Sex & Drugs: Pathophysiology of Drug Induced Sexual Dysfunction in Men & Women

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Scope of the Problem: Epidemiology of Sexual Dysfunction: Men

- Common problem worldwide
  - 30 million in US; 152 million worldwide
  - 31% incidence of *any* dysfunction in men 18-59 years old
  - Erectile dysfunction (ED) most commonly reported, but effects on libido also occur
- ED may be age related
  - US: Complete impotence increased from 5% in men 40 years old to 15% in 70 years old
  - Netherlands: ED 22% men 50-54, increased to 54% in 70-78 year old

Feldman et al J. Urol 1994;151:54-
Steftel J. Urol 2003;169:1999-2007
Laumann et al JAMA 1999;281:537-544
Blanker et al Urology 2001;57:763-

Spectrum of Potential Sexual Dysfunction in Men

Alterations in Desire
- Hyposexuality
- Inhibition of desire
- Aversion
- Hypersexuality
- Panic/phobia
- Obsessive-compulsive

Erection Abnormalities
- Inability/difficulty obtaining erection
- Inability/difficulty maintaining erection
- Decreased firmness of erection
- Ejaculation through flaccid or semi-erect penis
- Painful erection
- Peyronie's disease
- Priapism
- Decreased or absent nocturnal/morning erections

Infertility
- Decreased or malformed spermatogenesis
- Decreased sperm motility
- Hypogonadism
- Testicular atrophy

Orgasm/Ejaculation Disorders
- Ejaculatory incompetence (inability)
- Ejaculatory inhibition (delay)
- Ejaculation without orgasm
- Orgasm without ejaculation
- Retrograde ejaculation
- Decreased ejaculatory volume
- Anesthetic ejaculation
- Spontaneous orgasm
- Painful ejaculation
- Premature ejaculation

Dyspareunia
- Pain during intercourse
- Pain after intercourse
- Painful ejaculation

Breasts
- Galactorrhea
- Gynecomastia
- Breast pain/tenderness

Paraphilia

Crenshaw & Goldberg. Sexual Pharmacology. Drugs That Affect Sexual Functioning. WW Norton & Co. New York 1996

Etiology of ED

Anatomical causes

- Congenital Deformities
- Testicular Fibrosis

Cardio-Respiratory causes

- Coronary or pulmonary insufficiency, MI

Drugs

- **Alcohol**, Beta blockers
- Anti-depressants, Amphetamines
- Antiandrogens ,
  Monoamine oxidase inhibitors
- **Nicotine**, Narcotics
- Barbiturates
- Cimetidine, Clonidine

Endocrine Causes

- **Diabetes**
- Age related decline in T
- Hyperprolacteinemia

Genitourinary causes

- Phimosis, Priapism

Hematological Causes

- Sickle cell anemia
- Acute and chronic Leukemia's

Infectious cause

- Elephantiasis, Urethritis
- Mumps
- Genital TB

Neurologic Causes

- Cerebral Palsy
- Spinal cord transection or tumors
- Multiple sclerosis
- PID

Vascular causes

- Thrombotic obstruction
- Aneurysm
- Arteritis
- Impaired blood flow

Miscellaneous causes

- CRF, Cirrhosis, Obesity

Psychogenic ED

Developmental Factors

- Maternal or paternal dominance
- Conflicted parent-child relationship
- Severe negative family attitude toward sex
- Child abuse
- Traumatic coital experience
- Gender identity conflict

Affective actors

- Anxiety- performance and size
- Guilt
- Depression
- Poor self esteem
- Hypochondria
- Fear of VD

Cognitional factors

- Acceptance of cultural myths
- Paraphilias

Interpersonal factors

- Poor communication
- Hostility toward partner
- Lack of physical attraction to partner

Scope of the Problem: Epidemiology of Sexual Dysfunction: Women

- Female dysfunction can be subdivided into disorders of desire, arousal, orgasmic, pain
- Incidence varies depending upon ascertainment methodology
  - 40% women 18-59 years
    - Low desire 22%, arousal problems 14%, pain 7%

Phillips N. Am Fam Physician 2000;62:127-136
Laumann et al. JAMA 1999;281:537-544

Spectrum of Potential Sexual Dysfunction in Women

Alterations in Desire
- Hyposexuality
- Inhibition of desire
- Aversion
- Hypersexuality
- Panic/phobia
- Obsessive-compulsive

Lubrication Disorders

Orgasmic Disorders
- Orgasmic inhibition
- Anorgasmia
- Diminished number of orgasms
- Altered perception
- Anesthetic orgasm
- Spontaneous orgasm

Dyspareunia
- Pain during intercourse
- Pain after intercourse
- Painful orgasm

Menstrual Disorders
- Dysmenorrhea
- Menorrhagia
- Amenorrhea

Clitoral Hypertrophy

Infertility
- Decreased frequency of ovulation
- Decreased quality of egg
- Hypofertility

Breast Disorders
- Galactorrhea
- Gynecomastia
- Pain/tenderness

Paraphilia

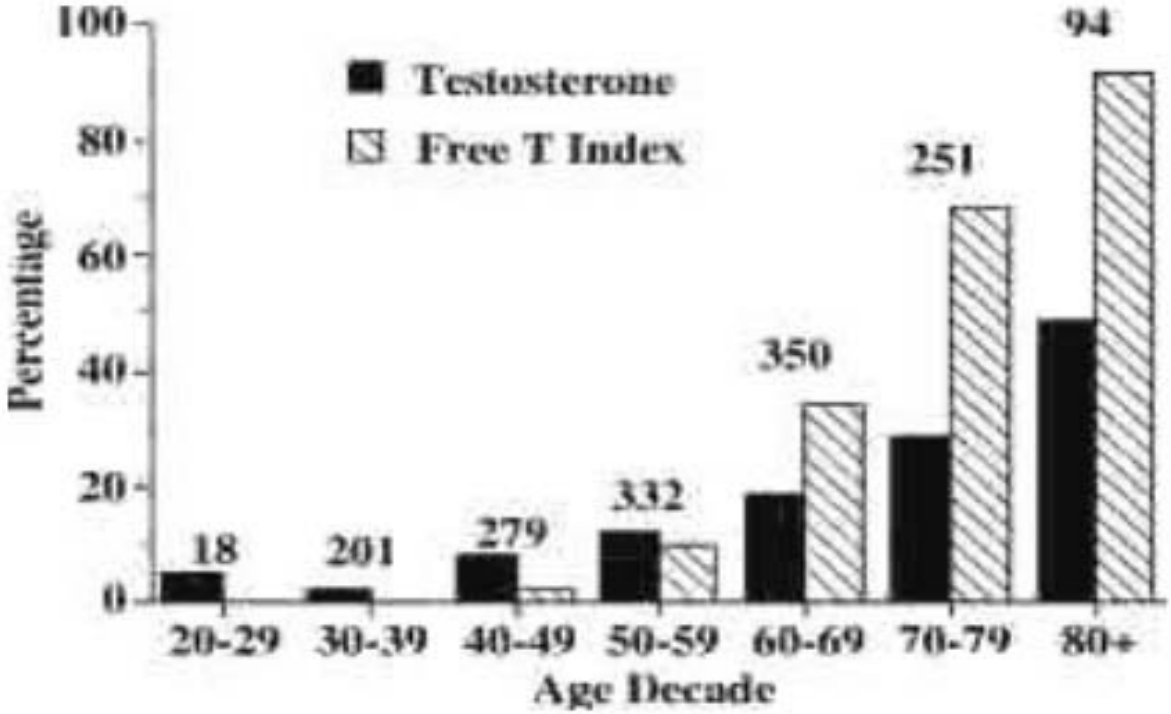
Crenshaw & Goldberg, Sexual Pharmacology, Drugs That Affect Sexual Functioning, WW Norton & Co. New York 1996

