

Psychiatric Disorders and Sexual Dysfunction

ISSWSH Fall Course 2014

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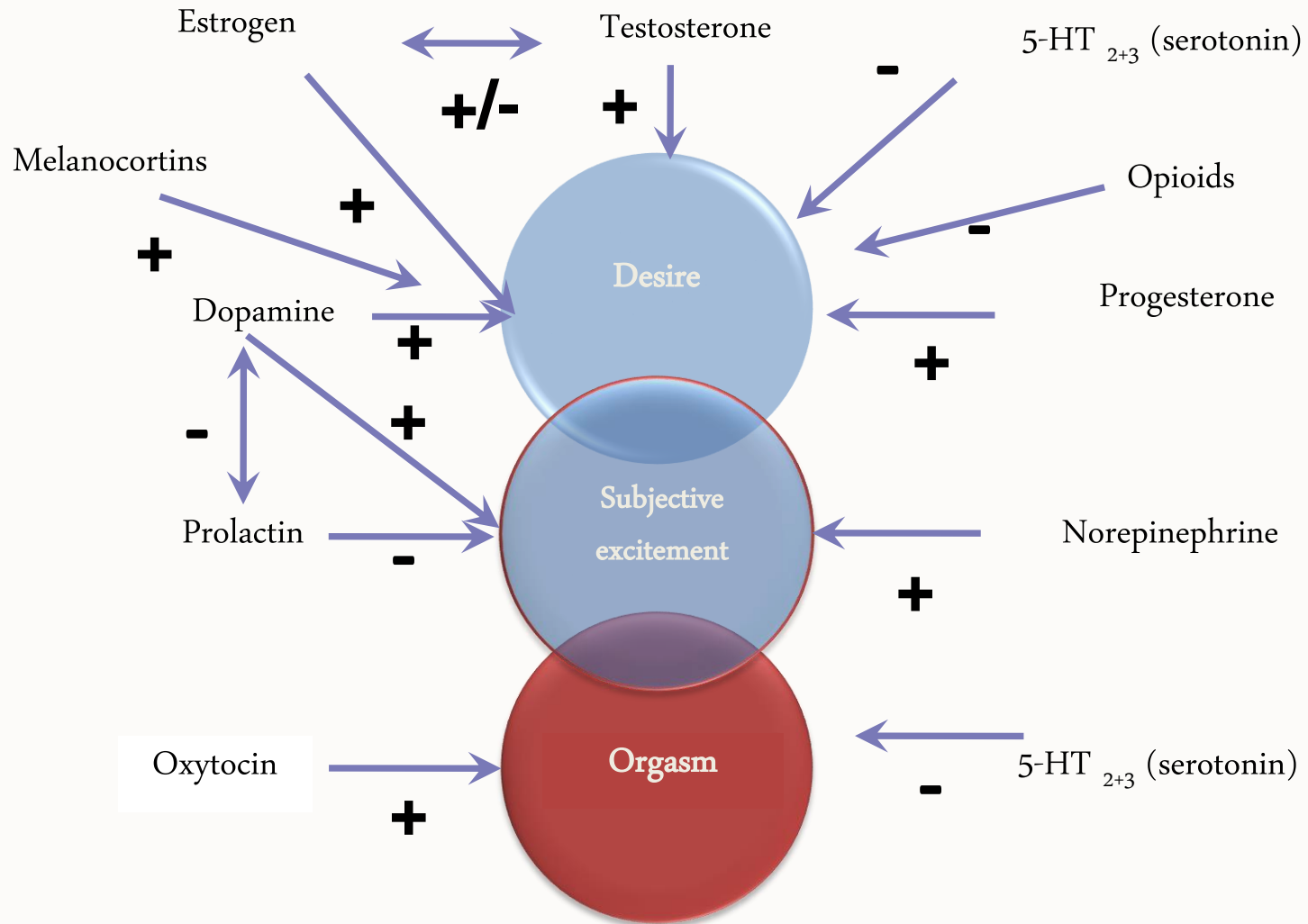
Disclosures

