

SEXUAL DYSFUNCTION CAUSED BY DEPRESSION AND ANTIDEPRESSANTS

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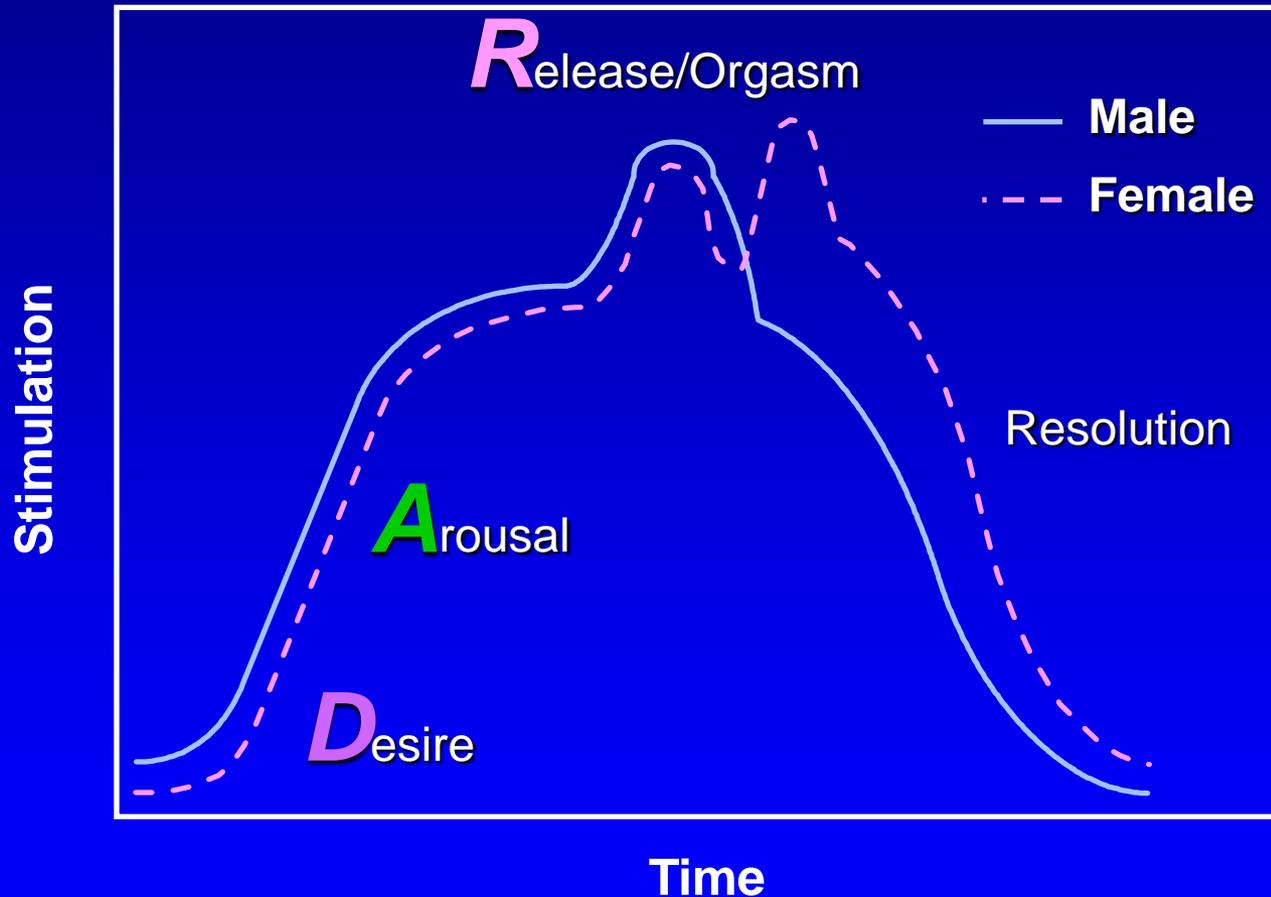
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Why Discuss This?

- **Antidepressants (and other psychotropics) often produce sexual dysfunction**
- **Substance-Induced Sexual Dysfunction (SISD) adversely affects Quality of Life and compliance**
- **SISD symptoms can often be alleviated**
- **Identification and treatment of SISD require clinician awareness**

The Sexual Response Cycle



Modified from Masters WH, Johnson VE, Kolodny RC.
In: *Human Sexuality*. 4th ed. New York, NY: Macmillan; 1992:69–94.

Sexual Dysfunction Requires A Differential Diagnosis That Includes:

- **Primary Sexual Disorders**
- **Medical Illnesses**
- **Recreational Substances**
- **Prescribed Medications**
 - **Nonpsychiatric**
 - **Psychiatric**

DSM IV TR Sexual Disorders of Desire, Arousal, and Orgasm

- **Disorders of Desire**
 - **Hypoactive Sexual Desire Disorder** 302.71
 - May affect 15% of men
 - May affect 35% of women
 - **Sexual Aversion Disorder** 302.79
- **Disorders of Arousal**
 - **Male Erectile Disorder** 302.72
 - **Female Sexual Arousal Disorder** 302.72
- **Female Orgasmic Disorder (5-30%)** 302.73
- **Male Orgasmic Disorder (5%)** 302.74
- **Premature Ejaculation (35%)** 302.75

DSM IV TR Sexual Dysfunction due to a General Medical Condition

May affect desire, arousal, pain, or other aspect(s) of functioning

- Neurologic
 - Neuropathy
 - Spinal injury
 - Postoperative
- Hormonal
 - Diabetes
 - Hypogonadism
 - Hyperprolactinemia
- Vascular
 - Arteriosclerosis

