Management of Depression Complicated by Sexual Dysfunction

Depression is one of the most prevalent disorders in the United States, with a high incidence of morbidity and mortality.[1] Although usually responsive to pharmaco-therapy, it is a condition that is often undetected or under-treated.[1,2] When appropriately administered, the newer antidepressant agents have efficacy comparable to tricyclic antidepressants, with fewer side effects.[3,4] However, most antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are associated with sexual dysfunction as an emergent adverse event.[5] Treatment-related adverse events are a frequent cause of noncompliance and subsequent treatment failure in depression.[3]

Most cases of depression are diagnosed by a primary care physician (PCP).[6] Furthermore, most patients who are diagnosed with depression are managed by their PCP.[1] The purpose of this Continuing Medical Education (CME) monograph is to enhance the skills of these healthcare providers in detecting and managing depression, especially when it is complicated by sexual dysfunction.

The learning objectives of this monograph are:

- Know the strengths and weaknesses of psychological screening devices that can be used to identify patients with a depressive disorder
- Know the causes and risks of noncompliance with antidepressant therapy
- Be able to name the types of sexual dysfunction that are associated with depression, comorbid medical conditions or treatments, or specific antidepressant agents
- Be able to discuss the principles of an interview style that is structured to successfully identify patients with depression complicated by sexual dysfunction
- Be able to describe the strategies for managing patients with depression complicated by sexual dysfunction

After completing this CME program, you should have a better understanding of the prevailing theories about both depression and sexual dysfunction: their underlying causes, the ways each is manifested, how to identify patients with either, and the

current strategies for managing depression and for resolving sexual dysfunction when it is an emergent adverse event.

Depression Update

Depression can present as one or more of several depressive disorders, all characterized by a mood impairment, and disturbances in social ability, productivity, and somatic functions — affecting sleep, appetite, and physical energy.[1,7,8] In addition to feeling or appearing sad most of the time, symptoms of a depressive disorder include marked apathy or anhedonia most of the time; psychomotor agitation or retardation most of the time; significant, unintentional change in weight; insomnia or hypersomnia; anergy or fatigue most of the time; feeling worthless or guilty; distracted or indecisive most of the time; and preoccupied with death or suicide most of the time. The course of a depressive disorder is often chronic, with periods of remission and recurrence.[1,9]

Perhaps as a reflection of the waxing and waning nature of depressive symptoms, additional disorders that do not satisfy the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnostic criteria for major or minor depression also can be associated with considerable disability and impairment, and should be considered clinically significant as well.[9] Table 1 lists the types of depressive disorders and diagnostic criteria.

Table 1. Depressive Disorders[7-9]

Disorder Type	Diagnostic Criteria
Major Disorder	
Major depressive disorder (MDD)	Five or more depressive symptoms for at least 2 weeks
Minor Disorder	
Dysthymic disorder	Feeling sad most of the time for at least 2 years, plus 2 or more depressive symptoms less severe than MDD
Additional Disorders	
Minor depressive disorder	Fewer than 5 depressive symptoms, for at least 2 weeks
Recurrent brief depressive disorder	Episodes of 2-14 days at least once a month for 12 months

Functional impairments associated with untreated depression can result in significant morbidity, disrupting virtually every aspect of a patient's life.[1,3] A depressive disorder can diminish one's physical health, social life, and ability to fulfill one's professional potential.[1] In addition, patients with depressive disorders have a higher mortality rate than those who are not depressed, not just due to an increase in the incidence of suicide, but also relative to matched cohorts who are afflicted with a comorbid medical disorder.[1,3] Fortunately, nearly two dozen antidepressant agents are available today

(listed in Table 3) that can reduce depressive symptoms in up to 75% of all patients with a depressive disorder.[1,3,4]

Diagnosis of Depression

Most measures of the prevalence of depressive disorders have been surveys of adults seeking medical treatment at a primary care facility, using a standardized, criterion-based interview for diagnosis, such as the Center for Epidemiological Studies Depression Scale.[10] On average, at least 15% of this population met the criteria for a depressive disorder.[6,9-11] These surveys also found a consistently high rate of undiagnosed, untreated patients; typically, half of all patients who screened positive for a depressive disorder had not received a prior diagnosis of depression.[2,9,12] As a rule, only patients with the most severe depressive symptoms or disabilities are detected or treated by primary care physicians (PCPs).[6,12]

The high incidence of undiagnosed depression in a primary care practice is certainly understandable. The time pressures created by managed care especially challenge PCPs, who are the frontline of health care.[12] Furthermore, most patient visits to a PCP are for physical, not psychological complaints. Often patients with a depressive disorder, for a variety of reasons, do not actively seek treatment of their depression.[12] Some depressive symptoms may be attributed incorrectly to a somatic condition or social complication, especially in patients over 65 years old.[13] It is not surprising then that a hurried physician, who is concentrating on physical complaints, may fail to detect the subtle symptoms of depression.[12] Nevertheless, greater detection of depression and delivery of the appropriate treatment is called for; when untreated, these prevalent disorders have a significant risk of morbidity and mortality.[14]