Hormonal Changes in the Aging Patient

HORMONE	CHANGE
Testosterone	Decreased ↓
Bioactive testosterone	Decreased ↓
Dihydroepiandrosterone	Decreased ↓
Sex hormone binding globulin (SHBG)	Increased ↑
Lutenizing hormone (LH)	Increased ↑

Steftel J Urol 2003;169:1999-2007

Testosterone levels with Age

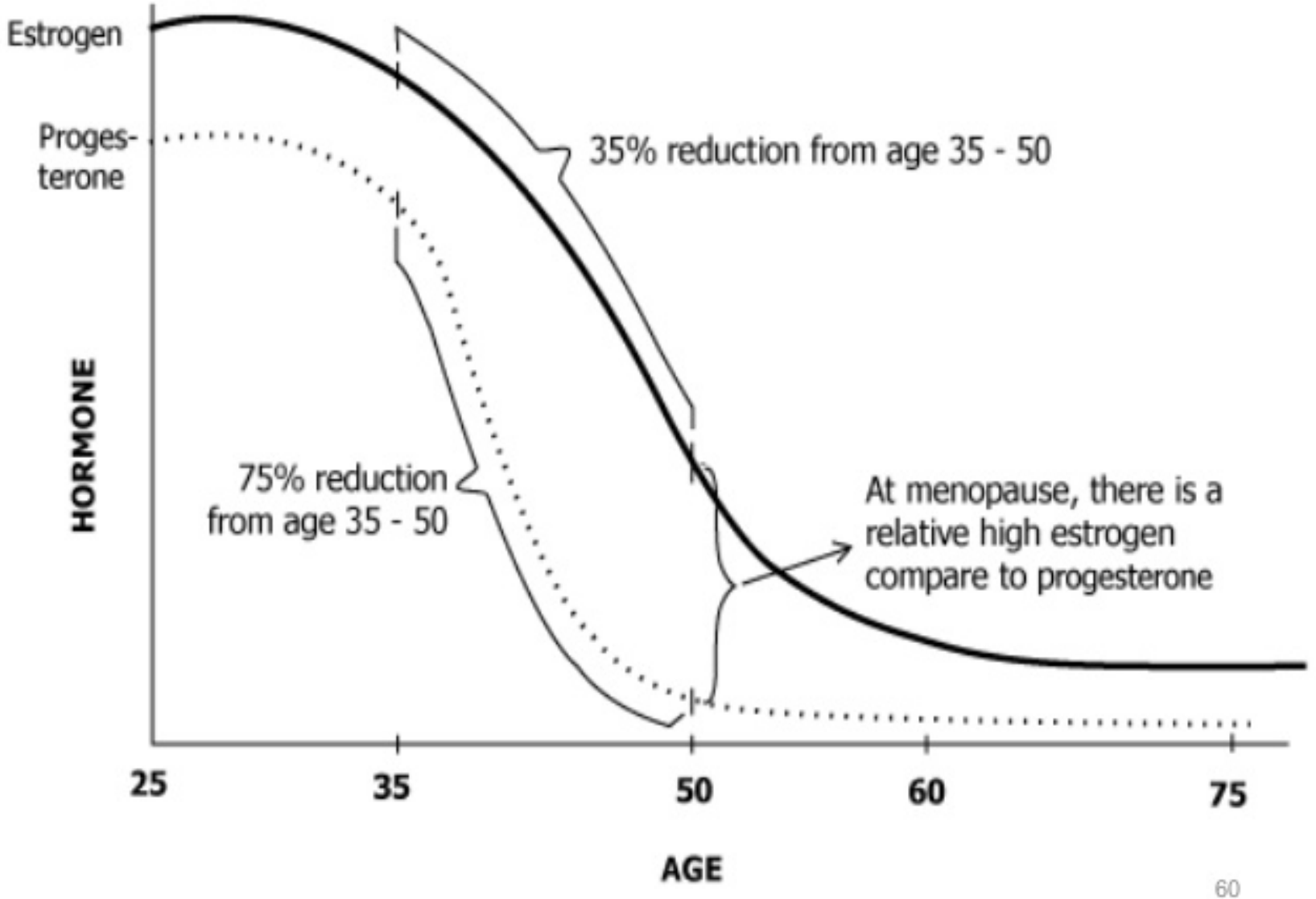


Hypogonadism in aging men.
Total testosterone less than 11.3 nmol/L (325 ng/dL) (*shaded bars*).
Total testosterone/SHBG (free T index) less than 0.153 nmol/Ls (*striped bars*).
Numbers above each pair of bars indicate the number of men who were studied.

Signs and Symptoms of the Andropause

Endocrine	Somatic	Sexual	Psychological.
• Erectile dysfunction • Reduced erectile quality • Diminished nocturnal erections	• Decreased vigor • Easily fatigued • Poor exercise tolerance • Diminished strength and muscle mass • Decrease in bone mineral density	• Decreased Libido • Decreased Sexual Activity • Limited Quality Of Orgasm • Reduced Ejaculate Strength • Reduced Ejaculate Volume	• Mood changes • Poor concentration • Loss of motivation • Reduced initiative • Memory impairment • Anxiety, Depression, Irritability, Insomnia

Hormonal changes over age in female



Assessment of Sexual Adverse Effects: How good is the data?

