Pathophysiology, Assessment, and Treatment of Sexual Dysfunction

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Faculty Disclosure

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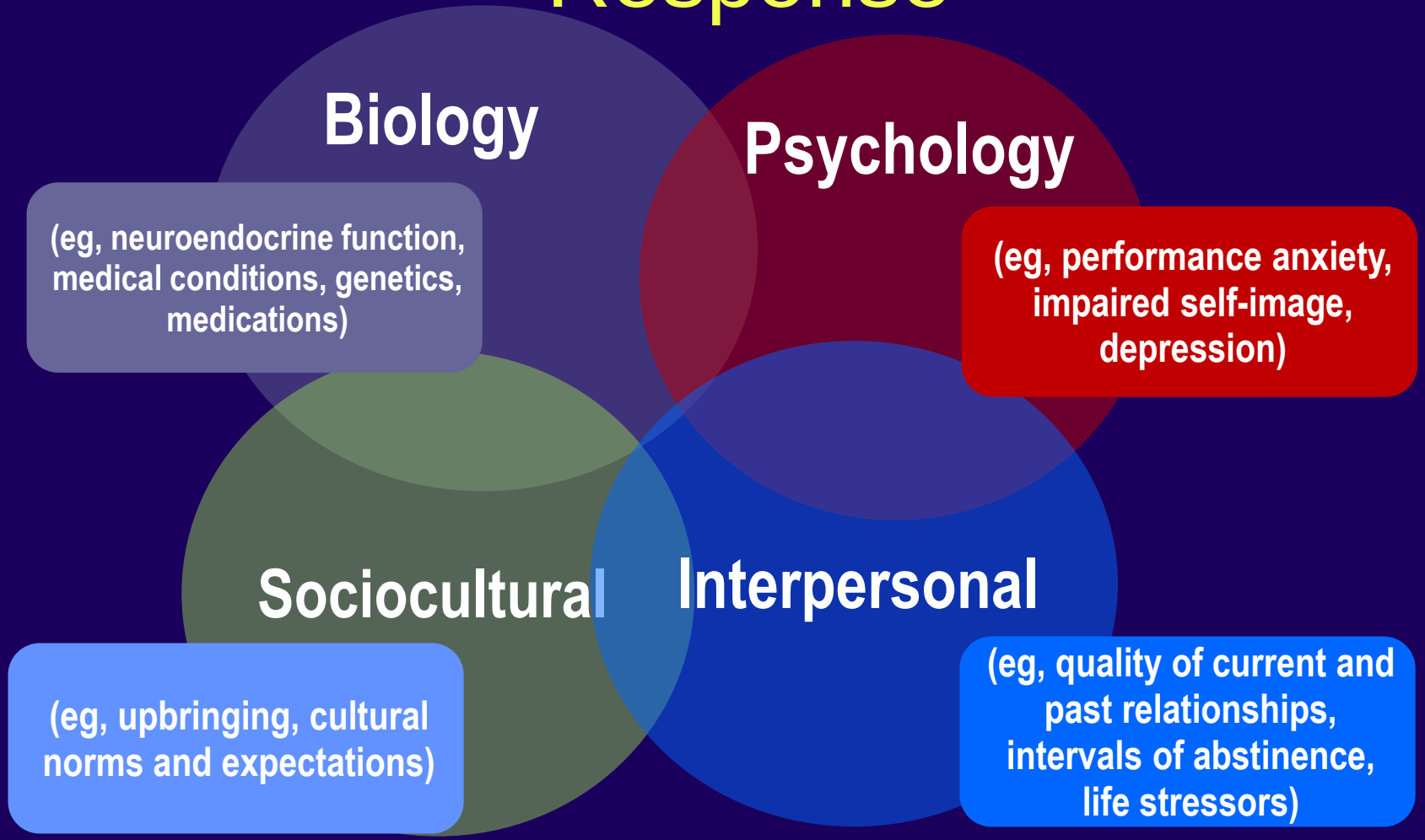
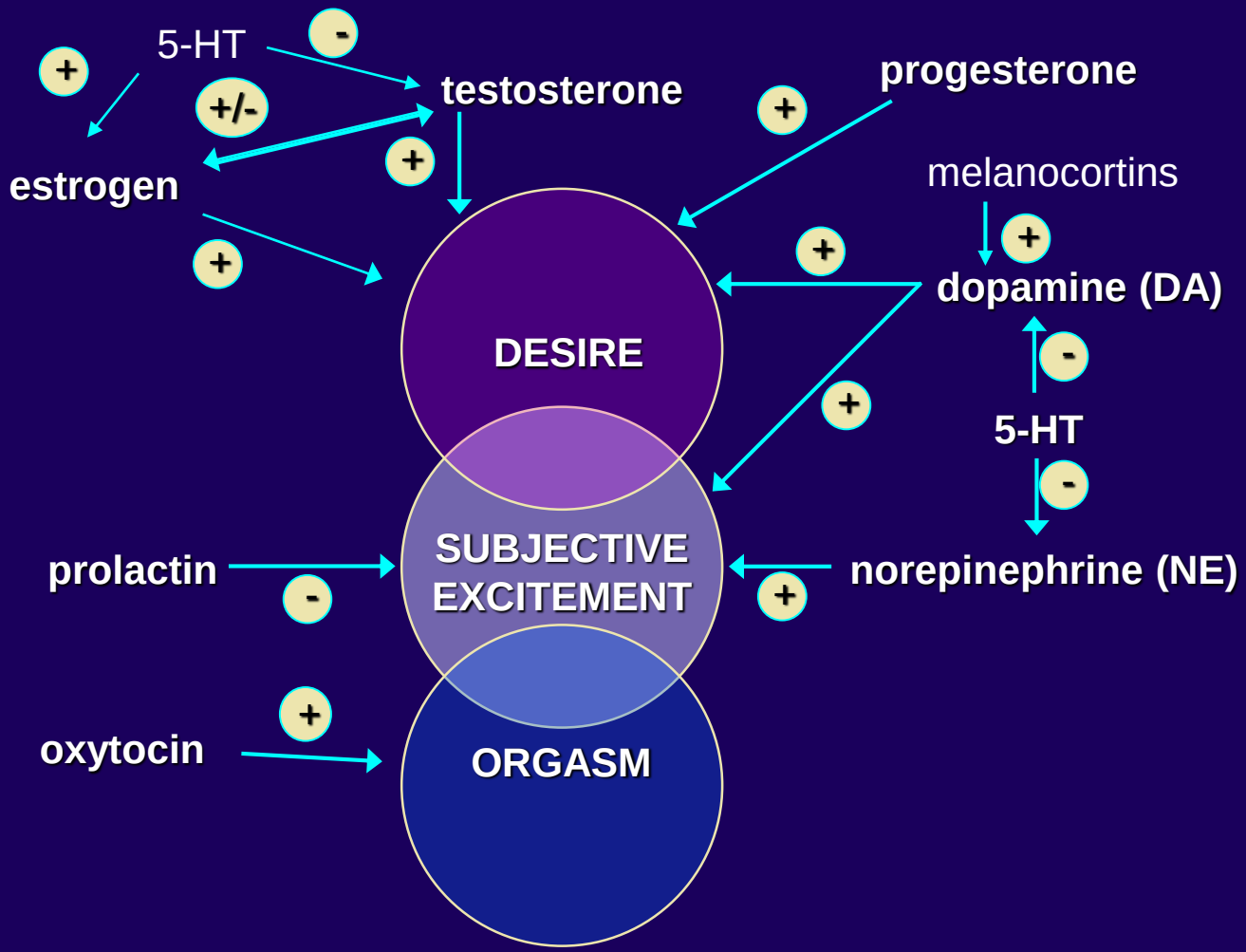
Biopsychosocial Model of Sexual Response



