Antidepressant Drug-induced Sexual Dysfunction (ADISD)

Rajnish Mago, MD
Founder and Editor-in-Chief
SimpleandPractical.com
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Clinical Presentation of Sexual Dysfunction

- Sexual dysfunction can include disorders of¹:
  - Sex drive (loss of libido)
  - Arousal (women: clitoral engorgement and lubrication; men: erectile function)
  - Orgasm and ejaculation

- Complaints may include:
  - A reduction in desire or libido²
  - Diminished arousal²
  - A decline in frequency of intercourse²
  - Undesirable delay in achieving orgasm²
  - Dyspareunia (painful sex)¹,³
  - Priapism (a prolonged and usually painful erection)¹,⁴

- The main type of disorder resulting from depression is low sex drive¹
  - Arousal and orgasm/ejaculation disorders occur less frequently

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Prevalence of Sexual Dysfunction

General Population

- In an analysis of data from a 1992 National Health and Social Life Survey pertaining to sexual behavior, a demographically representative cohort of United States (US) adults (N=3159) reported a sexual dysfunction prevalence of 43% for women and 31% for men.

Patients With Depression

- In a series of 4 studies in which 1345 patients with MDD were evaluated for sexual dysfunction utilizing the Arizona Sexual Experiences Scale (ASEX), 59.3% met criteria at baseline (may be attributable to depression itself):
  - Of the patients not meeting baseline criteria, 28.8% in the placebo group developed sexual dysfunction during the study.

Patients Being Treated With an Antidepressant Medication

- A large (N=6268) observational study conducted in >1000 US primary care clinics measured sexual functioning associated with antidepressant use via the Changes in Sexual Functioning Questionnaire (CSFQ) and reported:
  - A prevalence of 37% in the overall clinical population across all antidepressant medications evaluated.
  - A prevalence of 24% in a subgroup free of other probable causes of sexual dysfunction across all antidepressant medications.

Neurotransmitters in Sexual Function

- Specific neurotransmitters and receptors are thought to contribute to phase-specific sexual functions

**Neurotransmitter Contributions in Sexual Response Phases**

- **Libido**
  - Dopamine

- **Dopamine**
  - Acetylcholine
  - Nitric oxide

- **Orgasm**
  - Serotonin
  - Norepinephrine
  - Prolactin

**Serootonin Receptor Subtype Contributions in Sexual Response Phases**

- 5-HT$_{1A}$
  - Stimulation facilitates erection and ejaculation

- 5-HT$_{2A}$
  - Stimulation believed to have negative effects on sexual function
  - A distinct 5-HT$_{2A}$ SNP appears to correlate with lower scores of sexual arousal

- 5-HT$_{2C}$
  - Stimulation facilitates erection and ejaculation

- 5-HT$_3$
  - Excess activation inhibits ejaculation and orgasm

5-HT$_{xx}$, serotonin receptor subtype XX; SNP, single-nucleotide polymorphism.

<table>
<thead>
<tr>
<th>Neurotransmitter Modulation</th>
<th>Effects on sexual response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D&lt;sub&gt;2&lt;/sub&gt; agonism</strong></td>
<td>Increased sexual desire (anticipation of reward)</td>
</tr>
<tr>
<td><strong>D&lt;sub&gt;2&lt;/sub&gt; antagonism</strong></td>
<td>Decreased sexual desire, sexual activity, erection, and ejaculation</td>
</tr>
<tr>
<td><strong>5-HT&lt;sub&gt;2&lt;/sub&gt; agonism</strong></td>
<td>Delay of orgasm</td>
</tr>
<tr>
<td><strong>5-HT&lt;sub&gt;1a&lt;/sub&gt; agonism</strong></td>
<td>Activation of sexual behavior, facilitation of orgasm</td>
</tr>
<tr>
<td><strong>5-HT&lt;sub&gt;2a&lt;/sub&gt; and 5-HT&lt;sub&gt;2c&lt;/sub&gt; antagonism</strong></td>
<td>Probable stimulation of sexual behavior</td>
</tr>
</tbody>
</table>
| **α<sub>1</sub> antagonism** | Central effect: decrease of erection, lubrication, and ejaculation  
Peripheral effect: may have a stimulating effect on, e.g. erection |
| **α<sub>2</sub> antagonism** | Stimulation of erection |
| **H<sub>1</sub> antagonism** | Indirect effect on sexual performance through sedation |
| **M<sub>1</sub> antagonism** | Decreased erection and lubrication |

5-HT<sub>1XXX</sub>, serotonin (receptor subtype X/XX) ; α, alpha receptor; D, dopamine receptor; H, histamine receptor; M, muscarinic receptor.