Depression is a syndrome that is diagnosed by symptomatic behavior, unlike most medical conditions that can be quantified by objective measures.[14] This absence of biological markers that can be measured in everyday clinical practice reinforces the current misconception that psychological disorders are distinct, and perhaps less

significant than medical disorders. The first molecular explanation of depression, the monoaminergic hypothesis, was based on inferences made from the ability of certain drugs to elevate mood.[4] Decades later, researchers are still seeking to identify a central defect in patients with an established diagnosis of a depressive disorder. To date, monoaminergic regulation of the neuroendocrine system seems the most likely site of the central defect, but a quantifiable marker has not been identified yet.[15] As our understanding of the connection between biology and behavior advances, this will hopefully change.[1]

The clinical diagnosis of depression must be made by observing or eliciting reports of characteristic symptoms. In a busy primary care practice, a brief, universal screen is the best way to detect depression. Most diagnostic instruments are designed to screen for diagnostic criteria and risk factors, taking into consideration the uniqueness of a given population: how symptoms are presented, as well as the magnitude and prevalence of relevant risk factors. A diagnostic screen is evaluated by its ability to reliably diagnose depression in a given population. Two measures of this ability are the *sensitivity* of a diagnostic screen — its lack of false positive or negative diagnosis, and the *specificity* of a diagnostic screen — its accuracy in establishing a differential diagnosis. The predictive ability of a diagnostic instrument also can be described as its likelihood ratio (LR): a positive LR measures the degree of sensitivity, and a negative LR measures the degree of specificity.[16]

Standard diagnostic screens, such as the Beck Depression Inventory or Geriatric Depression Scale, have been used by clinical and research mental health practitioners for years.[17,18] However, these and more recently introduced diagnostic instruments take time to administer and interpret, and in a busy primary care practice, brevity is a priority.[10] Furthermore, a high rate of sensitivity is more important than specificity when screening a general population for depressive symptoms. As a rule, abbreviated depression screens designed for use in primary care practices have a higher rate of sensitivity (89% to 96%) than specificity (51% to 72%).[10]

A patient questionnaire, based on the primary diagnostic criteria of anhedonia[7] and the need for brevity, was recently proposed as a diagnostic screen for depression in primary care practices.[10] This two-question survey, which has 96% sensitivity and 57% specificity, could be incorporated easily into a written form completed by patients when they are waiting to be seen, or a verbal history taken when they are interviewed.[10] A positive response to either question should be considered positive for depressive symptoms.[10]

Two-question diagnostic screen for depression[10]

- During the past month, have you often been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things?

Once a patient has been identified as experiencing depressive symptoms, a differential diagnosis for medical, psychological, or social causes, or comorbid conditions will guide you in determining the appropriate treatment.[4] Table 2 lists medical conditions and drugs that have been associated with depressive symptoms.[4] Psychological conditions other than depression — such as somatization and borderline personality disorders — may present initially as depression.[4,13] Patients who test positive for depression on a brief, sensitive screen should undergo a second, more comprehensive screen with a higher rate of specificity, designed to differentiate psychological conditions. One recently developed instrument, the Symptom-Driven Diagnostic System-Primary Care Screen (SDDS-PC), is designed for use in the primary care setting.[19]

Table 2. Possible Medical Causes of Depressive Symptoms[4]

Conditions	Drugs
Endocrine disorders	Drugs of abuse
Hypothyroidism	alcohol
Hyperthyroidism	sedatives-hypnotics
Cushing's disease	opiates
Addison's disease	marijuana
Hypoparathyroidism	cocaine
Hyperparathyroidism	amphetamines
Hypoglycemia	phencyclidine
diabetes mellitus	Antihypertensive drugs
ovarian failure	propranolol
testicular failure	reserpine
Vascular diseases	methyldopa
Cardiomyopathy	guanethidine
cerebral ischemia	clonidine
congestive heart failure	Gastrointestinal drugs
myocardial infarction	cimetidine
Neurological disorders	Corticosteroids
Alzheimer's disease	Oral contraceptives
Parkinson's disease	Cytotoxic agents
multiple sclerosis	
Neoplastic diseases	
pancreatic cancer	
lung cancer	
endocrine cancers	
brain tumors	
Nutritional deficiencies	
Folate	
vitamins B_1, B_2, B_6, B_{12}	
iron	

Management of Depression

Next to antimicrobials, antidepressants are one of the most effective forms of pharmacotherapy, and the prognosis can be improved if treatment is initiated early.[1,3,4] The goal of therapy is remission of the depressive episode. However, outcomes in clinical trials usually are reported as a response rather than a full remission, quantified as a 50% or better reduction in the severity of depressive symptoms, often assessed by the Hamilton Rating Depression Scale.[13,20]

Another therapeutic approach to treating depression is psychotherapy, either alone or in combination with pharmacotherapy. The three major pharmacotherapeutic approaches to depression are psychodynamic, cognitive-behavioral, and interpersonal.[21] The basic difference of this approach from pharmacotherapy is the assumption that depressive symptoms are caused by personality disorders that can be corrected through various forms of communication and education.

