Antidepressant-Induced Sexual Dysfunction and Its Management

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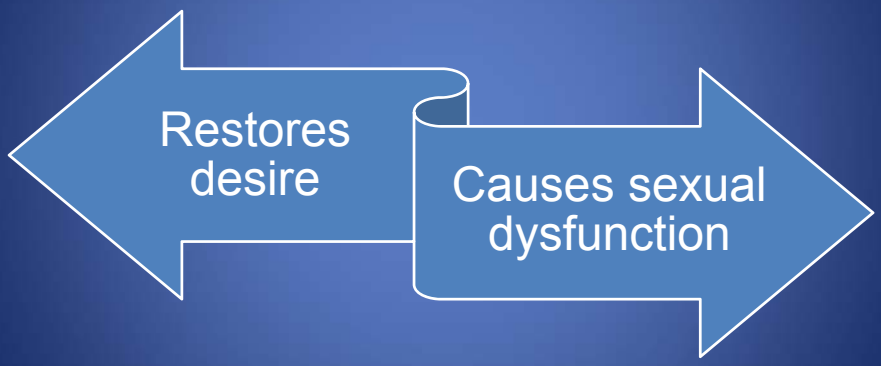
Learning Objectives

- Discuss the clinical features, epidemiology, and etiology of antidepressant-induced sexual dysfunction.
- Summarize important assessment & counseling points as relates to antidepressant-induced sexual dysfunction.
- Describe the strategies that can be used to manage antidepressant-induced sexual dysfunction.
- Cite medications that are considered useful add-on therapies for management of antidepressant–induced sexual dysfunction.

Antidepressant Treatment Paradox



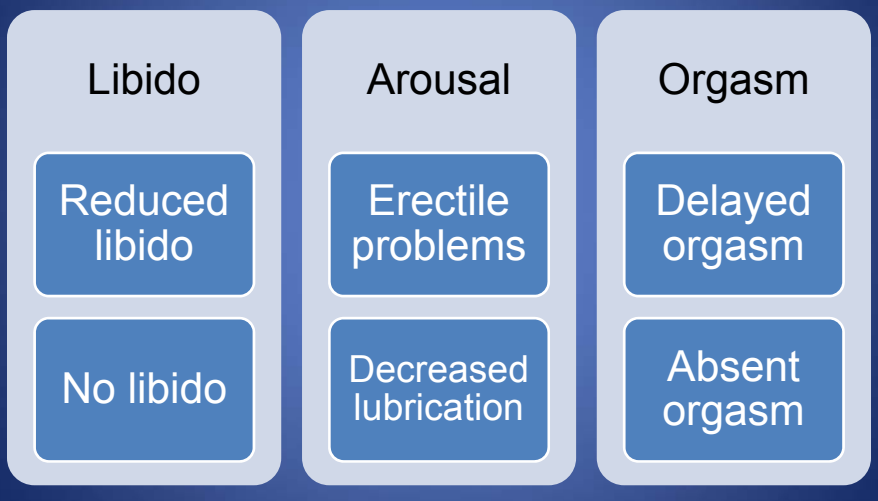
Introduction

- Considered one of the most common and bothersome adverse effects of antidepressants
- Patients are usually quite displeased and distressed about sexual adverse effects
- Can have a major impact on:
  - Adherence to therapy
  - Recovery from illness
  - Self-esteem
  - Quality of life
  - Interpersonal relationships

Clinical Features

- Antidepressants can affect all phases of sexual function
  - Libido
  - Arousal
  - Orgasm/ejaculation
- An individual patient can experience dysfunction in one or more phases
- Sexual phases can have varying degrees of dysfunction
- Orgasm disturbances are the most common type for newer antidepressants

Clinical Features (cont.)



Clinical Features (cont.)

- Dose – dose-related
- Onset – typically occurs early in treatment
- Duration – typically persists throughout treatment
- Resolution – typically resolves after discontinuation of the offending agent
  - Post-SSRI sexual dysfunction (?)

