

Sexual Dysfunction and Depression: Treatment Considerations

ISSWSH Annual Meeting 2016
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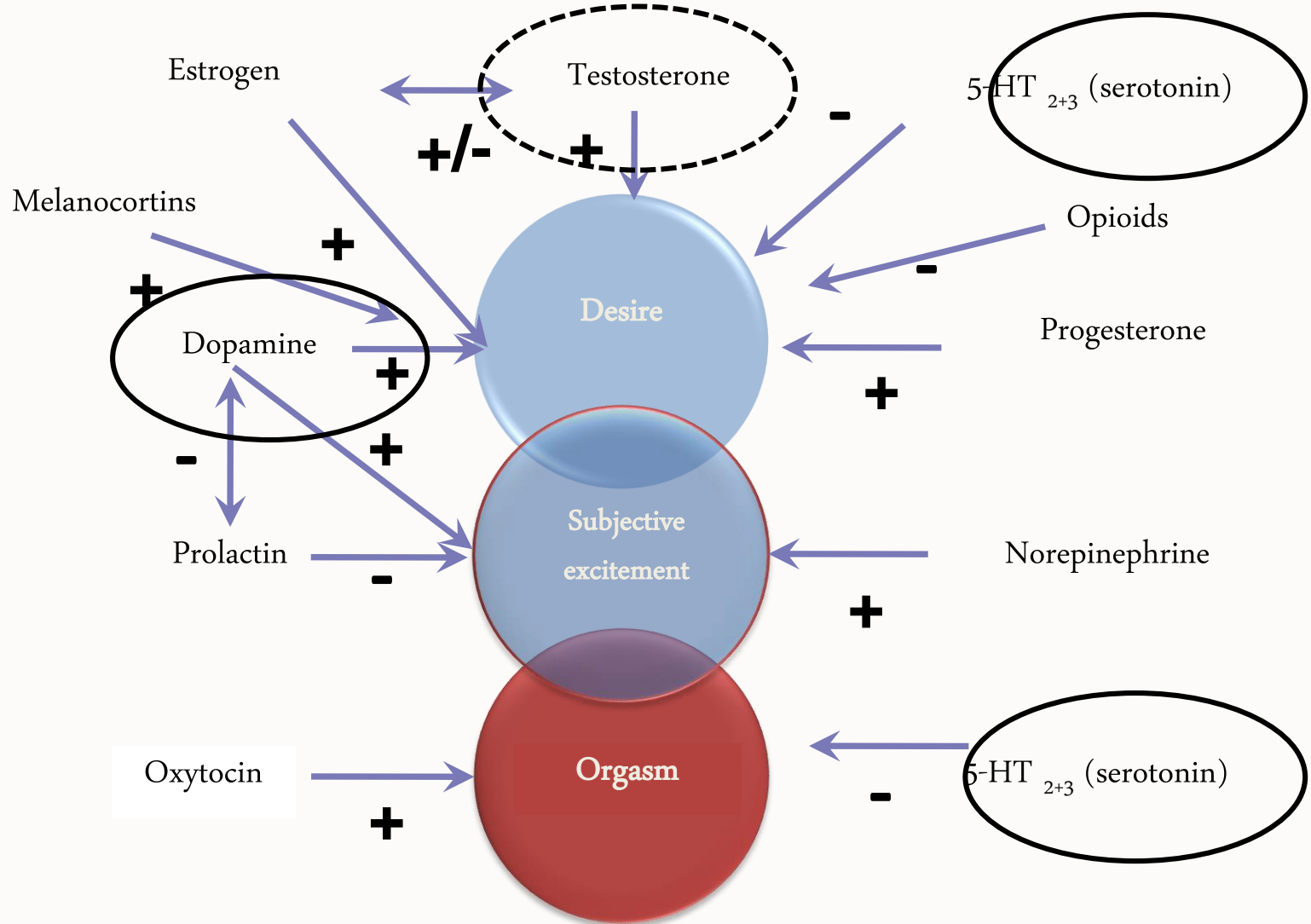
Disclosures

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

Objectives

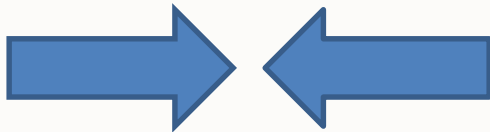
- **Describe the relationship between common psychiatric disorders in women, particularly depression, and female sexual dysfunctions**
- **Provide an evidenced-based approach to the appropriate use of psychopharmacological agents in this clinical context**

Central Effects of Neurotransmitters and Hormones on Sexual Functioning



Bidirectional Association between Depression and Sexual Dysfunction

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



Altantis, Sullivan, J Sex Med 2012;9:1497-1507.