There are currently five major classes of antidepressant agents available for the treatment of non-psychotic depression (listed in Table 3), differentiated by the degree to which various neurotransmitter systems are affected.[1,22] The prevailing theory for the mechanism of antidepressant action is that the agents induce receptor accommodation — a down-regulation of receptor sensitivity — in the neurotransmitter systems they affect. This would explain the delayed onset of efficacy usually experienced by patients. However, this theory does not seem to apply to newer and experimental agents, which may normalize neuronal communication in the brain by some other mechanism.

Table 3. Antidepressant Agents[1,3,13,22]

Generic name	Proprietary name
Tricyclic antidepressants	
Secondary amines	
desipramine	e.g., Norpramin®
nortriptyline	e.g., Aventyl®, Pamelor®
protriptyline	Vivactil®
maprotiline	Ludiomil®
Tertiary amines	
imipramine	e.g., Tofranil®
amitriptyline	e.g., Elavil®, Endep®
trimipramine	Surmontil®
doxepin	e.g., Sinequan®
clomipramine	Anafranil®
amoxapine	Asendin®
Monoamine oxidase inhibitors	
Isocarboxazid	Marplan®
phenelzine	Nardil®
tranylcypromine	Parnate®
SSRIs	
fluoxetine	Prozac®
sertraline	Zoloft®
paroxetine	Paxil®
fluvoxamine	Luvox®
citalopram	Celexa®
Aminoketones	
bupropion	Wellbutrin®
Triazolopyridines	
nefazodone	Serzone®
trazodone	Desyrel®
Atypicals	
venlafaxine	Effexor®
mirtazepine	Remeron®

Antidepressant therapy should be tailored to the individual patient. The first goal of treatment choice is to select the therapy with the greatest likelihood of response. If the underlying central defect of a depressive disorder were known, its site of action would dictate the choice of pharmacological agent. Unfortunately, research has yet to identify neurobiological predictors of antidepressant response.[4]

It is believed that a patient's depressive symptoms may be markers for underlying neurotransmitter dysfunctions. This is the therapeutic rationale for matching a class of antidepressant therapy with a depressive disorder.[4,13] Effects on psychomotor retardation, apathy and anhedonia are the best prognostic indicators, while changes in sleep and appetite disturbances are not.[4] The side effects associated with a class of antidepressant should be judged for their potential benefit as well; an adverse event in one patient may be therapeutic in another.[3,4] Table 4 lists receptor-related effects associated with central neurotransmitter systems affected by antidepressant agents. However, the symptomatic profile for each disorder is more of a guide than an absolute; patients may display individual variations, which should be considered when deciding on a course of therapy.[1,4]

Table 4. Receptor-related Effects of Major Antidepressant Classes[1,3,4]

Antidepressant Class	Receptor Type	Common Effects
Tricyclic agents	Noradrenergic	tachycardia, jitteriness, erectile and ejaculatory dysfunctions
	Histaminergic	sedation, weight gain, hypotension
	Muscarinic	constipation, cognitive dysfunction, dry mouth, blurred vision
SSRIs	Serotonergic	anorexia, insomnia, anxiety, diarrhea, delayed ejaculation, anorgasmia
Aminoketones	Dopaminergic	psychomotor activity, anxiety, weight loss

Patients should be followed closely, especially during the induction phase of treatment.[1] A patient's ability to function productively is a rapid yet effective measure of a patient's therapeutic response to an antidepressant agent.[23] In a primary care practice, this can be accomplished by asking a few questions at every follow-up visit.[23] Here are two sample questions that can evaluate a therapeutic response to antidepressant therapy with high predictability.

Sample Questions to Evaluate Antidepressant Efficacy[23]

- Is your level of productivity or efficiency lower than expected?
- Do you work more slowly or are you taking longer to complete projects than expected?

A subtherapeutic dose can compromise a favorable response to therapy, often a cause of treatment failure with tricyclic antidepressant (TCA) therapy. While efficacy is dose-dependent, so are many of the side effects associated with TCA therapy, and physicians mistakenly may prescribe insufficient doses of a TCA in an attempt to minimize side effects.[1] TCAs are the most common cause of overdose in the United States; subtherapeutic dosing with TCAs also may be a misguided attempt to guard against their use to commit suicide.[3]

Unfortunately, a positive outcome is not lasting in many patients. Among patients who achieved remission of a first episode of depression, up to 50% will experience a recurrence at some time in their life; after a second episode, the risk of a subsequent recurrence jumps to 90%.[1] In addition to an appropriate dose, a sufficient length of therapy is necessary for a positive outcome. A therapeutic dose should be maintained for four to six months after resolution of the first episode of a depressive disorder, one year after resolution of the second episode, and indefinitely after the third.[1]