- **Advisory Board:** Sprout, Pfizer, SST, Emotional Brain, Apricus
- **Speaker: Pfizer**

Objectives

- Describe the relationship between common psychiatric disorders in women, particularly depression, and female sexual dysfunctions
- Provide an evidenced-based approach to the appropriate use of psychopharmacological agents in this clinical context

Central effects of neurotransmitters and hormones on sexual functioning



Depression and sexual function: females

- **50% low sexual desire and arousal problems**
- **40% lubrication problems**
- **35% Lower interest in sexually explicit material**
- **15% Delay with orgasm**

Baldwin D.S. Expert Opinion Drug Saf. 2004; 3(5):457-70

Bidirectional Association between Depression and Sexual Dysfunction

- **Depression increased risk of sexual dysfunction in pooled unadjusted (RR/OR 1.52) and adjusted (RR/OR 1.71)**
- **Sexual dysfunction increased odds of depression in pooled unadjusted (OR 2.30) and adjusted (or 3.12)**
- **Meta-analyses**
- **12 studies, approx 15,000 subjects**

Altantis, Sullivan, JSM 2012:9:1497-1507.

Prevalence of Sexual Dysfunction: Role of Depression

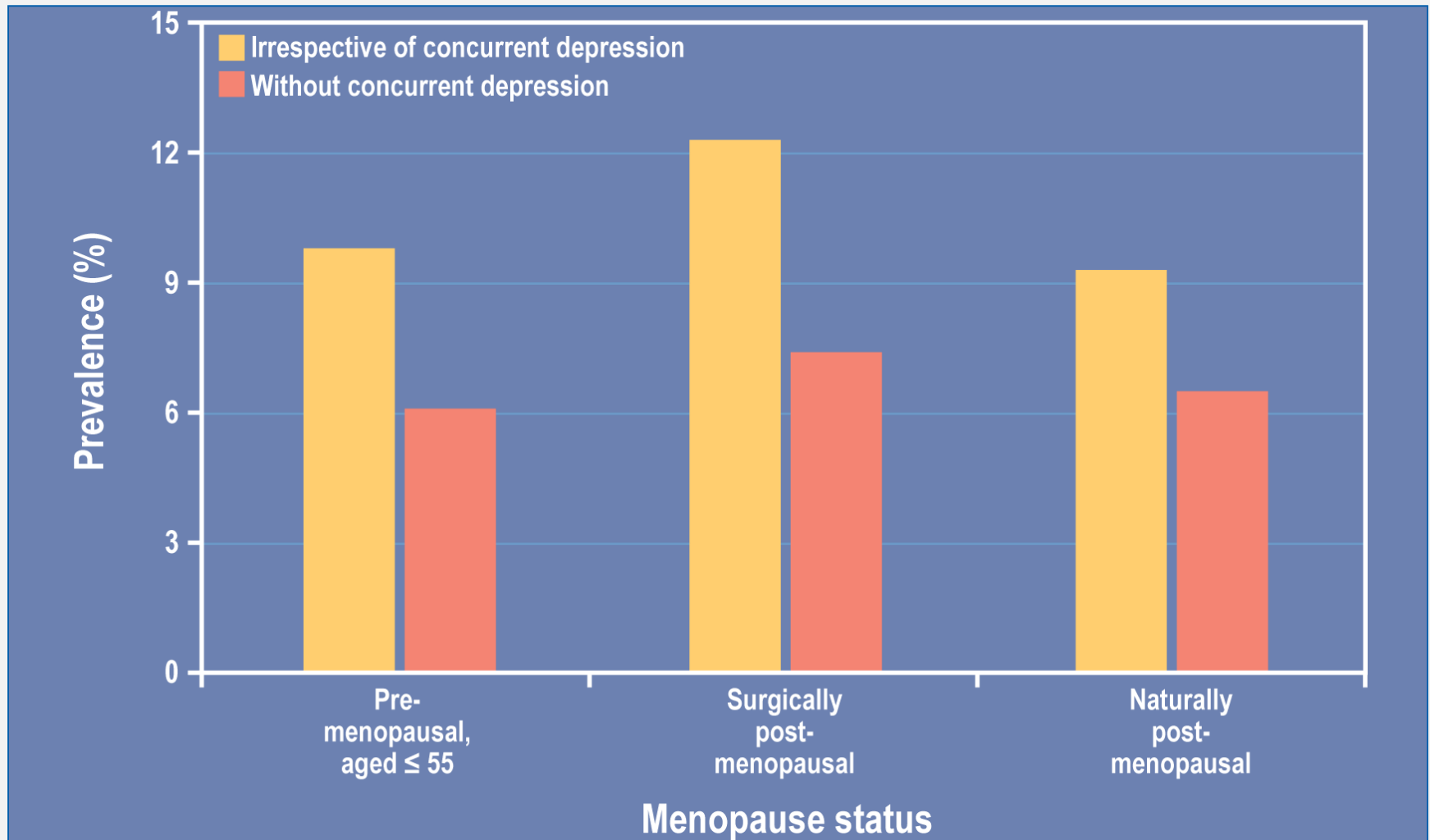
SEXUAL COMPLAINT	SEXUAL PROBLEM	PROBLEM PLUS DISTRESS	FSD WITHOUT DEPRESSION
Desire	38.7%	10%	6.3 – 8.8%
Arousal	26.1%	5.4%	3.3 – 4.7%
Orgasm	20.5%	4.7%	2.8 – 4.1%
Any Dysfunction	44.2%	12%	7.6 – 10.7%