Epidemiology – Historical Context

- Used to be underappreciated and underreported
- Now far more commonly reported due to various factors:
  - Growing awareness of the problem
  - Increased willingness to discuss sexual problems
  - Greater biological emphasis in treating depression
  - Lower threshold for prescribing antidepressants
  - More clinicians prescribing antidepressants
  - Increased use of antidepressant combination therapy
  - Expanded indications for antidepressants

Epidemiology – Incidence

- Reported rates vary widely between studies
- Approx. 20-50% of antidepressant-treated patients experience sexual dysfunction
- Most frequent adverse effect of certain antidepressants
- Risk varies by drug/class (next 2 slides)

Epidemiology – Risk by Drug/Class

Large, prospective trial

Citalopram
Paroxetine
Venlafaxine
Sertraline
Fluvoxamine
Fluoxetine

—

Mirtazapine
Nefazodone

2009 meta-analysis

Sertraline
Venlafaxine
Citalopram
Paroxetine
Fluoxetine
Imipramine
Phenelzine
Duloxetine
Escitalopram
Fluvoxamine

—

Bup, Mirt, Nefaz

Epidemiology – Risk by Drug/Class

Higher risk

- SSRIs
- SNRIs
- TCAs
- MAOIs

Lower risk

- Bupropion
- Mirtazapine
- Nefazodone
- Trazodone
- Vilazodone (?)
- Vortioxetine (?)

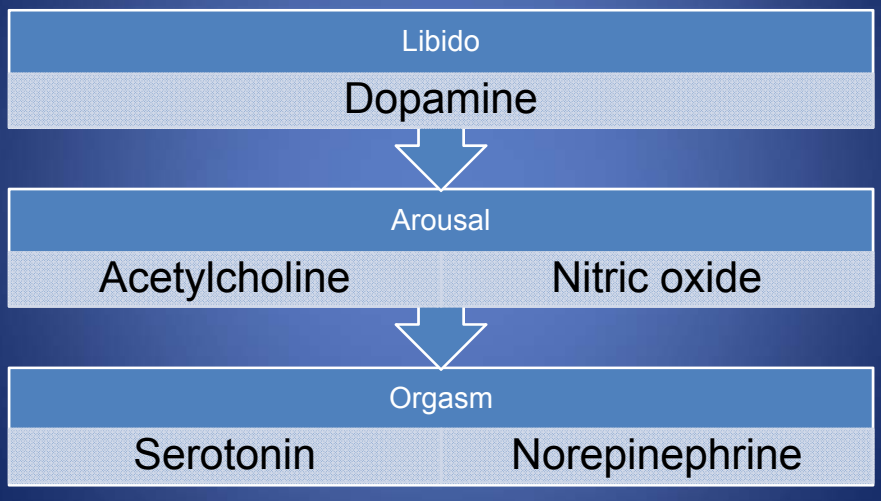
Epidemiology – Patient Acceptance

- In one large study, patients had differing acceptance levels of sexual dysfunction:
  - 27% had good tolerance (no concern)
  - 35% had fair tolerance (some concern; no plan to discontinue therapy)
  - 38% had poor tolerance (very concerned; serious risk of noncompliance)
- In one large survey, sexual dysfunction was cited among the most common (50%) adverse effects leading to treatment dropout

Epidemiology – Gender Issues

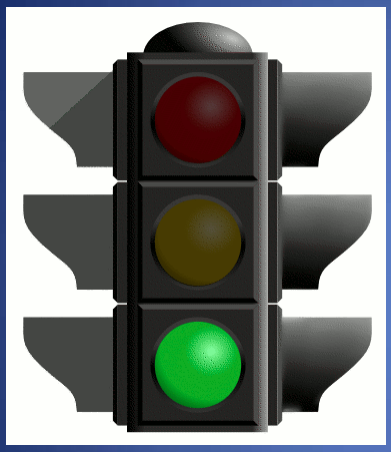
- Which gender bears the greater burden?
- Fairly similar rates of antidepressant-induced sexual dysfunction in men and women
  - Women are generally less likely to discuss adverse sexual effects with clinicians
  - Women may very well be more likely to attribute sexual dysfunction to other causes
- A few prospective trials show higher incidence rates in men, but greater severity in women
- Management strategies appear to be just as applicable to women

