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%	Men 45%
32% lack interest	31% premature ejaculation
26% inability to orgasm	18% performance anxiety
23% absent pleasure	15% lack interest
21% lubrication problems	10% erectile dysfunction
15% dyspareunia	8% inability to orgasm
12% performance anxiety	8% absent pleasure

Laumann E et al. JAMA. 1999;281:537-544.
Numberg H. Drugs Today 2008;44(2):147-168.

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

Sexual dysfunction in MDD

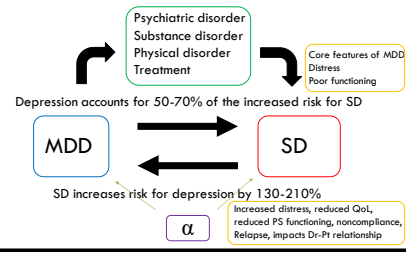
Sexual dysfunction and MDD

- 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 (2)
  - 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

1. Angst J. Int Clin Psychopharmacol. 1998 Jul;13 Suppl 6:S1-4. 2. Kennedy S et al. J Affect Disord. 1999 Dec;56(2-3):201-8.
3. Bonierbale M et al. Curr Med Res Opin. 2003;19:114-124. 4. Cyranowski J et al. Arch Sex Behav. 2004;33:539-48.
5. Baldwin D et al. J Psychopharmacol. 2006;20:91–6. 6. Baldwin D et al. Hum Psychopharm Clin. 2008;23:527–32.

The relationship between MDD and SD

Clayton A et al. J Sex Med. 2009 May;6(5):1200-11. Kennedy S et al. J Clin Psychopharmacol 2009;29(2):157-64. Gregorian R et al. Ann Pharmacother. 2002;36(10):1577-89. Rosenberg K et al. J Sex Marital Ther. 2003;29(4):289-96.



Antidepressant-induced SD

Antidepressant-induced SD

- Worsening of pre-existing SD or new-onset SD
- Only ¼ will disclose
  - Spontaneous disclosure 14% vs 60% on questionnaire
- AISD in women
  - 27-65%
  - More SD than men
  - More interest and 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

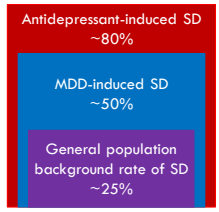
Serretti A and Chiesa A. J Clin Psychopharmacol. 2009;29(3):259-266. Montejo A et al. J Clin Psychiatry. 2001;62(suppl3):10-21.
Williams V et al. J Clin Psychiatry. 2006;67:204–10. Williams V et al. J Psychopharmacol. 2010;24:489–96. Reichenpfader U et al. Drug Safety 2014; 37:19–31.

Consequences of AISD

- Non-adherence
  - SD is one of the most common side-effects leading to treatment discontinuation
  - 42% of men and 15% women discontinue antidepressants due to concerns about SD
- Depressive relapse
- Reduced quality of life
- Tolerance for AISD reduces with increasing time in recovery

Rosenberg K et al. J Sex Marital Ther 2003;29:289-296. van Geffen E et al. Eur J Clin Pharmacol. 2007;63:1193-1199.
Gregorian R et al. Ann Pharmacother. 2002;36(10):1577-89. Clayton A et al. J Sex Med. 2009 May;6(5):1200-11.Reichenpfader U et al. Drug Safety 2014. 37;1:19-31.

SD: attributable fractions



Meta-analysis of AISD

Serretti A and Chelsa A. J Clin Psychopharmacol 2009;29(3):259-266.

SD occurs across all phases with all antidepressants, except where exceptions are noted
Mean total placebo rate of SD was14.2%

>placebo		≤placebo
HIGHEST RISK	MIDDLE RISK	LOWEST RISK
Sertraline 80%	Imipramine 44%	Mirtazapine 24%**
Venlafaxine 80%	Phenelzine 42%	Bupropion 10%***
Citalopram 79%	Duloxetine 42%	Moclobemide 4%
Paroxetine 71%	Escitalopram 37%*	Agomelatine 4%
Fluoxetine 70%	Fluvoxamine 26%	Vortioxetine^

* Escitalopram has a placebo level of desire dysfunction
** Mirtazapine has only desire dysfunction
*** Bupropion has only arousal dysfunction
^ Not part of this study, but −placebo (with and without baseline SD) a pooled analysis of 7 RCTs