N=31,581. Definition of depression: Self-reported depressive sx's + AD use; AD use without current depressive sx's; Depressive symptoms without AD use

Shifren J et al. Obstet Gynecol 2008;112:970-978.

Johannes CB et al. J Clin Psychiatry 2009;70(12):1698-1706.

Comparison of Distressing Low Desire in PRESIDE, Irrespective and Without Concurrent Depression



Johannes et al., J Clinical Psychiatry, 2009; 70:1698.

Rosen et al., J Sexual Med, 2009; 6:1549.


Correlates of Sexual Problems With Distress: Results of Multiple Logistic Regression, PRESIDE

Variable	Sexual Problems With Distress			
	Desire	Arousal	Orgasm	Any
Current depression	++	++	++	++
Chronic medical conditions				
Arthritis	+	+	+	+
Anxiety	+	+	+	+
Thyroid problem	+	+	+	+
Inflammatory/irritable bowel disease	+	+	+	+
Urinary incontinence	+	+	+	+

Note: ++ Odds ratio (OR) ≥ 2 ; + OR > 1 but < 2 ; — OR < 1 ; + or — (95% confidence interval for OR includes 1)

Other variables in the models: race, parity, current use of hormone therapy, current use of antihypertensive or cholesterol-lowering medications, current smoking, cancer, ulcer, hypertension, asthma, diabetes, heart disease, and chronic pain.

Correlates of Sexual Distress in Women With Low Sexual Desire

Variable	Adjusted Odds Ratio ^a (95% CI)
Current partner (Yes vs. No)	4.63 (4.11 – 5.22)
Current depression (SF-12)	
None	1.00 (Reference)
With antidepressant use	1.53 (1.32 – 1.77)
Without antidepressant use	 1.91 (1.62 – 2.24)
Anxiety (Yes vs. No)	1.61 (1.40 – 1.85)
Urinary incontinence (Yes vs. No)	1.22 (1.02 – 1.46)
Hormone medication use (Yes vs. No)	1.27 (1.10 – 1.47)
Other sexual problems present ^b	1.15 (1.03 – 1.28)

^a Logistic regression with backward selection.