Prevalence of Sexual Dysfunction: Role of Depression

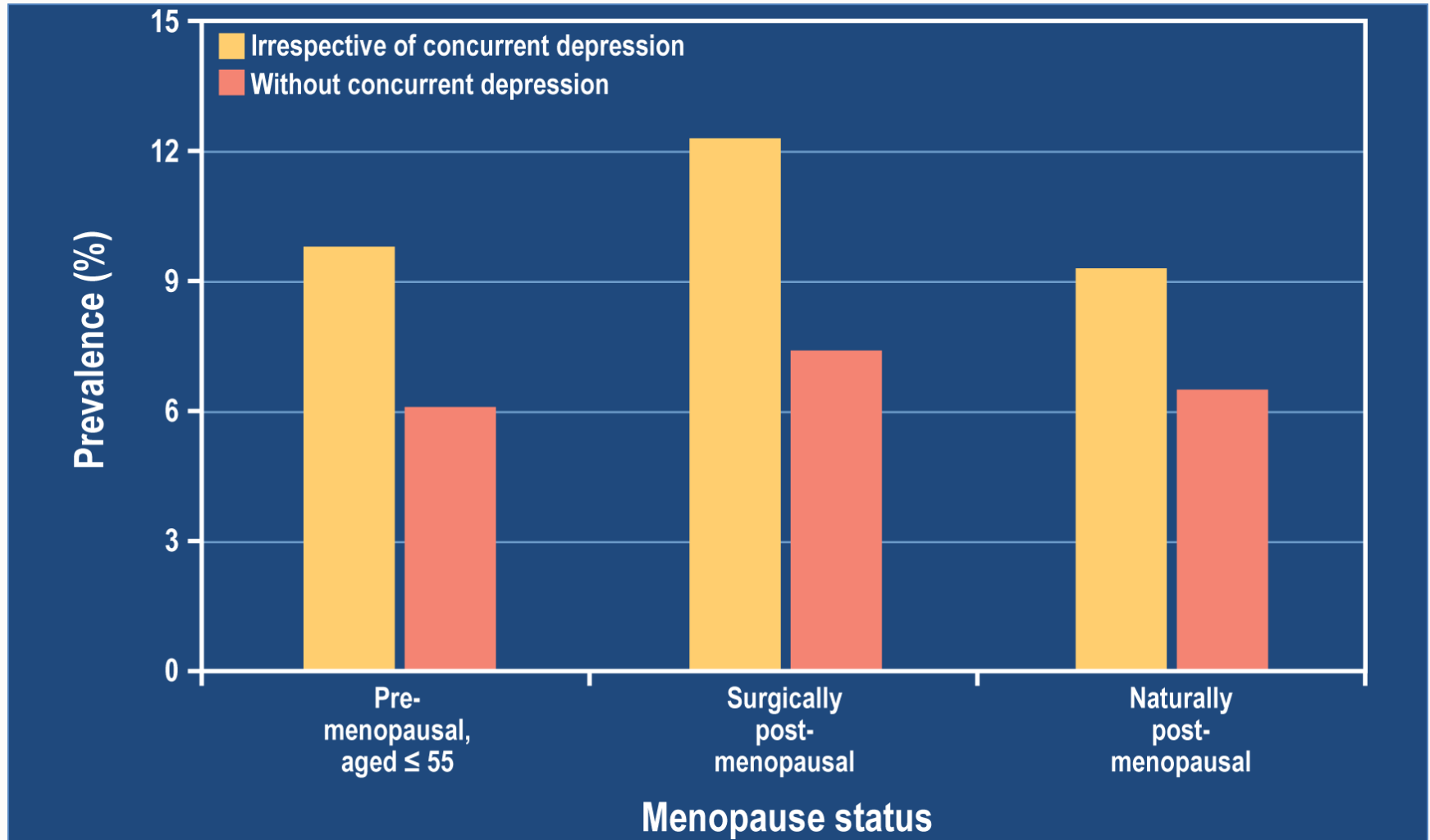
SEXUAL COMPLAINT	SEXUAL PROBLEM	PROBLEM PLUS DISTRESS	FSD WITHOUT DEPRESSION
Desire	38.7%	10%	6.3 – 8.8%
Arousal	26.1%	5.4%	3.3 – 4.7%
Orgasm	20.5%	4.7%	2.8 – 4.1%
Any Dysfunction	44.2%	12%	7.6 – 10.7%

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

- N=1088 premenopausal women
- Depression defined: current diagnosis, symptoms (PHQ-9), 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 with HSDD 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

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.

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



Simon et al. Menopause 2013;20:1027-1035.