- Many studies retrospective in nature
- Many studies lack controls
- Imprecise classification/description of medical and/or psychiatric comorbidities
- Insufficient data on drug exposure (how many, how long, previous exposure, doses, etc…)
- Patient self report vs clinician interview

Assessment of Sexual Dysfunction

- Early clinical studies rarely detect sexual dysfunction
  - Few studies systematically evaluate for this adverse effect
- Post-marketing surveillance studies also historically report low incidence
- Relatively few physicians (~50%) routinely obtain sexual history from their patients
  - Direct inquiry yields higher reporting rates as compared with spontaneous reports (58% vs 14%)

Bull et al Sex Tram Dis 1999;26:584-589
Montejo-Gonzalez et al J Sex Marital Ther 1999;23:176-194

Neurophysiology of Sexual Response

The Sexual Response

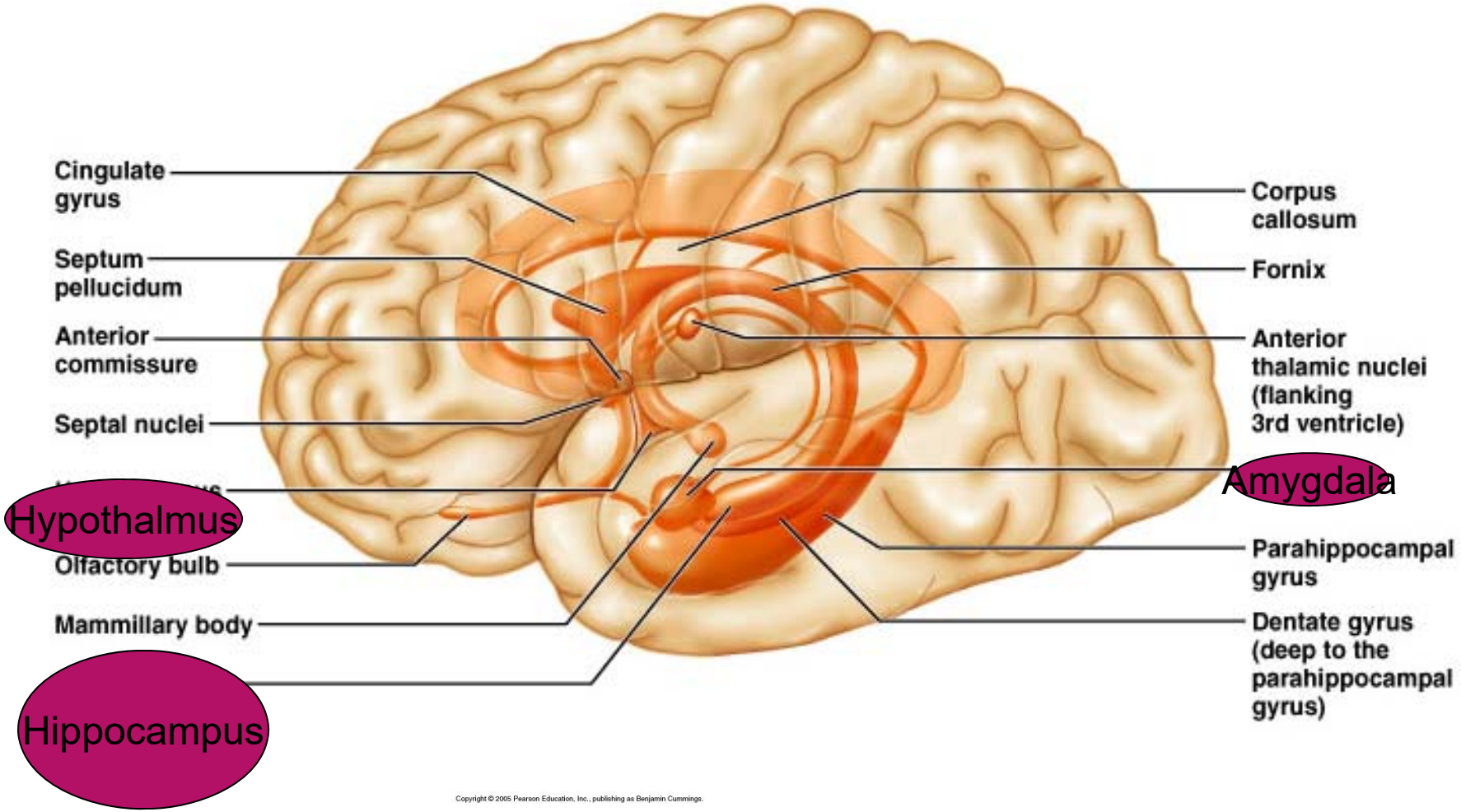
- Sexual response is a complex, multifactorial process
  - Sexual dysfunction may result from a disturbance in 1 or more domains including
    - Cognitive
    - Psychosocial
    - Neurological
    - Vascular

Neurophysiology of Sexual Response

- Requires intact libido and arousal response
  - Libido (desire) involves both affective and cognitive processes
  - Arousal (capacity to respond to stimuli) depends on neural, muscular and vascular response
- Sexual response is under control of both central & peripheral neural systems

