“SEX, DRUGS AND ROCK N’ ROLL”
Good Sexual Function & What Can Go Wrong!

Mary A. Gutierrez, PharmD, BCPP
Professor of Pharmacy Practice
Chapman University School of Pharmacy
Irvine, California

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Learning Objectives:
Sex, Drugs, & Rock N' Roll (Part 1)
Be able to:
Discuss the four components necessary for good sexual function.
Identify drugs that may adversely affect sexual function.
List the advantages & disadvantages of the available treatment options for sexual dysfunction.

Psychopharm PK/PD Clinical Pearls (Part 2)
Address questions and cases on psychotropic drugs’ pharmacokinetics and pharmacodynamics differences with gender and age.
Recognize and minimize clinically significant psychotropic drug interactions.
What is the most common type of sexual dysfunction reported with males?

1. Hypoactive sexual desire
2. Erectile dysfunction
3. Premature ejaculation
4. Delayed ejaculation
5. Anorgasmia


What is the most common type of sexual dysfunction reported with females?

1. Hypoactive sexual desire
2. Sexual arousal disorder
3. Orgasmic disorder
4. Dyspareunia
5. Vaginimus
Sexual Dysfunction in the U.S.

• Survey of >3,100 sexually active American men & women (18-59 y/o) found 43% women & 31% men reported SD.
• 140 males and 240 females excluded d/t sexual inactivity → Underestimation…incidence may be higher!
• Sexual problems are widespread and influenced by poor physical and emotional health → impaired quality of life for many individuals.


Sexual Dysfunction in the U.S.

• Latest review (2015) → most frequent sexual dysfunctions for women are desire and arousal dysfunctions, with a large proportion of women who experience multiple sexual dysfunctions.
• For men, premature ejaculation and ED are the most common sexual dysfunctions, with less comorbidity of sexual dysfunctions for men compared with women.

* These data need to be treated with caution with high level of variability across these studies with the differences in assessment of sexual dysfunction.


Women Sexual Dysfunction…Starting from?...

Unsatisfying encounters

Inadequate simulation

Increased desire

Increased arousal

Decreased desire

Decreased arousal

Sexual dysfunction vaginismus

Painful sex
Orgasms

- Males:
  - 75% always
  - 20% usually
- Females:
  - 29% always
  - 42% usually
  - 19% infrequent
  - 10% never

Intense physical and emotional sensations experienced at the peak of sexual excitation, usually with male ejaculation and in female vaginal contractions every 0.8 seconds.

Which of the following hormones has the most effect on increasing libido in men?

1. Estrogen
2. Progesterone
3. Prolactin
4. Testosterone

Which of the following hormones has the most effect on increasing libido in women?

1. Estrogen
2. Progesterone
3. Prolactin
4. Testosterone
Hormones Effects on Sexual Function
 Derived from Greek word = to arouse/to excite/to urge

• Testosterone: Ratio in men:women = 10-15:1
  Sexual thoughts/fantasies, desires, & assertiveness.
  Increase in puberty, peaks at 20s;
  declines esp. after age 50;
  20-30% of men > 65y/o w/ low TT

Estrogen: promotes sexual drive, vaginal lubrication;
generates attractive body odor & texture. Low estrogen can
→ vagina dryness → painful intercourse

Which of the following hormones can be increased
with dopamine blockers (e.g., antipsychotics)
that can inhibit sexual desire?
1. Estrogen
2. Testosterone
3. Progesterone
4. Prolactin

Which of the following atypical antipsychotics
has the least effect on increasing prolactin?
1. Risperidone (Risperdal)
2. Paliperidone (Invega)
3. Quetiapine (Seroquel)
4. Aripiprazole (Abilify)
Hormones Effects on Sexual Function

- Prolactin: Directly inhibits sexual desire; ↑ in pregnancy & nursing mothers; ↑ by dopamine-blockers & opiates; ↓ by testosterone & dopamine
- Dehydroepiandrosterone (DHEA): precursor to testosterone & estrogen, ↓ with age; stimulates sex drive? (reported esp. for women). OTC DHEA content not regulated...efficacy? ADRs of acne and hirsutism
- Thyroid hormone:
  - Hypothyroidism → ↓ testosterone → ↓ libido
  - Hyperthyroidism → ↑ prolactin → ↓ libido;
    ↑ vasoconstriction → ↑ arousal problems

Progesterone increases dopamine’s metabolism by which of the following mechanism?

1. Monoamine amine oxidase induction
2. CYP2D6 enzymes inhibition
3. Glucuronidation UGT enzymes inhibition

Hormones’ Effects on Sexual Function

- Progesterone: ↓ DA → ↓ sex drive
- PG ↑ during second half of menstrual cycle & drops abruptly prior to menses → Ratio of TT: PG ↑ → days prior to menses sexual desire ↑
  When progesterone levels fall → ↓ GABA_A receptor activitives → peak irritability and sleep disturbances
Chemistry of Attachment & Bonding

- Oxytocin: released with touching, hugs, sex, orgasms → promotes bonding & affectionate behavior. Peaks at orgasm with massive release from the pituitary gland → higher in women …also known as the "cuddling hormone".
- Vasopressin: released in response to touch; promotes attachment & bonding, esp. for males. Has a reputation as the "monogamy hormone".