Neurotransmitters in Sexual Function

- Sexual function can be impacted by treatment with antidepressant medication\(^1\)
  - The specific sex phase affected and the degree of symptom severity are influenced by the type and number of receptors targeted by individual medications\(^1\)

Neurotransmitter Contributions Towards Sexual Dysfunction\(^1\)

- Cholinergic and \(\alpha\) adrenergic receptor blockade
- Decreased dopaminergic activity
- Excess serotonin at 5-HT\(_2\) and 5-HT\(_3\) receptors
- Nitric oxide synthetase inhibition
- Elevation of prolactin levels

5-HT\(_X\), serotonin receptor X; \(\alpha\), alpha receptor.

Sex Differences in Depression and ADISD

• Men more frequently report problems with desire and orgasm, while women more frequently report decreased arousal

• A prospective observational, open study assessing the incidence of selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction via questionnaire* in outpatients (N=344) reported:
  – The overall incidence of sexual dysfunction in male study participants was 61.8% (94/152) compared with 52.5% (106/192) in female participants
  – In these patients who reported sexual dysfunction, additional comparisons between men (n=94) and women (n=106) were performed, which observed:
    • A more severe decrease in libido in females than males (Score: 2.06 vs 1.44; P=0.0001†)
    • A more severe delay of orgasm or ejaculation in females than males (Score: 2.44 vs 2.04; P=0.05†)
    • More severe anorgasmia or no ejaculation in females than males (Score: 1.81 vs 0.88; P=0.0001†)
  – The incidence of ADISD was greater in men, while the severity of ADISD was greater in women

*Questionnaire results utilized an intensity scale for the specific dysfunction severity (0=nil, 1=mild, 2=moderate, 3=severe)
†P-value assessed via chi-squared test.
Treatment Effect Differences in Sexual Dysfunction

• All 3 sexual response phases can be affected by both depression itself, as well as treatment with antidepressant drugs.

• To date, no medication is indicated for treating sexual dysfunction associated with antidepressant treatment.

• The frequency of sexual dysfunction as a side effect of treatment with antidepressant medication differs by mechanism of action.

<table>
<thead>
<tr>
<th>Sexual Dysfunction by Antidepressant Pharmacotherapy Class</th>
<th>Frequency of sexual dysfunction as treatment-related side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors</td>
<td>57% to 72%</td>
</tr>
<tr>
<td>5-HT₂ blockers</td>
<td>8% to 4%</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>~4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sexual Dysfunction Prevalence in Various Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy individuals</td>
</tr>
<tr>
<td>10% to 52% (men) 25% to 63% (women)</td>
</tr>
</tbody>
</table>

ASSESSMENT AND MANAGEMENT OF ADISD
The Relevance of Sexual Dysfunction Evaluation in the Treatment of Depression

• The evaluation of sexual dysfunction is relevant to the treatment of depression\(^1\)
  – Sexual dysfunction impacts quality of life and is important to most patients
  – It can be an additional source of distress, potentially impacting illness severity/course
  – Sexual dysfunction can lead to treatment nonadherence

Under-recognition of Sexual Dysfunction in Depression

- Sexual dysfunction is often underdiagnosed, underreported, and underestimated in prevalence by physicians

### Contributing factors to the under-reporting of sexual dysfunction

- Patients may be hesitant or embarrassed to report
- Physicians may believe depression to be the cause of the sexual dysfunction
- Physicians may have limited knowledge of appropriate symptom management
- Physicians consistently underestimate the prevalence of sexual dysfunction experienced by patients
Identifying and Evaluating ADISD in Patients With Depression

- Patients’ spontaneous report of sexual dysfunction can be unreliable
- Adequate assessment involves evaluation of sexual function prior to, and periodically during, treatment
  - Should involve the use of validated and specific questionnaires that encompass multiple aspects of sexual functioning

Evaluation criteria should include:

1. Comprehensive assessment of patient factors (e.g., age, relationships, use of alcohol/other substances)
2. Comorbid psychiatric and medical conditions
3. Detailed psychosexual history

Identifying and Evaluating ADISD in Patients With Depression

- Physicians can use structured scales in order to measure ADISD as an adverse event.
- These scales may allow improved detection of sexual dysfunction, thereby possibly improving treatment adherence and lowering risk of depression recurrence.