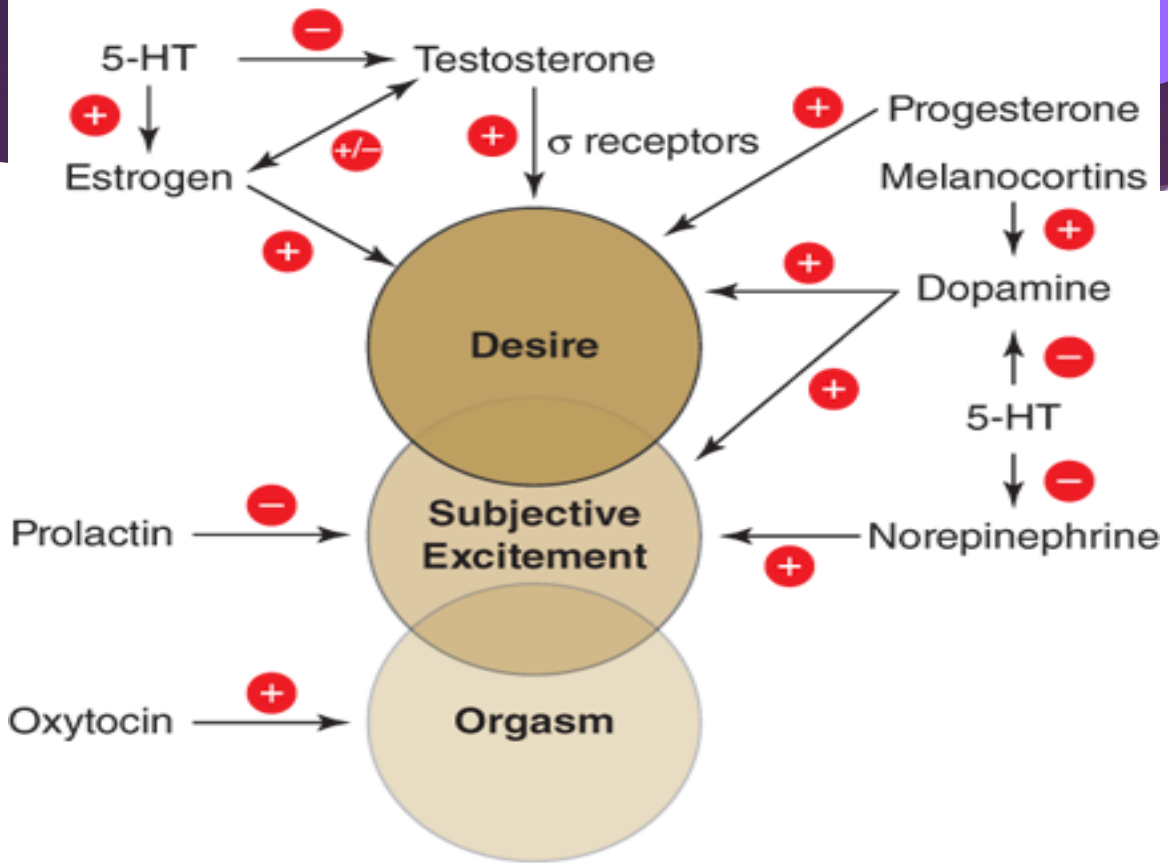
Argiolas & Melis. J Endocrinol Invest 2003;26(Suppl 3):20-22

Limbic system & Hypothalmus



Adapted: Marieb. Human Anatomy 4th Ed.

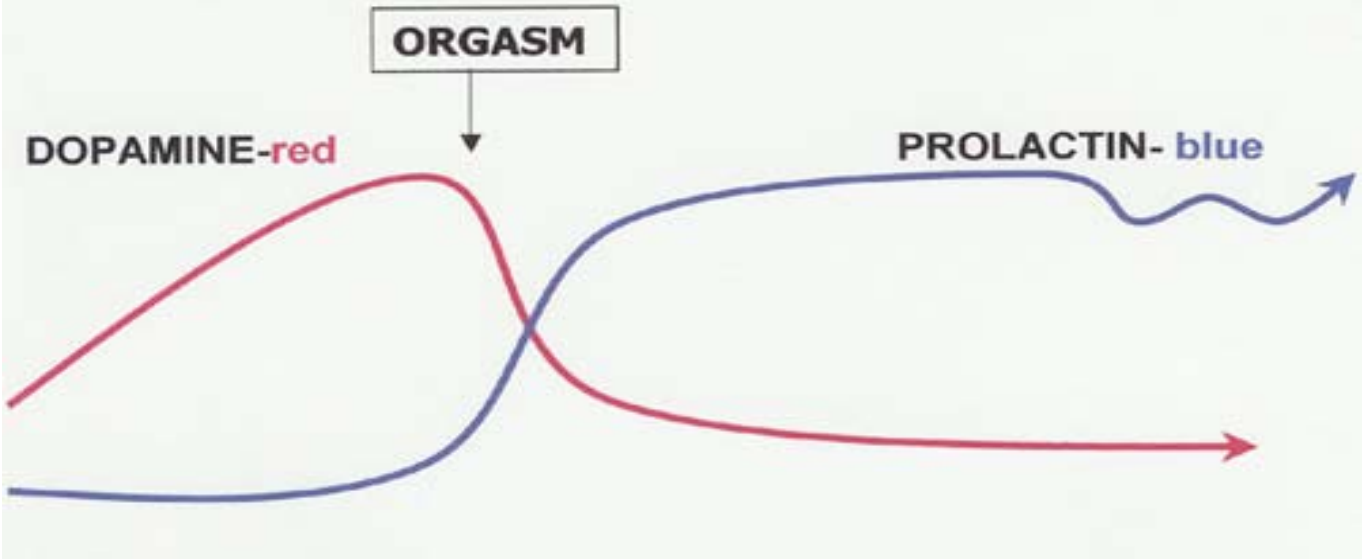
Central Effects on Sexual Function



Source: J.B. Halter, J.G. Ouslander, S. Studenski, K.P. High, S. Asthana, M.A. Supiano, C. Ritchie, W.R. Hazzard, N.F. Woolard: Hazzard's Geriatric Medicine and Gerontology, Seventh Edition, www.accessmedicine.com

PROLACTIN – DOPAMINE RELATIONSHIP

- At orgasm dopamine drops and prolactin shoots up.
- Prolactin functions to shut down sexual desire.
- Prolactin continues to be released in surges for up to two weeks after orgasm.
- There is an inverse relationship between dopamine and prolactin- when one is high the other is low.



Positive Modulators of Sexual Response: Neurotransmitters & Neuropeptides

NATURALLY OCCURRING
ENDOGENOUS SUBSTANCES
WITH GENERALLY EXCITATORY
SEXUAL ACTIONS
(Increase in dose or activity favorable to sex;
decrease in dose or activity unfavorable to sex.)

Adrenergic ($Alpha_1$) Activity
Adrenergic ($Beta_2$) Activity
Calcitonin-Gene-Related-Peptide (CGRP)
Cholinergic Activity
Dehydroepiandosterone (DHEA/DHEAS)
Dopamine (DA)
Endothelium-derived Relaxing Factor (EDRF)
Estrogen (female only)
Excitatory Peptides
Growth Hormone (GH)
Histamine
Luteinizing Hormone Releasing Hormone (LHRH)
Nitric Oxide (NO)
Oxytocin
Prostaglandins
Substance P (SP)
Testosterone
Vasoactive Intestinal Peptide (VIP)
Vasopressin
Zinc (replacement value only)