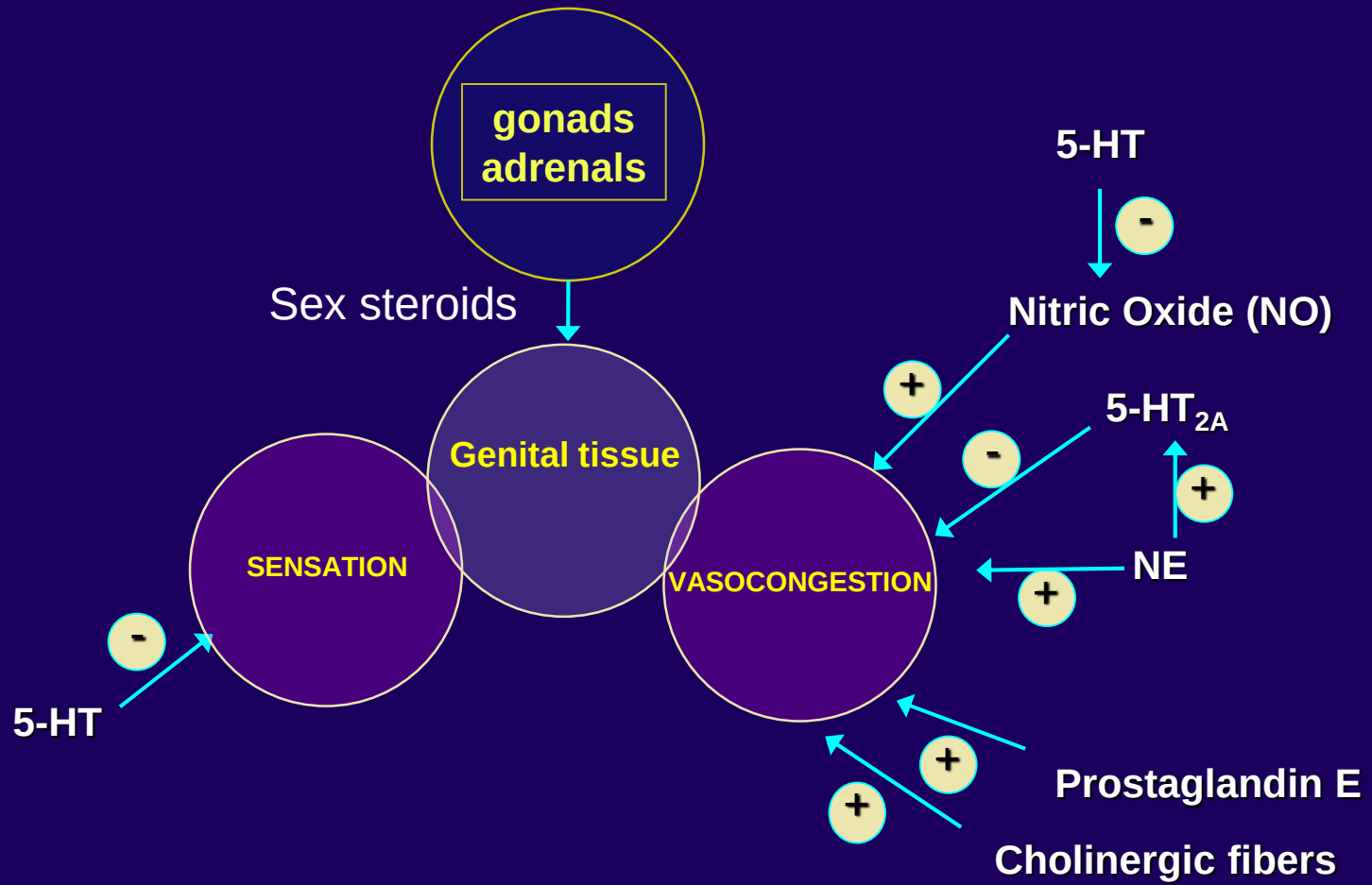
Althof SE, et al. *J Sex Med.* 2005;26:793-800.
Rosen RC, Barksy JL. *Obstet Gynecol Clin North Am.* 2006;334:515-526.