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 & 24 weeks
- Postmenopausal women age 40 with moderate to severe VMS
- 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***

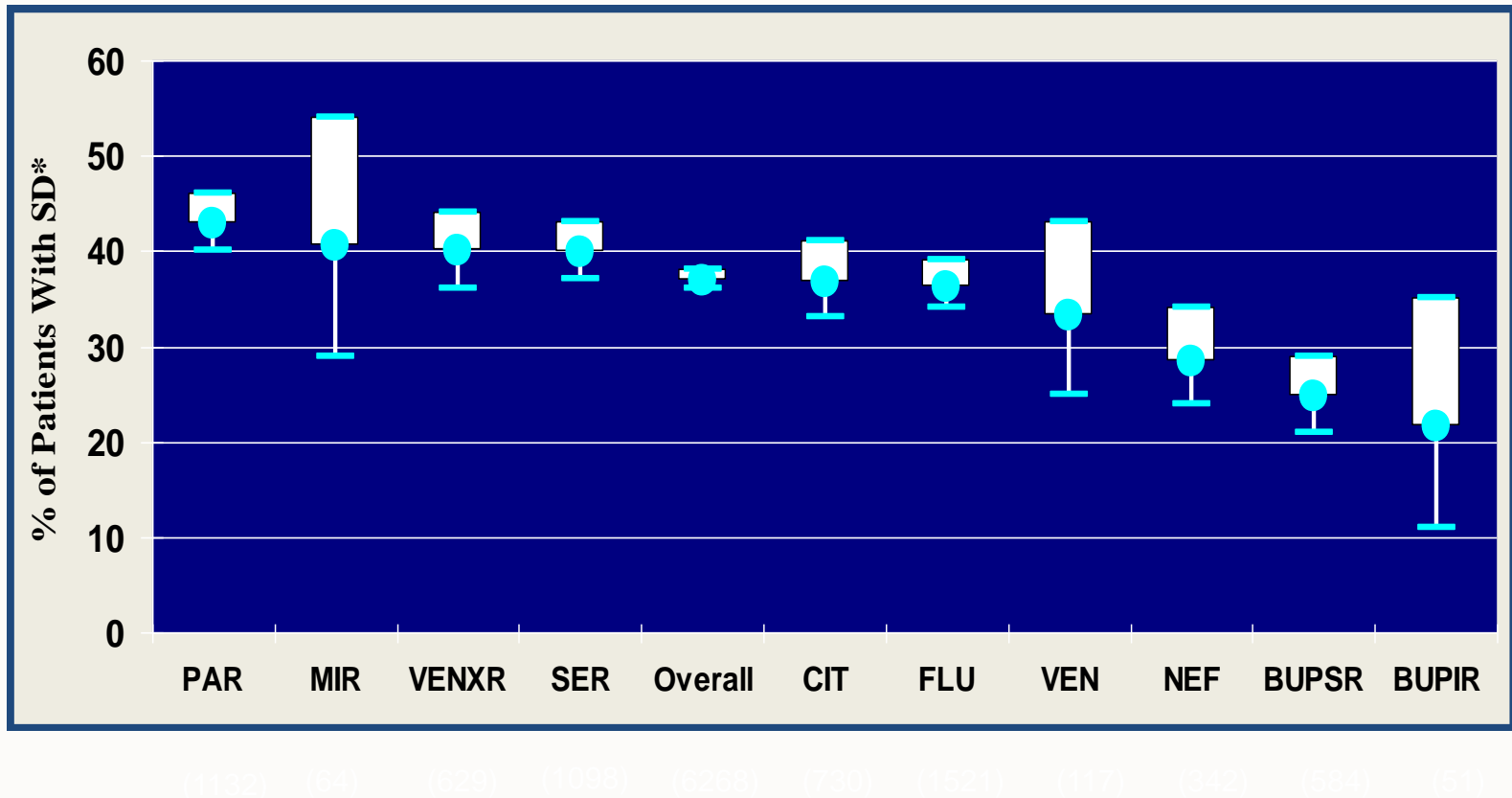
SSRI-Induced FSD

- **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.