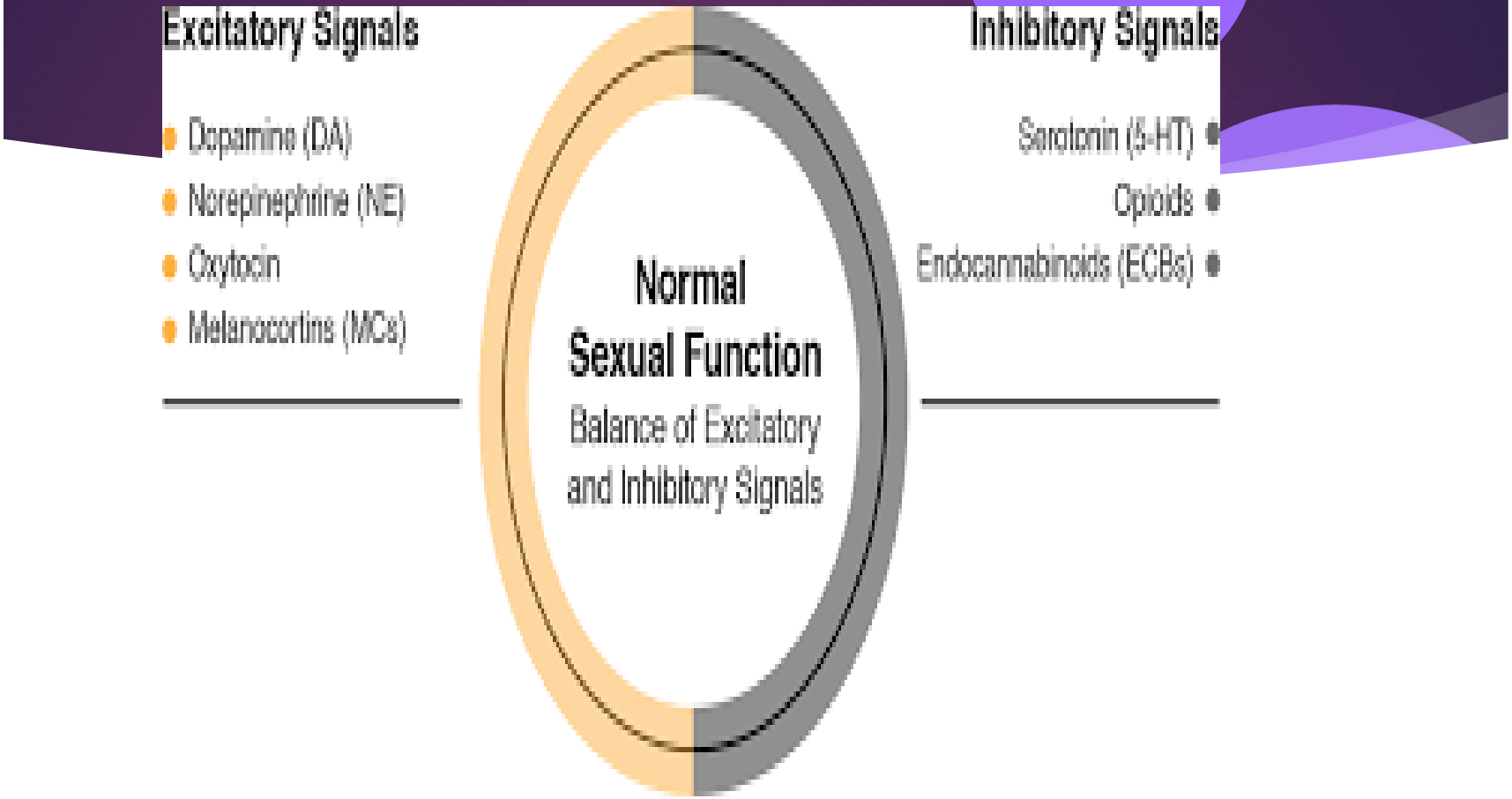
Crenshaw & Goldberg. Sexual Pharmacology. Drugs That Affect Sexual Functioning. WW Norton & Co. New York 1996

Inhibitory Modulators of Sexual Response: Neurotransmitters & Neuropeptides

NATURALLY OCCURRING ENDOGENOUS SUBSTANCES WITH GENERALLY INHIBITING SEXUAL ACTIONS
(Increase in dose or activity unfavorable to sex; decrease in dose or activity favorable to sex.)

Adrenergic ($Alpha_2$) Activity
Angiotensin II (Ang II)
Cortisol
Estrogen (male only)
Melatonin
Monoamine Oxidase (MAO)
Neuropeptide Y (NPY)
Opioids
Progesterone
Prolactin
Serotonin (5-HT) (5HT 1B, 2C,2A,3)
Thyroid Hormone*
Vasoconstrictive Peptides (Ang II and NPY)

Crenshaw & Goldberg. Sexual Pharmacology. Drugs That Affect Sexual Functioning. WW Norton & Co. New York 1996


Excitatory Signals
Dopamine (DA)
Norepinephrine (NE)
Oxytocin
Melanocortins (MCs)
Inhibitory Signals
Serotonin (5-HT)
Opioids
Endocannabinoids (ECBs)
Normal
Sexual Function
Balance of Excitatory
and Inhibitory Signals

Neurophysiology of Sexual Response: Inhibitory Effects

- GABA, opioid peptides reduces activation of nitric oxide synthase, and impairs erection
- Increased serotonin neurotransmission in lateral hypothalmus can result in decreased libido and impaired orgasm, ejaculation
  - Variable effects depending on 5-HT receptor subtype being stimulated
  - Postulated mechanisms include modulation of CNS dopamine, inhibition of NO synthase

Hyperprolactinemia

- Linked to impaired arousal
- Associated with D2 receptor, histamine and cholinergic receptor antagonism
- Associated with impaired orgasm & ejaculation

Control of Sexual Response: Sex Steroids

- Estrogen
  - Effect on sexual desire relatively small in both men and women
  - Does appear important in maintaining arousal in women
  - Hypothalmic aromatase suggests some central conversion of testosterone to estradiol
- Androgens
  - Male sexual behavior largely modulated by testosterone and DHT
  - Androgens important in maintaining arousal in women
  - Very low levels of testosterone consistently associated with decreased desire and occasionally ED
  - Supra-physiologic concentrations of testosterone ***do not*** modify desire or behavior

Rochira et al. J Endocrinol Invest 2003;26(Suppl 3):29-36

Local Control of Sexual Response: Modulation of Cavernosal Smooth Muscle

- Involvement of adrenergic & cholinergic systems
  - Alpha Adrenergic stimulation → contraction of cavernosal tissue → flaccid
    - B_2 activation → positive
    - B_2 blockade → inhibitory

    Cholinergic inhibitory control → relaxation of cavernosal tissue → erection
  - Neuronal & endothelial derived nitric oxide → activation of guanylate cyclase → ↑cyclic GMP → relaxation of smooth muscle → erection
  - VIP, NPY prostaglandins also involved in control of erection

Sexual Dysfunction

LOOKING AT THE WHOLE PATIENT: THE ROLE OF CO-MORBID DISORDERS

Medical Conditions Associated with SD

- Adrenal disease
- Alcoholism
- Atherosclerosis
- Cardiac disease
- CNS disease
- Diabetes
- Liver disease
- Peripheral nervous system disease
- Pituitary disease
- Thyroid disease
- Physical Trauma
- Psychiatric Illness