DEPRESSION AND HYPOACTIVE SEXUAL DESIRE

Percentage with HSDD

Source

- 31% Mathew et al, PB, 1980
- 67% Starkstein, JNNP, 1990
- 62% Kivela and Pahkula, IJSP
- 72% Casper, AGP, 1985

NOCTURNAL PENILE TUMESCENCE AND DEPRESSION

- **Diminished NPT time and diminished penile rigidity. Thase et al. BP, 1988**
- **Loss of NPT during depressive episode. Roose et al. BPB, 1982**
- **Reduced NPT time with depression. Thase et al. AJP, 1987**

DEPRESSION IN THE ELDERLY

- **Study of elderly in Ahtari, Finland**
- **Loss of libido distinguishes depressed men from nondepressed, ages 60-69 and over 70.**
- **Loss of libido distinguishes depressed women from nondepressed women, ages 60-69, but not in those over 70.**

Substance-Induced Sexual Dysfunction Definition (DSMIV)

- **Clinically significant dysfunction**
 - **marked distress or interpersonal difficulty**
- **Onset fully explained by substance use**
- **Not better accounted for by another diagnosis**
- **Specify with impaired desire, arousal, orgasm, or with sexual pain**
- **Code 292.89 with medication, or by substance when associated with recreational drug**

ANTIDEPRESSANTS AND SEXUAL SIDE EFFECTS

Some antidepressants have minimal negative impact on sexual function

- Nefazodone
- Trazodone
- Tranylcypromine
- Bupropion
- Mirtazapine

Antidepressants And Sexual Side Effects

Many antidepressants decrease/ eliminate sexual dysfunction by reducing depression and/or by direct effects on sexual function

- Clomipramine
- Phenezine
- SSRIs
 - Fluoxetine
 - Sertraline
 - Paroxetine
 - Fluvoxamine (possibly lower risk)
 - TCAs (less than SSRIs) imipramine and probably others

Antidepressants Are An Effective Pharmacotherapy for Some Cases of Premature Ejaculation

- **Clomipramine**
 - 25-50 mg 6 h before intercourse
- **Fluoxetine 20 mg/d**
- **Sertraline 50 mg/d**
- **Paroxetine 40 mg/d**

Harvey and Balon: Ann Clin Psychiatry 7:189-201, 1995

TREATMENT OF PREMATURE EJACULATION

- **Double-blind study of men with premature ejaculation**
- **25 mg or 50 mg clomipramine or placebo 6 hours prior to coitus**
- **6 min delay on 25 mg; approx. 8 min delay on 50 mg**

PAROXETINE AND PREMATURE EJACULATION

- 14 patients completed 6 week trial double-blind placebo study
- 20 mg paroxetine for one week then 40 mg for 5 weeks or placebo
- Assessment at weeks 3 and 6
- Ejaculatory latency increased from 30 seconds pretreatment to 7.5 minutes at 3 weeks and 10 minutes at 6 weeks

Waldinger et al. AJP, 1994

BENZODIAZEPINES (LORAZEPAM, VALIUM) CAN BE OF HELP IN TREATING PREMATURE EJACULATION

- **LORAZEPAM: Case report of successful treatment of widower with premature ejaculation 1-2 mg prior to coitus¹**
- **VALIUM: Double-blind placebo study of 8 female volunteers on escalating dose schedule 2, 5, 10 mg showed delay of orgasm with increasing doses²**

¹Segraves et al. *AJP*, 1987; ²Riley & Riley, *SMT*, 1986

ANTIDEPRESSANTS AND ADVERSE SEXUAL SIDE EFFECTS

Some antidepressants adversely affect desire, arousal, and/or orgasmic function

- TCAs
- MAOIs
- SRIs

MONTEIRO ET AL. BJP, 1987

- **Double-blind study, clomipramine, placebo in OCD**
- **23/24 (96%) developed anorgasmia or delayed orgasm on clomipramine**
- **No difficulties on placebo**
- **Problem started at low dosages (25-50 mg)**
- **Total anorgasmia at 100-150 mg**
- **Minimal tolerance with continued use**

HARRISON ET AL. JCP, 1986

- Double-blind study of imipramine, phenelzine, placebo
- RDC criteria major, minor, intermittent depressive disorder
- 60-90 mg phenelzine, 200-300 mg imipramine
- 6 weeks of treatment, n=82
- Sexual function questionnaire
- Phenelzine and imipramine impaired libido and orgasm in both sexes
- Phenelzine caused more impairment

HARRISON ET AL. JCP, 1986

- **Decreased libido on placebo** **8%**
- **Decreased libido on imipramine** **20%**
- **Decreased libido on phenelzine** **30%**

