Sexual Dysfunction and psychiatric disorder and psychiatric drugs

American Society Clinical Psychopharmacology

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 antidepressants 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. gransitron
- 4. sildenafil

Question 3

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

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

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;Kivela & Palhala, IJSP,1988;Aizenberg et al, JCP,1995;Aversa et al, IJA, 1996;Bodinger et al, JCP,2002; Aksaray et al, JSMT;Figueira et al, ASB,2001

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 phenylzine 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 or more severe in females

- Zajecka et al, 1997; Labbate et al, 1998; 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 US, UK, Spain, Sweden 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
- 2. Large clinical series
- 3.Efficacy in treatment of rapid ejaculation

Controlled Studies with Direct Inquiry

1. Clomipramine (Anafranil) > placebo
2. Sertraline (Zoloft) > nefazodone (Serzone)
3. Sertraline (Zoloft) > bupropion (Wellbutrin)
4. Paroxetine (Paxil) > duloxetine (Cymbalta)> placebo
5. Fluoxetine (Prozac) > bupropion (Wellbutrin)
6. Citalopram (Celexa) = paroxetine (Paxil)

1.Monteiro et al, BJP,1987; 2. Harrison et al, JCP,1986; 3. Feiger et al, JCP,1996 ,Ferguson et al, JCP, 2001; 4. Segraves et al, JCP,200; Kavoussi et al, JCP, 2001, Croft et al, JCP, 1999; 4. Delgado et al, JCP,2005; 6. 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

- 1. Sexual side effects more frequent in men
- 2. Sexual side effects more severe in women
- 3. Spontaneous remission at 6 months 10%
- 4. 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 SR)	6.7%
• Sertraline (Zoloft)	26%
• Paroxetine (Paxil)	25.8%
• Fluoxetine (Prozac)	22.9%
• Citalopram (Celexa)	30%
• Venlafaxine (EffexorCR)	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

- Treatment of rapid ejaculation

Controlled studies on Ejaculatory latency**

• Placebo	1.5 fold increase
• 100 mg fluvoxamine	1.9 fold increase
• 20mg fluoxetine*	6.6 fold increase
• 20mg paroxetine*	7.8 fold increase
• 50mg sertraline*	4.4 fold increase

Waldinger & Olivier, J Clin Psychopharmacol.1998

Paroxetine and Citalopram

- Intravaginal ejaculatory latency time
- Stop watch, 6 weeks treatment

- 20mg paroxetine 8.9 fold
- 20mg citalopram 1.8 fold

- Waldinger, J Clin Psychopharmacol, 2001

Summary Slide

- Causes significant delay ejaculation
- 1. Paroxetine (Paxil)
- 2. Sertraline (Zoloft)
- 3. Fluoxetine (Prozac)
- 4. Clomipramine (Anafranil)
- 5. Citalopram (Celexa)

1. Waldinger et al, AJP, 1994, Waldinger at al, BJU, 1997; McMahon et al, JU, 1999
2. Waldinger et al, JCP, 1998;Mendels et al, JCP,1995;McMahon , JU, 1998;
3. Waldinger etal, JCP,1998;kara et al, JU,1996;Haensel et al, JCP,1998; Biri et al, IVN,1999
4. Strassberg et al, JSMT,1999;Segraves et al, JSMT,1993;Althof et al, JCP,1995
5. Atmaca et al, IJIR,2002

Rapid Ejaculation Summary Slide

- Minimal or no delay
  - 1.Fluvoxamine (Luvox)
  - 2.Nefazodone (Serzone)
  - 3.Mirtazapine (Remeron)
  - 4.Citalopram (Celexa) at 20mg dose

1. Waldinger et al, JCP,1988; 2. Waldinger et al, JCP,1998
2. Waldinger etal, JCP,2001 3. Waldinger , JU, 2002
3. Waldinger, JCP,2001

Controlled Comparisons

- 1. Clomipramine > Sertraline> Fluoxetine
- 2. Paroxetine>Fluoxetine>Sertraline
- Fluvoxamine=placebo
- 3. 40mg fluoxetine=50mg sertraline
- 4. Paroxetine=clomipramine=sertraline