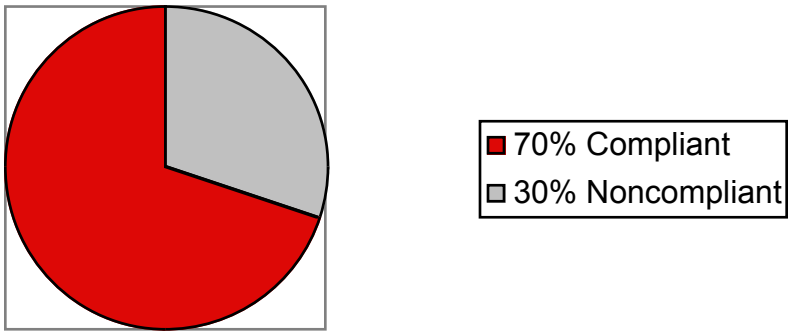
Suicide is a significant risk, especially during the delayed-onset phase that precedes the onset of effect. Approximately 15% of all patients with depression commit suicide.[3] Clinicians should not be afraid to ask a patient about suicidal thoughts; a sensitive inquiry will not encourage a patient to commit suicide.[1] However, any patient who has a

specific plan for committing suicide is at risk of carrying out the plan, and should be considered a candidate for hospitalization or some other form of protective action.[1]

Patients should be encouraged to regard their diagnosis of depression as they would any other treatable disease.[1] Patients should have realistic expectations about their condition and response to treatment, especially the delayed onset of effect.[1] Patients should be encouraged to self-monitor for side effects to therapy, and after the discontinuation of therapy, for early signs of a recurrent episode.[1,3]

The most important factor determining treatment outcome in depression is compliance.[1] Since depression is not a condition commonly understood, patient education may play an important role in improving compliance. At least 30% of outpatients treated for depression are thought to be noncompliant, often due to treatment-emergent adverse events.[3]

Treatment Compliance



An analysis of the potential risks and benefits of a course of therapy also should consider its safety and manageability based on each patient's unique circumstances. Safety issues include the potential compatibility of an agent with comorbid medical conditions or concomitant medications. For example, TCA therapy is contraindicated in patients with cardiovascular disease, because the high incidence of associated anticholinergic side effects raises the risk of cardiotoxic reactions.[1] Similarly, drug-drug interactions are a concern when prescribing SSRIs, which have been shown to alter the

serum concentration of compounds metabolized by the cytochrome P450 isozyme CYP2D6.[3,13] Inhibition of CYP2D6 by fluoxetine and paroxetine, and to a lesser extent sertraline, can result in the accumulation of a variety of drugs, including antiarrhythmic agents, ß-adrenergic receptor antagonists, morphine derivatives, neuroleptics, TCAs, and other SSRIs.[24] A comparison of antidepressant safety issues, organized by drug class, is listed in Table 5.

Table 5. Comparison of Antidepressant Classes[13]

Consideration	TCAs	SSRIs	Triazolopyridines	Aminoketones	MAOIs
Safety	Serious systemic toxicity can result from overdose	No serious systemic toxicity demonstrated	Minimal serious systemic toxicity due to acute over-dose	Seizures as primary acute systemic toxicity due to acute overdose; easily managed in medical setting	Serious systemic toxicity can result from acute ingestion
Tolerability	Generally good with secondary amine TCAs, superior to tertiary amine TCAs	Generally good, especially if dose is kept to effective minimum dose	Sedation and cognitive slowing are frequently problems even at effective minimum dose	Generally good, especially if dose is kept to effective minimum dose	Generally good except for the occurrence of hypotension and the need for dietary restrictions

Table 5. Comparison of Antidepressant Classes, cont.[13]

Consideration	TCAs	SSRIs	Triazolopyridines	Aminoketones	MAOIs
Pharmacokinetic Interactions	Can be affected by other drugs (e.g. SSRIs) to a clinically significant extent but do not affect other drugs	Can inhibit oxidative metabolism of a variety of drugs but considerable differences exist in terms of magnitude and duration of effect. No known clinically significant effect of other drugs on SSRIs	Neither affected by nor have affect on other drugs in a clinically significant way	Can be affected by some SSRIs (e.g. fluoxetine) and possibly others in a clinically significant way. No know effect on the metabolism of other drugs	Neither affected by nor have affect on other drugs in a clinically significant way

Table 5. Comparison of Antidepressant Classes, cont.[13]

Consideration	TCAs	SSRIs	Triazolopyridines	Aminoketones	MAOIs
Pharmaco-dynamic Interactions	Multiple, due to the large number of effects of TCAs. Can be agonistic (additive or potentiating) or antagonistic, more likely and more significant with tertiary amines	See MAOI interaction. May occur with other serotonin agonists. Fluoxetine can have agonistic interaction with dopamine agonists in terms of extrapyramidal effects	Can have interactions with other agents which decrease arousal or impair cognitive performance. Can interact with adrenergic agents affecting blood pressure regulation. Complex interactions with other serotonin-active agents	Can have interactions with dopamine agonists and antagonists	Clinically significant interactions with tyramine and sympathomimetic agents on blood pressure and serotonin-active agents inducing the central serotonin syndrome