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

1. Gartlehner G et al. Ann Intern med 2011;155(11):772-85.

The clinical management of AISD

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

Scale	No. of items	Method of administration	Time required (mins)	Gender Versions?	Comments
ASEX	5	Clinician	5-10	Yes	Simple design
CSFQ-short	14	Self	5	Yes	Has long version
PRSexDQ or SALSEX	7	Clinician	5	Yes	Specific to AISD
SexFX	11	Clinician/self	5-10	Yes	Specific to AISD
Direct enquiry					

ASEX: Arizona Sexual Experiences Scale McGahuey C et al. J Sex Marital Ther 2000;26:25-40.
CSFQ: Changes in Sexual Functioning Questionnaire Clayton A et al. Psychopharmacol Bull 1997;33:731-745.
PRSexDQ: Psychotropic-related Sexual Dysfunction Questionnaire Montejo A et al. J Clin Psychiatry 2001;62:10-21.
SexFX: Sex Effects Scale Kennedy S et al. J Clin Psychiatry 2000;61(4):276-281.

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
  - Behavioural
  - 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

1. Lorenz T et al. Ann Behav Med 2012;43(3):352-61.
2. Lorenz T et al. Depress Anxiety 2014;31(3):188-95.

Pharmacological management of AISD

- Watchful waiting
- Scheduling sexual activity
- Dose reduction
- Drug holiday
- Switch
- Augment

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

1. Ashton A et al. J Clin Psychiatry 1998;59(3):112-5. 2. Montejo A et al. J Clin Psychiatry 2001;61(suppl3):10-21. 3. Clayton A et al. J Clin Psychiatry 2006 (suppl6):33-7.
4. Montejo-Gonzalez A et al. J Sex marital Ther 1997;23(3):176-94.

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

- 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

Drug holiday

- Temporary reduction or suspension of antidepressant
- Most methods use a brief abstinence strategy
  - E.g. cease after 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 recommend if in full remission and SD impairment is so severe that the sufferer would otherwise cease treatment

1. Montejo A et al. J Clin Psychiatry 2001;61(suppl3):10-21.

Switch

- Change antidepressant to a lower SD risk alternative
  - Agomelatine, vortioxetine, bupropion, moclobemide, mirtazapine
  - SSRI to SSRI probably wont work, though SSRI to SNRI might
- Where
  - Suboptimal efficacy
  - Treatment refusal due to SD
- High likelihood of alleviating AISD
- 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 SSRI (citalopram, paroxetine, sertraline) whilst maintaining efficacy (1)

1. Clayton A et al. Expert Opin Drug Saf 2014;13(10):1361-1374.

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 (eg 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
      - Women had reduced orgasm disturbance
    - Tadalafil (2 studies (5-6))
      - ED due to antidepressants
  - Bupropion
    - 150mg BD (3 studies (7-9)) > placebo with no deterioration in mood
    - 150mg OD (2 studies (10-11)) = placebo
    - 'The most promising approach in studies so far' in women with AISD

1. Taylor M et al. Cochrane Database of Systematic Reviews 2013, 5. Art. No.: CD003282. 2. Nurnberg H et al. JAMA 2008;300(4):395-404. 3. Nurnberg H et al. JAMA 2003;289(1):56-64.
4. Fava M et al. J Clin Psychiatry 2006;67(2):240-6. 5. Srilanyagle Y et al. Urology 2011;78(5):1137-41. 6. Segraves R et al. J Clin Psychopharmacol 2007;27(1):62-66.
7. Gitlin M et al. J Sex Marital Ther 2002 ; 28 : 131 – 138. 8. Horden M . Depression 1994 ; 12 :109 – 112. 9. Safarinejad M. BJU Int 2010 ; 106 : 840 – 847.
10. Safarinejad M. J Psychopharmacol 2011 ;25 : 370 – 378. 11. Thase M. J Clin Psychiatry 2005 ; 66 : 974 – 981.

Other 'antidotes'

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

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
- Cyproheptdine/loratadine
- Yohimbine
- Dopamine agonists: amantadine, bromocriptine and psychostimulants
- Anticholinergics

NOT RECOMMENDED

Other 'antidotes'

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