16]. In one case series comprising four patients, trazodone (total daily doses ranging from 100 to 500 mg) was successfully used to treat an array of behavioral disturbances, including ISB [122]. Clomipramine was used successfully to treat ISB in a case series of two elderly men with doses ranging from 150 to 175 mg daily [123]. Prescribers should be aware of specific risks of priapism with trazodone and orthostasis with tricyclic antidepressants like clomipramine [16, 123].

Anxiolytics: Buspirone, typically used to treat anxiety spectrum disorders, is a partial agonist at the serotonin 5-HT_{1A} receptor and has a weak affinity for the 5-HT_2 receptor [124]. There is one case report of successful treatment of ISB with this agent. An 80-year-old man with vascular dementia, agitated behaviors, and sexual aggression responded to buspirone 5 mg three times daily for 6 weeks [125]. It is important to note that there are no reports of treatment of ISB with benzodiazepines and these medications should be used with caution in elderly patients [126•].

Antipsychotics: Antipsychotics are frequently used to treated agitation and other behavioral disturbances in patients with dementia despite a lack of FDA approval for this indication. Antipsychotics may be effective at treating hypersexuality because of known sexual side effects attributed to hyperprolactinemia, decreased dopamine activity, and alpha 1-receptor blockade [118, 127]. Antipsychotics associated with hyperprolactinemia such as haloperidol, risperidone, paliperidone, and amisulpride may be more likely to cause decreased libido and arousal and to be effective at treating ISB [118]. Quetiapine 75 mg nightly was successfully used to treat frontal lobe signs including inappropriate sexual behavior in a 60-year-old woman with Lewy body dementia [128]. In another case report, quetiapine 25 mg improved ISB in a patient with dementia and parkinsonism [129]. Treatment with risperidone had a positive effect in reducing ISB in one of three patients included in a recent case series. However, one patient's symptoms worsened and another developed significant extrapyramidal signs during treatment [18]. In that same series, all six patients prescribed olanzapine for ISB improved though two patients had to discontinue treatment due to side effects [18]. Elderly patients may be more susceptible to side effects and drug interactions when prescribed antipsychotics [130]. Providers considering antipsychotics in patients with dementia should carefully weigh the potential risks (including the FDA's "black box

warning" on this class of medication) and benefits with the patient/surrogate decision-maker.

Anticonvulsants and Mood Stabilizers: Anticonvulsants and mood stabilizers may reduce behavioral disturbances, including ISB, in patients with dementia [16]. Two case reports support the use of carbamazepine [131, 132]. In the first, a 78-year-old man with ISB that was refractory to treatment with donepezil, galantamine, and piamperone responded to carbamazepine 200 mg daily (higher doses were not tolerated due to dizziness) [131]. In the second, a 78-year-old man with frontotemporal dementia and ISB (unresponsive to paroxetine) was successfully treated with carbamazepine 800 mg daily for 6 months before he was lost to continued follow-up [132]. Providers should be aware of potentially severe adverse reactions, including sedation, ataxia, hyponatremia, blood dyscrasias, and Stevens-Johnson syndrome associated with the use of carbamazepine [132]. Gabapentin, in doses ranging from 900 to 2700 mg daily, has been successful in curbing ISB in several cases [16]. A 62-year-old man with vascular dementia improved with gabapentin 300 mg three times per day [133], and two case series by Alkhalil et al. demonstrated similar outcomes in several patients with Alzheimer's and vascular dementia [134, 135]. No other recent case reports using mood stabilizers or anticonvulsants to treat ISB were found in an extensive literature search.

Cholinesterase Inhibitors: Cholinesterase inhibitors have been shown to mitigate behavioral and psychological symptoms associated with Alzheimer's disease [136]. Limited data exist describing their efficacy to specifically target ISB. Rivastigmine, one of three acetylcholinesterase inhibitors approved for treatment of mild-moderate Alzheimer's disease, has shown success treating inappropriate sexual behaviors in dementia [16]. In a case report of an 81-year-old man who presenting with a 1-year history of memory and attention deficits, depression, and behavioral disturbances (increased libido, sexual comments, and excessive kissing), sexual symptoms were successfully treated with 9.5 mg/day of transdermal rivastagmine [19]. Rivastigmine was also effective in managing sexual aggressiveness in a 72-year-old woman with mixed dementia (Alzheimer's and vascular) [137]. Alternatively, donepezil was associated with increased libido in one case report and was ineffective at treating sexual aggression in another [131, 138].