Table 5. Comparison of Antidepressant Classes, cont.[13]

Consideration	TCAs	SSRIs	Triazolopyridines	Aminoketones	MAOIs
Ease of administration	Excellent, generally can be administered QD	Excellent for sertraline due to QD dosing. Good for fluoxetine typically administered QD but long-half-life of parent compound and active metabolite makes dose titration difficult	Satisfactory but requires multiple dosing for antidepressant effect	Satisfactory but requires multiple dosing for antidepressant effect	Satisfactory but clinical practice is generally to give in divided doses

Treatment-related adverse events, which can occur at anytime during a course of therapy with many antidepressants, are another reason to closely monitor each patient's response to therapy. For example, TCAs have a narrow therapeutic index and their metabolism can vary from patient to patient. Serum concentrations should be evaluated if a toxic reaction is suspected.[1]

A number of studies have found that physicians should probe for treatment-emergent events.

Reliance on patients to self-report adverse events, particularly sexual dysfunction, will result in significant under reporting.[25] Patients, especially female patients, are reluctant to discuss sexual problems.[5,26-28] Treatment-emergent sexual dysfunctions are estimated to affect a large portion of all adult males and females treated with one of the antidepressant agents, except bupropion and nefazodone.[1,26,27,29] Due to this significant threat to patient compliance and treatment outcome, the managing physician needs to be skilled in understanding, detecting, and managing treatment-emergent sexual dysfunction.[26,27]

Sexual Dysfunction

The human sexual response is one of man's most basic instincts, promoting mutual affection and pleasure, and survival of the species.[30] Human sexuality is strongly influenced by multiple physiological and psychological factors, and an imbalance in any one of these factors can interfere with the sexual response. According to the DSM-IV standard for classifying human sexual dysfunction, sexual dysfunction is an impairment in sexual behavior or performance that can occur during one or more of the three phases of a sexual response: desire, arousal, and orgasm.[7] An impairment can occur as either an increase or a decrease in function, relative to a subjectively defined norm. The forms of sexual dysfunction are listed in Table 6.

Table 6. Forms of Sexual Dysfunction[7,31]

Phase of Sexual Response	Decreased Function	Increased Function
Desire	Hyposexuality, or asexuality; decrease in sexual thoughts	Hypersexuality; obsession with sex or pornography
Arousal	Absent, partial, or short-lived erection (impotence); insufficient production of vaginal lubrication	Persistent, painful erection (priapism)
Orgasm	Retarded ejaculation; decreased emission; delayed or absent orgasm (anorgasmia)	Premature ejaculation

One of the most common sexual dysfunctions experienced by men is premature ejaculation (PE).[32] Masters and Johnson defined PE as the inability to inhibit ejaculation long enough for one's sexual partner to reach orgasm 50% of the time.[32] Regardless of quantifiable parameters, the relative responsiveness of one's sexual partner is an important, yet highly variable factor in the diagnosis of PE.[32]

Perhaps due to limitations in methodology, far fewer studies have investigated the physiological aspects of the sexual response in women than in men.[25,28] It is easier to directly quantify changes that occur during a man's sexual response than it is to obtain a precise measure of the subtle, internal changes involved in the physical manifestations of a woman's sexual response.[5] Furthermore, the physical aspects of a woman's sexual response do not correlate well with the psychological component of a

woman's sexual response.[25,33] A retrospective analysis of 22 general population surveys estimated that 30% or more of women may have an orgasm disorder, and up to 35% may have a disorder of diminished sexual desire.[30]

Neurochemistry of the Sexual Response

Knowledge of the mechanisms involved in the sexual response is essential to understanding sexual dysfunction. Although our comprehension of the neurochemical control of sexual function is incomplete, it is known to involve a complex interaction of central and peripheral nerves, including dopaminergic, serotonergic, adrenergic, and muscarinic systems.[28]

Sexual desire is believed to originate in the limbic region of the central nervous system (CNS).[28,33] Psychotropic agents that elevate central serotonergic activity, such as SSRIs, monoamine oxidase inhibitors (MAOIs) and clomipramine, are associated with a high incidence of decreased libido.[34] A normal level of testosterone also appears to be essential for normal sexual desire in both men and women.[31]

Studies in men have identified CNS mechanisms that regulate sexual arousal. Researchers have found a significant correlation between centrally-active dopamine agonists and enhanced or spontaneous erections, and between dopamine blockers and erectile dysfunction.[27,35] Not surprisingly, serotonergic antidepressants appear to have the same inhibitory effect on sexual arousal as they do on sexual desire.[34]

