ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

Jon-Paul Khoo

Objectives

- To appreciate the relationship between major depressive disorder, its treatment and sexual dysfunction
- To review the assessment of sexual function
- An approach to the clinical management of antidepressant-induced sexual dysfunction

What is sexual dysfunction, how frequently does it occur and how do we evaluate it?

Sexual dysfunction (SD)

- Dysfunction in phases of the sexual response cycle
  - Desire: low/absent
  - Arousal: erectile dysfunction/reduced vaginal lubrication
  - Orgasm: delayed/anorgasmia/spontaneous; ejaculatory disorder
  - Pain and sensory changes
  - (What about too much sexual function?)

SD in the general population

US epidemiological data, 18-59yo

Women 30%

- 32% lack interest
- 26% inability to orgasm
- 23% absent pleasure
- 21% lubrication problems
- 1.5% dyspareunia
- 12% performance anxiety

Men 45%

- 31% premature ejaculation
- 18% performance anxiety
- 15% lack interest
- 10% erectile dysfunction
- 8% inability to orgasm
- 8% absent pleasure

Assessment of sexual functioning

- Assess premorbid/baseline sexual functioning
- Consider psychiatric and psychological issues that might contribute to sexual difficulties
- Consider physical health comorbidities and concomitant medication
- Consider alcohol and illicit substance usage
- Assess intra-morbid sexual functioning in current (and past) depressive episodes
- Current psychosocial context
- Personal importance of sexual activity and current relationship impact of SD
In untreated depressed patients (MDD, dysthymia, recurrent brief depression), SD occurs in up to 50% (40-65%) vs 24% controls (1,2).

MDD-induced SD:
- Low interest: 40% men and >50% women
- Arousal dysfunction 40-50%
- Orgasm difficulty 15-20%

Greater depressive severity, duration and recurrence predicts more SD (3,4).

Antidepressant treatment improves SD in those with depression-induced SD (5,6): NB attribution bias.

The relationship between MDD and SD:
- Depression accounts for 50-70% of the increased risk for SD.
- SD increases the risk for depression by 130-210%.

SD increases the risk for depression by 130-210%.

Antidepressant-induced SD:
- Worsening of pre-existing SD or new-onset SD.
- Only 1/2 will disclose.
- Spontaneous disclosure 14% vs 60% on questionnaire.
- AISD in women:
  - 27-65% more SD than men.
  - More interested in orgasm dysfunction than men.
  - Less likely to discuss SD and more likely to attribute SD to other causes.
- AISD in men:
  - 26-57%
  - More severe SD than women
  - More arousal dysfunction than women.

Consequences of AISD:
- Non-adherence
- SD is one of the most common side-effects leading to treatment discontinuation.
- 42% of men and 13% of women discontinue antidepressants due to concerns about SD.
- Depressive relapse
- Reduced quality of life
- Tolerance for AISD reduces with increasing time in recovery.
Antidepressant-induced SD ~80%
MDD-induced SD ~50%
General population background rate of SD ~25%

Meta-analysis of AISD

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Highest Risk</th>
<th>Middle Risk</th>
<th>Lowest Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>76%</td>
<td></td>
<td></td>
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<tr>
<td>Fluoxetine</td>
<td>70%</td>
<td></td>
<td></td>
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<tr>
<td>Venlafaxine</td>
<td>79%</td>
<td></td>
<td></td>
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<tr>
<td>Mirtazapine</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>71%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapoxetine</td>
<td>39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agomelatine</td>
<td>4%</td>
<td></td>
<td></td>
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<tr>
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<td>Venlafaxine</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>26%</td>
<td></td>
<td></td>
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<tr>
<td>Vortioxetine^</td>
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</table>

* Escitalopram has a placebo level of desire dysfunction.
** Mirtazapine has only desire dysfunction.
*** Bupropion has only arousal dysfunction.
^ Not part of the study; referred to another database/baseline SD.

