Sexual dysfunction , psychiatric disorder and psychiatric drugs

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Teaching Points

- Many psychiatric drugs are associated with sexual dysfunction
- Drug-induced sexual dysfunction may be an unspoken cause of treatment non-compliance
- In most cases, sexual side effects can be medically managed

Abbreviated Outline

A. Co-morbidity of sexual dysfunction and psychiatric disorders
B. Need for direct inquiry
C. SSRIs and sexual dysfunction
D. Benzodiazepines and SD
E. Lithium and SD
F. Anticonvulsants and SD
G. Antipsychotics and SD

Pre-Lecture Exam Question 1

- Which antidepressant appears to have a very low incidence of drug-induced sexual dysfunction?
- 1. paroxetine
- 2. fluoxetine
- 3. serteraline
- 4. bupropion

Question 2

- Which drug has been shown in double-blind trials to reverse SSRI-induced sexual dysfunction?
- 1. mirtazapine
- 2. yohimbine
- 3. granisetron
- 4. sildenafil

Question 3

- Which antipsychotic appears to have the lowest incidence of drug-induced sexual dysfunction?
- 1.olanzapine
- 2.risperidone
- 3.thioridazine
- 4. haloperidol

Question 4

- True or false
- Case reports suggest that sildenafil may be helpful in reversing antipsychotic-induced sexual dysfunction.
- True
- False

Question 5

- Studies indicate that which of the following may be successful in reversing SSRI-induced sexual dysfunction.
- 1. 15 mg buspirone
- 2. 60mg buspirone
- 3. 50mg amantadine
- 4. 15mg yohimbine

Sexual Co-Morbidity

- Major depressive disorder
- Obsessive compulsive disorder
- Posttraumatic stress disorder
- Anorexia nervosa
- Schizophrenia
- Social phobia
- Panic disorder

Lindal & Steffansonn, SPPE,1993;Wiederman et al, IJED,1996;Kennedy et al, JAD,1999;Kockott et al, CP,1996;Minnen & Kampman, SRT,2000;Zemishlany & Weizman ,APM 2008; Malik JCP 2011; Bodinger et al, JCP,2002

History

- 1. 1971 :first report of female orgasm delay on monoamine oxidase inhibitors
- 2. 1985 :double-blind study indicated high rate of orgasm/libido problems on both phenelzine and imipramine
- 2. 1987 :Double-blind study indicated orgasm problems on benzodiazepines
- 3. 1976-Reports of orgasm delay on antipsychotics

Harrison et al, PB, 1985; Monteiro et al, BJP, 1987; Segraves et al,JCP, 2000

Sex Differences

- PDR initially only indicated that sexual problems occurred in males
- Early clinical reports indicated that sexual problems more common in men than women on SSRIs
- Recent reports indicate somewhat similar rates of SSRI-induced sexual dysfunction in both sexes

- Nkanginieme & Segraves, 2001

Need for Physician Inquiry

- Only about 1/4 of patients experiencing drug-induced sexual dysfunction will report this to their physician unless directly asked

Problem with patient self-report

- Studies in multiple countries have compared estimates of incidence of drug-induced SD obtained by patient spontaneous self-report vs direct inquiry by physician. Direct inquiry by MD reveals more SD than patient spontaneous report.
    - 96% vs 33%
    - 58% vs 14%
    - 80% vs 15%
    - 41% vs 6%

Monteiro et al, BJP, 1987; Montejo-Gonzales et al, JSMT, 1997;Montejo, JCP,2001;Landen et al, JCP,2005

Evidence Concerning Rates of Drug-induced Sexual Dysfunction

- 1.Controlled trials (usually financed by pharmaceutical companies)
- 2. Large clinical series
- 3. Case reports

Controlled Studies with Direct Inquiry

Studies have found minimal consistent differences in incidence of treatment emergent sexual dysfunction between SSRIS and SNRIs or within classes of antidepressants

Possible exception is that paroxetine may have higher incidence of drug-induced sexual dysfunction than other SSRIs or SNRIs

Labbate, APM 2008 ; Feiger et al, JCP,1996; Ferguson et al, JCP, 2001; Segraves et al, JCP,200; Kavoussi et al, JCP, 2001, Delgado et al, JCP,2005; Landen et al, JCP, 2005