A sexual orgasm is the subjective perception of pleasure, which is believed to take place in the sensory cortex. It is not completely understood how the different neurochemical systems interact to promote ejaculation, but studies have shown that central serotonergic activity can suppress it and dopaminergic activity can stimulate it.[32] As seen with sexual desire and arousal, antidepressants that elevate central serotonergic activity are associated with ejaculatory dysfunction, delayed orgasm, and

anorgasmia.[32,34] Dopamine agonists, such as apomorphine, promote ejaculation, and dopamine antagonists capable of crossing the blood-brain barrier suppress it.[32]

Diagnosis of Sexual Dysfunction

A sexual dysfunction is believed to have either an organic or psychogenic basis. A sexual dysfunction is classified as organic when it develops as a consequence of an unrelated medical disorder or medication. Table 7 lists examples of common conditions or treatments that can interfere with one or more phases of the sexual response.

Table 7. Potential Causes of Organic Sexual Dysfunction[5,28,30,31,32,36]

Medical Conditions	Medications
Vascular diseases stroke coronary artery disease Urologic disorders benign prostatic hypertrophy prostatitis Peyronie's disease penile deformity Gynecologic disorders tipped uterus endometriosis Endocrine disorders diabetes mellitus hypothyroidism Neurologic disorders Parkinson's disease Post-surgical procedures prostate surgery pelvic surgery Nutritional deficiencies zinc Liver diseases Pulmonary disorders	Psychotropic drugs TCAs SSRIs MAOIs trazodone lithium anxiolytics antipsychotics drugs of abuse Prescription drugs antihypertensives diuretics antiepileptics statins antiparkinsonian agents indomethacin phentolamine Over-the counter drugs pseudoephedrine HCl ephedrine sulfate phenylpropanolamine

The classification of a sexual dysfunction as psychogenic is essentially a diagnosis of exclusion.[37] Non-medical conditions, such as interpersonal distress, possibly due to

cultural influences, social conditions or inadequacies, can lead to the psychogenic development of a sexual dysfunction.[28] Most clinicians today regard severe depression or anxiety as primary causes of psychosexual dysfunction. Depressive symptoms also may develop as a consequence of an organic sexual dysfunction.

As with the diagnosis of depression, current diagnostic tools are not able to identify all organic causes of sexual dysfunction.[28,37] Some conditions currently regarded as a psychosexual dysfunction may actually be due to an underlying but yet unknown neurochemical imbalance.[37]

Sexual Dysfunction Associated with Antidepressant Therapy

Many of the neurochemical systems controlling sexual function are the same monoaminergic systems believed to be involved in regulating mood and affect. In fact, some disorders of mood and of sexual function may have a common cause.[38] It is not surprising, then, that most of the antidepressant agents that relieve depressive symptoms also alter one's sexual function.[38]

Detecting Patients with Treatment-Emergent Sexual Dysfunction

It is extremely difficult to distinguish sexual dysfunction due to depression from sexual dysfunction due to the treatment of depression.[30,39] Although reports of the incidence of treatment-emergent sexual dysfunction vary widely, most reports based on post-marketing experience exceed the incidence found in pre-marketing studies.[28] As a class, the risk of a sexual dysfunction occurring during therapy with a TCA is lower than with a SSRI: approximately 10% with a TCA and 50% with a SSRI.[28]

Thus, an important consideration whenever managing any patient with depression is the possible presence of a sexual dysfunction. The presence of a sexual dysfunction, of course, can occur regardless of a patient's relationship status or sexual orientation. In fact, a sexual dysfunction may diminish a patient's interest in pursuing a relationship.

A patient's baseline sexual function should be established before initiating therapy with any antidepressant, and monitored at every follow-up visit. Surprisingly, a study found that most patients were not upset when their physician monitored their sexual function.[30] When the patient is in an intimate relationship, it may be helpful to include the partner in the interview.

The accuracy of a sexual history depends on a patient's ability to recognize and report a sexual dysfunction. The challenge in conducting a sexual interview is to ask questions that are explicit enough to be understood, without causing a reluctance to respond. A sexual history should be obtained with direct but non-assuming questions, asked in a confidential setting, with a respectful and non-judgmental attitude. By starting with general questions that are easy to answer, the patient can become comfortable with the process, enabling one to proceed to more specific issues.[25] Encourage the patient to use his or her own sexual terms, but ask for clarification of general or euphemistic phrases. Ask open-ended questions and invite elaboration of responses.[40] When time is limited, a two-question sexual inquiry can generate valuable information.[40]

Questions for a Limited Sexual Inquiry[40]

- Are you sexually active, with whom, and under what circumstances?
- What questions, concerns, or difficulties are you having at the present time?

Management of Depression Complicated by Sexual Dysfunction

There are a number of effective management strategies one can employ to preserve a therapeutic response to antidepressant therapy that has been complicated by sexual dysfunction. The first step, of course, is to rule out other causes such as a coexistent medical condition or its treatment. An evaluation of the therapeutic response to the

antidepressant should rule out the possibility that the sexual dysfunction is symptomatic of refractory depression or a subtherapeutic dose of an antidepressant agent.