1. Kim & Sue, JU, 1998; 2. Waldinger et al, JCP,1998;
3. Murat et al, AEU,1999

On Demand

- Clomipramine 25mg effective
- Paroxetine = placebo

Waldinger et al, EU,2004

Bottom line

- 1. Good data that bupropion, nefazodone , and possibly mirtazapine have low levels SD
- 2. Celexa at usual dose levels has high rates of SD
- 3. Good data that clomipramine & paxil have high rates of SD
- 4. Duloxetine probably has intermediate rates of SD

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) *

- Fluvoxamine (Luvox)
- Mitazapine (Remeron)

* 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
Nefazodone	150mg PRN
Bupropion	100mg bid
Mirtazapine	15-45mg qd
Sildenafil	50-100mg PRN
Bethanechol	10-50mg PRN
Methyphenidate	5-40mg qd
Neostigmine	50-200 mg PRN
Pemoline	18.75-75mg qd

Zajecka, JCP,2001

- 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
- Interim analysis of study in progress suggest that 25-50mg may be effective in reversing SSRI-induced SD in women

Nurnberg et al, JAMA,2003: Nurnberg et al, McGill, 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. Gransitron (5HT3 antagonist) ineffective

1.Michelson et al,JPR,2002 2. Meston et al, JSMT,2004 3. DeBatista et al, JCP,2005 ; Masand et al, AJP 2001 4. Clayton et al, JCP, 2001; Clayton et al, JCP. 2004
5. Michelson et al, AJP, 2000 6. Landen et al, JCP, 1999 7. Nelson et al, JCP,2001

Mechanism

- Descending inhibition by 5HT projection from nucleus paragigantocellularis
- Paroxetine potent inhibitor of NOS
- Probably involves 5HT2
- Inhibition of mesolimbic DA pathways by 5HT

Sussan & Genshey,1998, Alcantara,SMT,1999;Stable, 1998;Lauerman, APS,1996
marson & McKenan, JCN,1996;McKenna, SDM,2001

Benzodiazepines

- Numerous case reports of anorgasmia on benzodiazepines
- One double-blind, placebo-controlled study
- Orgasm by vibrator in laboratory
- Dose response delay in orgasm by diazepam

Riley & Riley, SMT,1986;Fossey & hammer, 1994;
Segraves & Balon, In Press

Lithium and Sexual Dysfunction

- Case reports suggest that lithium may impair libido and erectile function
- One double blind study found that 2/10 of bipolar patients developed erectile problems on therapeutic doses of lithium
- 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

Anticonvulsants

- Case reports of anorgasmia on gabapentin and carbamazepine
- Case reports of decreased libido, impaired arousal and anorgasmia on valproate monotherapy
- Case reports of improved erectile function in epileptics on lamotrigine

Schnech et al, JCP,2002; Husain et al, SMJ,2002;
Leris et al, BJU,1997;Labbate & Rubey,AJP,1999

Anticonvulsants

- Carbamazepine (Tegretol) increases serum hormone binding globulin and thus decreases bioavailabilty of androgens

- Oxcarbamazpine (Trileptal) does not influence androgen bioavialabilty

Rattya, Neurology, 2001

- 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
- Evidence is not consistent

Report of SD on Antipsychotics

- Studies in Spain and the Netherlands have found dramatic under reporting of sexual side effects.

- 10% vs 60%
- 15% vs 80%
-

Knegtering et al, 2002; Montejo et al, 1998

- Most evidence consists of case repots 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

Loxapine (Loxatine)

- Clinical series, computerized questionnaire
- Dickson-Glazer Sexual Function Scale
- 40% decrease libido
- 30% erectile problems
- 36% ejaculation problems

Dickson, APA, Chicago, 2000.