Normal Sexual Functioning

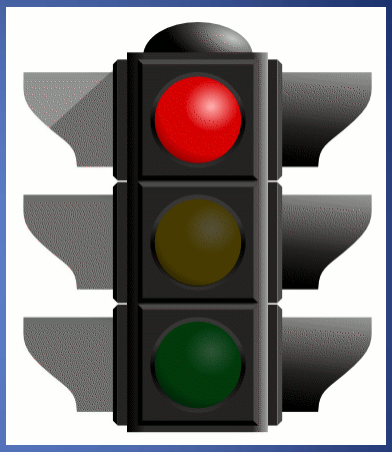


How Antidepressants Affect Sexual Functioning

- Neurotransmitters involved in normal sexual functioning are targeted by antidepressants
- Serotonin is particularly important
  - Almost all antidepressants increase serotonin levels
  - In general, likelihood of sexual dysfunction is correlated with serotonergic activity of the drug
  - Serotonin can actually affect functioning in all 3 sexual phases
  - Effects differ based on receptor subtype:
    - 5-HT_{2A} stimulation = negative effects
    - 5-HT_{1A} stimulation = positive effects

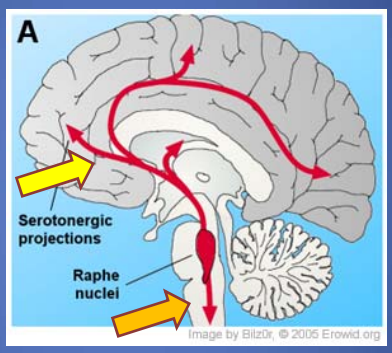


Dopamine

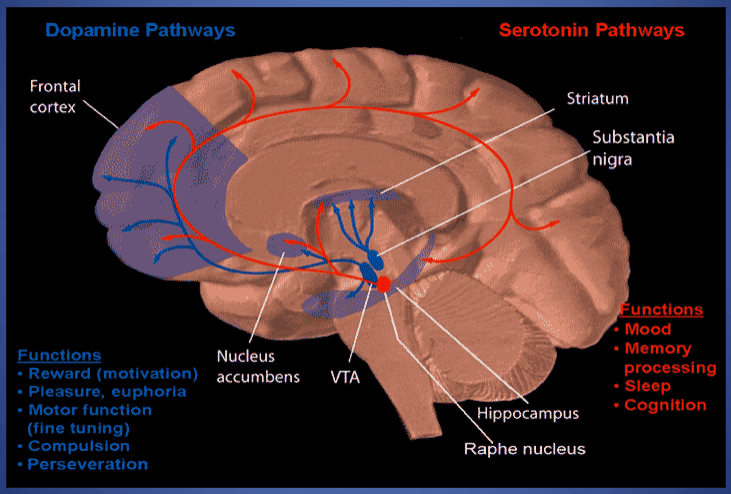


Serotonin

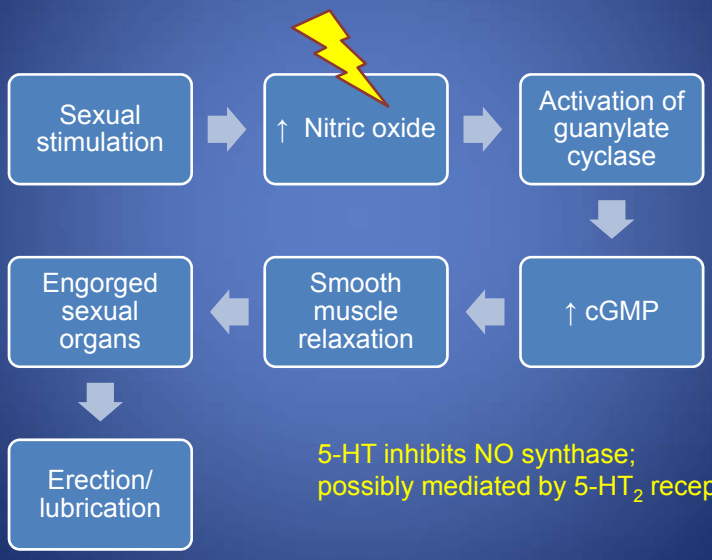
Diminished libido



Inhibited arousal & orgasm



Serotonin & Nitric Oxide



5-HT inhibits NO synthase;
possibly mediated by 5-HT_2 receptors

Clinical Approach

Screen
- Is sexual dysfunction present?

Assess
- Is sexual dysfunction due to the antidepressant?

Manage
- Which strategy is best for the particular patient?

Screening

- Important monitoring parameter of anti-depressant therapy
- Needs to be methodical in terms of both specificity and timeliness
- Likelihood of detection is highly dependent upon method used:

  direct questioning >> spontaneous reports
- Various scales are available; examples include ASEX and CSFQ

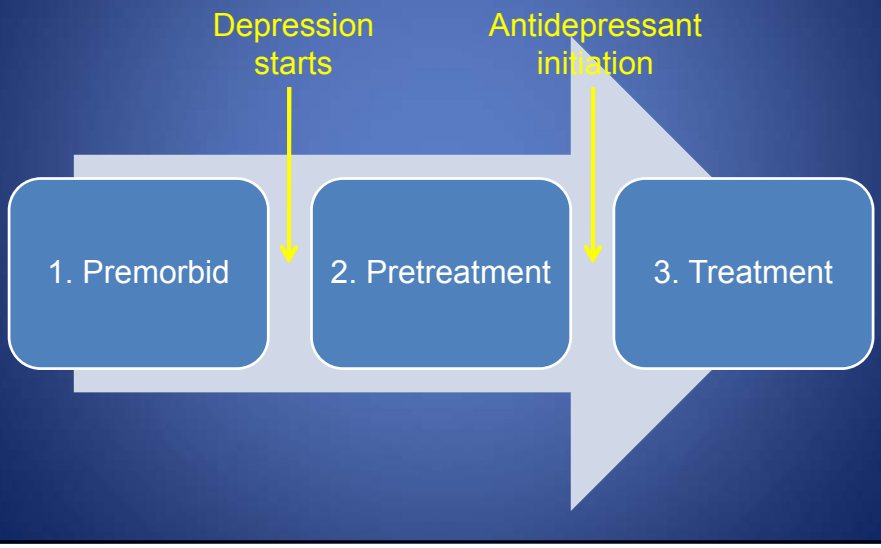