A treatment-emergent sexual dysfunction, like other adverse events associated with antidepressant therapy, can be transient. Unless the dysfunction is causing discomfort, it may be prudent to maintain the dose and wait several months.[38] With sertraline and phenelzine, treatment-related anorgasmia has resolved spontaneously on occasion.[29]

With some antidepressants, sexual dysfunctions are dose-dependent side effects. A reduction in the concentration of the drug may relieve a sexual dysfunction without compromising a therapeutic response. Administration of an antidepressant at a time likely to follow sexual activity may be sufficient to resolve a sexual dysfunction. This approach has been successful with sertraline and clomipramine.[29] A dose reduction has been an effective treatment of sexual dysfunction associated with fluoxetine, which has a relatively long half-life. There have been reports that brief treatment holidays from SSRIs with a shorter half-life, sertraline and paroxetine, permitted a significant improvement in sexual functioning without a significant return of depressive symptoms.[41,42]

Drug substitution is the next step, if the sexual dysfunction has not spontaneously resolved and dose reduction is not effective. Switching from a tertiary amine TCA to a secondary amine TCA can reduce the incidence of sexual dysfunction.[38] Several studies have reported that switching patients from TCA, SSRI, or MAOI therapy to bupropion resulted in the most predictable resolution of sexual side effects, possibly due to its mild dopaminergic action.[43-45] In fact, bupropion may be the drug of choice for all depressed patients concerned about preserving sexual function.[44] The only caveat is that bupropion is not indicated for the treatment of depression with a comorbid anxiety disorder.[42]

Coadministration of one of a number of drugs has been successful in countering sexual dysfunction associated an antidepressant. The cholinergic agent, bethanechol, has been reported to reverse anorgasmia secondary to therapy with TCAs such as

protriptyline, amoxapine, and imipramine.[29] The potent anti-serotonergic agent cyproheptadine has been effective in returning normal orgasm function to patients treated with imipramine, nortriptyline, fluoxetine, fluvoxamine, clomipramine, and citalopram.[29,46] However, it can reduce the efficacy of the antidepressant therapy.[46] A low-dose psychostimulant, such as methylphenidate, which may have a pressor effect, has been useful in augmenting a patient's response to SSRI therapy.[47] These agents have also been reported to reverse inhibited sexual function associated with fluoxetine, sertraline, paroxetine, and phenelzine.[35,48] The alpha$_2$ antagonist yohimbine has been used to reverse anorgasmia associated with clomipramine, fluoxetine, sertraline, paroxetine, or fluvoxamine therapy.[29] The glutamatergic agent amantadine has also been used to reverse fluoxetine-induced anorgasmia.[29] In a small clinical study, the addition of anxiolytic buspirone improved sexual functioning in patients treated with fluoxetine, sertraline, or paroxetine, possibly by its action as an alpha$_2$ antagonist, or partial serotonin agonist.[49]

Table 8. Management of Depression Complicated by Sexual Dysfunction[29]

1. Rule-out causation by coexistent medical condition or treatment
2. Rule-out causation by uncontrolled depression
3. Observe and wait for dysfunction to disappear
4. Reduce serum antidepressant level
    a. timing of drug administration
    b. dose reduction
    c. treatment holiday
5. Switch antidepressant therapy
    a. alternative agent within class
    b. alternative agent in another class
        i. bupropion
        ii. nefazodone
6. Supplement existing antidepressant therapy
    a. cyproheptadine
    b. methylphenidate
    c. bethanechol
    d. yohimbine
    e. amantadine
    f. buspirone

Conclusions

Depression is a disabling, prevalent condition in our country. Due to inadequate screening, or lack of patient self-awareness or reluctance to seek help, depressive disorders are often unreported and untreated. Treatment with virtually every antidepressant agent is associated with a significant incidence of sexual dysfunction. A treatment-emergent adverse event, such as sexual dysfunction, is the most common cause of patient noncompliance and treatment failure.

Sexual dysfunctions are even more prevalent than depressive disorders, probably due to the fact that many medical conditions and drugs can lead to organic sexual dysfunction. The incidence of sexual dysfunction is higher in patients with depression than in the general population. A baseline evaluation of a depressed patient's sexual function should be conducted prior to initiating antidepressant therapy. Explicit monitoring during therapy is necessary to identify patients with treatment-emergent sexual dysfunction.

The cause of a sexual dysfunction must be established before planning a treatment strategy. When managing treatment-emergent sexual dysfunction, the simplest treatment plan may be to switch to an antidepressant with a minimal risk of sexual dysfunction, if the patient is an appropriate candidate.

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Recommended Reading

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After reading this monograph, you may obtain three Continuing Medical Education credits by scoring [[number]]% or better on the following exam. Using the detachable answer sheet, place an "X" in the box that corresponds with your answer. Fill in the identifying information blanks, and mail the answer sheet, according to the mailing instructions below, before [[date]].