Central Effects on Sexual Function



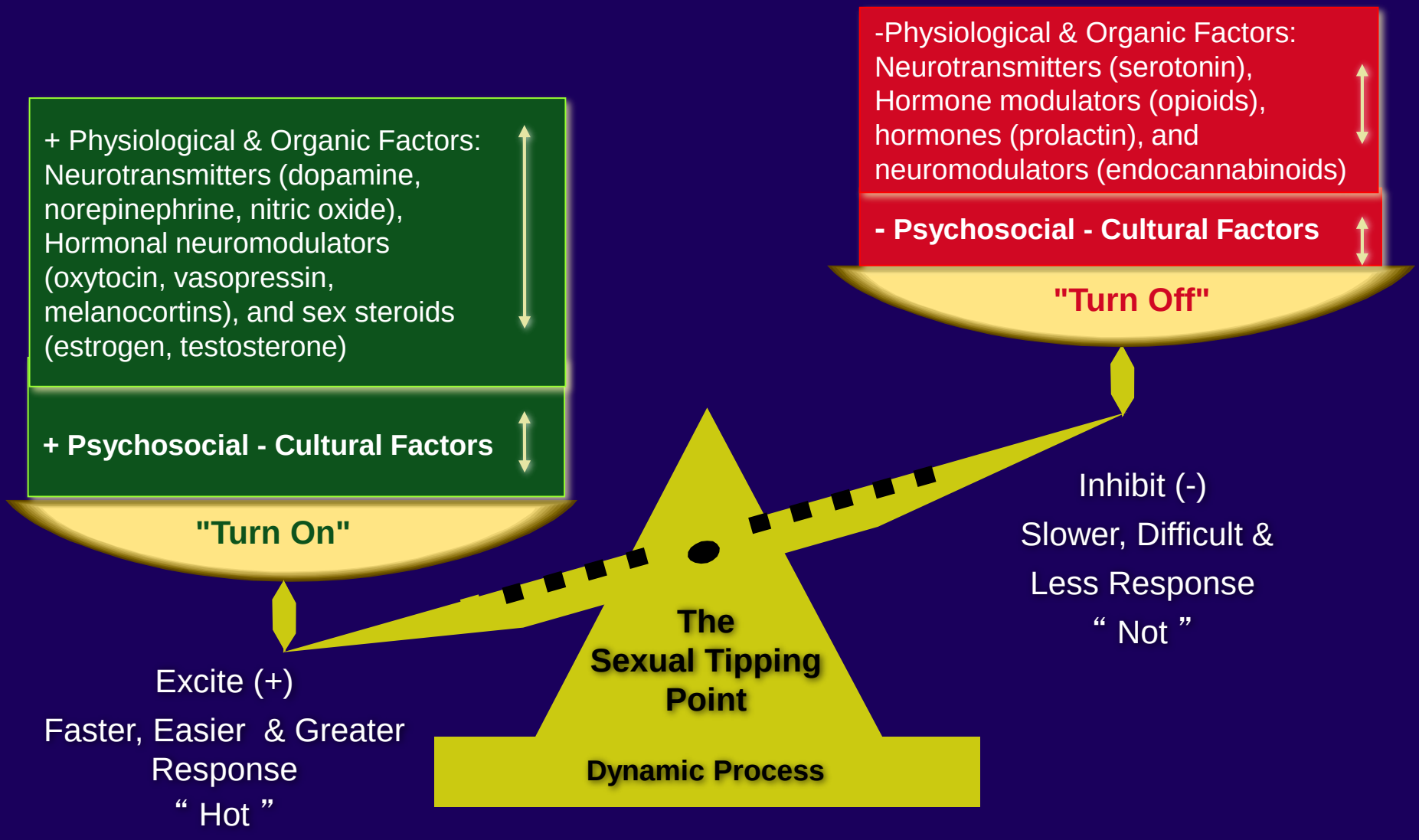
Modified from Clayton AH. *Psych Clin NA.* 2003;26:673-682; Cohen AJ. AD-induced SD associated with low serum free testosterone 2000. http://www.mental-health-today.com/rx/testos.htm.

