

Male erectile dysfunction: integrating psychopharmacology and psychotherapy

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ABSTRACT

Objective: Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance, is the most common sexual problem in men. ED arises when there is disruption of the complex interplay between vascular, neurologic, hormonal and psychologic factors necessary for normal erectile function. It may have a significant effect on quality of life and portend undetected cardiovascular disease. Risk factors for development of ED include advancing age, tobacco use, a history of pelvic irradiation or surgery and antipsychotic use (Table 1) [1]. Treatment guidelines continue to evolve for optimal management of ED. In this article, we review diagnostic and treatment strategies for ED relevant to psychiatrists.

Method: We present an integrative approach to the treatment of ED based on a review of the urologic and psychiatric literature.

Results: ED is multifactorial in origin and responsive to a variety of therapeutic interventions, including psychopharmacology and psychotherapy in which cognitive underpinnings of poor sexual performance, including diminished self-esteem, lack of confidence and perceived failures in the male role, are examined.

Conclusions: Psychiatrists can readily perform a basic workup for ED as they integrate both a medical and therapeutic model when confronted with such patients.

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1. Epidemiology of erectile dysfunction (ED)

As life expectancies increase worldwide, the prevalence of ED is expected to dramatically increase. By 2025, the World Health Organization predicts that 15% of the world's population will be over the age of 65 years [2]. As advancing age is a risk factor for the development of ED, health care professionals can expect to see more men presenting for treatment. On occasion, ED will present initially to a psychiatrist who, in turn, will need to initiate an adequate initial workup and history, if not a full physical examination.

In a population-based study of US health professionals, the prevalence of ED in men younger than 59 years was found to be 12%, 22% in those 60 to 69 years of age and 30% in those older than 69 years [3]. In the landmark Massachusetts Male Aging Study (MMAS), the prevalence of impotence in all degrees in men older than 40 years was 52% [4]. Despite effective ED therapies, 70%–90% of affected men do not receive treatment.

2. Causes of ED

ED has several causes, with an estimated 75%–80% of cases attributed to vascular disease. *Vascular* changes leading to ED are

seen primarily in patients with diabetes and hypertension. *Anatomic/local tissue* causes of ED include Peyronie's disease and atherosclerosis, which cause chronic ischemia and abnormal collagen deposition, leading to corporal fibrosis in male sexual organs [5]. *Endocrine* abnormalities, including diabetes mellitus, hyperprolactinemia, hyper/hypothyroidism and hypogonadism, are well-established causes of ED. *Neuropsychiatric* disorders associated with ED include Alzheimer's disease, Parkinson's disease, major depressive disorder, schizophrenia and anxiety. *Iatrogenic* causes include the development of ED secondary to postoperative tissue and neural changes (postprostatectomy, transurethral resection of the prostate) and the use of certain types of medications, including antihypertensives and antidepressants.

3. Diagnosis and evaluation of ED

The American Urological Association recommends that the initial evaluation of ED include sexual, medical and psychosocial histories, as well as laboratory tests to identify comorbid conditions that may predispose the patient to ED [6]. Laboratory evaluation should include a fasting serum glucose level and lipid panel, thyroid-stimulating hormone level, complete blood count, prostate-specific antigen, prolactin and free/total testosterone levels [7]. History may reveal causes or comorbidities associated with ED, including cardiovascular disease, diabetes, alcoholism and depression. A thorough sexual history should screen for diminished libido, strength of erection,

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Table 1
Risk factors for erectile dysfunction.

Psychogenic
Performance anxiety
Loss of attraction
Relationship difficulties
Stress
Psychiatric
Depression
Neurogenic
Spinal cord injury
Pelvic surgery
Pelvic radiotherapy
Multiple sclerosis
Diabetes mellitus
Alcohol
Endocrine
Testosterone deficiency
Hyperprolactinemia
Raised sex-hormone binding globulin
Arteriogenic
Hypertension
Smoking
Hyperlipidemia
Peripheral vascular disease
Metabolic syndrome
Venous
Functional impairment of veno-occlusive mechanism

quality and timing of orgasm, penile curvature, and volume and appearance of ejaculate. Attention should be paid to potentially modifiable risk factors, including obesity, cigarette smoking and sedentary lifestyle. A focused physical examination should also be performed. For a concise treatment algorithm, see Fig. 1 [7].