Causes of Sexual Dysfunction: Effect of Co-morbid disorders

Endocrine	*Gastrointestinal*	*Gynecological*	*Immunological*	*Neurological*	*Urological*	*Vascular*
Acromegaly	Constipation	Dysfunctional bleeding	AIDS/HIV	Alzheimer's disease	Chronic kidney disease	Arteriosclerosis
Adrenal dysfunction	Diarrhea	Dyspareunia	Arthritis & other bone/joint disorders	Brain lesions	Cystitis (acute, chronic & postcoital)	Fistula
Diabetes mellitus	Irritable bowel syndrome	Endometriosis	Cancer	Dementia	Epididymitis	Hypertension
Hyperprolactinemia	Ulcerative colitis	Genital warts	Chronic fatigue syndrome	Diabetic neuropathy	Peyronie's disease	Ischemia
Hypogonadism		Infertility/ pregnancy	Respiratory diseases	Epilepsy	Priapism	Myocardial infarction
Thyroid dysfunction		Menopause		Multiple sclerosis	Prostatitis	Stroke
		Menstrual cycle disorders		Parkinson's disease	Renal failure	Transient ischemic attacks (TIAs)
		PMS		Spinal injury or tumors	Urethrocele/ cystocele	Venous insufficiency
		Vaginismus		Stroke	Urinary incontinence	
		Vaginitis (bacterial, fungal, trichomonal, viral)				

Crenshaw & Goldberg. Sexual Pharmacology. Drugs That Affect Sexual Functioning. WW Norton & Co. New York 1996

Drug type	Examples that cause SD
Antihypertensive agents (Beta Blockers Calcium channel blockers)	Propranolol, metoprolol, nadolol, timolol, atenolol Nifedipine, verapamil, diltiazem
Antidepressants –SSRIs, MAO TCAs	
CNS depressants	Barbituates, benzodiazepines, alcohol
Neuroleptic antipsychotics	Chlorpromazine, haloperidol, olanzipine
Anticholinergics	benztropine
Anticonvulsants	Phenobarbital, phenytoin, carbazepine
Antiulcer drugs (H2-receptor blocker)	Cimetidine

Sexuality and MS

- Sexual difficulties may occur early in the course of MS.
- Predictive factors of sexual dysfunction include:
  - Increased disease activity
  - Depression and fatigue
  - Long duration of disease
  - Spasticity, bladder and bowel symptoms

Parkinsons Disease

Table 1 Sexual Dysfunction in Parkinson's Disease

	Symptoms	Definition	Prevalence in PD	Studies
Women	Decreased libido; deficiency or absence of desire for sexual activity	Female hypoactive sexual desire dysfunction[a]	46.9%–84%	Bronner et al. (2004), Sakakibara et al. (2001), and Waters and Smolowitz (2013)
	Difficulties in reaching orgasm	Female orgasmic dysfunction[a]	75%	Bronner et al. (2004)
	Increased libido and repetitive behaviors toward sexual gratification outside the accepted social and personal bounds	Hypersexuality	0.5%	Weintraub et al. (2010)
Men	Decreased libido; deficiency or absence of desire for sexual activity	Male hypoactive sexual desire disorder[a]	83%	Sakakibara et al. (2001)
	Decrease in penile erection; inability to attain or maintain penile erection sufficient for sexual intercourse	Erectile dysfunction[a]	42.6%–79%	Bronner et al. (2004), Kummer et al. (2009), and Sakakibara et al. (2001)
	Significant decrease in latency time to ejaculation	Premature ejaculation[a]	40.6%	Bronner et al. (2004)
	Decrease in ejaculation; absence of normal ejaculation	Anejaculation[a]	79%	Sakakibara et al. (2001)
	Decrease in orgasm; inability to reach orgasm	Anorgasmia[a]	87%	Sakakibara et al. (2001)
	Increased libido and repetitive behaviors toward sexual gratification outside the accepted social and personal bounds	Hypersexuality	5.2%	Weintraub et al. (2010)

[a]Consensus Statement from the Fourth International Consultation on Sexual Medicine (McCabe et al., 2016).

Epilepsy

- Sexual dysfunction described in 30-60% of men and women with epilepsy
  - Men report less sexual experience, anorgasmia and high incidence of ED
  - Low testosterone concentrations, and impaired nocturnal penile tumescence reported
  - Both men and women with temporal lobe epilepsy demonstrate diminished physiologic arousal (genital blood flow) in response to visual erotic stimuli
  - Likelihood of sexual dysfunction may increase in patients with continued seizures, and those with a longer history of seizures

Morrell Epilepsia 1991;32(Suppl 6):38-45
Morrell et al Neurology 1994;44:243-247
Fenwick et al Acta Neurol Scand 1985;71:428-435
Herzog et al Arch Neurol 1986;43:347-350

Epilepsy & Sexual Dysfunction in Women

- Herzog et al 2003
  - Sexual dysfunction scores significantly higher in women with temporal lobe epilepsy vs control (right > left)
  - Inverse relationship between bioactive testosterone sexual dysfunction
  - Serum estradiol lower in women with epilepsy vs controls

Herzog et al. Epilepsy & Behavior 2003;4:407-413

ASM Effects on Sexual Function: Potential Mechanisms

- Older AEDs (phenytoin, carbamazepine, phenobarbital & primidone) induce hepatic drug metabolism
- CytochromeP450 isozymes participate in metabolism of estradiol and testosterone
- Increased hepatic synthesis of sex hormone binding globulin (SHBG) → ↓ concentrations of bioactive androgen

Differential ASM Effects on Sexual Dysfunction in Women

- Morrell et al 2004
  - Women with epilepsy (31± 5.6 years) more likely to report sexual dysfunction than were healthy controls
  - Women receiving enzyme inducing drugs, particularly phenytoin or phenobarbital had significantly lower sexual arousal scores as compared to controls
  - As compared to controls, depression was more common in women with partial seizures
  - Effects were modestly correlated with reduced androgen (DHEAS) concentrations