Hormonal Antiandrogens: Medroxyprogesterone acetate (MPA) and cyproterone acetate (CPA) are the most commonly used hormonal antiandrogens and exert their effect by reducing serum testosterone levels through inhibition of pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH) [16, 17•]. In a retrospective chart review, five patients with ISB were treated with MPA (doses ranged from 100 mg monthly to 500 mg weekly), all with good response [18]. A case series of four patients treated with MPA 300 mg intramuscularly on a weekly basis reported remission of ISB at 1-year follow up in three of the four [139]. Additional case series of similar sizes (two to five patients) report comparable results [140, 141]. Side effects associated with MPA include sedation, increased appetite, weight gain, fatigue, loss of body hair, hot and cold flashes, mild diabetes, decreased ejaculatory volume, and depression [16]. Use of hormonal agents may raise ethical concerns related to chemical castration and patient autonomy [16]. These should be addressed with

patients and/or their surrogate decision-makers prior to initiation of treatment.

Other Hormonal Agents: Leuprolide, a gonadotropin-releasing hormone, also inhibits testosterone by acting on FSH and LH [16]. Case report data has found leuprolide to be effective at reducing ISB in a patient with vascular dementia [18]. Although no adverse events were reported in that particular case, side effects may include hot flashes, erectile dysfunction, decreased libido, and irritation at the injection site [16]. Diethylstilbestrol (DES), an estrogen compound which acts via a similar mechanism as leuprolide, has also been effective at treating ISB in some case reports [16]. Doses ranged from 0.635 to 1 mg orally and from 0.05 to 0.1 mg when using the patch formulation [16, 117, 142]. As with MPA, ethical concerns inherent in the use of hormonal agents for this purpose should be carefully considered prior to use [16].

Nonhormonal Antiandrogens: Cimetidine, a histamine H_2-receptor antagonist with antiandrogen properties, was shown in one retrospective case series to successfully treat hypersexuality in dementia patients. Doses ranging from 600 to 1600 mg/day were used, and 14 out of 20 patients responded to cimetidine alone. An additional six patients had a positive response to cimetidine plus a second antiandrogen medication such as ketoconazole (100 to 200 mg/day) or spironolactone 75 mg/day. Eighty-five percent of patients were men and the most frequently reported side effects were nausea, arthralgia, and headache [143].

Beta-Blockers: Pindolol may treat ISB by decreasing adrenergic drive [16]. There is one case report of successful treatment of ISB in a 75-year-old man when pindolol 40 mg daily was added to his existing regimen of haloperidol and hydroxyzine [144].

Non-pharmacologic

Non-Pharmacologic: Prior to initiating treatment with medication(s), providers should attempt non-pharmacological interventions such as behavioral redirection, changing environment, simplifying tasks, establishing structured routines, and providing education to caregivers [16, 126•, 145]. Treatment plans should be individualized to patients to target specific behavioral concerns [145]. Additionally, it is important to distinguish between ISB and inappropriate of expression of normal sexual drive, which may be easily accommodated with conjugal visits or private rooms for those living in supported care environments [16].

Conclusion

Most older adults remain sexually active but can face age-specific obstacles to maintaining normal sexual function. Both men and women experience sexual disorders more often with age; yet, there is a lack of evidence to support most interventions in the elderly, particularly in women and those with ISB due to dementia. Psychiatrists should be attuned to all aspects of their patients' psychological needs, including their sexual health given its impact on overall quality of life. The geriatric psychiatrist, in particular, should be vigilant against ageist stereotypes about sexual behaviors in older populations. While many of the interventions for these disorders may require collaboration with primary

care or other specialties, the psychiatrist has an important role in identifying these needs and limiting their impact on patients' lives by providing psychosocial support, adjusting psychotropic medications, and performing adjunctive psychotherapy when indicated.