Antipsychotics and SD

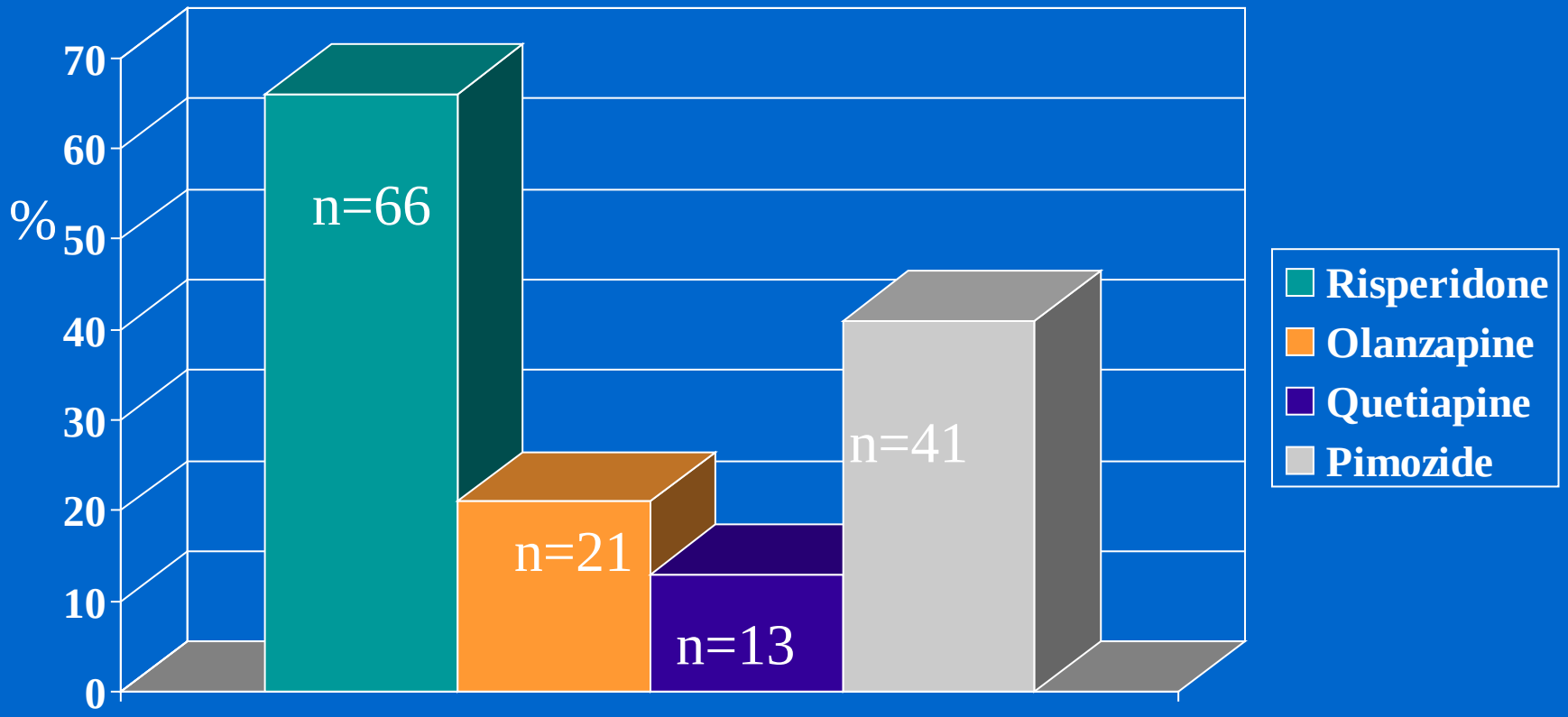
- Open label study of 106 outpatients

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

Montejo et al, 1998 APA NR