Peripheral Effects on Sexual Function



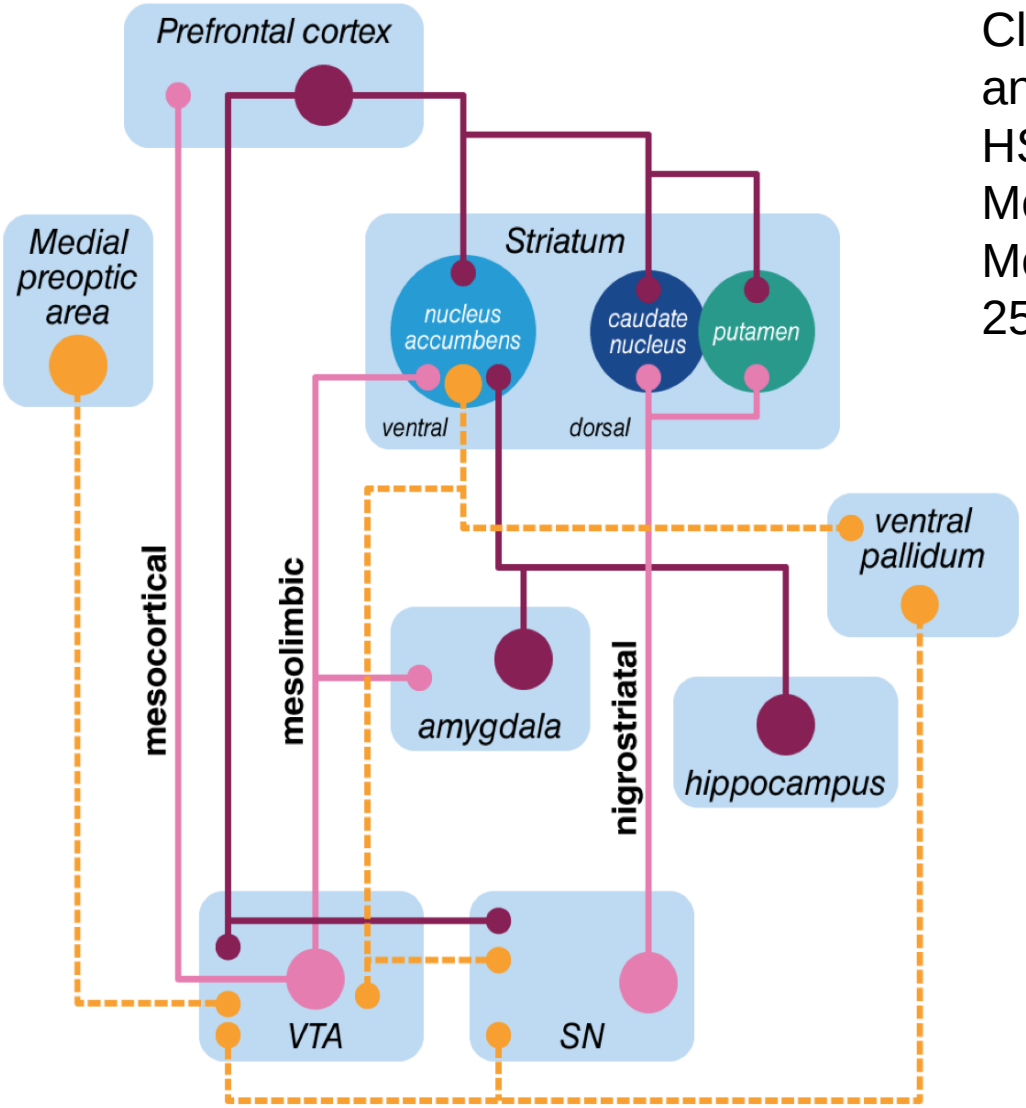
Modified from Clayton AH. *Psychiatric Clinics of North America*. 2003;26:673-682.