- Large Clinical Series

Observation in Clinical Settings

- 5 year open label prospective study of treatment emergent sexual dysfunction
- 1022 patients (610 women, 412 men)
- Average age 39.8 years
- Standard questionnaire used at multiple clinical sites in Spain

Montejo et al, J Clin Psychiatry,2001

Sexual Side Effect Profile

• Citalopram (Celexa)	73%
• Paroxetine (Paxil)	71%
• Venlafaxine (Effexor CR)	67%
Sertraline (Zoloft)	63%
• Fluoxetine (Prozac)	58%
• Mirtazapine (Remeron)	24%
• Nefazodone (Serzone)	8%

Montejo et al, JCP, 2001

Additional Observations

- Spontaneous remission at 6 months 10%
- Most common problems-delayed orgasm or ejaculation and decreased libido

Montejo et al, JCP, 2001

General Practice Setting

- Multicenter cross sectional study
- Study of 6297 patients in 1101 sites
- Standard Questionnaire given to patients on antidepressants
- Average age 43
- 72% female
- 70% married

Clayton et al, JCP, 2002

General Practice Study

% Experiencing Sexual Dysfunction

- Paroxetine (Paxil) 43%
- Mirtazapine (Remeron) 41%
- Venlafaxine (EffexorCR) 40%
- Sertraline (Zoloft) 40%
- Citalopram (Celexa) 37%
- Fluoxetine (Prozac) 36%
- Nefazodone (Serzone) 28%
- Bupropion (WellbutrinSR) 25%

Clayton et al, 2002

Subgroup Analysis

- Bupropion (Wellbutrin) 6.7%
- Sertraline (Zoloft) 26%
- Paroxetine (Paxil) 25.8%
- Fluoxetine (Prozac) 22.9%
- Citalopram (Celexa) 30%
- Venlafaxine (Effexor) 30%

Time Course

- By day seven, patients on sertraline had more orgasm delay than placebo
- By day 42, less desire disorder on bupropion than placebo or sertraline
- By day 56, more arousal disorder on sertraline than bupropion

Croft et al, JCP.1999

Summary Statement

- Minimal differences between SSRIs and SNRIs or within classes
- Bupropion and nefazodone both found to have very low incidence of SD
- Mirtazapine may have a lower incidecnee of sexual dysfunction

Schweitzer et al, ANZJP 2009; Serretti et al, JCP, 2009

Case Reports

- There have been case reports of spontaneous orgasm with most of the SSRIS
- There have also been reports of both transient and persistent genital anesthesia with SSRIs
- Bolton et al , JSMT,2006; Virit & Savas, JCP 2008

Solutions to Anorgasmia secondary to serotonergic drugs

- Dose reduction
- Switch antidepressant
- Drug holiday
- Antidotes
- Wait for adaptation

Knangienime & Segraves, 2001
Segraves & Balon, Sexual Pharmacology, 2003

Drug Substitution

- Bupropion (Wellbutrin)*
- Nefazodone (Serzone) *

* Controlled studies

Antidotes-Case Reports

• Yohimbine	1-2 tablets PRN
• Cyproheptadine	4-8 mg PRN
• Amantadine	100-400mg PRN
• Dextroamphetamine	20mg PRN
• Gingko bilboa	120mg qd
• Mirtazapine	15-45mg qd
• Bethanechol	10-50mg PRN
• Methyphenidate	5-40mg qd
• Neostigmine	50-200 mg PRN
• Pemoline	18.75-75mg qd
• Pregabalin	75-150 mg qd

Zajecka, JCP,2001; Oulis et al, JCP 2008

- Controlled studies of antidotes

Antidotes

- Double-blind studies have established that buspirone 60 mg daily will reverse serotonergic antidepressant -induced sexual dysfunction in both sexes
- Failure reported at lower doses

Landen et al, 1999; Michelson et al, AJP, 1998

Sildenafil

- A double-blind multi-site study found that 50-100mg sildenafil PRN reversed SSRI-induced sexual dysfunction in men
- Subsequent analysis indicates effect mainly restricted to subgroup with ED
- Multi-site study found that sildenafil reversed SSRI-induced sexual dysfunction in women