HIGHEST RISK
Sertraline 80%
Imipramine 76%
Mirtazapine 64%
Venlafaxine 79%
Fluoxetine 70%
Duloxetine 39%
Bupropion 10%
Citalopram 37%
Dapoxetine 37%
Agomelatine 4%
Paroxetine 71%
Sertraline 80%
Imipramine 44%
Mirtazapine 24%
Venlafaxine 66%
Duloxetine 42%
Bepridil 10%
Clonazepam 79%
Doxepin 42%
Mirtazapine 24%
Reboxetine 10%
Pimozide 2%
Reboxetine 10%
Buspirone 37%
Agomelatine 4%

Important observations regarding AISD

- Minimal clinical differences in AD efficacy, but differences in onset, adverse events (AISD) and rates of discontinuation (1)
- Intra- and inter-class variation
- Dose-related
- Usually occurs early in treatment
- Typically persists throughout treatment
- Typically resolves on discontinuation of the offending treatment

The clinical management of AISD

- Assessment of sexual functioning prior to treatment
- (A priori) prescription of low SD risk treatment in those already suffering SD or very concerned about developing it
- Validated tools for qualifying/quantifying SD

Validated depression-specific SD questionnaires

<table>
<thead>
<tr>
<th>Scale</th>
<th>No. of Items</th>
<th>Method of Administration</th>
<th>Time required (mins)</th>
<th>Gender</th>
<th>Versions</th>
<th>Comments</th>
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<tr>
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<td>Clinician</td>
<td>5-10</td>
<td>Yes</td>
<td>Yes</td>
<td>Simple design</td>
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<td>CSFQ</td>
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<td>Self</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Has long version</td>
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<tr>
<td>PRSexDQ or SALSEX</td>
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<td>Clinician</td>
<td>5-10</td>
<td>Yes</td>
<td>Yes</td>
<td>Specific to AISD</td>
</tr>
<tr>
<td>SexFX</td>
<td>11</td>
<td>Clinician/self</td>
<td>5-10</td>
<td>Yes</td>
<td>Yes</td>
<td>Specific to AISD</td>
</tr>
</tbody>
</table>

ASEX: Arizona Sexual Experiences Scale
CSFQ: Changes in Sexual Functioning Questionnaire
PRSexDQ: Psychotropic-Related Sexual Dysfunction Questionnaire
SALSEX: Sexual Arousal and Libido Scale
SexFX: Sex Effects Scale

Direct enquiry

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Footnotes:
### Clinical Management of AISD

- **Assessment of sexual functioning prior to treatment**
  - A priori prescription of low SD risk treatment in those already suffering SD or very concerned about developing it
  - Validated tools for qualifying/quantifying SD
  - Rule out causes unrelated to depression or ADT
    - Physical/medication/substance/psychological/social
    - Target baseline
    - Explanation and education
  - Specific strategies
    - Behavioral
    - Pharmacological

### Behavioural management of AISD

- **Exercise**
  - 3/52 moderate strength training and aerobic exercise 30/60 before sexual activity improved sexual desire and function in women (1)

- **Scheduling sexual activity**
  - May increase orgasm function in women (2)

- **Changing sexual technique**
  - Vibratory stimulation

- **Psychotherapy**
  - There are no RCTs of behavioural strategies

### Pharmacological management of AISD

- **Watchful waiting**
  - Waiting for tolerance
    - Adaptation occurs in ~5-10% over 4-6/12 (1-3)
  - Where patient is
    - Experiencing good antidepressant efficacy;
    - Considered to be on short-term treatment; and
    - Accepting AISD as a "price worth paying"
  - Very ineffective: the vast majority will have no improvement over 6/12 (4) therefore such should not be expected

- **Dose reduction**
  - AISD appears to be dose-related
  - Lowest therapeutic treatment dose ("dose inflation")
  - Strategies usually recommend a 50% dose reduction
  - Where
    - Antidepressant has a flat dose-response curve
    - Patient is experiencing good antidepressant efficacy
    - Difficulties include reducing SD at the cost of symptom control, discontinuation and nonadherence

### Scheduling

- Schedule sexual activity at trough serum level
  - Where
    - Antidepressant has short half-life (eg sertraline, paroxetine, clomipramine)
    - Limited benefit for the majority and reduces spontaneity

### Dose reduction

- Where
  - Antidepressant has flat dose-response curve
  - Patient is experiencing good antidepressant efficacy
  - Difficulties include reducing SD at the cost of symptom control, discontinuation and nonadherence