Compliance with ethical standards

Conflict of interest

Phelan E. Maruca-Sullivan declares that she has no conflict of interest. Sarah A. Kleinfeld declares that she has no conflict of interest. Kirsten M. Wilkins declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and recommended reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. AARP. Sexuality at Midlife and Beyond: 2004 update of Attitudes and Behaviors, 2005. https://assets.aarp.org/rgcenter/general/2004_sexuality.pdf.
2.• Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762–74.

Comprehensive epidemiological review of sexual health in older populations

3. Sarrel PM. Sexuality and menopause. Obstet Gynecol. 1990;75(suppl):26S–30S.
4.• Agronin ME. Sexuality and aging. In: Steffens DC, editor. The American Psychiatric Publishing textbook of geriatric psychiatry. Fifth edition. Washington, D.C.: American Psychiatric Publishing; 2015.

Comprehensive and updated overview of sexual health in late life.

5. Thomas DR. Medications and Sexual function. Clin Geriatr Med. 2003;19(3):553–62.
6. Dhringa I, De Sousa A, Sonavane S. Sexuality in older adults: clinical and psychosocial dilemmas. J Geriatr Ment Health. 2016;3(2):131–9.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, D.C.: American Psychiatric Pub; 2013.
8.• Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. Expert Opin Pharmacother. 2015;16:555–63.

Review of recent advances in pharmacotherapy for FSD.

9.• Faubion SS, Rullo JR. Sexual dysfunction in women: a practical approach. Am Fam Physician. 2015;92(4):281–8.

Useful overview of diagnosis and treatment of female sexual disorders.

10. Rew KT, Heidelbaugh JJ. Erectile dysfunction. Am Fam Physician. 2016;94(10):820–7.
11. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M. The multinational Men's attitudes to life events and sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin. 2004;20(5):607–17.
12. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol. 1994;151(1):54–61.
13. Aversa A, Bruzziches R, Francomano D, Natali M, Gareri P, Spera G. Endothelial dysfunction and erectile dysfunction in the aging man. Int J Urol. 2010;17(1):38–47.
14. Chew K, Bremner A, Stuckey B, Earle C, Jamrozik K. Sex life after 65: how does erectile dysfunction affect ageing and elderly men? Aging Male. 2009;12(2/3):41–6.
15. Shiri R, Koskimäki J, Häkkinen J, Tammela TL, Huhtala H, Hakama M, et al. Effects of age, comorbidity and lifestyle factors on erectile function: Tampere ageing male urological study (TAMUS). Eur Urol. 2004;45(5):628–33.
16. Ozkan B, Wilkins K, Muralee S, Tampi RR. Pharmacotherapy for inappropriate sexual behaviors in dementia: a systematic review of literature. Am J Alzheimers Dis Other Demen. 2008;23(4):344–54.
17.• Torrisi M, Cacciola A, Marra A, De Luca R, Bramanti P, Calabrò RS. Inappropriate behaviors and

hypersexuality in individuals with dementia: an overview of a neglected issue. Geriatr Gerontol Int. 2017;17(6):865–74.

Excellent review of diagnosis and management of ISB.