IMPRAMINE VS PAROXETINE

- **38 outpatients received double-blind treatment**

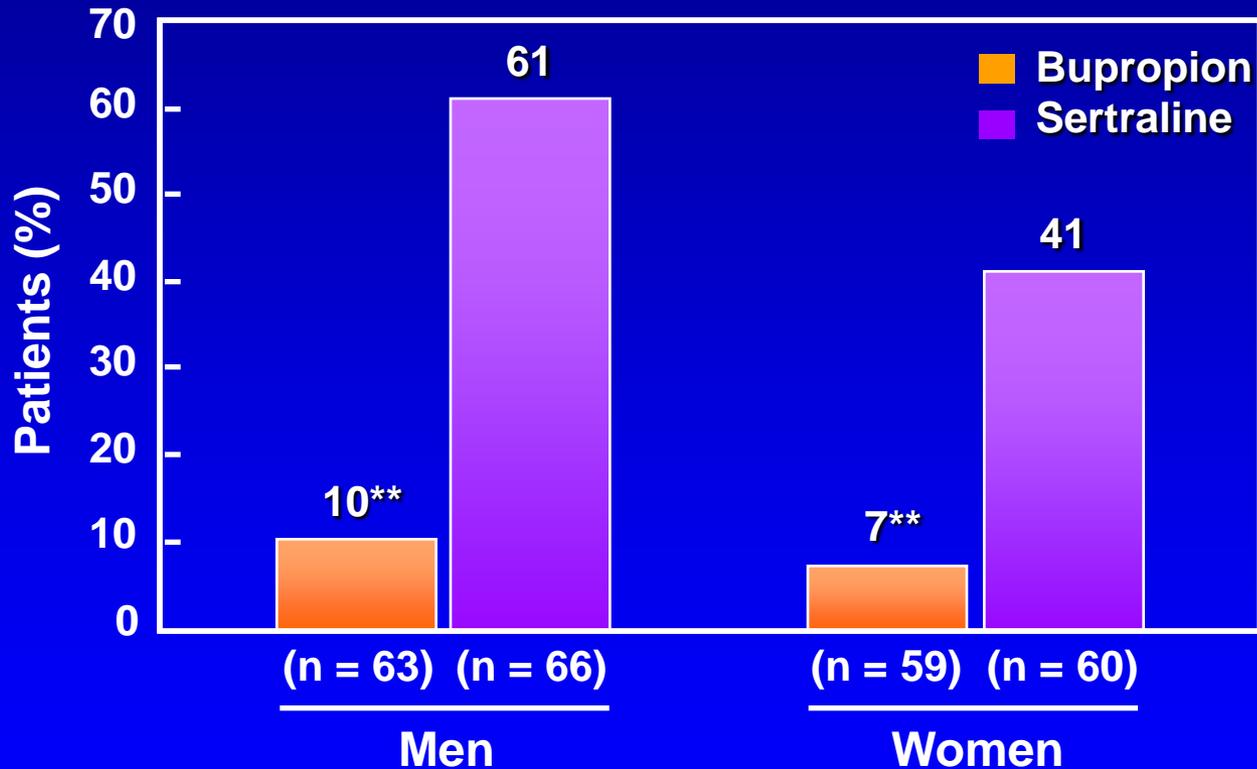
15% on imipramine and 35% on paroxetine had sex problems

Mainly decreased ability to become aroused

Ontiveros et al. Biol Psychiatry

16-Week Double-Blind Comparison of Bupropion* vs Sertraline

Self-Report of Orgasm Dysfunction at Any Time During Study



*Sustained-release formulation.

** $P < 0.001$ vs sertraline.

Kavoussi RJ et al. *J Clin Psychiatry*. 1997;58:532–537.

TRAZODONE AND LIBIDO

- Case reports of increased libido above premorbid baseline in both sexes

Gartrell, AJP, 1986

Sullivan, JCP, 1988

Sullivan, AJP, 1987

ERECTILE FAILURE AND ANTIDEPRESSANT THERAPY

- Imipramine (Tofranil)
- Desipramine (Norpramin)
- Nortriptyline (Pamelor)
- Amitriptyline (Elavil)
- Doxepin (Sinequan)
- Clomipramine (Anafranil)
- Protriptyline (Vivactil)
- Tranylcypromine (Parnate)
- Trazodone (Desyrel)
- Maprotiline (Ludiomil)
- Lithium (Lithobid)
- Paroxetine (Paxil)
- Bupropion (Wellbutrin)
- Sertraline (Zoloft)
- Amoxapine (Asendin)
 - Lithium also reported

KOWALSKI ET AL. BJP, 1985

- **Double-blind, three way crossover design**
- **6 normal males, 3 nights NPT**
- **Amitriptyline, mianserin, placebo x14 days**
- **Both amitriptyline, mianserin reduced maximum NPT and duration of NPT**

ERECTILE FUNCTION AND ANTIDEPRESSANTS

- **Multisite double-blind titrated dose study**
- **Comparison of sertraline (Zoloft) vs nefazodone (Serzone)**
- **No significant effect of either drug on erections**

Feiger et al, JCP, 1995

CHARACTERISTICS OF DRUG-INDUCED ORGASM/EJACULATION PROBLEMS

- Onset 1-2 weeks after initiation or dose increase
- Generalized sexual problem not specific to a situation
- Desire is usually normal but orgasm is impaired
- Dissipates with drug discontinuation

SEROTONIN AND EJACULATION

- **Ascending serotonergic projections to medial preoptic area which may be inhibitory to ejaculation**
- **Descending serotonergic pathways to lumbosacral motor nuclei**

LUVOX VS ZOLOFT

- **Multicenter double-blind 7 week study**
- **50-150 mg fluvoxamine (Luvox)**
- **50-150 mg sertraline (Zoloft)**
- **Outpatient major depression**
- **Equal efficacy**
- **Zoloft higher incidence of sexual dysfunction including orgasm, libido problems**

SERTRALINE (ZOLOFT) VS NEFAZODONE (SERZONE)

- **Multisite, double-blind titrated dose, double dummy study**
 - Used sexual questionnaire
- **Women have difficulty achieving orgasm**
 - 47% on Zoloft
 - 17% on Serzone
- **Men having ejaculatory delay**
 - 67% on Zoloft
 - 18% on Serzone