Nurnberg et al, JAMA,2003: Nurnberg et al, JAMA 2008McGill, 2002

Antidote Studies

- 1. Mirtazapine, yohimbine, placebo ineffective
- 2. Ephedrine ineffective
- 3. 150mg bupropion inefffective
- 4. 300mg bupropion effective
- 5. 20mg buspirone & 50mg amantadine ineffective
- 6. 20-60mg buspirone effective
- 7. Gransiteron (5HT3 antagonist) ineffective

Michelson et al,JPR,2002 ; Meston et al, JSMT,2004 ;DeBatista et al, JCP,2005 ; Masand et al, AJP 2001 ;. Clayton et al, JCP, 2001; Clayton et al, JCP. 2004 ;Michelson et al, AJP, 2000 ; Landen et al, JCP, 1999 ; Nelson et al, JCP,2001; Ozmenler et al, HP 2008

Adaptation

- Spontaneous remission of SSRI-induced sexual dysfunction at 6 months occurs in 10-30% of patients

- Haberfellner & Rittmansberger, Pharmacopsychiatry 2004

Benzodiazepines

- Numerous case reports of anorgasmia on benzodiazepines
- One double-blind, placebo-controlled study
- Found dose response delay in orgasm by diazepam

Riley & Riley, SMT,1986;Fossey & Hammer, 1994;
Labbatte APM, 2008

Lithium and Sexual Dysfunction

- Case reports and clinical series suggest that lithium may impair libido and erectile function
- It is difficult to discriminate between a drug side effect, phase of the disease, and a treatment effect

Vinarova et al , 1976;Aizenberg et al, 1996;Labbatte, APM, 2008;

Anticonvulsants

- Case reports of anorgasmia on gabapentin, carbamazepine ,topiramate, oxcarbazepine
- Case reports of decreased libido, impaired arousal and anorgasmia on valproate monotherapy
- Case reports of erectile dysfunction with topiramate

Schnech et al, JCP,2002; Husain et al, SMJ,2002; Vivaldi et al, CNN 2011;Newman et al, Neurol 2005; Calabro et al, 2010;Lasaosa et al, Neurol 2008

Anticonvulsants

- Data from clinical series suggest that sexual dysfunction is less common with lamotrigine and oxycarbazepine than with carbamazepine and phenytoin

Rattya, Neurology, 2001; Svalheim et al, EB 2009; Labbatte APM,2008

- ANTIPSYCHOTIC DRUGS

Antipsychotic Drugs and Sexual Dysfunction

- In general evidence suggests that newer prolactin sparing antipsychotics are less likely to cause sexual dysfunction that older agents causing prolactin elevation
- However, evidence is not consistent
- Difficulty separating effect of disease from effect of treatment
- Problem of under reporting
- Wirshing et al, Psych Cl NA 2003; Serretti & Chiesa, IJP 2011

Report of SD on Antipsychotics

- Studies in multiple countries have found dramatic under reporting of sexual side effects in patients taking antipsychotic drugs.

- 10% vs 60%
- 15% vs 80%
- Knegtering et al, 2002; Montejo et al, 1998

- Most evidence consists of case reports and clinical series.

Early Case Report

- Sexual interviews, n=87
- Difficulty with erections in 44% of patients on thioridazine (Mellaril) versus 19% on other antipsychotics
- Ejaculatory problems in 49%

Kotin et al, 1975

Antipsychotics and SD

- Open label study of 106 outpatients

• Risperidone (Risperdal)	82%	(5.5mg/d)
• Haloperidol (Haldol)	25%	(5.8mg/d)
• Olanzapine (Zyprexa)	2%	(9.4 mg/d)
• Clozapine (Clozaril)	0%	(115mg.d)

Montejo et al, 1998 APA NR

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- Various open label studies by Knegtering of patients with schizophrenia monitoring sexual side effects by direct inquiry have found higher incidence of sexual side effects with prolactin elevating antipsychotics

EIRE Study

- Multi-site cross sectional study of patients with schizophrenia on either haloperidol, risperidone, olanzapine or quetiapine
- UKU rating scale
- N=636
- 61% male
- 71% single
- Average age 35