18. Bardell A, Lau T, Fedoroff JP. Inappropriate sexual behavior in a geriatric population. Int Psychogeriatr. 2011;23(7):1182–8.
19. Canevelli M, Talarico G, Tosto G, Troili F, Lenzi GL, Bruno G. Rivastigmine in the treatment of hypersexuality in Alzheimer disease. Alzheimer Dis Assoc Disord. 2013;27(3):287–8.
20. Tosto G, Talarico G, Lenzi GL, Bruno G. Effect of citalopram in treating hypersexuality in an Alzheimer's disease case. Neurol Sci. 2008;29(4):269–70.
21. Wilkins KM, Warnock JK. Sexual dysfunction in older women. Prim Psychiatry. 2009;16:59–65.
22. Lichtenberg PA. Sexuality and physical intimacy in long term care settings. Occup Ther Health Care. 2014;28(1):42–50.
23. Friend T. Why ageism never gets old. New Yorker November 20, 2017.
24. Ishak WW, Bokarius A, Jeffrey JK, Davis MC, Bakhta Y. Disorders of orgasm in women: a literature review of etiology and current treatments. J Sex Med. 2010;7:3254–68.
25. Smith LJ, Mulhall JP, Deveci S, Monaghan N, Reid MC. Sex after seventy: a pilot study of sexual function in older persons. J Sex Med. 2007;4(5):1247–53.
26. Albersen M, Orabi H, Lue TF. Evaluation and treatment of erectile dysfunction in the aging male: a mini-review. Gerontology. 2012;58(1):3–14.
27. El-Sakka AI, Yassin AA. Amelioration of penile fibrosis: myth or reality. J Androl. 2010;31(4):324–35.
28. Rudner XL, Berkowitz DE, Booth JV, Funk BL, Cozart KL, D'Amico EB, et al. Subtype specific regulation of human vascular α 1-adrenergic receptors by vessel bed and age. Circulation. 1999;100(23):2336–43.
29. Christ GJ, Stone B, Melman A. Age-dependent alterations in the efficacy of phenylephrine-induced contractions in vascular smooth muscle isolated from the corpus cavernosum of impotent men. Can J Physiol Pharmacol. 1991;69(7):909–13.
30. Wespes E. The ageing penis. World J Urol. 2002;20(1):36–9.
31. Seftel A. Erectile dysfunction in the elderly: epidemiology, etiology and approaches to treatment. J Urol. 2003;169:1999–2007.
32. American Urological Association. The management of erectile dysfunction: an update, 2005, revised 2011. http://www.auanet.org/guidelines/erectile-dysfunction-(2005-reviewed-and-validity-confirmed-2011.
33. Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. Expert Opin Pharmacother. 2005;6(1):75–84.
34. Yuan J, Zhang R, Yang Z, Lee J, Liu Y, Tian J, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol. 2013;63(5):902–12.
35. Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol. 2002;168(4):1332–6.
36. Evans JD, Hill SR. A comparison of the available phosphodiesterase-5 inhibitors in the treatment of erectile dysfunction: a focus on avanafil. Patient Prefer Adherence. 2015;9:1159.
37.• Shamloul R, Ghanem H. Erectile Dysfunction. Lancet. 2013;381:153–65.

Comprehensive review of erectile dysfunction pathophysiology, diagnosis, and treatment.

38. Lee DM, Nazroo J, Pendleton N. Erectile dysfunction and phosphodiesterase type 5 inhibitor use: associations with sexual activities, function and satisfaction in a population sample of older men. Int J Impot Res. 2015;27:146–51.
39. Melnik T, Soares BG, Nasello AG. The effectiveness of psychological interventions for the treatment of erectile dysfunction: systematic review and meta-analysis, including comparisons to sildenafil treatment, intracavernosal injection, and vacuum devices. J Sex Med. 2008;5(11):2562–74.
40.• Melnik T, Abdo CH, de Moraes JF, Riera R. Satisfaction with the treatment, confidence and 'naturalness' in engaging in sexual activity in men with psychogenic erectile dysfunction: preliminary results of a randomized controlled trial of three therapeutic approaches. BJU Int. 2011;109(8):1213–9.

Investigation of the role of psychotherapy in the treatment of erectile dysfunction.

41. Williams G, Abbou CC, Amar ET, Desvaux P, Flam TA, Lynch SF, Morgan RJ, Müller SC, Porst H, Pryor JP, Ryan P. Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. MUSE Study Group Br J Urol 1998:81(6):889–94.
42. Mikhail N. Does testosterone have a role in erectile function? Am J Med. 2006;119(5):373–82.
43. Seidman SN. The aging male: androgens, erectile dysfunction, and depression. J Clin Psychiatry. 2003;64:31–7.
44. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf. 2014;13(10):1327–51.
45. Bolona ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;82(1):20–8.
46. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med. 2004;350(5):482–92.
47. Elkhoury FF, Rambhatla A, Mills JN, Rajfer J. Cardiovascular health, erectile dysfunction, and testosterone