^b Problems with arousal, orgasm, or both.

HSDD Registry and Depression

- Depression defined: current diagnosis, symptoms (PHQ), use of antidepressant medication (AD)
- 34% depressed, of whom 56% took AD medication
- Sexual function significantly lower in women with current depression ($p < 0.001$)
- AD users: inadequately treated depression assoc. with increased severity of HSDD ($p = 0.02$) compared with women in remission.
- ADs not otherwise associated with sexual function differences among women with HSDD and depression

Relationship and Lifestyle Factors

- **Depressed women are more likely:**
 - **unhappy in their current partner relationship**
 - **trouble forming and/or maintaining relationships**
- **Depressed women have lower frequency of sex with their partner than women without depression**
- **Depressed women more likely to engage in binge drinking and screen positive for alcohol and substance abuse**
- **Depression & HSDD are frequently co-morbid**
- **Relationship likely due to overlap of neurotransmitter and neuroendocrine systems affected**

Managing Menopausal Symptoms

- **Address hot flashes with hormonal treatments, lifestyle interventions, and anti-depressants**
 - Diet, exercise, supplements
 - Interaction of estrogen/ androgens and central serotonin receptors
 - CEE, CEE-BZA, Estradiol
 - Venlafaxine, desvenlafaxine
 - Escitalopram 10-20 mg (MFLASH)
 - Paroxetine 7.5 mg (low-dose mesylate salt) – FDA approved
- **Address sleep**
 - Powerful relationship between sleep and depression
 - Sleep quality and quantity
 - Non-prescription approaches

Low Dose Paroxetine and Sexual Function

- *Portman et. al. Menopause 2014;21:1082-1090*
- Pooled analysis of 1,184 enrolled in 2 phase 3 trials – 12 and 24 weeks
- Postmenopausal women age 40 with moderate to severe VM sx
- Arizona Clinical Experience Scale (ASEX)
- Assesses: Sex drive, arousal, lubrication, orgasm or satisfaction
- 58% baseline sexual dysfunction
- *“No clinically meaningful or statistically significant change from baseline” in sexual function*