Sexual Function Starts in the Brain!

- Frontal cortex - stores consolidated memories of past sexual encounters; guides sexual choices & strategies
- Limbic system - routing & processing of sensory input (5 senses + sexual thoughts and fantasies) → libido
- Circuit via the limbic septum -> basal ganglia → charging & potentiating sexual feelings -> anterior hypothalamus → active sexual responses & behavior
- Pituitary gland - produces & distributes hormonal messages to the body → regulates other sex hormone production & metabolism

Libido (Sexual Desire)

- Psychogenic stimuli
  - visual, tactile, olfactory, gustatory, auditory, & imaginative stimuli (fantasies/sexual thoughts)
- Hormonal factors
  - Men & women: androgens (testosterone)
  - Normal circulating testosterone in men exceeds threshold levels needed for sexual desire. Women are more sensitive to low libido secondary to low testosterone or to any anti-androgen agents
  - Hypogonadism: induced lack of libido may benefit from exogenous testosterone treatment
Stages of Sexual Response

**Libido** – needs hormonal, neurologic & psychogenic input

**Arousal** – needs hormonal, neurologic, vascular input
- => erectile tissue engorgement
- => glandular secretions

**Orgasm** – needs correct balance of
- PNS and SNS => contraction of smooth and striated muscles

**Resolution** – detumescence to baseline state genitalia & vital signs

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The monthly supply (6-8 doses/month) for Viagra and other ED medications is based on the average frequency of sexual activities for an individual in the U.S. (True or False?)

1. True
2. False

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Sexual Activity “Norm” in the U.S.

- Frequency:
  - 1/3 ≥ 2x/week
  - 1/3 at least a few times/month
  - 1/3 a few times/year or none
  - Average frequency: 6-7 x per month
  - determines HMO allowance for ED drugs (e.g., Viagra) = 4-8 doses/month
Which of the following medications can increase libido?

1. Vicodin
2. Tagamet
3. Levodopa
4. Oral contraceptives
5. Proscar

Finasteride (Proscar and Propecia)

- In 2012, the FDA announced changes to the labelling for Propecia (finasteride 1 mg) and Proscar (finasteride 5 mg) to expand the list of sexual adverse events reported to FDA. The new label changes include a revision to:
  - “Propecia label to include libido disorders and orgasm disorders that continued after discontinuation of the drug.”
  - “Proscar label to include decreased libido that continued after discontinuation of the drug.”
  - “Propecia and Proscar labels to include reports of male infertility and/or poor semen quality that normalized or improved after drug discontinuation.”
Drugs => Decrease Libido
- Opiates (codeine, heroin), cimetidine, spironolactone are antiandrogens \(\rightarrow\) decrease TT
- Dopamine blockers (e.g., haloperidone & other APs, risperidone, paliperidone, metoclopramide) \(\rightarrow\) increase prolactin \(\rightarrow\) decrease TT
- SSRIs and SNRIs \(\rightarrow\) increase 5HT-2 \(\rightarrow\) decreased DA
- Oral contraceptives: oral estrogen \(\rightarrow\) increase sex hormone binding globulin \(\rightarrow\) binds to TT, progestin \(\rightarrow\) decrease TT

Estrogen \(\rightarrow\) ↑ Sex Hormone Binding Globulin
- Oral contraceptives and estrogen therapies increase sex hormone-binding globulin, the primary binding protein for testosterone \(\rightarrow\) decrease free testosterone concentrations
- Using alternative forms of contraception or transdermal estrogen therapy that does not increase SHBG levels can prevent lowering of free testosterone concentrations

Female Sexual Dysfunction
- Your patient noted lower libido after use of oral contraceptives, what can you recommend?
- Explain mechanism – oral contraceptives (estrogen) can increase sex hormone-binding globulin, which binds to testosterone \(\rightarrow\) lowers libido
- Recommend alternative forms of contraception or transdermal estrogen therapy (patches) that do not increase sex hormone-binding globulin (SHBG) \(\rightarrow\) do not affect free testosterone
Which of the following antidepressants does not increase serotonin-2 and 3 → minimal sexual ADRs?

1. Zoloft
2. Effexor
3. Wellbutrin
4. Remeron
5. 3 and 4

Dopamine ←→ Serotonin-2 & 3
• Increased serotonin (5HT-2) decreases the release of dopamine in the mesolimbic “pleasure center” → negatively affects sexual function. Increased 5HT-3 activities can delay orgasms or cause anorgasmia
• SSRIs, SNRIs = 5HT-2/3 agonists → SD ADRs
• Remeron = 5HT-2/3 antagonists → little SD ADRs
• Wellbutrin = no 5HT effects → least SD ADRs

Which of the following OTC or Rx hypnotic medications can negatively affect sexual arousal?