BUPROPION VS SERTRALINE

- **Multisite, double-blind study, double dummy**
- **Wellbutrin SR 100-300 mg/d**
- **Zoloft 50-200 mg/d**
- **Equal efficacy**
- **Significantly higher incidence of sexual dysfunction on Zoloft as early as day 7**

VINAROVA ET AL. ACTIV NERV, 1972

- **Lithium carbonate, bipolar disorder**
- **Placebo-controlled, double-blind**
- **2/10 erectile failure on lithium**
- **No problems on placebo**

ANTIDEPRESSANT-INDUCED ANORGASMIA

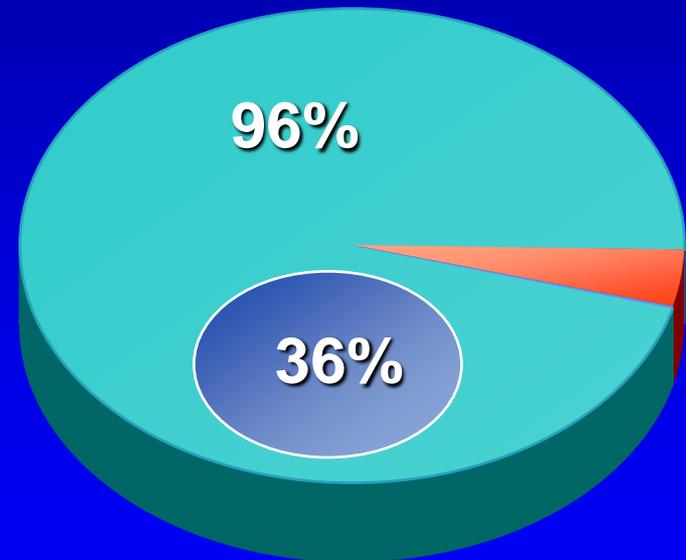
- Phenezine (Nardil) 30%
- Clomipramine (Anafranil) 96%
- Imipramine (Tofranil) 40%
- Fluoxetine (Prozac) 20-75%
- Sertraline (Zoloft) 20-70%
- Paroxetine (Paxil) 20-30%
- Venlafaxine (Effexor) 20-30%

Evaluation of SISD

- **History**
 - Assess premorbid functioning in 3 phases
 - Assess treatment of psychiatric disorder
 - Assess medical factors
 - Assess non-psychiatric medications' roles
 - Assess situational/relationship factors
 - ?Use of questionnaires
- **Physical examination/laboratory testing**
 - Consider referral to Internal Medicine/Urology

Most Patients Report Sexual Dysfunction Only in Response to Direct Inquiry

- On direct questioning, 96% of patients in one study reported drug-induced anorgasmia
- Of these patients, 36% had not acknowledged any drug-induced sexual dysfunction on a side-effect questionnaire



SISD: Treatment Approaches

- Stop the *offending* medication
- Do *nothing*
- Change medication *schedule*
 - Change timing of doses
 - Try drug holiday
- Switch to a *better* medication
- Add a medication *antidote*

“Do Nothing”^{1,2,3}

- **Orgasm is frequently impaired.^{1,2}**
 - In both men and women
 - Unlikely to spontaneously normalize
- **Arousal may return to baseline levels after several months¹**
- **Desire may improve over time**
 - For prospectively studied group of women, desire and arousal improved over 6 weeks of SSRI treatment³

¹Grimes JB: *New Research Abstract 95, APA Proceedings 1996*; ²Labbate et al: *J Sex Marital Ther* 24:3-12, 1998; ³Piazza et al: *AJP* 154:1757, 1997

NURNBERG & LEVINE, AJP, 1987

- **Phenelzine-induced anorgasmia**
- **3 case reports**
- **Spontaneous improvement after 6-20 weeks of treatment**