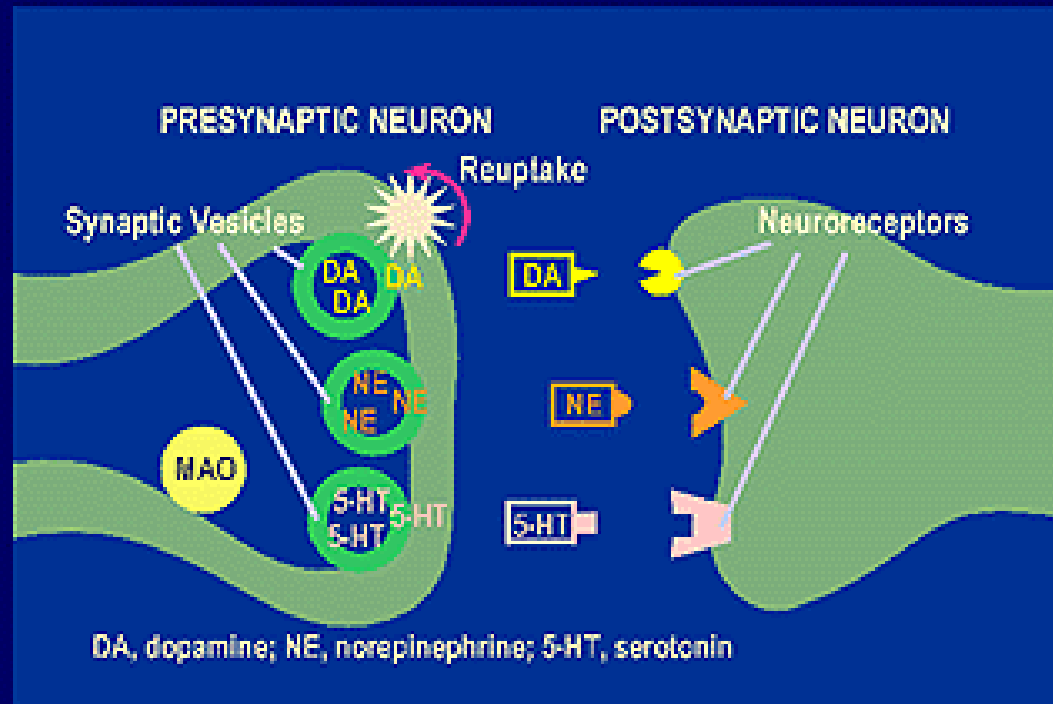
SSRI-Induced FSD

- **Diminished libido^{1,2}**
 - Reduced testosterone levels, dopamine transmission
 - Prevalence: up to 50%
- **Diminished arousal^{1,2}**
 - Negative effects on nitric oxide system and sensation
 - Prevalence: 5%
- **Delayed, reduced or absent orgasm^{1,2}**
 - 5-HT-2 and other receptors
 - Prevalence: up to 66%
- **Sexual side effects: noncompliance, discontinuation, decreased recovery²**
- **Patients report 2x physicians' perceptions**

1. Kennedy SH, et al. J Clin Psychiatry. 2000;61:276-281.