4. Sexual dysfunction in patients with depression

Sexual dysfunction refers to any reduction in desire to libido, diminished arousal (erectile dysfunction, reduced vaginal lubrication), a decrease in frequency of intercourse, or delay in or inability to achieve orgasm [8]. In the depressed population, the occurrence of sexual dysfunction is significantly higher than in the general

population [9]. In a prospective Swiss study, the overall prevalence of sexual problems in patients with depression was almost twice that of control subjects (50% vs. 24%) [10]. The MMAS demonstrated that men with depression had a 1.8 times higher likelihood of experiencing ED than their nondepressed counterparts. The prevalence rates of ED also increased as the severity of depression increased [11].

The most commonly reported sexual problem in untreated, depressed patients is diminished libido, with secondary reports of difficulties with tumescence/ejaculation and orgasm [12]. An association between prevalence of sexual dysfunction and increased duration, severity and recurrence of a depressive episode has also been identified [13]. Up to 25% and 12% of men have concurrent depressive or anxiety disorders, respectively [14]. Depression and anxiety may increase the risk of ED, and ED may further exacerbate psychiatric disease, implicating a bidirectional relationship.

Up to 60% of patients taking selective serotonin reuptake inhibitors (SSRIs) report some form of treatment-emergent sexual dysfunction [15–17]. These effects are postulated to be secondary to stimulation of serotonin, which may inhibit sexual desire, ejaculation, and orgasm by causing a reduction in dopamine levels in the brain. Medications that inhibit serotonin reuptake, without exerting similar effects on dopamine reuptake inhibition, have a greater incidence of sexual dysfunction. SSRIs also stimulate prolactin secretion, which has been shown to cause negative effects on libido and sexual performance. Other mechanisms have also been proposed, including cholinergic receptor blockade and nitric oxide synthase-inhibiting effects. These effects have been observed with paroxetine, an SSRI with the greatest associative incidence of sexual dysfunction [18].

A large-scale, nonrandomized, retrospective study of 167 men using one of four SRIs (paroxetine, fluoxetine, sertraline, venlafaxine) for ≥6 months demonstrated an overall rate of sexual dysfunction of 23% and a rate of ED of 10% [19]. In a prospective multicenter study of 152 male outpatients taking one of four SRIs, the incidence of ED ranged from 10% (fluvoxamine) to 34% (paroxetine) depending on the antidepressant prescribed [20]. Labbate and colleagues found decreased erection scores in 12 patients with major depressive disorder after 1 and 2 months, with almost 60% of men reporting this after 1 month of SRI therapy [21].