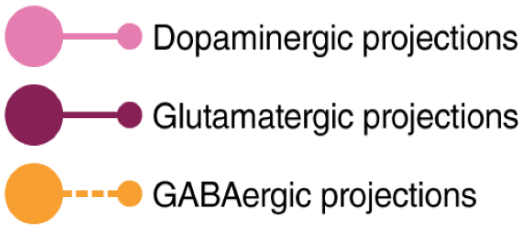
Excitation vs. Inhibition



Adapted from: Perelman, In Balon & Segraves, 2005; Perelman, UCNA, 2005

Sexual Reward System Circuitry

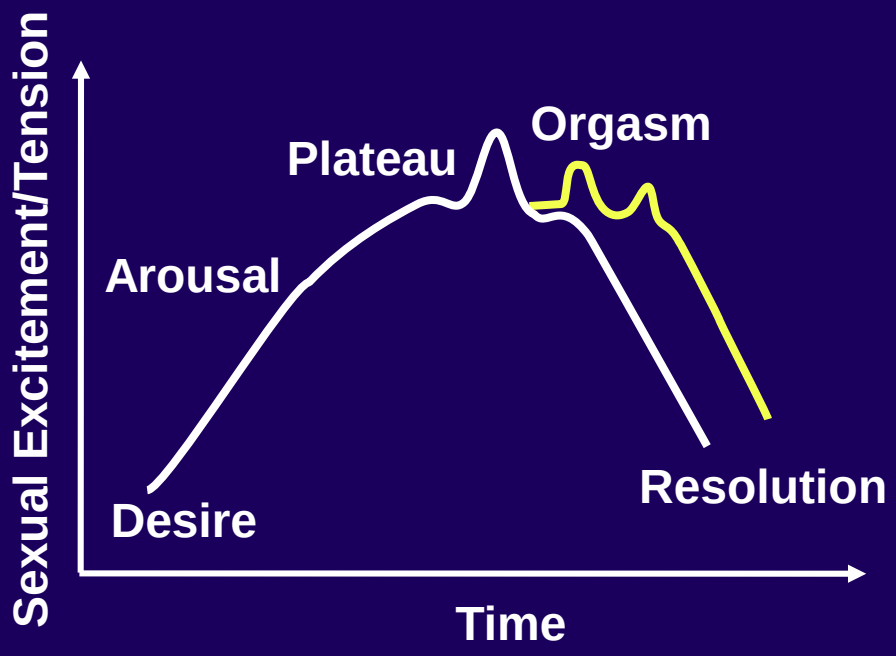




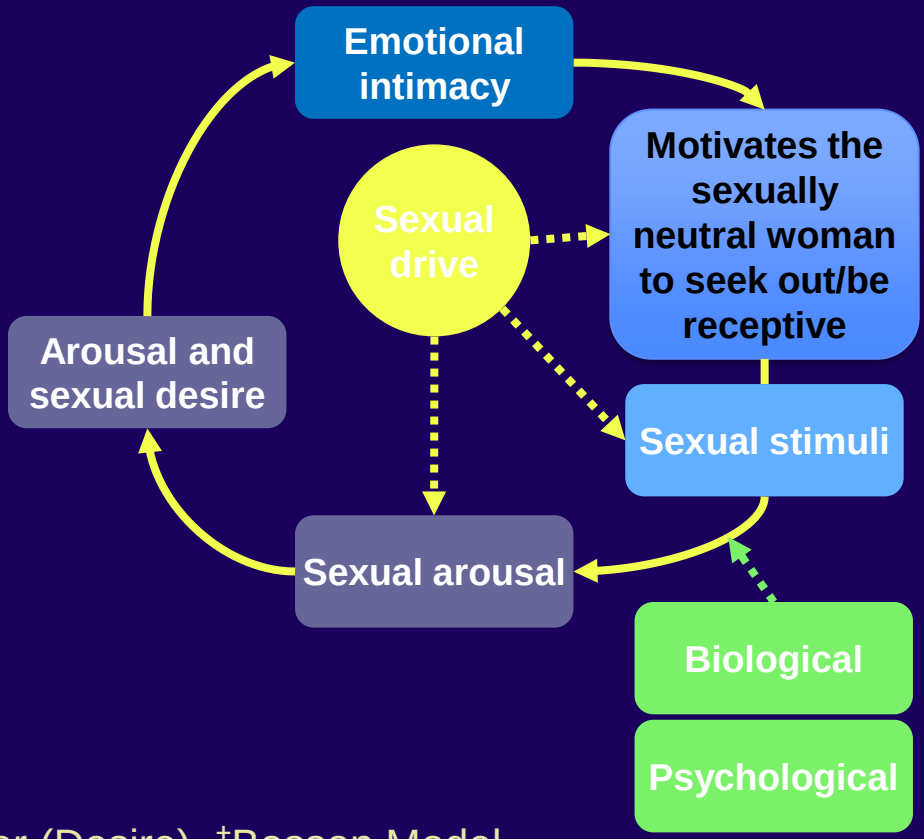
Clayton et al. The neurobiology and efficacy of bremelanotide in HSDD. Poster at 20th World Meeting on Sexual Medicine/ISSM, September 22-25, 2016, Beijing, China

Theoretical Models of Sexual Response

Linear Model[1,2,3*]



Circular Model[3†]



*Masters & Johnson Model with Kaplan Modifier (Desire). †Basson Model.