2. Clayton AH, et al. J Sex Med. 2009;6:1200-1211.

Neurotransmitters and antidepressants



NE and 5-HT: TCAs, HCAs, MAOIs, venlafaxine (Effexor)

NE and DA: bupropion, Wellbutrin, dextroamphetamine (Dexedrine), methylphenidate (Ritalin), pemoline (Cylert)

5-HT₂ antagonists: trazodone (Desyrel), nefazodone (Serzone)

5-HT reuptake blockade: fluoxetine (Prozac), sertraline, (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa)

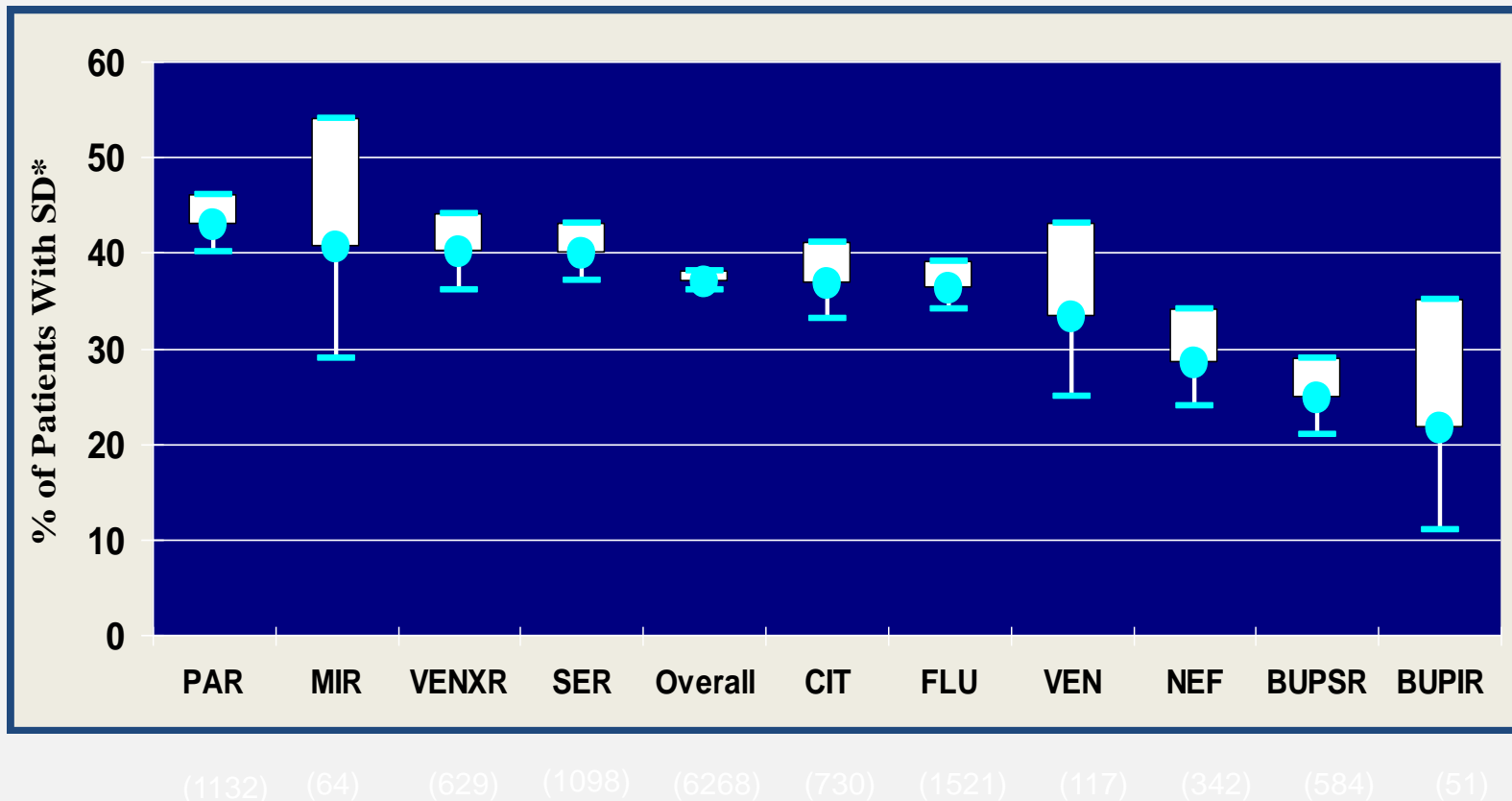
α_2 -antagonists: mirtazapine (Remeron)