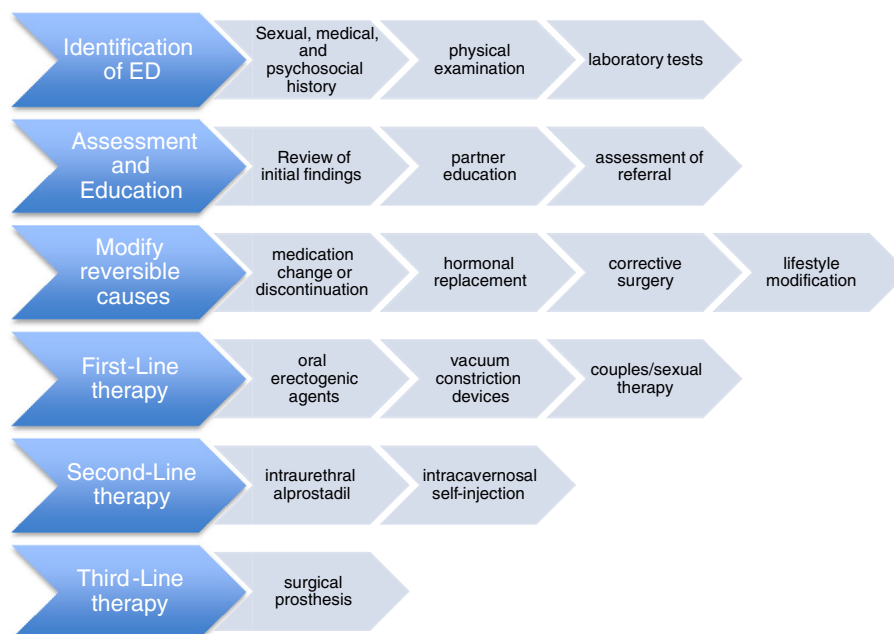


Fig. 1. Algorithm for the diagnosis and treatment of erectile dysfunction. Adapted from Levine, L. Diagnosis and treatment of erectile dysfunction. 2000;109(9):6S [7].

5. Sexual dysfunction in patients with schizophrenia

Sexual dysfunction is highly prevalent in both untreated and treated patients with schizophrenia. Sexual dysfunction affects 30%–80% of women and 45%–80% of men [22–24]. Possible reasons for this include core psychopathology, long-term duration of symptoms unique to schizophrenia (e.g., disturbed psychomotor performance, negative symptoms and a diminished desire, opportunity or ability to form sexual relationships), treatment effects and comorbid medical illness, including hyperlipidemia and type 2 diabetes [25]. Lambert et al. reported that patients who were treated with antipsychotics and consequently developed sexual side effects were at greater risk of developing a negative attitude towards treatment and nonadherence to treatment [26]. Accordingly, psychiatrists should routinely question patients with schizophrenia about their sexual health. This may improve the therapeutic alliance, improve the patient's quality of life, and confront and mitigate negative attitudes to therapy and treatment noncompliance.

Antipsychotic medications induce sexual dysfunction secondary to activity at dopaminergic, cholinergic, histaminergic and α -adrenergic receptors. Binding at these receptors affects sexual functioning by increasing sedation, reducing peripheral vasodilation and inhibiting reward and motivation. Blockade of certain dopamine D2 receptors within the tuberoinfundibular pathway may lead to hyperprolactinemia, which is an endocrine state known to inhibit prosexual behavior mediated by dopamine. The incidence of sexual dysfunction also differs depending on the antipsychotic used. Several studies have reported an incidence of sexual dysfunction of 25%–60% in patients treated with first-generation agents [27] or risperidone [28]. Knegtering et al. reported olanzapine-induced sexual dysfunction in 27% of their patients [28], with other studies reporting a rate up to 35% in their patient population. Quetiapine and aripiprazole induced the lowest rate of sexual dysfunction (18.2%), and risperidone the highest (43.2%) [29]. The relative effects of various antipsychotics on sexual function serve as useful guides when initiating neuroleptic treatment, in order of decreasing effect on erectile function: risperidone>typical antipsychotics (haloperidol)>olanzapine>clozapine>quetiapine>aripiprazole [30].

The use of atypical antipsychotics as augmentation agents in major depression has also become increasingly common. Efficacy in improving mood is theorized to be due to blockade of 5-HT_{2A} and 5-HT_{2C} receptors [31]. These agents may cause increased sexual side effects as augmentation therapy.

6. Sexual dysfunction in patients with anxiety

The benzodiazepines (BDZs) inhibit central nervous system (CNS) functioning through actions at the gamma-aminobutyric receptor. While the BDZs have not been consistently shown to negatively influence sexual function, high doses have been reported to increase risk for sexual dysfunction. Lydiard and Howell reported that men and women who had received high doses of alprazolam (3–10 mg/day) for panic disorder experienced erectile dysfunction, diminished sex drive and/or reduced ability to obtain orgasm in 50% of encounters [32].

7. Current treatments for ED

Therapies for ED include (a) phosphodiesterase 5 (PDE5) inhibitors, including sildenafil, tadalafil and vardenafil; (b) psychopharmacology and psychotherapy; (c) intraurethral suppository and intracavernosal injection treatments; (d) CNS-acting agents; (e) hormone replacement and (f) surgical intervention. The first two modalities are discussed, as the average psychiatrist is most likely to utilize each as treatment in routine clinical practice.