replacement: controversies and correlations. Urology. 2017;110:1–8.
48. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med. 2013;11(1):108.
49. Kloner RA. Testosterone and cardiovascular health: safety of treatment of hypogonadism. Sex Med Rev. 2015;3(1):56–62.
50. American Urological Association Position Statement on Testosterone Therapy, Revised August 2015. http://www.auanet.org/guidelines/testosterone-therapy.
51.• Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310(17):1829–36.
Important study informing FDA decision to require warning about CVD risk with testosterone supplementation.
52.• Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PloS One. 2014;9(1):e85805.
Important study informing FDA decision to require warning about CVD risk with testosterone supplementation.
53. United States Food and Drug Safety Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. 2015. https://www.fda.gov/Drugs/DrugSafety/ucm436259.htm.
54.• Corona G, Rastrelli G, Maseroli E, Forti G, Maggi M. Sexual function of the ageing male. Best Pract Res Clin Endocrinol Metab. 2013;27(4):581–601.
Thorough review of sexual health and the treatment of sexual dysfunction specific to elderly populations.
55. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology. 2000;56(2):302–6.
56. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'andrea F, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004;291(24):2978–84.
57. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011;171(20):1797–803.
58. Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. J Urol. 2004;172(1):255–8.
59. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med. 2003;139(3):161–8.
60. Schmidt HM, Munder T, Gerger H, Frühauf S, Barth J. Combination of psychological intervention and phosphodiesterase-5 inhibitors for erectile dysfunction: a narrative review and meta-analysis. J Sex Med. 2014;11(6):1376–91.
61. Banner LL, Anderson RU. Psychology: Integrated sildenafil and cognitive-behavior sex therapy for psychogenic erectile dysfunction: a pilot study. J Sex Med. 2007;4(4ii):1117–25.
62. Melnik T, Abdo CH. Psychogenic erectile dysfunction: comparative study of three therapeutic approaches. J Sex Marital Ther. 2005;31(3):243–55.
63. Pahlajani G, Raina R, Jones S, Ali M, Zippe C. Vacuum erection devices revisited: its emerging role in the treatment of erectile dysfunction and early penile rehabilitation following prostate cancer therapy. J Sex Med. 2012;9(4):1182–9.
64. Kucuk EV, Tahra A, Bindayi A, Onol FF. Erectile dysfunction patients are more satisfied with penile prosthesis implantation compared with tadalafil and intracavernosal injection treatments. Andrology. 2016;4(5):952–6.
65. DeRogatis L, Rosen RC, Goldstein I, Werneburg B, Kempthorne-Rawson J, Sand M. Characterization of hypoactive sexual desire disorder (HSDD) in men. J Sex Med. 2012;9(3):812–20.
66. Segraves RT. Management of hypoactive sexual desire disorder. In: Balon R, editor. Sexual dysfunction: the brain body connection. Advances in Psychosomatic Medicine, vol. 29. Basel: Karger Publishers; 2008. p. 23–32.
67. Bloch M, Meiboom H, Zaig I, Schreiber S, Abramov L. The use of dehydroepiandrosterone in the treatment of hypoactive sexual desire disorder: a report of gender differences. Eur Neuropsychopharmacol. 2013;23(8):910–8.
68. O'Carroll R, Bancroft J. Testosterone therapy for low sexual interest and erectile dysfunction in men: a controlled study. Br J Psychiatry. 1984;145(2):146–51.
69. Schiavi RC, White D, Mandeli J, Levine AC. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. Arch Sex Behav. 1997;26(3):231–41.
70. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281:537–44.
71. Kara H, Aydin S, Agargun MY, Odabas O, Yilmaz Y. The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind placebo controlled study. J Urol. 1996;156(5):1631–2.
72. Murat BM, Atan A, Yildiz M, Baykam M, Aydogănli L. Comparison of sertraline to fluoxetine with regard to their efficacy and side effects in the treatment of premature ejaculation. Arch Esp Urol. 1999;52(9):1008–11.
73. Haensel S, Klem T, Hop WC, Slob AK. Fluoxetine and premature ejaculation: a double-blind, crossover,