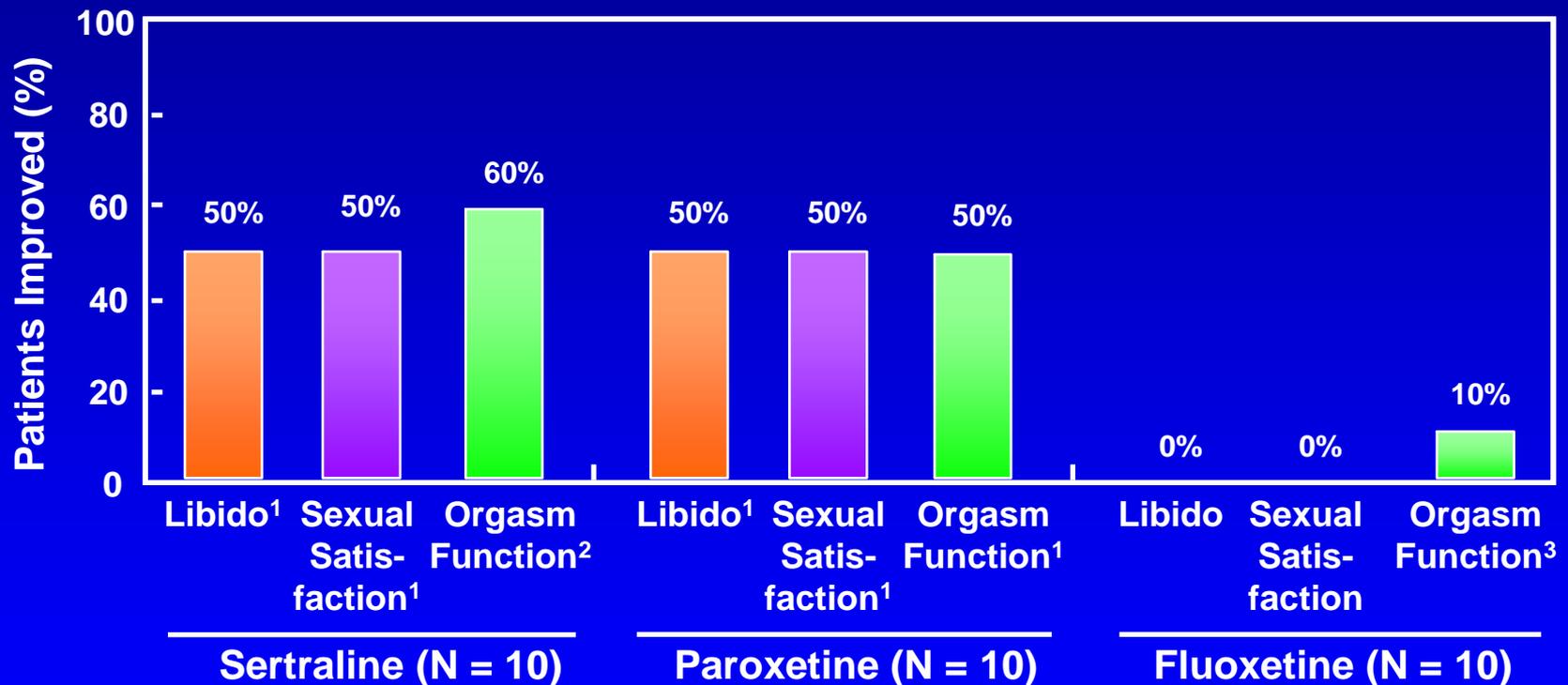
Schedule Changes

- **Rationale: Minimize drug level at time of sexual activity**
- **Change in daily timing of doses**
- **Weekend “drug holidays”***
- **Works better with shorter half-life drugs**
- **Discontinuation symptoms?**
- **Relapse symptoms?**

**Rothschild: Am J Psychiatry 152:1514-1516, 1995*

SSRI-Induced Sexual Dysfunction Efficacy of a Drug Holiday

Patients Taking SSRIs Who Reported “Much” or “Very Much” Improved Sexual Functioning for at Least 50% of Four Weekend Drug Holidays



¹Improvement in two of five women and three of five men.

²Improvement in three of five women and three of five men.

³Improvement in none of six women and in one of four men.

Rothschild AJ. *Am J Psychiatry*. 1995;152:1514–1516.

SISD: “Better” Antidepressants

- **Are the SSRI’s equivalent?**
 - Paroxetine most likely to interfere with ejaculation
 - Is fluvoxamine less likely to cause SISD?
 - How is information obtained
 - Spontaneous reporting/package insert data
 - Case reports
 - Retrospective survey
 - Prospective study
 - Animal model
 - Normal volunteers vs patients

SISD: Is Fluvoxamine Better ?

- **Prospective study:**
 - Dble-blind pla-cont. tx of rapid ejaculators with paroxetine (20 mg/d), fluoxetine (20 mg/d), or sertraline (50 mg/d) increased IELT significantly more than did fluvoxamine (100 mg/d) or placebo¹
- **Animal model:**
 - Paroxetine, sertraline slightly more detrimental to rat sexual behavior than clomipramine, fluvoxamine, fluoxetine²
- **Normal volunteers vs patients**
 - Fluvoxamine 150 mg/d x 4 weeks produced 35% rate of sexual dysfunction in healthy volunteers³

1. Waldinger et al 1998; 2. Mos et al 1999 ;
3. Nafziger et al 1999

SISD: Are Non-SSRIs Better?

- **Non-SSRI antidepressants: Pros and Cons**
 - **Bupropion**
 - **Nefazodone**
 - **Mirtazapine**