PDE5 inhibitor therapy is the *first-line* therapy in the medical management of erectile dysfunction. The PDE 5 inhibitors are generally well tolerated and safe. Side effects include peripheral vasodilation, facial flushing, nasal congestion, headache and dyspepsia. PDE 5 inhibitor therapy is contraindicated in patients taking organic nitrates due to the potential for clinically significant and severe hypotension.

Sildenafil was the first PDE5 inhibitor prescribed for the treatment of ED. Peak plasma concentrations are reached in 30 to 120 min, with a median time of 60 min. Postmarketing studies have demonstrated onset of action as early as 14 min. The recommended starting dose for the average adult male is 50 mg, but in those patients with hepatic impairment or severe renal insufficiency, 25 mg is advocated. Studies have shown Viagra to be helpful in ED of several etiologies, including 70% of patients with hypertension, 42% to 72% of radical prostatectomy patients, 76% of patients with depressive disorder and 80% of patients with spinal cord injury [33].

Peak plasma concentrations of tadalafil are reached in 2 h. The half-life of tadalafil is 17.5 h in young men and 22.5 h in the elderly. Onset of action is typically 16 to 45 min, with standard doses ranging from 10 to 20 mg.

Peak plasma concentrations of vardenafil are reached in approximately 1 h. Half-life is 4 to 5 h, and onset of action is 25 min. Standard doses are 5–20 mg.

8. Potential for abuse

In prescribing PDE5 inhibitors, physicians should be mindful of their potential for abuse, as reports of recreational use and misuse continue to appear in the literature. In both young, healthy patients and those with chronic illnesses, including HIV and cancer, PDE5 inhibitors are often combined with club drugs, including 3,4-methylenedioxy-N-methylamphetamine MDMA/ecstasy ("Sextasy"), methamphetamine ("Tina") and ketamine. Access to the PDE5 inhibitors via the Internet may facilitate this behavior and increase the potential for harmful or fatal drug interactions [34]. Given this reality, physicians should continue to screen for a history of substance abuse, as a positive history may be predictive of future substance abuse.

8.1. Psychopharmacology

Current treatments for depression, schizophrenia and anxiety, while effective in treating the primary psychiatric condition, may cause burdensome sexual side effects. This may serve to not only reduce treatment adherence and compliance, but also further weaken interpersonal relationships already strained due to the primary illness. Augmentation or combination agents may be necessary to offset side effects from the initial treatment.

For the patient with depression, the use of bupropion as an adjunctive treatment has been shown to mitigate some of the sexual side effects of serotonergic agents [35]. Placebo-controlled trials have demonstrated the efficacy of PDE5 inhibitors such as sildenafil (50 to 100 mg prn). Augmentation with the D₂ partial agonist aripiprazole has led to improved libido. Anecdotal reports also describe potential benefits from yohimbine (2.7 mg prn to 5.4 mg tid), cyproheptadine (4–8 mg/day), amantadine (100–200 mg/day), buspirone (10–30 mg bid), mirtazapine (15–30 mg qhs), psychostimulants (methylphenidate 10–20 mg prn or bid), cholinergic agents (bethanechol 10–50 mg prn) and ginkgo biloba [36].

There is a paucity of clinical trials that have studied sexual dysfunction and use of antipsychotics. Few guidelines for the treatment of sexual dysfunction in a patient who has been prescribed an antipsychotic exist. Costa et al. performed a systematic review of available studies, which resulted in the identification of only 13 studies: eight were open-label, four were case reports, and only one study was a randomized trial (Table 2) [37]. Based on their analysis, an

Table 2
Main drugs and dosages used in treatment of antipsychotic-induced sexual dysfunction.