Assessment

- Clinician cannot assume that sexual dysfunction is due to the antidepressant
  - Sexual dysfunction is fairly common in the general population
  - Sexual dysfunction is very common in the depressed population (pretreatment)
- Sexual dysfunction has numerous potential causes (next slide)
- The cause of sexual dysfunction is frequently multifactorial

Assessment – Differential Diagnosis

Primary sexual dysfunction: Desire disorders Arousal disorders Orgasm disorders Sexual pain disorders	Psychosocial factors: Stressors Relationship difficulties
Medical and psychiatric issues: Depression Hypertension Diabetes Hypothyroidism	Medications and drugs: Antidepressants Other psychotropics Antihypertensives Hormones Alcohol Illicit drugs

Screening/Assessment Time Frames



Sexual History

- Questions should relate to:
  - Satisfaction with sexual activity
  - Frequency of sexual activity
  - Functioning within each sexual phase
- Important aspects of any identified problems:
  - Specific type/phase of dysfunction
  - When it first occurred
  - How often it occurs
  - In which type of situation does it occur

Sexual History – Types of Questions

Before therapy

- How important is sexual activity in your life?
- Are you happy with your sexual performance?
- Have you experienced a decreased interest in sex?
- Have you experienced any changes in sexual performance?
- Have you experienced any difficulty in reaching orgasm?