Morrell M et al, Submitted Epilepsy & Behavior 2004

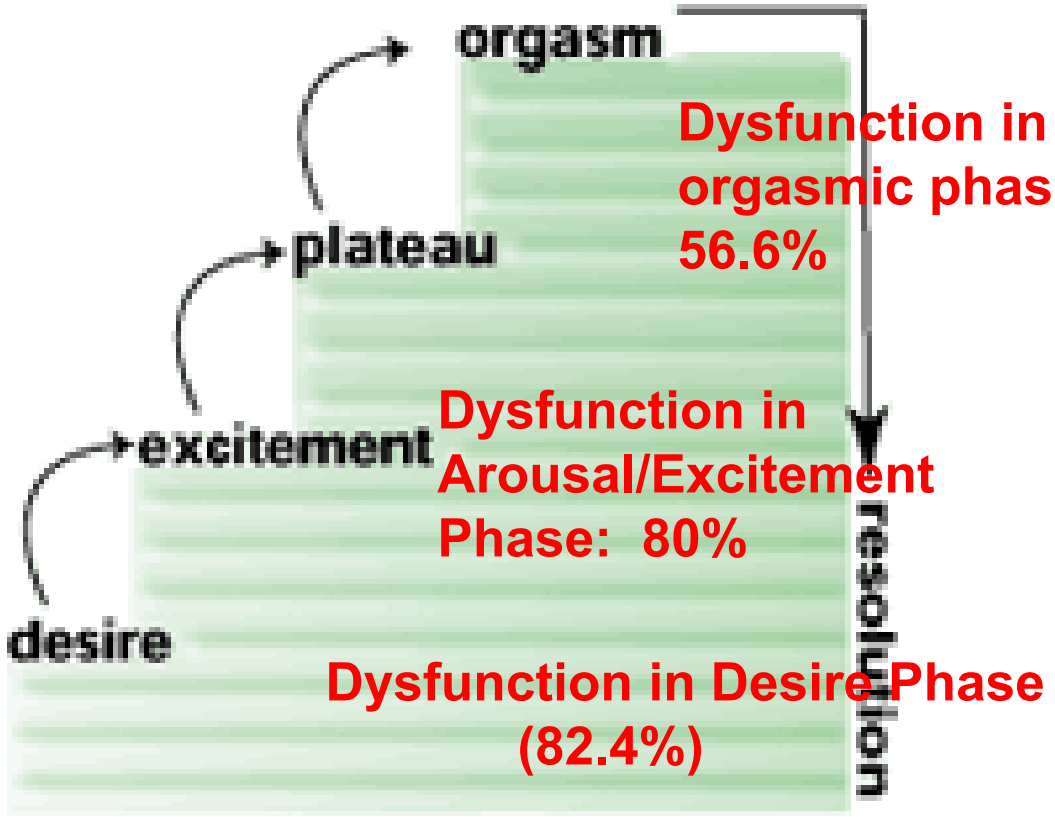
Depression

- Sexual dysfunction is correlated with depression…Changes in sexual function (particularly libido) can be symptoms of depression
  - Treatment emergent sexual dysfunction noted in 50-60% of men and women

  Common complaints in include declines in libido, difficulty achieving orgasm, and ED
  - Men may have nearly 2-fold increase in ED
  - Prevalence of ED may increase with severity of depression
- Sexual side effects has a negative impact on medication adherence.

Fava J Clin Psych 2002;63(Suppl 5):13-16
Aranjo et al. Psychosom Med 1998;60:458-465
Laumann et al. JAMA 1999;281:537-544
Shabsigh et al Urology 1998;52:848-852

Participants without global sexual dysfunction

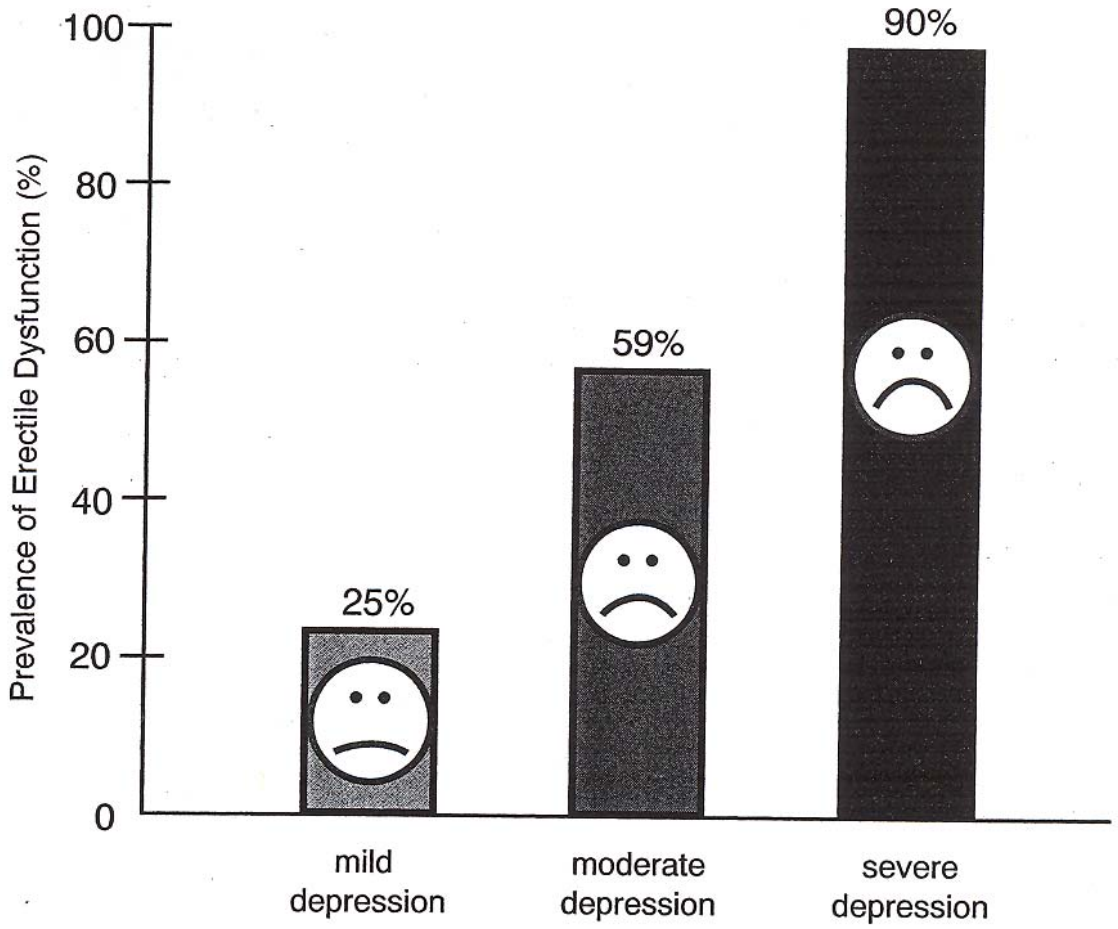


Only 6.5% were free of sexual dysfunction.