Drug	Dose	Mechanism of action for sexual dysfunction	Side effects
Bromocriptine	2.5 mg po bid-tid	Dopamine agonist	Nausea/vomiting, constipation, headache, fatigue, dizziness, hallucinations/psychosis
Cabergoline	0.5 mg po twice/week	Dopamine agonist	Dizziness, fatigue, headache, constipation, somnolence, depression, orthostatic hypotension, abdominal pain
Cyproheptadine	4 mg po qid	Serotonergic (5 HT-2) antagonist	CNS depression, dry mouth, increased appetite, weight gain, nausea/vomiting, diarrhea
Amantadine	100–300 mg po daily	Increases dopamine release, reduces dopamine, norepinephrine reuptake	Insomnia (most common), dizziness, anxiety, confusion, agitation, hallucinations
Sildenafil	25–50 mg po 1 h prior to intercourse	PDE5 inhibitor	Flushing, dizziness, headache, dyspepsia, nasal congestion, priapism (rare)
Imipramine	25–50 mg po daily	tricyclic antidepressant; mechanism of action for sexual dysfunction unknown	Dry mouth, constipation, blurred vision, urinary retention
Selegiline	15 mg po daily	Selective monoamine oxidase B inhibitor	Abdominal pain, nausea, dizziness, lightheadedness, confusion, hallucinations

Adapted from Costa, AM, Silva de Lima, M, de Jesus Mari, J. A systematic review on clinical management of antipsychotic-induced sexual dysfunction in schizophrenia. Sao Paulo Med J 2006;124(5):291–7 [37].

algorithm for the treatment of antipsychotic-induced sexual dysfunction was proposed (Fig. 2) [37].

8.2. Psychotherapy

The introduction of sildenafil in 1998 profoundly altered the treatment landscape for sexual dysfunction. Sildenafil successfully restored potency in 50%–70% of men. In an elegant counterargument to a pure medical model, Althof and Wieder highlighted the large percentage of patients who discontinued pharmacotherapy despite the efficacy and safety of available medications [38]. Exploring this “discontinuation phenomenon,” the authors hypothesized that med-

ications only addressed the vascular and hormonal mechanisms of obtaining an erection and did little to address the psychological meaning of utilizing a medication to achieve physical intimacy [39]. Without discussion of relational issues that lead to ED, treatment would be limited. The authors reaffirmed the role of psychotherapy and advocated evaluating sexual dysfunction from a biopsychosocial perspective. By providing patients with an integrated medical and psychological approach, with efforts aimed at addressing the myths and cognitive distortions that often lead to ED, the effectiveness of interventions increased.

Schover [40] and Zilbergeld [41] describe such myths regarding sexual performance, including the following: (a) It is the