SSRIs: Prevalence of Sexual Dysfunction



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

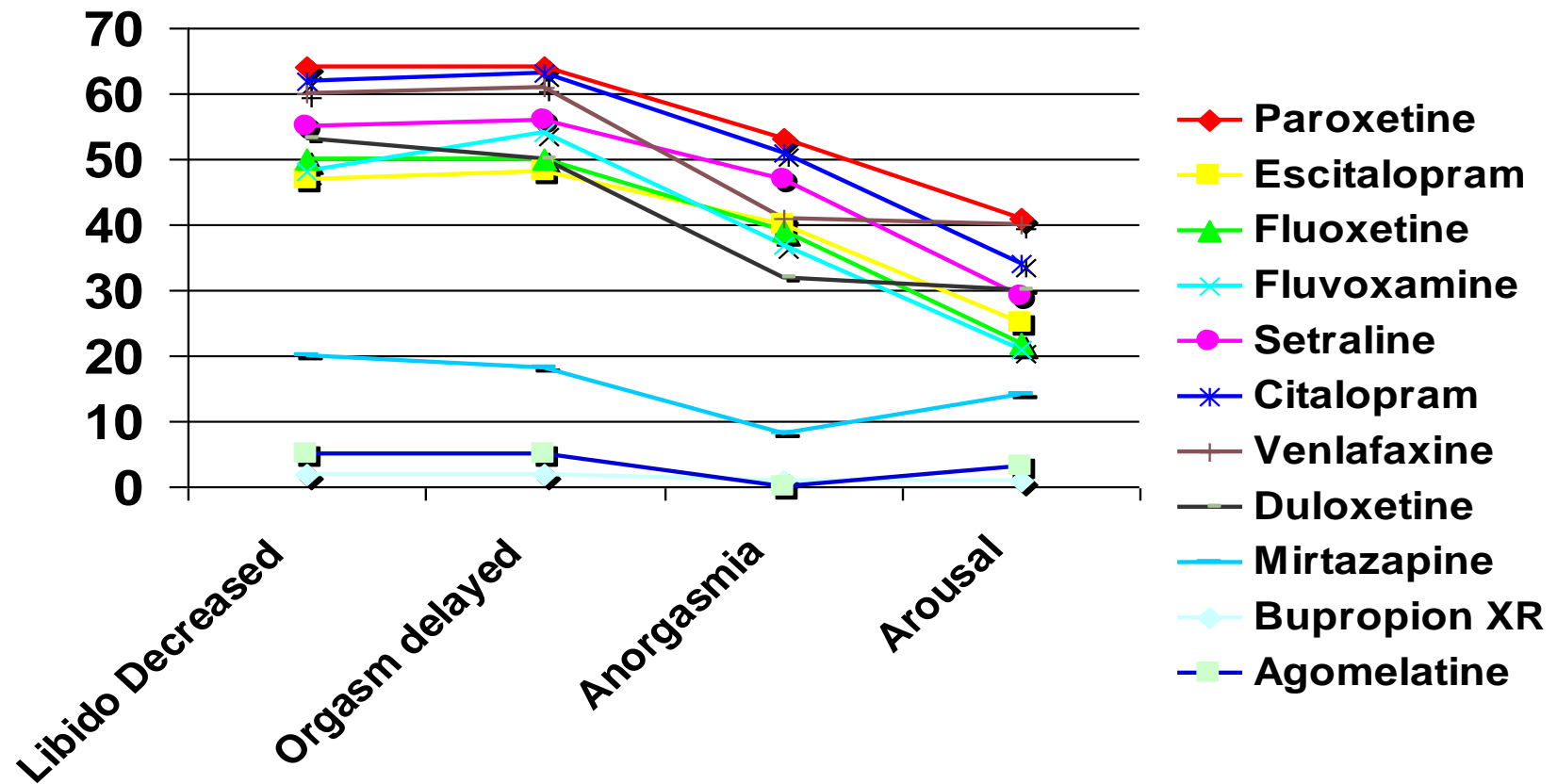
SD defined as at or below threshold total CSFQ Score
Clayton et al., J Clin Psych 2002

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

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 Al et al. (data on file 2008)

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: risperadone, 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%
- Small adverse impact (8% vs. 0.9%), 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 AD 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}
- Exercise
- Vibratory stimulation



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

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

SSRI Sexual Dysfunction: Management

- **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 arousal¹
- **Sildenafil:** small, significant improvement in Clinical Global Impression-sexual function scores²
- **Testosterone:** significant increase in SSEs in women with SSRI/SSNI –emergent loss of libido with 300 mcg TT³

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

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

3. Fooladi et al. J Sex Med 2014.

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

Flibanserin, Depression, SSRI/SNRIs

Division Summary, phase 3 placebo-controlled trials

SS/NRIs

- **Combination of flibanserin with SS/NRI** exacerbated dizziness and insomnia but does not appear to worsen psychiatric symptoms.
- **Adverse events exacerbated by concomitant use of flibanserin:** anxiety, somnolence, fatigue, insomnia, and dizziness.
Findings should not preclude concomitant use but consideration should be given...
- **Adverse events mapping to MedDRA Depression SMQ were more common among flibanserin treated subjects** than placebo; incidence is dose-proportional...no signal of an association between flibanserin treatment and suicidality
- **Flibanserin did not exacerbate depression or anxiety in patients taking SSRI or SNRI medication.**