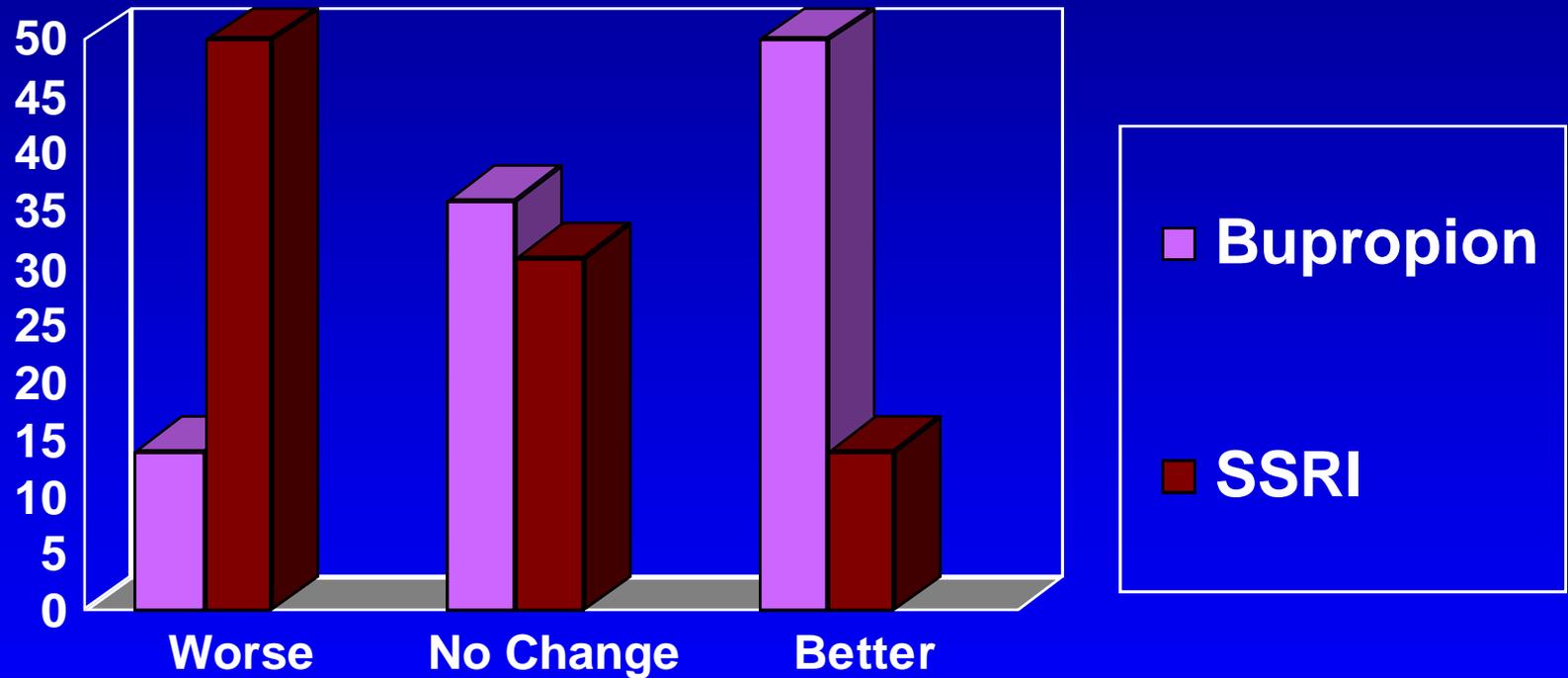
Bupropion (Wellbutrin)

- Rarely impairs libido, arousal, orgasm¹
- Has resolved SSID in male/female patients switched from fluoxetine²
 - Very significant level of improvement (>80%)
- Different spectrum of effectiveness and different contraindications from SRI's
- May have “prosexual effects”

¹Gardner and Johnston: *J Clin Psychopharm* 5:24-29, 1985

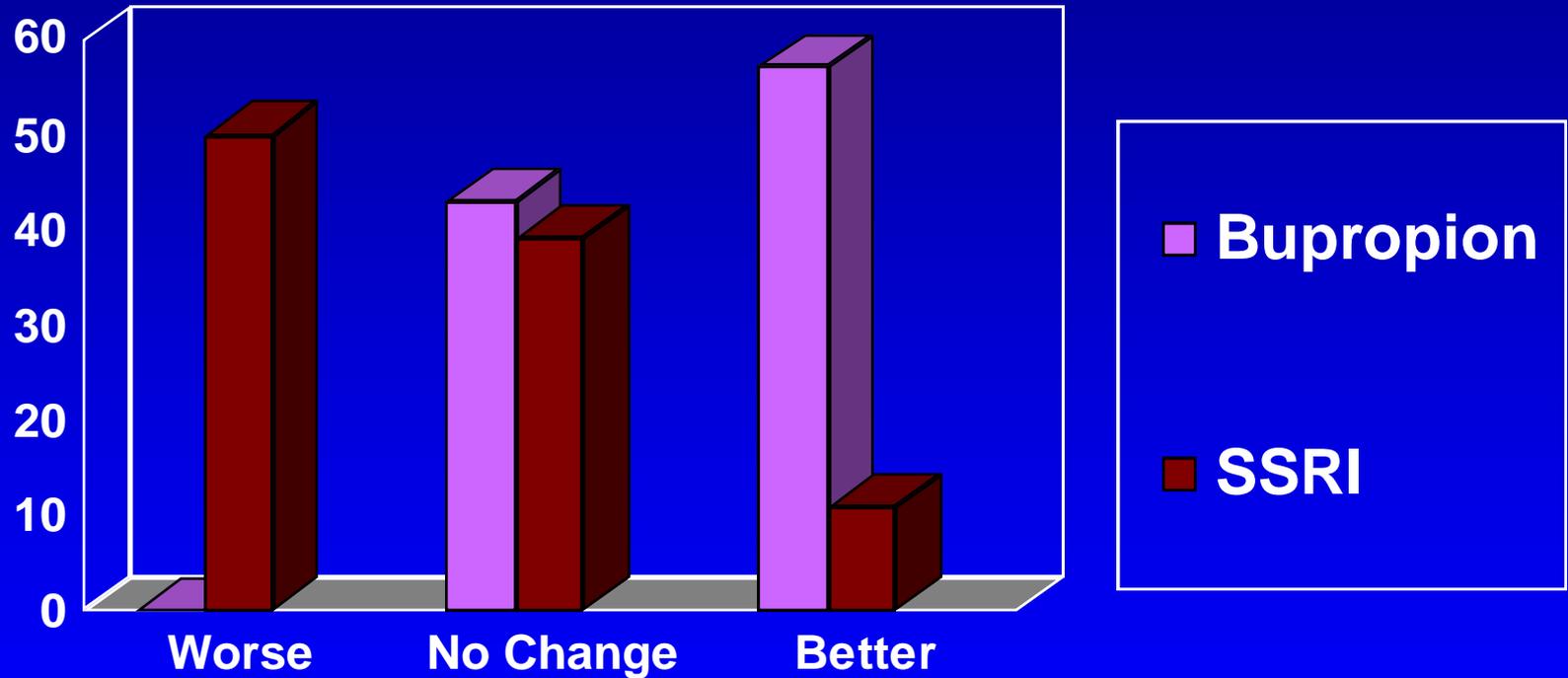
²Walker et al: *J Clin Psychiatry* 54:459-65, 1993