*The United States Food and Drug Administration has supported the use of these scales in registration trials for antidepressant medications.
ASEX, Arizona Sexual Experiences Scale; CSFQ, Changes in Sexual Functioning Questionnaire; PRSexDQ, Psychotropic-Related Sexual Dysfunction Questionnaire, SexFX, Sex Effects Scale.
# Validated Depression-specific Sexual Dysfunction Questionnaires

<table>
<thead>
<tr>
<th>Questionnaire*</th>
<th>Items, n</th>
<th>Time to Complete (minutes)</th>
<th>Domains Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASEX†</td>
<td>5</td>
<td>5–10</td>
<td>Drive, arousal, penile erection/vaginal lubrication, orgasm, satisfaction</td>
</tr>
<tr>
<td>CSFQ-long†</td>
<td>F: 34 M: 36</td>
<td>15–20</td>
<td>Desire—interest, desire—frequency, pleasure, arousal/excitement, orgasm/completion</td>
</tr>
<tr>
<td>SexFX†</td>
<td>11</td>
<td>5–10</td>
<td>Desire, arousal, orgasm, satisfaction with function</td>
</tr>
<tr>
<td>CSFQ-short‡</td>
<td>14</td>
<td>5</td>
<td>Desire—interest, desire—frequency, pleasure, arousal/excitement, orgasm/completion</td>
</tr>
<tr>
<td>PRSexDQ§</td>
<td>7</td>
<td>5</td>
<td>Desire, arousal, ejaculation/ orgasm, sexual dysfunction, tolerability of change in function</td>
</tr>
</tbody>
</table>

*Separate sex versions available for all questionnaires.
†Administered by either self-report or clinical interview.
‡Administered by self-report.
§Administered by clinical interview.

ASEX, Arizona Sexual Experiences Scale; CSFQ, Changes in Sexual Functioning Questionnaire; F, female; M, male; PRSexDQ, Psychotropic-Related Sexual Dysfunction Questionnaire; SexFX, Sex Effects Scale.

# Changes in Sexual Functioning Questionnaire Scale (CSFQ)

## Instructions for Completing and Scoring the CSFQ

Ask the patient to complete all 14 items on the clinical version of the CSFQ. The patient should place a check in the box corresponding to the response for that particular item. This is a questionnaire about sexual activity and sexual function. By sexual activity, it means intercourse, masturbation, sexual fantasies and other activity. A numerical value (1-5) or weight is indicated for a particular response. These values are summed for all 14 items.

1. Compared with the most enjoyable it has ever been, how enjoyable or pleasurable is your sexual life right now?
2. How frequently do you engage in sexual activity (sexual intercourse, masturbation, etc.) now?
3. How often do you desire to engage in sexual activity?
4. How frequently do you engage in sexual thoughts (thinking about sex, sexual fantasies) now?
5. Do you enjoy books, movies, music or artwork with sexual content?
6. How much pleasure or enjoyment do you get from thinking about and fantasizing about sex?
7. How often do you have an erection related or unrelated to sexual activity?
8. Do you get an erection easily?
9. Are you able to maintain an erection?
10. How often do you experience painful, prolonged erections?
11. How often do you have an ejaculation?
12. Are you able to ejaculate when you want to?
13. How much pleasure or enjoyment do you get from your orgasms?
14. How often do you have painful orgasm?

To calculate the Total CSFQ score, add up the values of the response for all 14 items. To calculate subscale scores, add up the values for only the items that correspond to a particular subscale.

To determine if sexual dysfunction is present, scoring is performed by referring to gender-specific scoring protocols.