[1]Masters WH and Johnson VW. *Human Sexual Response.* Boston: Little Brown; 1966; [2]Kaplan HS. *Disorders of Sexual Desire and Other New Concepts and Techniques in Sex Therapy.* New York: Brunner/Mazel; 1979; [3]Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. *Obstet Gynecol.* 2001;98(2):350-353.

Secondary Sexual Dysfunction

Illnesses Affecting Sexual Function

- Psychiatric illness
  - Mood disorders[1,17]
  - Anxiety disorders[2,3]
  - Psychotic illness[4]
- CV disease/HTN[5,6]
- Neurological disorders[7]
- Urological problems[8]
- Sexually transmitted infections[9]
- Gynecological problems: Pelvic floor disorders,[10] Postpartum[11]
- Endocrine disorders[12]
  - Diabetes[12,13]
  - Thyroid disorders[12]
  - Hyperprolactinemia[7]
  - Androgen deficiency[14]
- Other: Rheumatoid arthritis,[15] Psoriasis,[16] Cancer (breast,[17] prostate, etc.)

[1]Casper RC, et al. *Arch Gen Psychiatry*. 1985;42:1098-1104; [2] van Lankveld JJ, Grotjohann Y. *Arch Sex Behav*. 2000;29:479-498; [3] Shifren J, et al. *Obstet Gynecol*. 2008;112:970-978; [4] Friedman S, Harrison G. *Arch Sex Behav*. 1984;13:555-587; [5]Okeahialam BN, Obeka NC. *J Natl Med Assoc*. 2006;98:638-640; [6] Doumas M, et al. *J Hypertens*. 2006;24:2387-2392; [7] Rees PM , et al. *Lancet*. 2007;369:512-525; [8] Asian G, et al. *Int J Impot Res*. 2005;17:248-251; [9] Smith EM, et al. *Infect Dis Obstet Gynecol*. 2002;10:193-202. [12] Handa VL, et al. *Obstet Gynecol*. 2008;115:1045-1052; [13]Baksu B, et al. *Unt Urogynecol J*. 2007;18:401-406; [10]Bhasin S, et al. *Lancet*. 2007;369:597-611; [11]Yencilek F, et al. *Fertil Steril*. 2010.;94(5):1840-1843; [14] Turna B, et al. *Int J Imp Res*. 2005;17:148-153; [15] Abdel-Nasser A, Ali E. *Clin Rheumatol*. 2006;25:822-830; [16]Sampogna F, et al. *Dermatology*.2007;214:144-150; [17]Mathias C, et al. *Ann Oncol*. 2006;17:1792-1796; [18]Hou, Po-Hsun et al. *J Sex Med. 2018;15(2):183-191.*

Pharmacotherapies and Risk of SD

PSYCHOTROPIC MEDICATIONS	SSRIs/SNRIs/TCAs Mood stabilizers Antipsychotics	Benzodiazepines Antiepileptic drugs
ANTIHYPERTENSIVES	Beta-blockers Alpha-blockers	Diuretics
CARDIOVASCULAR AGENTS	Lipid-lowering agents Digoxin	
HORMONES	Oral contraceptives Estrogens Progestins	Antiandrogens GnRH agonists
OTHER	Histamine H2-receptor blockers Opioids NSAIDs	

Clayton & Ramamurthy in *Sexual Dysfunction: The Brain-Body Connection*. Ed: R Balon, Karger, Basel, Switzerland, 2008; Basson R, Schultz WW. *Lancet*. 2007;369:409-424; Kingsberg SA, Janata JW. *Urol Clin North Am*. 2007;34:497-506.

Bidirectional Relationship

- Meta-analysis identified 1022 citations, with 34 potentially-relevant citations, but 26 excluded due to inadequate predictor or outcome, 1 cross-sectional study, and 1 poster
- 8 citations included:
  - 6 studies on depression for risk of SD (n=3,285)
  - 6 studies on SD for risk of MDD (n=11,171)
- Depression was associated with a 50% – 70% increased risk of developing SD
- Sexual dysfunction was association with a 130% – 210% increased risk of developing MDD

Atlantis E and Sullivan T. *J Sex Med* 2012;9:1497-1507

Effect of Antidepressants on Sexual Function

- Associated with sexual dysfunction: SSRIs,[1] venlafaxine,[1] TCAs,[2] oral MAOIs[2]
- Few negative effects on sexual function with bupropion-SR,[1] mirtazapine,[3] nefazodone,[1] selegiline transdermal system,[4] reboxetine,[5,6] duloxetine,[7] desvenlafaxine,[8] vilazodone,[9,10,11] vortioxetine,[12,13] agomelatine[14,15]

[1]Clayton et al. *J Clin Psychiatry* 2002; 63:357-366; [2]Montgomery et al. *J Affective Dis* 2002;69 (1-3): 119-140; [3]Boyarsky et al. *Depression & Anxiety* 1999;9(4):175-179; [4]Clayton et al. *J Clin Psychiatry* 2007; 68:1860-1866; [5]Clayton et al. *Int Clin Psychopharm* 2003;18:151-156; [6]Baldwin D et al. *J Psychopharmacology* 2006;20(1):91-96. [7]Clayton et al. *J Sex Med*, 2007;4(4i):917-929; [8]Clayton AH et al. *Int Clin Psychopharmacology* 2015;30(96):307-315; [9]Clayton et al. *J Sex Med* 2013;10(10):2465-2474; [10]Clayton AH et al. *Int Clin Psychopharmacology* 2015;30(4):216-223; [11]JClayton AH, et al. *International Clinical Psychopharmacology*. 2017;32(1):27-35**;** [12]Jacobsen PL et al. *J Sex Med*, 2015;12:2036-2048; [13]Jacobsen PL et al. *CNS Spectrums*. 2015;17:1-12; [14]Montejo A et al. *J Psychopharmacology* 2010;24(1):111-120; [15]Kennedy SH et al. *J Clin Psychopharmacology* 2008;28(3):329-333.