Comparison of Bupropion vs SSRI Effects on Libido



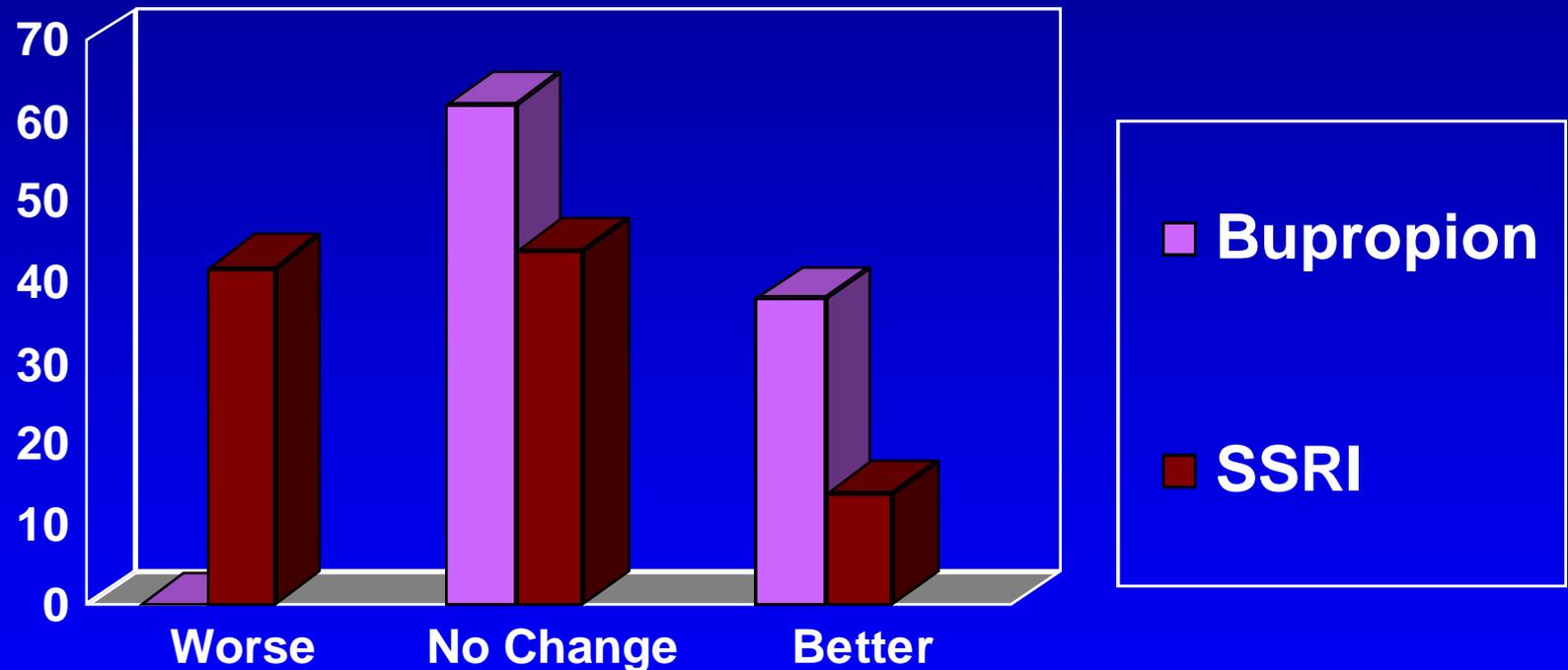
redrawn from Modell et al 1997

Comparison of Bupropion vs SSRI Effects on Arousal



redrawn from Modell et al 1997

Comparison of Bupropion vs SSRI Effects on Orgasm



redrawn from Modell et al 1997

Nefazodone (Serzone)

- **Low incidences¹ of:**
 - **Decreased libido**
 - **Anorgasmia**
 - **Abnormal ejaculation**
- **Comparison to sertraline:**
 - **Improvement of SISD in >50% of patients switched in double-blind study²**

¹Feiger et al *J Clin Psychiatry* 57Suppl2:53-62, 1996

²Ferguson et al, data presented at 1996 APA New Research

Strategic “Antidotes” for SISD

- Increase central dopamine +/- norepinephrine
- Decrease central serotonin
- Increase peripheral acetylcholine
- Mechanisms unknown

Popular Strategic Antidotes For Reducing Antidepressant-induced Sexual Dysfunction (All Co-prescribed With Primary Antidepressant)

- **Bupropion**
- **Amantadine**
- **Methylphenidate or Dexedrine**
- **Buspirone**
- **Cyproheptadine**
- **Ginkgo biloba**
- **Yohimbine**
- **Cholinergic agents**

Bupropion

- Case report: 50 year old man with dysfunction in libido, erection, orgasm helped with addition of bupropion 75 mg/d to fluoxetine 20 mg/d.¹
- 4 of 8 patients with SRI sexual dysfunction reported improvement after 1 month of augmentation with bupropion 75 mg/d²
- Potential pharmacokinetic interaction requires awareness, discussion, and monitoring³

¹Labbate and Pollack: *Ann Clin Psychiatry* 6:13-15, 1994; ²Labbate et al: *Ann Clin Psychiatry* 9:241-5, 1997; ³Hopkins: *Biol Ther in Psych* 19:31-2, 1996