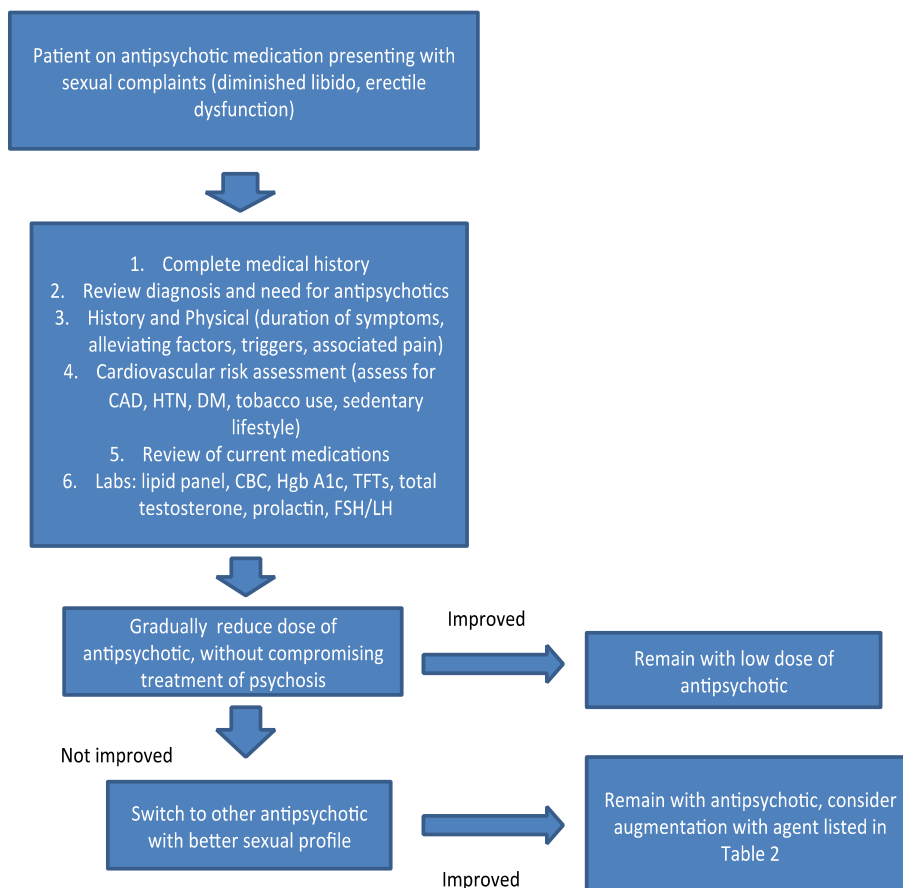


Fig. 2. Clinical management of antipsychotic-induced sexual dysfunction in schizophrenia. Adapted from Costa, AM, Silva de Lima, M, de Jesus Mari J. A systematic review on clinical management of antipsychotic-induced sexual dysfunction in schizophrenia. Sao Paulo Med J 2006;124(5):291–7 [37].

Table 3

Etiological background of sexual dysfunction: the biopsychosocial perspective.

Predisposing factors: associated with greater prevalence of sexual problems
1. Constitutional: congenital illness, anatomical deformities
2. Prior life experiences: unstable attachments, restrictive upbringing, critical or neglectful parents, history of sexual or physical abuse
Precipitating factors: trigger sexual problems
1. Separation and divorce
2. Disability due to an accident
3. Unsatisfying sexual experiences
4. Repeated humiliation from spouse
5. Infidelity
Maintaining factors:
1. Relationship conflict, performance anxiety, guilt, loss of sexual chemistry
2. Fear of intimacy, impaired self-image/esteem, restricted foreplay, lack of privacy
3. Psychiatric disorders
Contextual factors:
1. Environmental constraints
2. Anger or resentment towards partner

responsibility of the man to satisfy the woman; (b) firmness and size of the erect penis are determinants of the female partner's satisfaction; (c) a woman's favorite part of sex is intercourse; (d) a man always wants and is always ready to have sex; and (e) with age, all men lose their ability to achieve erections. Similarly, Rosen et al. [42] identified several cognitive distortions that may cause ED:

1. All-or-nothing thinking: "I am a complete failure because my erection was not 100% rigid."
2. Overgeneralization: "If I had trouble getting an erection last night, I won't have one this morning."
3. Disqualifying the positive: "My partner says I have a good erection because she doesn't want to hurt my feelings."
4. Mind reading: "I don't need to ask. I know how she felt about last night."
5. Fortune telling: "I am sure things will go badly tonight."
6. Categorical imperatives: presence of "should," ought to" and "musts" dominates thoughts about sexual function.
7. Catastrophizing: "If I fail tonight, my girlfriend will dump me."

Psychoeducation aimed at addressing these myths and distortions, with guidance and expertise from a psychiatrist, may be effective. Notably, neither psychotherapy nor medication alone is sufficient for lasting resolution of ED. Studies have demonstrated that men randomized to receive psychotherapy plus sildenafil showed more significant improvement in ED and were less likely to drop out of treatment, in comparison to men receiving only sildenafil [43]. There is a synergistic effect between both modalities. Assessment of sexual dysfunction should include a biopsychosocial formulation of predisposing, precipitating, maintaining and contextual factors (Table 3).

9. Conclusion

Management of ED continues to evolve. Patients who present with ED have access to a variety of effective therapies. The treatment of ED offers the health care professional a unique clinical opportunity to enhance the health and well-being of a patient who might otherwise suffer in silence. With concomitant surgical therapy, the current landscape in the treatment of ED is rich.

Still, our colleagues in the urologic and primary care disciplines have neither the intensive training nor the expertise in psychiatric illness to maximize the success of their interventions. Medications and surgical options are limited in their capacity to bridge the mind-body disconnect that often serves as the foundation of ED. In a post-Viagra practice, psychiatrists have a unique but familiar role to play, empowering patients to confront and process difficult issues that neither a pill nor a surgical procedure will ever fully address.

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