Other Psychiatric Medications Affecting SF

- Antipsychotic medications[1] with lower rates of SD:
  - D2 antagonist-partial agonist effects and/or 5-HT_2 antagonism e.g. aripiprazole, quetiapine, brexpiprazole, ziprasidone, olanzapine,[2,3] lurasidone[4]
  - 5-HT_{1A} agonists like aripiprazole, brexpiprazole, caripiprazine,[2,3] lurasidone[4]
- Negative effects of antipsychotics related to postsynaptic dopamine blockade and elevated prolactin (e.g. risperidone, paliperidone), α_1 receptor antagonism (priapism), perhaps cholinergic antagonism (arousal),[2,3,5] and persistent psychosis
- Decreasing impact on sexual function: thioridazine (60%), risperidone, clozapine (?), haloperidol, olanzapine, ziprasidone, quetiapine (16%), lurasidone[4] (?), aripiprazole[3]

[1]Montejo AL et al. *J Sex Med* 2010;7(10):3404-3413. [2]Park YW, et al. *World J Mens Health* 2012;30(3):153-159. [3]Serretti A and Chiesa A. *Int Clin Psychopharm*. 2011;26(3):130-140; [4]Clayton A et al.*J Clin Psychiatry.* In press. [5]de Boer MK et al. *Schizophr Bull* 2015;41(3):674-686

General Management

- Psychiatric/Medical conditions: treat to remission to decrease disease effects
- Proactive avoidance/eliminate contributing factors: Medications/substances, smoking, relationship difficulties, partner SD, impact of sexual trauma, psychosocial issues
- Psychological interventions
- Approved medications for primary sexual disorders

Management of Medication-Induced SD

- Substitute meds with fewer negative effects on sexual function - possibly less efficacy or tolerability[1]
- Add antidotes (off-label) - possible drug interactions/side effects and increased cost[2]
- Acupuncture[3]
- Lower dose – possible re-emergence of symptoms
- Talk with patient and partner – change approach to sexual activity
- Not recommended: drug holidays – leads to nonadherence

[1]Park YW et al. *World J Mens Health* 2012;30(3):153-159.[2]Clayton, AH, et al. *Expert Opinion on Drug Safety*, 2014 Oct; 13(10): 1361-1374.
[3]Khamba et al. *J Altern Complement Med* 2013;19(11):862-869

SRI-Induced Sexual Dysfunction

- Substitute meds eg, bupropion,[1] mirtazapine,[2] seligiline transdermal system,[3] vilazodone,[4] desvenlafaxine,[5] duloxetine,[6] vortioxetine[7]
- Add antidotes (off-label) including bupropion,[8] buspirone,[9] testosterone,[10,11,12] sildenafil,[13] mirtazapine,[14,15] flibanserin,[16] DHEA (OTC)

[1]Clayton AH et al. *J Clin Psychiatry.* 2002;63(4):357-366; [2]Boyarsky BK et al. *Depress Anxiety.* 1999;9(4):175-179; [3]Clayton AH et al. *J Clin Psychiatry.* 2007;68(12):1860-1866; [4]Clayton AH et al. *J Sex Med*. 2013;10(10):2465-2474; [5]Clayton AH et al. *Int Clin Psychopharmacol*. 2015;30(6):307-315; [6]Clayton A et al. *J Sex Med.* 2007;4(4 Part 1):917-929. [7]Jacobsen PL et al. *J Sex Med* 2015;12:2036-2048; [8]Clayton AH et al. *J Clin Psychiatry.* 2004;65(1):62-67; [9] Landen M et al. *J Clin Psychopharmacol.* 1999;19(3):268-271; [10]Sherwin BB. *J Clin Endocrinol Metab.* 1991;72(2):336-343; [11]Warnock JK et al. *J Sex Marital Ther.* 1999;25(3):175-182; [12]van Anders SM et al. *J Sex Marital Ther.* 2005;31(3):173-185; [13]Nurnberg HG et al. *JAMA.* 2008;300(4):395-404; [14]Ozmenler NK et al. Hum *Psychopharmacol Clin Exp* 2008;23:321-326. [15]Atmaca M et al. *Psychiatry Investig* 2001;8:55-57; [15]Clayton AH et al. *J Sex Med* 2018;15(1):43-51.