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CME Exam

1. A depressive disorder can have a negative effect on
   a. somatic health
   b. social interactions
   c. professional performance
   ✓d. all of the above

2. Patients with a depressive disorder and a comorbid disease have a higher mortality rate than those without depression in an otherwise matched population.
   ✓a. True
   b. False

3. Patients with an endocrine disorder or vascular disease are at risk of having a comorbid depressive disorder.
   ✓a. True
   b. False

4. In a diagnostic screen designed to detect depression in primary care patients, a high degree of sensitivity is more important that a high degree of specificity.
   ✓a. True
   b. False

5. The likelihood ratio for a depression risk factor reflects
   a. its likelihood of association with depression
   b. the prevalence of a depressive disorder in a given population
   c. its predictive probability
   ✓d. all of the above

6. The delayed onset of efficacy associated with many antidepressant agents is thought to be due to
   a. the time required to obtain a steady-state level
   b. the time required to induce an activating enzyme
   ✓c. the time required to down-regulate synaptic receptor sensitivity
   d. the time required to accumulate neurotransmitters in the synapse

7. The most important factor determining treatment outcome in depression is
   a. an appropriate diagnosis
   b. an appropriate therapy at the therapeutic dose
   c. sufficient duration of therapy
   ✓d. patient compliance

8. The effect of an antidepressant on a sleep or appetite disorder is a good indicator of an agent's therapeutic efficacy.
   a. True
   ✓b. False

9. A quick yet reliable measure of a patient's response to therapy is the change in a patient's level of
   a. physical activity
   b. social activity
   ✓c. professional productivity
   d. emotional affect

10. What percent of patients experience a recurrent episode of depression after remission from their first episode?
   a. 25%
   ✓b. 50%
   c. 75%
   d. 90%

11. Among the most common causes of noncompliance with an antidepressant agent is treatment-emergent adverse events.

✓a. True

b. False

12. Inhibition of a P450 isozyme by an SSRI can cause the accumulation of a concomitantly administered drug.

✓a. True

b. False

13. Which class of antidepressant agents has a narrow therapeutic index?

✓a. TCAs

b. MAOIs

c. SSRIs

d. Aminoketones

14. The incidence of treatment-emergent sexual dysfunction is

a. is probably low due to under-reporting

b. Is difficult to establish due to the difficulty in distinguishing from sexual dysfunctions caused by a depressive disorder

c. is highest with SSRI therapy

✓d. all of the above

15. A sexual dysfunction cannot occur if a patient is not in a sexual relationship.

a. True

✓b. False

16. In most post-marketing reports, the incidence of a treatment-emergent sexual dysfunction exceeds the incidence reported in pre-marketing studies.

✓a. True

b. False

17. The incidence of a sexual dysfunction associated with SSRI therapy is lower than that associated with TCAs.

a. True
✓b. False

18. Depressive disorders are more prevalent than sexual dysfunctions.
a. True
✓b. False

19. One of the most common sexual dysfunctions
a. in men is a pathologic increase in orgasmic function
b. in women is a pathologic decrease in orgasmic function
c. is dependent upon the sexual function of the partner
✓d. all of the above

20. Impotence is
a. a pathologic decrease in sexual desire
✓b. a pathologic decrease in sexual arousal
c. a pathologic decrease in orgasmic function
d. all of the above

21. Many of the neurochemical systems controlling sexual function are the same monoaminergic systems regulating mood and affect.
✓a. True
b. False

22. An increase in serotonin activity is believed to suppress the sexual response.
✓a. True
b. False

23. An increase in dopaminergic activity is believed to suppress the sexual response.
a. True
✓b. False

24. Possible causes of organic sexual dysfunction include
a. endocrine disorders

b. vascular disorders and their treatments

c. drugs of abuse

✓d. all of the above

25. Depression can lead to

a. increased sexual activity

b. decreased sexual activity

c. decreased satisfaction with sexual activity

✓d. all of the above

26. The classification of a sexual dysfunction as organic is essentially a diagnosis of exclusion.

a. True

✓b. False

27. A sexual interview should

a. be conducted with a nonjudgmental attitude

b. build from general questions to specific questions

c. be conducted at every visit with depressed patients

✓3d. all of the above

28. The strategies for managing a sexual dysfunction associated with antidepressant therapy are designed to maximize the therapeutic effect of the agent

a. True

✓b. False

29. The alternate antidepressant that most reliably resolves sexual dysfunction associated with antidepressant therapy is

a. desipramine
b. fluoxetine
c. sertraline
✓d. bupropion

30. Coadministration of a low-dose psychostimulant

a. can augment a patient's response to SSRI therapy
b. can reverse an inhibited sexual dysfunction
c. can have a pressor effect
✓d. all of the above

Answer Sheet

To earn CME credit, place an "X" in the box that corresponds with your answer, provide the identifying information requested in the blanks, and follow the mailing instructions.

	a	b	c	d
1.	☐	☐	☐	☐
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