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Drug holiday

- Temporary reduction or suspension of antidepressant
- Most methods use a brief abstinence strategy
- E.g. cease other dose on Thursday - restart Sunday (1): improved sexual function 50% of the time on weekends without mood deterioration
- Where
  - Patient is experiencing good efficacy
  - Antidepressant has a shorter half-life
  - Sexual activity is relatively infrequent
- Overall, not very effective
- Difficulties include discontinuation, relapse, reduced spontaneity, conflicting messages about adherence
- ONLY recommended if in full remission and SD impairment is so severe that the sufferer would otherwise cease treatment

Switch

- Change antidepressant to a lower SD risk alternative
- Agomelatine, vortioxetine, bupropion, moclobemide, mirtazapine
- SSRIs to SNRIs probably won’t work, though SSRIs to SNRIs might
- Where
  - Suboptimal efficacy
  - Treatment refusal due to SD
  - High likelihood of alleviating SD
- Difficulties include other side-effects and risks with new treatment, potential loss of efficacy, potential crossover
- Single RCT
  - Vortioxetine > Escitalopram in improving AISD in those taking SSRIs (citalopram, paroxetine, sertraline) whilst maintaining efficacy (1)

Augmentation “antidote”

- Adding a second treatment to improve sexual functioning
- Pulse vs regular?
- Where
  - Patient is experiencing good efficacy
  - Patient accepting additional medication
- Difficulties include drug-drug interactions, side-effect synergy, increased cost, the complexity of treatment regimen might reduce adherence, and, in Australia, none are indicated or reimbursed
- Some adjunctive therapies might also enhance antidepressant response (e.g., bupropion, mirtazapine, agomelatine)
- Limited database

Which ‘antidotes’?

- Cochrane database review 2013 (1)
- PDE inhibitors
  - Sildenafil (3 studies (2–4)): Men and women reported improved sexual function and satisfaction
  - Most favoured strategy for men with erectile dysfunction
  - Tadalafil (2 studies (5–6)): ED due to antidepressants
  - Vardenafil (3 studies (7–9): placebo with no deterioration in mood
  - Bupropion 150mg OD (2 studies (10–11): placebo
  - ‘The most promising approach in studies so far’ in women with AISD

Other ‘antidotes’

- Controlled data
- Case reports/series
- Complimentary therapies with controlled data

- Mirtazapine
- Aripiprazole
- Testosterone
**Other ‘antidotes’**

- Controlled data
- Case reports/series
- Complimentary therapies with controlled data

- Buspirone
- Cyproheptadine/loratadine
- Yohimbine
- Dopamine agonists: amantadine, bromocriptine and levodopa/psychostimulants
- Anticholinergics

- Maca root
- Saffron
- SAMe

**Take home messages**

**Objective 1: take home message**

- The relationship between major depressive disorder, its treatment and sexual dysfunction
  - AISD includes both aggravations of existing SD and new onset SD
  - In the depressed individual on treatment who experiences SD, the cause may be due to the underlying depressive morbidity, to the treatment, or to some pre-morbid background physiological, illness, substance or psychosocial variable

**Objective 2: take home message**

- The assessment of sexual function
  - Premorbid/baseline sexual functioning
  - Psychiatric and psychological issues associated with SD
  - Physical health comorbidities and concomitant medication
  - Alcohol and illicit substance usage
  - Intra-morbid sexual functioning in current (and past) depressive episodes
  - Current psychosocial context
  - Personal importance of sexual activity and current relationship impact of SD

**Objective 3: take home message**

- The clinical management of AISD
  - Rule out causes unrelated to depression or the antidepressant
  - If existing SD, or very concerned about developing it, use a first-line antidepressant with a more favourable SD profile
  - Bupropion, agomelatine, vortioxetine, mirtazapine and moclobemide
  - For AISD where a change in treatment is not deemed reasonable, adding an ‘antidote’ is the most effective strategy
  - Also consider watchful waiting, scheduling sexual activity, dose reduction, drug hold, holiday, and/or behavioural and/or complimentary intervention.
  - For AISD where a treatment change can be considered, switch to an agent with lower SD risk (as above)