Bobes et al, JSMT,2002

Frequency of Sexual Side Effects

- Haloperidol (Haldol) 38%
- Risperidone (Risperdal) 43%
- Olanzapine (Zyprexa) 35%
- Quetiapine (Seroquel) 18%

Bobes et al, JSMT,2003

Other Findings

- Most common problem erectile dysfunction and loss of sexual desire in men
- In women, lost of sexual desire most common
- Frequency of side effects appeared to be dose related

Bobes et al, JSMT,2003

Intercontinental Schizophrenia Outpatient Health Outcome Study

570 patients started on clozapine, olanzapine, quetiapine, riperidone, haloperidol

Sexual dysfunction assessed at baseline, 3 and 6 months

Less sexual dysfunction on olanzapine

Bitter et al, ICP, 2005

Side Effect Burden

- Patient ratings of burden

- Akinesia 40%
- Weight gain 37%
- Anticholinergic 33%
- Sexual problems 31%

- Weiden & Mitler, JPP,2001

Bottom Line

Risperidone (Risperdal) and tradtional antipsychotics probably have highest incidence of sexual side effects

- Olanzapine (Zyprexa)and quetiapine) Seroquel) probably have the lowest incidence of sexual side effects
- Data available suggests that Abilify (aripiprazole) and ziprasidone (Geodon) have minimal sexual side effects

Management of Sexual Side Effects

- 1. Dose reduction
- 2. Antidotes
- 3. Switch drugs

Antidotes

- 1.Sildenafil reverses ED
- 2. Case report so success using amantadine (Symmetrel), bromocriptine and cabergoline (Dostinex) to restore libido and orgasm
- 3. No success with selegiline (Eldepryl)

Salerian et al, !999: Valevski et al, 1998; Tollin, 2000;
Benatov et al, 1999, Kodesh et al, 2003; Aviv etal. JCP,2004

Switching Drugs

1. Switch to quetiapine or aripiprazole from risperidone

2. Switch to olanzapine from risperidone

3. Switch to aripriprazole from ziprasidone

1.Keller & Mongibe, NS, 2002; 2. Ahi et al, ANYAS,2004; 3. Angelesc & Wolf, JCP, 2004;Chen et al, PCN 2011

Mechanism

- Prolactin elevation interfering with dopamine synthesis
- Alpha-1 blockade
- Direct effect D2 blockade

Segraves & Balon, 2002

Priapism

- 1.Risperidone (Risperdal)
- 2.Ziprasidone (Geodon)
- 3.Aripiprazole (Abilify)
- 4.Quetiapine (Seroquel)
- 5.Olanzapine (Zyprexa)
- 6.Clozapine (Clozaril)

1,5,6, Reeves & Mack, P, 2003; 2. Reeves & Kimble, JCP, 2003
3. Nagin & Murphy, JAACAp, 2005; Daval & Rukstais, 2005

Summary

- Numerous psychiatric drugs affect human sexuality
- Sexual side effects may be cause of treatment noncompliance
- Sexual side effects may be reversible

Post-Lecture Exam Question 1

- Which antidepressants appears to have a very low incidence of drug-induced sexual dysfunction?
- 1. paroxetine
- 2. fluoxetine
- 3. sertraline
- 4. bupropion

Question 2

- Which drug has been shown in double-blind trials to reverse SSRI-induced sexual dysfunction?
- 1. mirtazapine
- 2. yohimbine
- 3. granisteron
- 4. sildenafil

Question 3

- Which antipsychotic appears to have the lowest incidence of drug-induced sexual dysfunction?
- 1.aripiprazole
- 2.risperidone
- 3.thioridazine
- 4. haloperidol

Question 4

- True or false
- Case reports suggest that sidlenafil may be helpful in reversing antipsychotic-induced sexual dysfunction.
- True
- False

Question 5

- Studies indicate that which of the following may be successful in reversing SSRI-induced sexual dysfunction.
- 1. 15 mg buspirone
- 2. 60mg buspirone
- 3. 50mg amantadine
- 4. 15mg yohimbine

Answers to
Pre & Post Lecture Exams

1. 4
2. 4
3. 1
4. True
5. 2