### Table: Subscore Measure and Items Included for Scoring

<table>
<thead>
<tr>
<th>Subscore Measure</th>
<th>Items Included for Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleasure</td>
<td>Item #1</td>
</tr>
<tr>
<td>Desire/Frequency</td>
<td>Item #2 and Item #3</td>
</tr>
<tr>
<td>Desire/Interest</td>
<td>Item #4 – Item #6</td>
</tr>
<tr>
<td>Arousal/Erection</td>
<td>Item #7 – Item #9</td>
</tr>
<tr>
<td>Orgasm/Ejaculation</td>
<td>Item #11 – Item #13</td>
</tr>
<tr>
<td>Total CSFQ Score</td>
<td>Item #1 – Item #14</td>
</tr>
</tbody>
</table>

# The Arizona Sexual Experiences Scale (ASEX)

For each item, please indicate your **OVERALL** level during the past **WEEK**, including **TODAY**.

1. **How strong is your sex drive?**
   1. Extremely strong
   2. Very strong
   3. Somewhat strong
   4. Somewhat weak
   5. Very weak
   6. Absent

2. **How easily are you sexually aroused?**
   1. Extremely easily
   2. Very easily
   3. Somewhat easily
   4. Somewhat difficult
   5. Very difficult
   6. Never

3. **(For men only) Can you easily get and keep an erection?**
   1. Extremely easily
   2. Very easily
   3. Somewhat easily
   4. Somewhat difficult
   5. Very difficult
   6. Never

4. **(For women only) How easily does your vagina become moist?**
   1. Extremely easily
   2. Very easily
   3. Somewhat easily
   4. Somewhat difficult
   5. Very difficult
   6. Never

5. **How easily can you reach orgasm?**
   1. Extremely easily
   2. Very easily
   3. Somewhat easily
   4. Somewhat difficult
   5. Very difficult
   6. Never

6. **Are your orgasms satisfying?**
   1. Extremely satisfying
   2. Very satisfying
   3. Somewhat satisfying
   4. Somewhat unsatisfying
   5. Very unsatisfying
   6. Never achieve orgasm

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Nonpharmacological Management Strategies for ADISD

**Drug Holiday**
- With some antidepressant medications, brief so-called “drug holidays” may allow for significant improvement in sexual functioning without a significant return of depressive symptoms

**Adaptation**
- In an open-label study of 1022 outpatients with MDD being treated with antidepressant medication, spontaneous total remission of sexual dysfunction was reported in 9.7% of patients at the end of 6 months of treatment and 1.7% within the first 3 months

**Lifestyle Modification: Exercise**
- One study of 52 women experiencing antidepressant drug-induced sexual side effects found that exercise immediately prior to sexual activity significantly improved sexual desire and, for women with sexual dysfunction at baseline, global sexual function
- A regimen of 30 minutes of vigorous exercise 3 times per week was recommended (immediately prior to sexual activity for maximal benefit)

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Pharmacologic Management Strategies for ADISD

Dose Reduction

- Dose reduction, if feasible, can be considered because ADISD can be dose-dependent with some SSRIs.\(^1,2\)
- However, dose reduction is not commonly used, as it is difficult to achieve a dose reduction that relieves sexual side effects without also allowing the return of depressive symptoms\(^3\)

Medication Switching

- Dopaminergic antidepressant medications have demonstrated smaller impact on sexual function than SSRIs in randomized clinical trials\(^4-6\)
- Switching from an SSRI to a dopaminergic antidepressant agent to reduce ADISD may be acceptable, but has not been evaluated in clinical trials
- Data evaluating the addition of a dopaminergic antidepressant to help ADISD caused by an SSRI is contradictory, and further studies are needed to conclusively evaluate the efficacy of this strategy\(^7-11\)

References:
Pharmacologic Management Strategies for ADISD

Management Strategies

- **Treatment with PDE-5 inhibitors in anticipation of sexual intercourse**
  - A significant improvement in sexual function was observed following antidote treatment with PDE-5 inhibitors versus placebo in US double-blind studies in both men and women with ADISD1-4

- **Supplement or substitute SSRI regimen with anxiolytics with 5-HT1A activity**
  - Anxiolytics with partial agonist activity at 5-HT1A activity have demonstrated efficacy in a limited number of placebo-controlled trials, and demonstrated variability of their respective efficacies based on individual drugs and between sexes5-7

- **Treatment with testosterone gel**
  - When compared to placebo, depressed men treated with testosterone gel had significant improvements in erectile function8

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5-HTxx, serotonin receptor subtype XX: PDE-5, phosphodiesterase type 5.

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