During therapy

- Is your sex life different now than it was before therapy began?
- Have you experienced a decreased interest in sex?
- Have you experienced any changes in sexual performance?
- Have you experienced any difficulty in reaching orgasm?
- Do you care that your sexual performance has been altered by taking an antidepressant?

Counseling Patients

- Counseling is critical; discussion should be honest & forthright
  - Helps to build a therapeutic alliance
  - Promotes full adherence to therapy
- Counseling points:
  - Approximate likelihood of sexual dysfunction
  - Signs of sexual dysfunction
  - What to do should sexual dysfunction occur
  - Possible management strategies

Dealing with Antidepressant-Induced Sexual Dysfunction

Try to avoid it

Live with it

Manage it

Minimizing the Risk

- Bupropion
  - Reason: dopamine reuptake inhibition; lack of serotonin reuptake inhibition
  - Problem: seizure risk
- Mirtazapine
  - Reason: 5-HT_{2A} antagonism
  - Problem: sedation and weight gain
- Nefazodone
  - Reason: 5-HT_{2A} antagonism
  - Problem: hepatotoxicity (black box); very limited usage

Minimizing the Risk (cont.)

- Trazodone
  - Reason: 5-HT_{2A} antagonism
  - Problem: sedation; very limited usage as antidepressant
- Vilazodone
  - Reason: 5-HT_{1A} partial agonism
  - Problem: relatively new agent; impact on sexual functioning is perhaps greater in men vs. women
- Vortioxetine
  - Reason: 5-HT_{1A} agonism
  - Problem: relatively new agent

Managing Sexual Dysfunction

- Watchful waiting
- Dosage reduction
- Drug holiday
- Timing method
- Switching antidepressants
- Add-on therapy

Watchful Waiting

- Continue therapy and wait for tolerance
- May be considered when:
  - Therapy is still in initial phase
  - Patient is experiencing very good efficacy
  - Duration of therapy is considered short-term
- Pro: preserves efficacy of antidepressant
- Con: not usually effective, as sexual adverse effects often persist

Dosage Reduction

- Downward titration of antidepressant dosage
- May be considered when:
  - Patient is experiencing very good efficacy
  - Antidepressant has relatively flat dose-response curve
- Pro: maintain therapy with same antidepressant, so may be able to preserve efficacy
- Con: increased likelihood of depressive relapse or recurrence

Drug Holiday

- Patient is allowed to skip 1 or more doses
- May be considered when:
  - Patient is experiencing very good efficacy
  - Antidepressant has a shorter half-life (ex: paroxetine)
  - Patient engages in relatively infrequent sexual activity
- Pro: possibly effective without regularly reducing the dosage
- Con: increased likelihood of depressive relapse or recurrence; possibility of withdrawal symptoms; may encourage nonadherence

Timing Method

- Schedule sexual activity just prior to the daily dose of antidepressant (i.e., at trough level)
- May be considered when:
  - Antidepressant has a shorter half-life (ex: paroxetine)
- Pro: preserves efficacy of antidepressant; avoids risks associated with drug holidays
- Con: questionable effectiveness

Switching Antidepressants

- Switch to antidepressant that is associated with lower incidence of sexual dysfunction
- May be considered when:
  - Antidepressant has not been optimally efficacious
  - Patient refuses to continue treatment with same antidepressant due to sexual dysfunction
- Switch from what to what?
  - SSRI → SSRI will probably not work
  - SSRI → SNRI might work
  - Best bet is to switch to bupropion, mirtazapine, or perhaps a newer antidepressant

Switching Antidepressants (cont.)