placebo-controlled study. J Clin Psychopharmacol. 1998;18(1):72–7.
74. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. Am J Psychiatr. 1994;151(9):1377–9.
75. Waldinger MD, Hengeveld MW, Zwinderman AH. Ejaculation-retarding properties of paroxetine in patients with primary premature ejaculation: a double-blind, randomized, dose-response study. BJU Int. 1997;79(4):592–5.
76. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. J Clin Psychopharmacol. 1998;18(4):274–81.
77. Mendels J, Camera A, Sikes C. Sertraline treatment for premature ejaculation. J Clin Psychopharmacol. 1995;15(5):341–6.
78. Althof SE, Levine SB, Corty EW, Risen CB, Stern EB, Kurit DMA. Double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. J Clin Psychiatry. 1995;56(9):402–7.
79. Balachandra K. Re: treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J Urol. 2001;166(6):2325.
80. Cormio L, Massenio P, La Rocca R, Verze P, Mirone V, Carrieri G. The combination of dapoxetine and behavioral treatment provides better results than dapoxetine alone in the management of patients with lifelong premature ejaculation. J Sex Med. 2015;12(7):1609–15.
81. Bai Y, Pu C, Han P, Li J, Yuan H, Tang Y, et al. Selective serotonin reuptake inhibitors plus phosphodiesterase-5 inhibitors for premature ejaculation: a systematic review and meta-analysis. Urology. 2015;86(4):758–65.
82. Atikeler MK, Gecit I, Senol FA. Optimum usage of prilocaine-lidocaine cream in premature ejaculation. Andrologia. 2002;34(6):356–9.
83. Sahin H, Bircan MK. Re: efficacy of prilocaine-lidocaine cream in the treatment of premature ejaculation. J Urol. 1996;156(5):1783–4.
84. Sadowski DJ, Butcher MJ, Köhler TS. A review of pathophysiology and management options for delayed ejaculation. Sex Med Rev. 2016;4(2):167–76.
85. de Carufel F, Trudel G. Effects of a new functional-sexological treatment for premature ejaculation. J Sex Marital Ther. 2006;32(2):97–114.
86. Masters WH, Johnson VE. Human sexual inadequacy. Boston: Little, Brown & Company; 1970.
87. Althof SE. Psychosexual therapy for premature ejaculation. Transl Androl Urol. 2016;5(4):475–81.
88. Cooper K, Martyn-St James M, Kaltenthaler E, Dickinson K, Cantrell A, Wylie K, et al. Behavioral therapies for Management of Premature Ejaculation: a systematic review. Sex Med. 2015;3(3):174–88.
89. Frühauf S, Gerger H, Schmidt HM, Munder T, Barth J. Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. Arch Sex Behav. 2013;42(6):915–33.
90. Nastri CO, Lara LA, Ferriani RA. Rosa-E-Silva AC, Fiqueiredo JB, martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2013;6:CD009672.
91. Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(10):3489–510.
92. Panjari M, Davis SR. Vaginal DHEA to treat menopause related atrophy: a review of the evidence. Maturitas. 2011;70:22–5.
93. Huang A, Yaffe K, Vittinghoff E, Kuppermann M, Addis I, Hanes V, et al. The effect of ultralow-dose transdermal estradiol on sexual function in postmenopausal women. Am J Obstet Gynecol. 2008;198(3):265.e1–7.
94. Penteado SR, Fonseca AM, Bagnoli VR, Abdo CH, Júnior JM, Baracat EC. Effects of the addition of methyltestosterone to combined hormone therapy with estrogens and progestogens on sexual energy and on orgasm in postmenopausal women. Climacteric. 2008;11(1):17–25.
95. Cui Y, Zong H, Yan H, Li N, Zhang Y. The efficacy and safety of ospemifene in treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy: a systematic review and meta-analysis. J Sex Med. 2014;11(2):487–97.
96. Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008;359(19):2005–17.
97. Nathorst-Böös J, Flöter A, Jarkander-Rolff M, Carlström K, Schoultz B. Treatment with percutanous testosterone gel in postmenopausal women with decreased libido–effects on sexuality and psychological general well-being. Maturitas. 2006;53(1):11–8.
98. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas. 1995;21(3):227–36.
99. American Geriatrics Society. 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
100. Portman DJ, Brown L, Yuan J, Kissling R, Kingsberg SA. Flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the PLUMERIA study. J Sex Med. 2017;14(6):834–42.
101. Chivers ML, Rosen RC. Phosphodiesterase type 5 inhibitors and female sexual response: faulty protocols or paradigms? J Sex Med. 2010;7(2 Pt 2):858–72.
102. Ferguson DM, Hosmane B, Heiman JR. Randomized, placebo-controlled, double-blind, parallel design trial of the efficacy and safety of Zestra in women with