Risk Factors for SSRI Sexual Dysfunction

- Older (at least 50 y.o.)
- Married
- < College education
- Not employed full-time
- Tobacco use (6-20x/day)
- ↑ Total daily doses of antidepressant
- Concomitant medications

- Comorbid illnesses
- Prior history of antidepressant-induced sexual dysfunction
- History ↓ sexual enjoyment
- Sexual functioning “not” or “somewhat” important

SSRIs: Prevalence of Sexual Dysfunction



Reproduced with permission, Clayton et al. J Clinical Psychiatry 2002;63:357-366.

SD defined as at or below threshold total CSFQ Score
Clayton et al., J Clin Psych 2002

Meta-analysis: Comparative Benefits

- Five trials & pooled analysis (N=2399) of 2 identical RCTs
- **Bupopriion:** lower rates of sexual dysfunction than escitolapram, fluoxetine, paroxetine, sertraline
 - Rates not always statistically significant
 - Underreporting in efficacy studies likely
- **Paroxetine:** higher rates compared with other second-generation antidepressants, esp. ejaculatory disorders

Table 1. Diagnosis Distribution (N = 1022)

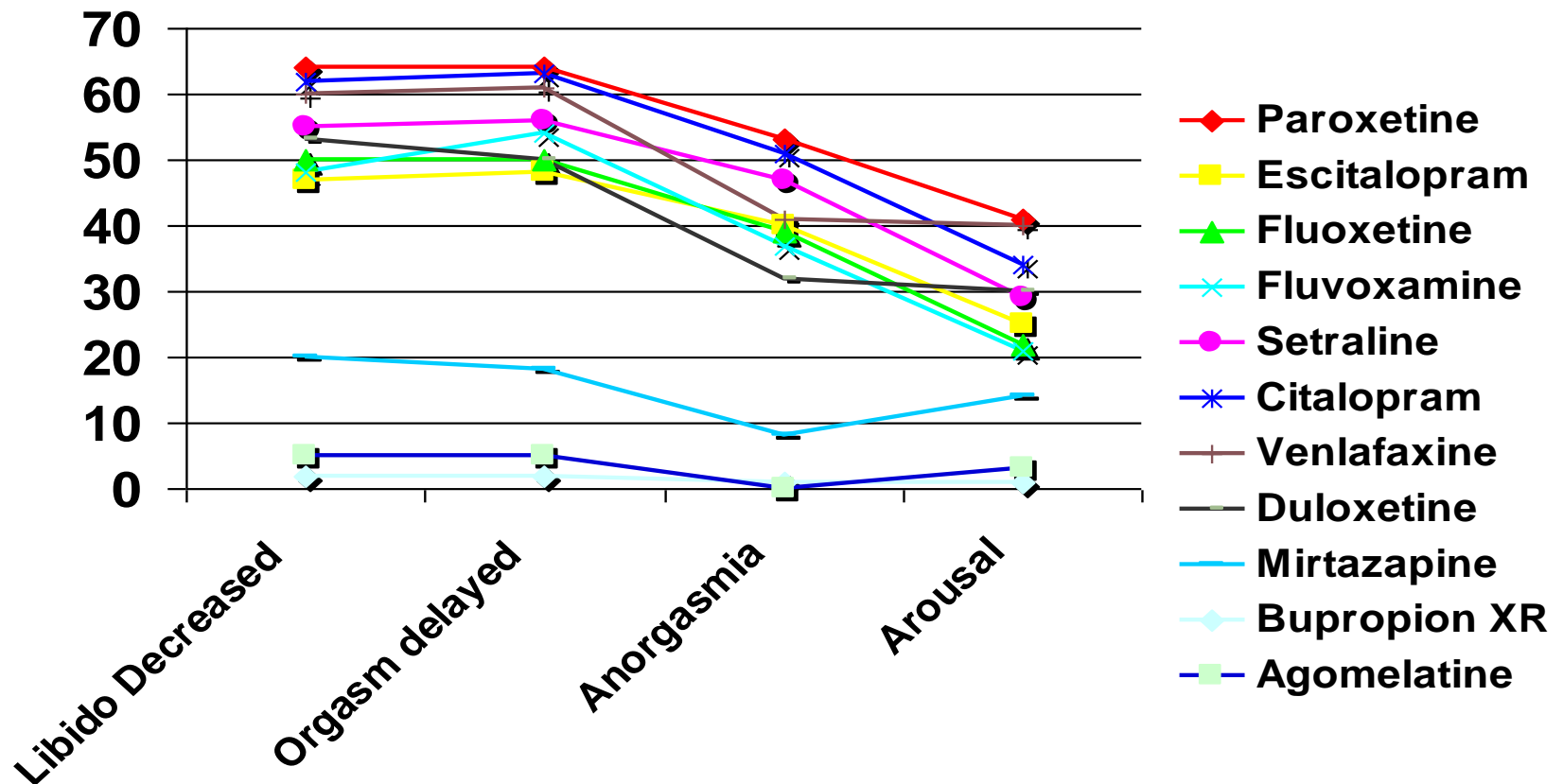
Diagnosis ^a	N	Women/ Men	Patients With Sexual Dysfunction	
			N	%
Major depression	614	349/265	346	56.3
Dysthymic disorder	177	119/58	97	54.8
Panic disorder	124	92/32	74	59.6
Obsessive-compulsive disorder	60	24/36	36	60.0
Others ^b	38	26/12	22	58.3

^aSome patients had more than one diagnosis.

^bOthers include personality disorder, bipolar disorder, anorexia/bulimia, phobias, etc.