- Pro: high likelihood of alleviating sexual dysfunction with proper medication selection
- Con: loss of efficacy from previous antidepressant and no assurance of efficacy from chosen antidepressant

Add-on Therapy

- Add medication to ongoing antidepressant therapy to treat the sexual dysfunction
- May be considered when:
  - Patient is experiencing very good efficacy
  - Patient is willing to accept additional medication
- How do add-on therapies work?
  - Dopamine modulation
  - Serotonin modulation
  - Norepinephrine modulation
  - Acetylcholine modulation
  - Phosphodiesterase inhibition

Add-on Therapy – Examples by Mechanism

Dopamine modulation: Amantadine Bupropion Dextroamphetamine Methylphenidate Ropinirole	Serotonin modulation: Buspirone Cyproheptadine Granisetron Mirtazapine Nefazodone Olanzapine
Norepinephrine modulation: Yohimbine	Phosphodiesterase inhibition: Sildenafil Tadalafil Vardenafil
Acetylcholine modulation: Bethanechol	Unknown: Ginkgo biloba

Add-on Therapy – Concerns

- Bupropion, mirtazapine, and nefazodone – see previous slide about avoiding sexual dysfunction
- Bupropion – can cause tremor and anxiety when coadministered with SSRIs
- Cyproheptadine – sedation and fatigue; can reverse antidepressant therapeutic effects
- PDE-5 inhibitors – should avoid in patients taking nitrates and those with significant CVD
- Stimulants – agitation and insomnia; potential for misuse
- Yohimbine – anxiety, nausea, and sweating

Add-on Therapy – Bonuses

- Some add-on therapies may also enhance the therapeutic effects of the antidepressant:
  - Bupropion
  - Mirtazapine
  - Buspirone

Add-on Therapy – Examples of Dosing

Drug	Dose per day
Amantadine	100-400 mg
Bupropion	75-150 mg
Buspirone	15-60 mg
Cyproheptadine	2-16 mg
Methylphenidate	10-25 mg
Mirtazapine	15 mg
Sildenafil	50-100 mg prn
Yohimbine	5.4-16.2 mg

Add-on Therapy (cont.)

- Dosing schedule of add-on medications
  - As-needed dosing may work, but some patients require routine dosing
  - Routine dosing is more likely to cause more adverse effects; as-needed dosing can spoil spontaneity
- Pro: preserves efficacy of antidepressant; may confer additional antidepressant benefits if certain medications are chosen
- Con: additional adverse effect burden; increased cost of therapy; possibility of drug interactions

Add-on Therapy (cont.)

- What is the evidence?
  - Numerous agents have been described as useful add-on therapies
  - There have been relatively few randomized controlled trials, and the results have been mixed
- 2013 Cochrane review
  - PDE-5 inhibitors: effective in men with erectile dysfunction; uncertain effectiveness in women
  - Bupropion: effective
  - Other agents: failed to demonstrate significant improvements vs. placebo

Question #1

Antidepressants can cause which of the following sexual dysfunctions?

A. Reduced libido
B. Erectile problems
C. Delayed orgasm
D. All of the above

Question #2

Which of the following antidepressants is MOST likely to cause sexual dysfunction?

A. Mirtazapine
B. Paroxetine
C. Imipramine
D. Vilazodone

Question #3

Which of the following statements concerning assessment of antidepressant-induced sexual dysfunction is TRUE?

A. Direct questioning is better than patient self-report to detect sexual dysfunction
B. It is rare for other factors besides antidepressant use to cause sexual dysfunction
C. Screening should begin 3 months after the antidepressant is initiated
D. Sexual histories should ignore functioning within specific sexual phases

Question #4

Which of the following medications can be added to a patient's antidepressant therapy to treat antidepressant-induced sexual dysfunction?

A. Propranolol
B. St. John's wort
C. Sildenafil
D. Esomeprazole

Question #5

A patient has received fluoxetine therapy (20 mg/day) for 6 weeks. His depressive symptoms have only minimally responded to treatment, and he has developed anorgasmia. Which of the following would be the BEST management strategy for this patient?

A. Wait for tolerance to develop
B. Try drug holidays on the weekends
C. Switch from fluoxetine to bupropion
D. Increase the dose to 40 mg/day