Primary Sexual Disorders

DSM-5 Sexual Dysfunctions

- DSM-IV: 3 criteria for each disorder:
  - Disturbance in phase(s) of the sexual response cycle or pain
  - Distress related to the sexual problem
  - Is not better accounted for by a medical or psychiatric condition or substance/medication use
- DSM-5 has sex-specific sexual dysfunctions
  - For women, merged disorders
    - Desire and arousal disorders combined into FSIAD
    - Genito-pelvic pain/penetration disorder combines vaginismus and dyspareunia
  - Dx's (except substance/medication-induced SD) require a duration of ≥6 months plus distress
  - Subtypes include lifelong vs. acquired and generalized vs. situational

ICD-11 Recommendations

- Geared toward clinical utility across multicultural and multidisciplinary sample
- Proposes separate chapter on Conditions Related to Sexual Health to integrate Mental Health & Behavioral and Genitourinary Disorders
- SD and sexual pain D/O=syndromes associated with difficulty experiencing personally satisfying, non-coercive sexual activities regardless of presumed etiology
- Classifications will apply to both men and women (desire and orgasmic dysfunctions) except for distinct clinical presentations (FSAD, ED)

Reed GM, Drescher J, Krueger RB, et al. *World Psychiatry* 2016;15:205-221.

Screening

Decreased Sexual Desire Screener (DSDS)

	NO	YES
1. In the past, was your level of sexual desire or interest good and satisfying to you?	☐	☐
2. Has there been a decrease in your level of sexual desire or interest?	☐	☐
3. Are you bothered by your decreased level of sexual desire or interest?	☐	☐
4. Would you like your level of sexual desire or interest to increase?	☐	☐
5. Please check all the factors that you feel may be contributing to your current decrease in sexual desire or interest:		
A. An operation, depression, injuries, or other medical condition	☐	☐
B. Medications, drugs or alcohol you are currently taking	☐	☐
C. Pregnancy, recent childbirth, menopausal symptoms	☐	☐
D. Other sexual issues you may be having (pain, decreased arousal or orgasm)	☐	☐
E. Your partner's sexual problems	☐	☐
F. Dissatisfaction with your relationship or partner	☐	☐
G. Stress or fatigue	☐	☐

Sensitivity 0.836, 0.946, 0.956, and specificity 0.878

Goldfischer ER et al. *Obstet Gynecol* 2008;111:109S
Clayton A et al. *J Sex Med* 2009;6:730–738
Nappi R et al. *J Sex Med* 2009;6(suppl 2):46

International Index of Erectile Function (IIEF-5)

Over the past 6 months:
1. How do you rate your **confidence** that you could get and keep an erection?
Very low 1, Low 2, Moderate 3, High 4, Very high 5
2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration?
Almost never/never 1, A few times/much less than half the time 2, Sometimes (about half the time) 3, Most times (much more than half the time) 4, Almost always/always 5
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?
Almost never/never 1, A few times/much less than half the time 2, Sometimes (about half the time) 3, Most times (much more than half the time) 4, Almost always/always 5
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?
Extremely difficult 1, Very difficult 2, Difficult 3, Slightly difficult 4, Not difficult 5
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?
Almost never/never 1, A few times/much less than half the time 2, Sometimes (about half the time) 3, Most times (much more than half the time) 4, Almost always/always 5

Rosen RC, et al. *Int J Impot Res.* 1999;11(6):319-26.

Strategies for Speaking About Sex

- Provider should initiate the conversation with non-threatening, non-judgmental attitude
- Utilize language appropriate to person's age and provider comfort level
- Do not assume heterosexual orientation
- Within the context of other health concerns
- Active listening and open-ended questions about each phase of the sexual response cycle
- Follow-up to clarify details

Key Points

- Screening tools
- Determine how the symptoms impact the patient
  - The discussion itself may be therapeutic
- If a sexual problem exists:
  - Identify modifiable factors
  - Determine timing of onset/duration
    - Acquired or a lifelong condition
    - Determine if situational or generalized
- Ask about all phases/symptoms (desire, arousal, orgasm and sexual pain)
- Additional information: Sexual hx (e.g. hx of trauma), PE as needed, laboratory studies as indicated

Treatment of Sexual Dysfunctions

- General approach
  - Manage modifiable factors
  - Provide education
  - Referral as needed
- For men:
  - Androgens/testosterone, PDE-5 inhibitors, external vacuum devices
- For women:
  - Postmenopausal women: Address pain first – usually due to GSM, so lubricants/moisturizers, sex steroids, ospemiphene (SERM), prasterone (DHEA vaginal insert)
  - Premenopausal women: flibanserin (5-HT 1A agonist, 5-HT 2A antagonist), pelvic floor PT, psychotherapy

Conclusions

- Sexual function is an important part of overall health and quality of life across the lifespan
- Multiple factors affect sexual functioning including genetic determinants, neuroendocrine systems, medical and psychiatric conditions, substance use, and relationship status
- Appropriate assessment regarding symptoms and modifiable factors is important and informs management
- Interventions for sexual dysfunctions may include eliminating known causes, psychotherapy, and avoidance of or counteracting mechanism(s) negatively impacting sexual function