96% of women and 98% of men had impairment in at least one phase of sexual functioning

80% had dysfunction in more than one phase

Clayton, A., Keller, A., and McGarvey, E.L. (2005). Burden of phase-specific sexual dysfunction with SSRIs. *Journal of Affective Disorders, 91*, (27-32).


Prevalence of Erectile Dysfunction (%)
100
80
60
40
20
0
25%
59%
90%
mild depression
moderate depression
severe depression

Ask about sexual dysfunction! Don't wait for patients to report!

Reported rates of sexual dysfunction due to SSRIs are most likely underestimates.

- Montejo-Gonzales et al. found that rates of sexual dysfunction due to SSRIs were reported to physicians at **14%** spontaneously but **58%** when physicians asked direct questions.
- Among patients treated with citalopram or paroxetine, Landen et al. found fewer patients (**6%**) reported SD spontaneously versus **41%** who reported it when directly questioned about it.

Haberfellner. A review of the assessment of anti-depressant-induced sexual dysfunction used in randomized, controlled trials. Pharmopsychiatry 2007; 40: 173-182.

Medication Effects on Sexual Function: Antidepressant Agents

- Erectile dysfunction (10-30%)
- Loss of libido (40-60%)
- Delayed orgasm (46-59%)
- Anorgasmia (31-48%)

Rosen & Marin. J Clin Psych 2003;64(Suppl 10):5-10

Incidence of Sexual Side-Effects of Antidepressants

- < 10%:
  - bupropion, mirtazepine, moclobemide, nefazodone
- 10%-30%
  - citalopram, duloxetine, venlafaxine
- >30%
  - fluoxetine, fluvoxamine, paroxetine and sertraline
- Incidence of TCA's and MAOI are similar to SSRIs and dual action antidepressants

Kennedy et al.2004

Psychotic Illness & SD

- 50% of men and 30% of women report SD
- Women are twice as likely to be in an intimate relationship (60%) as men
- 40% of both genders have never had a sexual relationship
- Compared with controls, men with schizophrenia report low sexual desire, erectile dysfunction, premature ejaculation, and orgasmic dissatisfaction

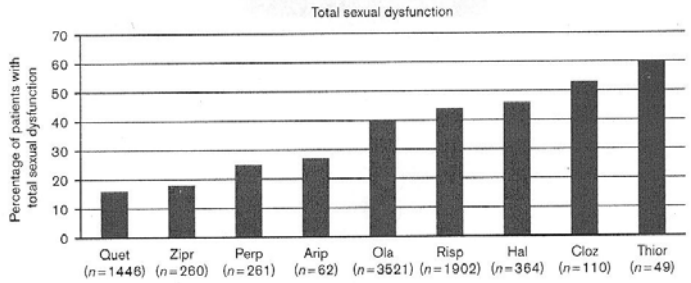
Bhui K, et al. *Soc Psychiatry Psychiatr Epidemiol.* 1997;32:459-467.
Macdonald S, et al. *Br J Psychiatry.* 2003;182:50-56.

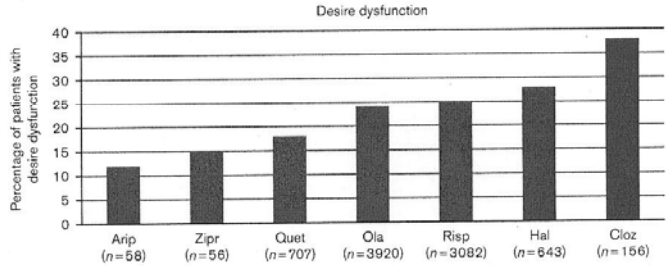
Antipsychotic Agents & Effect on Sexual Function

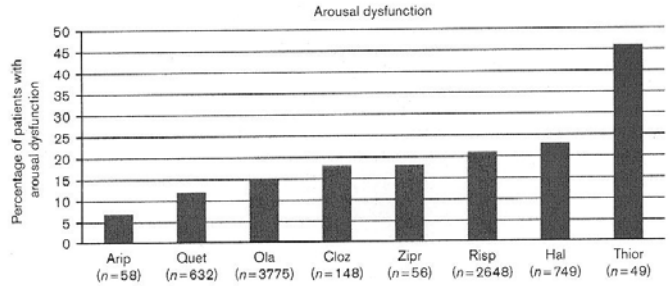
- Dose-related hyperprolactinemia due to dopaminergic antagonism in the tuberoinfundibular system
  - Prolactin increased with conventional antipsychotics and risperidone
  - Prolactin decreased with clozapine, aripiprazole (higher 5-HT_{2A}:D2 binding ratio?)
  - No change or slight decrease in prolactin with olanzapine, quetiapine, ziprasidone

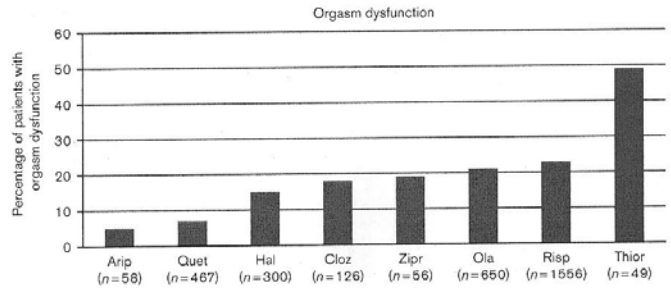
Goodnick PJ, et al. *Expert Opin Pharmacother*. 2002;3:1391-1391.

Sexual Dysfunction and Antipsychotic Drugs









Total and specific sexual dysfunction rates in patients taking different antipsychotics. Arip, aripiprazole; Cloz, clozapine; Hal, haloperidole; Ola, olanzapine; Perp, perphenazine; Quet, quetiapine; Risp, risperidone; Thior, thioridazine; Zipr, ziprasidone.

Serretti & Chiesa Int J Clin Psychpharmacol 2011;26:130-140

So, What do we do about this?: Sexual history taking

- Are you having sexual relations currently? If so, with men or women or both? If not, when did you last have sexual intercourse? Are you satisfied with the frequency and quality of your sexual experience? Do you have more than one sexual partner?

Sexual history taking: Get Specific

- Both: Assess libido/arousal: do you have sexual thoughts? How often do you want to have sex with your partner
- Men: how often do you get an erection when you want to have sex with your partner? Do you get nighttime erections? Is it difficult to ejaculate?
- Women: Can you lubricate? Does it hurt? Can you climax?

Conclusions

- Sexual dysfunction is a common problem
- Not limited to men
- Prevalence likely increased with advancing age
- Understanding drug/disease interactions a necessary 1st step in assessment
- Knowledge of drug M.O.A. valuable in predicting potential adverse effects
- Don't ask…Don't tell not a good approach