Amantadine

- **Based on case reports only**
 - **3 male patients¹**
 - **Decreased libido**
 - **Erectile difficulty**
 - **Anorgasmia**
- **DA agonist (increases presynaptic release)**
- **100 mg q d to bid**
- **Intermittent use: 100 mg 5 hr prior to activity²**

¹Balogh et al: *J Clin Psychiatry* 53:212-13, 1992

²Balon: *J Sex & Marital Therapy* 22:290-2, 1996

Methylphenidate/Dextroamphetamine

- Study: Methylphenidate or dextroamphetamine effective in 80% of 25 (11F, 14M) patients with SIRD due to SRI1
- Case report:: 53 year old man used dextroamphetamine 25 mg/d to reduce anorgasmia on phenelzine 75 mg/d²
- All phases of sexual function improved
- Reduce “Lag time” of 1 hour by sublingual absorption
- Side effects include insomnia

¹Bartlik et al: *New Research*, 1996 APA

²Gitlin: *J Clin Psychiatry* 56:124, 1995

Buspirone

- Study: Substantial improvement of SISD in 11 of 16 patients on SSRI¹
- *Use:* for reduced libido
- *Mechanism:* 5HT_{1A} agonist, D₂ antagonist, (1-PP is alpha NE antagonist)
- *Dose:* >30 mg/d, divided dosage
- *Side effects:* sedation, akathisia, dizziness, insomnia, nervousness, GI disturbance, nausea, headache; serotonin syndrome; pregnancy Category B; interactions

¹Norden: *Depression* 2:109-12, 1994

Cyproheptadine

- **Effective with a variety of antidepressants**
- **Wide dose range**
- **Significant side effect potential**
- **Data are from case reports only**

STEELE AND HOWELL, JCP, 1986

- 150 mg imipramine, complete anorgasmia
- Double-blind, lactose placebo-controlled, single-subject study
- 4 mg cyproheptadine (antiserotonergic, antihistaminic, anticholinergic)
- 10 mg diphenhydramine (anticholinergic, antihistaminic)
- Cyproheptadine more effective than diphenhydramine

Ginkgo Biloba

- **Used for at least 4000 years in China**
- **Concentrated, standardized extract (GBE)**
- **Mechanisms: Enhanced vascular flow, prostaglandin, and serotonin effects claimed**
- **Urologic Treatment of Erectile Dysfunction**
 - **50% improved after 60 mg/d x 6 mo.¹**
- **Side effects: increased bleeding time; large doses may produce nausea, restlessness, diarrhea, vomiting**

¹Sikora et al, J Urology 1989

Ginkgo Biloba

- Study: Over 60 pts (men and women) successfully treated in 1 uncontrolled series¹
 - Beneficial effects on all phases of SISD claimed
 - Dosage for SISD: GBE 50:1, 60 mg tid-qid
 - Prior failures with: SSRI's, venlafaxine, bupropion, cyproheptadine, amantadine, yohimbine, buspirone
 - Long-term (>1 yr) stability of improvement
- Cognitive benefits claimed
- Relief of fluoxetine induced genital anesthesia claimed

¹Cohen AJ: *New Research*, 1996 APA
and Cohen AJ personal communication

Yohimbine

- **Open trial: 54 outpatients with fluoxetine SISD ¹**
- **5.4 mg tid improved all phases of sexual response in men and women**
- **Discontinuation due to side effects in 10% of patients**
- **No patients had comorbid panic disorder**

¹Jacobsen: *J Clin Psychiatry* 53:119-22, 1992

Cholinergic Antidotes for Antidepressant-Induced Male Erectile Disorder

- Bethanechol: HCAs¹
- Neostigmine: HCAs²

¹Yager J. *J Clin Psychiatry*. 1986;47:210–211.

²Kraupl-Taylor F. *BMJ*. 1972;1:305.

Other Approaches to Treating Male Erectile Disorder (SISD or Other Etiology)

- Intracavernosal injections
- Vacuum devices
- Prostheses
- Urethral suppositories (PGE1)
- Oral agents
- Psychotropics
- Arginine
- DHEA
- Sildenafil (Viagra)

Male Erectile Disorder: Sildenafil

- GMP phosphodiesterase inhibitor
- Peripheral action -- increases NO availability
- Mild side effects: headache, dyspepsia, pelvic musculo-skeletal pain
- Excellent success rate with psychogenic impotence and organic impotence
- No specific data on antidepressant impotence

Boolell et al 1996

Where Does Treatment of Erectile Disorder Fit Into Psychiatric Practice?

- Establish a proper diagnosis
 - Take and record appropriate medical history
 - Perform and record appropriate physical examination (or ascertain that this has been done)
 - Consultation may be crucial because erectile dysfunction may result from undetected cardiovascular, endocrine, neurologic or other disease
- Establish an appropriate treatment regimen
- Maintain appropriate records

Viagra (Sildenafil) and Female Sexual Dysfunction

- At mean dose of 57 mg/d sildenafil helped libido, arousal, orgasm, and sexual satisfaction among women affected by antidepressant-induced sexual dysfunction in open study¹
- Several other open studies have confirmed this finding^{2,3,4}

¹ Fava et al, Psychother Psychosom 1998;

² Nurnberg et al, J Clin Psych 1999;

³ Nurnberg et al Psychiatr Serv 1999;

⁴ Salerian et al, J Sex Marital Ther 2000

Summary

- **Sexual Dysfunction is a frequent concomitant of antidepressant treatment**
- **Clinician awareness and direct inquiry are necessary to determine presence of sexual dysfunction**
- **A variety of treatment options are available**