Frequency of Sexual Dysfunction

PRSexDQ- SALSEX n =1205



Pooled data from different observational studies

Montejo AL et al. J Clin Psychiatry. 2001;62 Suppl 3:10-21.
Montejo AI et al (data on file 2008)

Table 2. Incidence of Sexual Dysfunction With Antidepressants Assessed by the Psychotropic-Related Sexual Dysfunction Questionnaire (N = 1022)^a

Drug ^a	N	Women/ Men	Mean Dose, mg	Patients With Sexual Dysfunction	
				N	%
Citalopram	66	36/30	28.7	48	72.7
Paroxetine	208	137/71	23.4	147	70.7
Venlafaxine	55	30/25	159.5	37	67.3
Sertraline	159	96/63	90.4	100	62.9
Fluvoxamine	77	33/44	115.7	48	62.3
Fluoxetine	279	166/113	24.5	161	57.7
Mirtazapine	49	28/21	37.7	12	24.4
Nefazodone	50	35/15	324.6	4	8.0
Amineptine	29	17/12	187.2	2	6.9
Moclobemide	26	16/10	265.6	1	3.9

^aOther groups (N = 24): clomipramine (N = 10), imipramine (N = 8), maprotiline (N = 4), phenelzine (N = 2), trazodone (N = 1).

Treatment-Emergent SD – *Meta-Analysis*

- Higher rate of total/specific treatment-emergent SD and specific phases of dysfunction compared with placebo
- Decreasing order: sertraline, venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine (25.8-80.3%)
- All phases, arousal more affected in women
- No difference with bupropion and mirtazipine
- Antipsychotics: risperidone, olanzapine, haloperidol (60-70%)
- Anxiolytic data mixed

Serreti A, Chiesa A. J of Clin Psychopharmacol 2009;29:259-266.

Serreti A, Chiesa A. Nature 2011;89:142-147.

Newer Antidepressants

- **Desvenlafaxine (SNRI)**
 - N=422, ASEX
 - 50 mg vs. placebo, 12 weeks, double-blind
 - Placebo poorer overall sexual functioning and orgasmic satisfaction
 - Represents disease state FSD in untreated depression
- **Vilazodone**, a novel chemical entity, is a dual-acting selective and potent serotonin-1A partial agonist and reuptake inhibitor (SPARI)
 - N=869, (2) 8 week RCTs; N=599, 52 week open label; 40 mg
 - High baseline FSD 68%, sexual function improved > 90%
 - Vilazodone : small adverse impact (8% vs. 0.9%), 9.3 %, decreased libido
 - » Clayton et al. J Sex Med 2013;10:768-776.
 - » Clayton et al. J Sex Med 2013;10:2465-2476.

Depression, T, Anti-depressant Treatment

- **Premenopausal women diagnosed with depression compared with controls (N=82)**
- **Depressed women had lower total and bioavailable testosterone and sexual dysfunction.**
- **With treatment, depression symptoms decreased, testosterone levels increased, but sexual disorders persisted.**

Kumsar et al. J Sex Med 2014;11:529-535.

SSRI Sexual Dysfunction: Management

- Dose reduction or await tolerance: low success¹
- “Drug holiday”: relapse, discontinuation syndrome¹
- Drug substitution: fear of failure^{1,2}
- Augmentation/antidote: cost, side effects, limited efficacy^{1,2}
 - Bupropion: improvements in self-reported feelings of desire and frequency of sexual activity, but no differences in global sexual functioning measured by CSFQ, orgasm, desire/interest measured by sexual thoughts, or self-reported arousal³
 - Sildenafil: small, significant improvement in Clinical Global Impression-sexual function scores⁴
 - Testosterone: significant increase in SSEs in women with SSRI/SSNI –emergent loss of libido with 300 mcg TT⁵

1. Balon R. Am J Psychiatry. 2006;163:1504-1509.

2. Taylor MJ, et al. J Affect Disord. 2005;88:241-254.

3. Clayton AH, et al. J Clin Psychiatry. 2004;65:62-67.

4. Nurnberg HG, et al. JAMA. 2008;300:395-404.

5. Fooladi et al. J Sex Med 2014.

6. Lan et al. J Sex Med 2013;10:74-82.