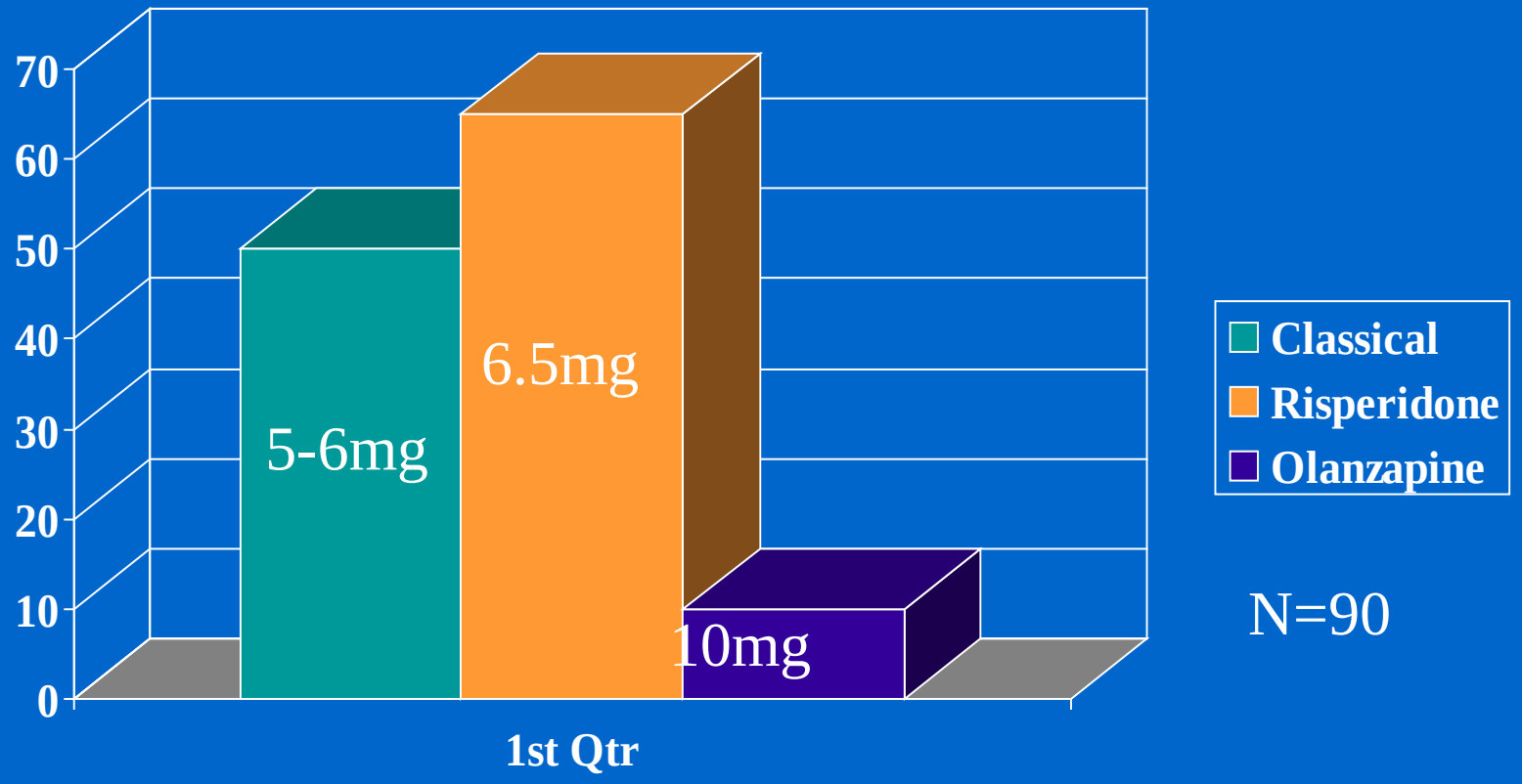
- Various open label studies by Knetering of patients with schizophrenia monitoring sexual side effects by direct inquiry