mixed desire/interest/arousal/orgasm disorders. J Sex Marital Ther. 2010;36(1):66–86.
103. Londoño DC, Slezak JM, Quinn VP, Van Den Eeden SK, Loo RK, Jacobsen SJ. Population-based study of erectile dysfunction and polypharmacy. BJU Int. 2012;110(2):254–9.
104. McKay A. Sexuality and substance use: the impact of tobacco, alcohol, and selected recreational drugs on sexual function. Can J Hum Sex. 2005;14(1/2):47.
105.• Segraves RT. Sexual dysfunction associated with antidepressant therapy. Urol Clin North Am. 2007;34(4):575–9.
Important review on the sexual side effects of antidepressant treatment and options for minimizing symptoms.
106. Gareri P, Castagna A, Francomano D, Cerminara G, De Fazio P. Erectile dysfunction in the elderly: an old widespread issue with novel treatment perspectives. Int J Endocrinol. 2014;2014:1–15.
107. Seidman SN, Roose SP, Menza MA, Shabsigh R, Rosen RC. Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatr. 2001;158(10):1623–30.
108.• La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: a critical review–part I: antidepressants. Pharmacopsychiatry. 2013;46(05):191–9.
Important review detailing the available data on medication-induced sexual dysfunction by class and by specific antidepressant agent.
109. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol. 1999;19(1):67–85.
110. Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. Perspect Psychiatr Care. 2002;38(3):111–6.
111.• Taylor MJ, Rudkin L, Hawton K. Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomized controlled trials. J Affect Disord. 2005;88(3):241–54.
Useful meta-analysis comparing sexual side effects for specific antidepressant agents.
112. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009;29(3):259–66.
113. La Torre A, Conca A, Duffy D, Giupponi G, Pompili M, Grözinger M. Sexual dysfunction related to psychotropic drugs: a critical review part II: antipsychotics. Pharmacopsychiatry. 2013;46(06):201–8.
114. Francois D, Levin AM, Kutscher EJ, Asemota B. Antidepressant-induced sexual side effects: incidence, assessment, clinical implications, and management. Psychiatr Ann. 2017;47(3):154–60.
115. Segraves RT, Lee J, Stevenson R, Walker DJ, Wang WC, Dickson RA. Tadalafil for treatment of erectile dysfunction in men on antidepressants. J Clin Psychopharmacol. 2007;27(1):62–6.
116. Guay DR. Inappropriate sexual behaviors in cognitively impaired older individuals. Am J Geriatr Pharmacother. 2008;6(5):269–88.
117. Lothstein LM, Fogg-Waberski J, Reynolds P. Risk management and treatment of sexual disinhibition in geriatric patients. Conn Med. 1997;61(9):609–18.
118. Montejo AL, Montejo L, Navarro-Cremades F. Sexual side-effects of antidepressant and antipsychotic drugs. Curr Opin Psychiatry. 2015;28(6):418–23.
119. Chen ST. Treatment of a patient with dementia and inappropriate sexual behaviors with citalopram. Alzheimer Dis Assoc Disord. 2010;24(4):402–3.
120. Jazi AN, Shebak SS, Kim KY. Treatment of hypersexuality in an elderly patient with frontotemporal dementia in a long-term care setting. Prim Care Companion CNS Disord. 2017;19(3)
121. Stewart JT, Shin KJ. Paroxetine treatment of sexual disinhibition in dementia. Am J Psychiatry. 1997;154(10):1474.
122. Simpson DM, Foster D. Improvement in organically disturbed behavior with trazodone treatment. J Clin Psychiatry. 1986;47:191–3.
123. Leo RJ, Kim KY. Clomipramine treatment of paraphilias in elderly demented patients. J Geriatr Psychiatry Neurol. 1995;8(2):123–4.
124. Loane C, Politis M. Buspirone: what is it all about? Brain Res. 2012;1461:111–8.
125. Tiller JW, Dakis JA, Shaw JM. Short-term buspirone treatment in disinhibition with dementia. Lancet. 1988;2(8609):510.
126.• De Giorgi R, Series H. Treatment of inappropriate sexual behavior in dementia. Curr Treat Options Neurol. 2016;18(9):41.
Excellent review of treatment options for ISB.
127. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual (Dys)function in schizophrenia: an overview of clinically relevant findings. Schizophr Bull. 2015;41(3):674–86.
128. Prakash R, Pathak A, Munda S, Bagati D. Quetiapine effective in treatment of inappropriate sexual behavior of lewy body disease with predominant frontal lobe signs. Am J Alzheimers Dis Other Demen. 2009;24(2):136–40.
129. MacKnight C, Rojas-Fernandez C. Quetiapine for sexually inappropriate behavior in dementia. J Am Geriatr Soc. 2000;48(6):707.
130. McKean A, Monasterio E. Indications of atypical antipsychotics in the elderly. Expert Rev Clin Pharmacol. 2015;8(1):5–7.
131. Freymann N, Michael R, Dodel R, Jessen F. Successful treatment of sexual disinhibition in dementia with carbamazepine – a case report. Pharmacopsychiatry. 2005;38(3):144–5.
132. Poetter CE, Stewart JT. Treatment of indiscriminate, inappropriate sexual behavior in frontotemporal dementia with carbamazepine. J Clin Psychopharmacol. 2012;32(1):137–8.