New Antipsychotics



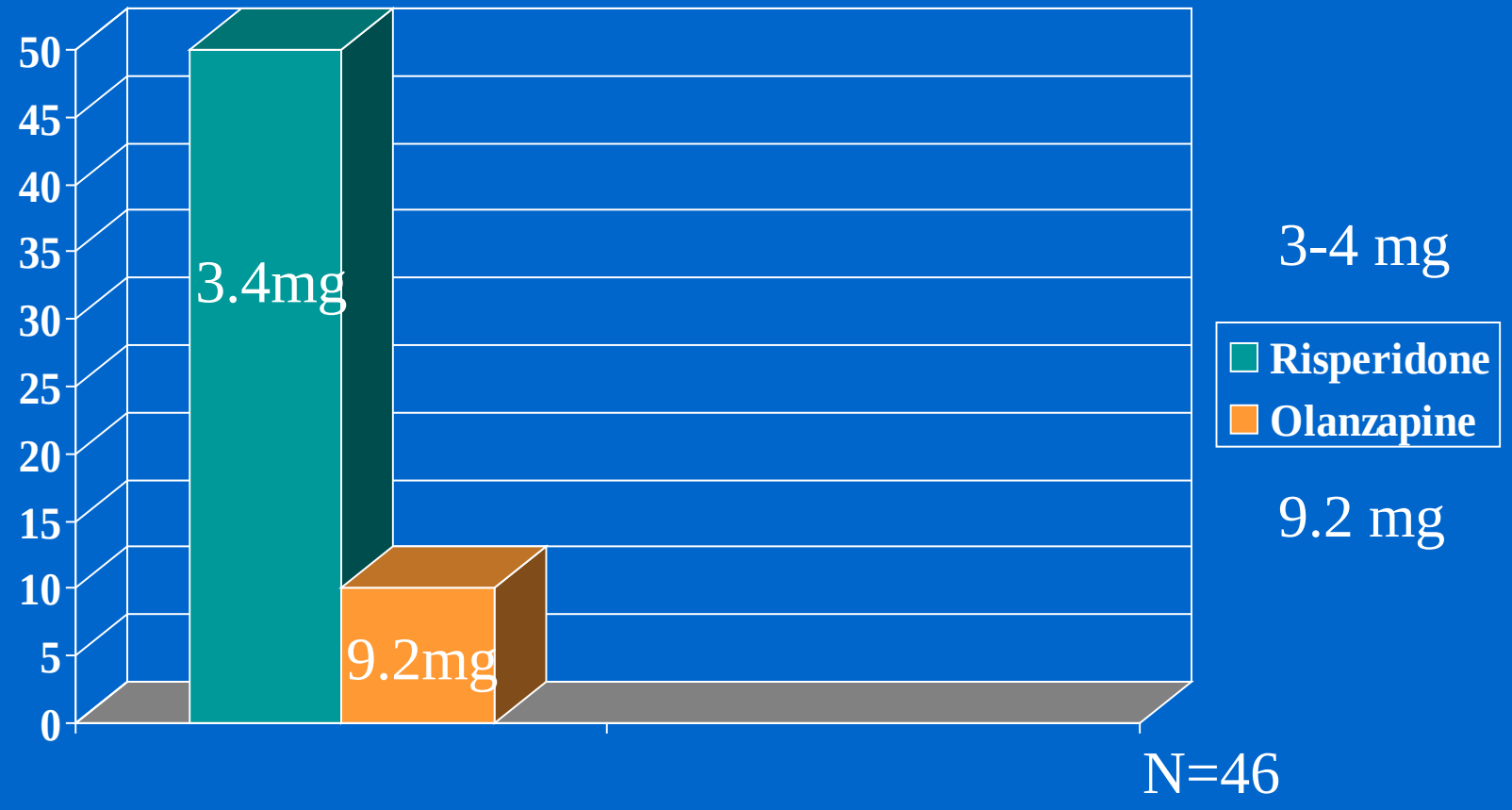
Knegtering et al, 2002

SD and Antipsychotic Drug Therapy



Knegtering et al, 2002

Risperidone vs Olanzapine



Knegtering et al, 2000

EIRE Study

- Multi-site cross sectional study of patients with schizophrenia on either haloperidal, 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

- Haloperidal (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

Controlled Study

- Randomly assigned to ziprasidone 40-80mg or risperidone 3-5 mg for 8 weeks
- Sexual dysfunction questionnaire
- Similar types and frequencies of sexual dysfucntion
- Except risperidone twice as much ejaculatory disorder (not statistically signif)

Addington et al, JCP, 2004

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

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 (Symmerel), 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 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

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 & Ruksta;is, 2005

Summary

- Numerous psychiatric drugs affect human sexuality
- Sexual side effects may be cause of treatment noncompliance
- Sexual side effects 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. 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. gransitron
- 4. sildenafil

Question 3

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

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