133. Miller LJ. Gabapentin for treatment of behavioral and psychological symptoms of dementia. Ann Pharmacother. 2001;35:427–31.
134. Alkhalil C, Hahar N, Alkhalil B, Zavros G, Lowenthal DT. Can gabapentin be a safe alternative to hormonal therapy in the treatment of inappropriate sexual behaviors in demented patients? Int Urol Nephrol. 2003;35:299–302.
135. Alkhalil C, Tanvir F, Alkhalil B, Lowenthal DT. Treatment of sexual disinhibition in dementia: case reports and review of the literature. Am J Ther. 2004;11:231–5.
136. Campbell N, Ayub A, Boustani MA, Fox C, Farlow M, Maidment I, et al. Impact of cholinesterase inhibitors on behavioral and psychological symptoms of Alzheimer's disease: a meta-analysis. Clin Interv Aging. 2008;3(4):719–28.
137. Alagiakrishnan K, Sclater A, Robertson D. Role of cholinesterase inhibitor in the management of sexual aggression in an elderly demented woman. J Am Geriatr Soc. 2003;51(9):1326.
138. Segrec N, Zaman R, Pregelj P. Increased libido associated with donepezil treatment: a case report. Psychogeriatrics. 2016;16(1):70–2.
139. Cooper AJ. Medroxyprogesterone acetate (MPA) treatment of sexual acting out in men suffering from dementia. J Clin Psychiatry. 1987;48(9):368–70.
140. Weiner MF, Denke M, Williams K, Guzman R. Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. Lancet. 1992;339(8801):1121–2.
141. Cross BS, DeYoung GR, Furmaga KM. High-dose oral medroxyprogesterone for inappropriate hypersexuality in elderly men with dementia: a case series. Ann Pharmacother. 2013;47(1):e1.
142. Kyomen HH, Nobel KW, Wei JY. The use of estrogen to decrease aggressive physical behavior in elderly men with dementia. J Am Geriatr Soc. 1991;39(11):1110–2.
143. Wiseman SV, McAuley JW, Freidenberg GR, Freidenberg DL. Hypersexuality in patients with dementia: possible response to cimetidine. Neurology. 2000;54(10):2024.
144. Jensen CF. Hypersexual agitation in Alzheimer's disease. J Am Geriatr Soc. 1989;37:917.
145. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015;350:h369.