1. Tylenol PM
2. Pseudoephedrine
3. Ambien
4. Buspirone
The Autonomic Nervous System

**Parasympathetic**  **Sympathetic**
- NTs: Acetylcholine  Norepinephrine
- Receptors: Cholinergic  Adrenergic

Erection (point)  Ejaculation (shoot)

Your patient taking daily muscle relaxant c/o erectile dysfunction associated with this medication. Which of the following muscle relaxants is the MOST likely agent to cause his ED?

1. Baclofen
2. Cyclobenzaprine
3. Orphenadrine
4. Methocarbamol

Medications → Sexual Dysfunction
- Flexeril (cyclobenzaprine)
  - similar structure to TCAs
  - highly anticholinergic → possible sexual arousal problems (ED or lack of vaginal lubrication)
- Tegretol, Equetro (carbamazepine)
  - similar structure to TCAs
  - highly anticholinergic → possible sexual arousal problems (ED or lack of vaginal lubrication)
Drugs => Decreased Sexual Arousal

• Parasympathetic antagonists - anticholinergic drugs
  [e.g., Cogentin, tricyclic antidepressants, OTC sleep aids (diphenhydramine, doxylamine), etc.]
• Drugs that decrease nitric oxide synthesis
  [e.g., selective serotonin reuptake inhibitors & dopamine blockers (e.g., antipsychotics)]
• Any drug that inhibits libido
  [e.g., cimetidine, antipsychotics, SSRIs, opiates]

Long-term use of which of the following medications can worsen premature ejaculation?

1. Hytrin
2. Prozac
3. Sudafed
4. None of the above

Drugs and Premature Ejaculation

1. Alpha-1 blockers (e.g., Hytrin, Minipress)
   ⇒ reports of delayed ejaculation and priapism
2. SSRIs (e.g., Prozac, Paxil)
   ⇒ frequent incidence of delayed ejaculation and anorgasmia
3. Oral decongestants (e.g., Sudafed)
   ⇒ sympathomimetic effects can worsen PE
Sexual Arousal

If drug-induced, disease states-induced, and psychological problems are all ruled out for the etiology of his/her low libido problem. What are the available treatments for male and female sexual desire dysfunction?

Testosterone Replacement Therapy

- Androgel FDA approved for hypogonadism-induced SD in males. QD application - rubbed onto skin and release into bloodstream
- Patches - 20% allergic reactions
- IM injections - q2wk, pain, peak in 3 days with rapid levels decline
- Increase libido, bone density, and energy levels
- Not effective for patients with normal testosterone levels; can exacerbate ED by increasing patient’s libido without improving ability to perform

Testosterone Pellets (Q3-6 Months)
Testosterone Replacement Therapy

- ADRs:
  - acne, gynecomastia, increase in male alopecia, prostate enlargement and cancer; female voice deepening, hirsutism clitoromegaly, and menstrual irregularities

Androgen Values in Premenopausal Women Without Sexual Dysfunction

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<th>AGE:</th>
<th>20-29 (n=17)</th>
<th>30-39 (n=23)</th>
<th>40-49 (n=20)</th>
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<td>DHEA-S (ug/dL)</td>
<td>177 – 214</td>
<td>139 – 171</td>
<td>125 – 156</td>
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<td>SHBG (nmol/L)</td>
<td>44 – 59</td>
<td>45 – 52</td>
<td>47 – 58</td>
</tr>
<tr>
<td>Tot T (ng/dL)</td>
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<td>28 – 40</td>
<td>27 - 39a</td>
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<tr>
<td>Free T (pg/ml)</td>
<td>1.4 – 1.6</td>
<td>1.0 – 1.2</td>
<td>0.9 – 1.1</td>
</tr>
<tr>
<td>FAI</td>
<td>3.7 – 5.0</td>
<td>2.0 – 3.0</td>
<td>2.0 - 2.9</td>
</tr>
</tbody>
</table>


Testosterone Patches in Surgically Menopausal Women

Sexual Arousal
For males & females, arousal is dependent on:
• Vascular - need good arterial inflow for male penile erection/female pelvic vasocongestion for lubrication
  – Penile erection needs a 6-fold increase in arterial blood inflow
  – HTN, atherosclerosis, damaged blood vessels, certain drugs => decrease in arterial inflow => erectile dysfunction

Sexual Arousal
• Parasympathetic stimulation (females)
  => erectile tissue congestion in the clitoris
  => vaginal lubrication from
  – Bartholin’s glands
  – Cervix
  – Vaginal wall

Non Rx Treatment Options for Vagina Dryness & Pain
Which of the following is a FDA-approved treatment for female sexual dysfunction?

1. EROS-CTD (clitoral therapy device)
2. DHEA
3. Testosterone patch
4. All of the above

Current FDA-Approved Treatments for Female SD

1. The Eros clitoral stimulator, approved in 2000 for female sexual arousal disorder
2. Premarin (conjugated estrogen vaginal cream), approved in 2008 for treatment of moderate to severe vagina dryness and dyspareunia
3. Osphena (osphemifene) approved in 2013 for treatment of moderate and severe dyspareunia d/t menopause
4. Addyi (flibanserin) approved in 2015 for acquired, generalized hypoactive sexual disorder. “Acquired” = previously had no problems with sexual desire. “Generalized” = HSDD that occurs regardless of the type of stimulation, situation, or partner

EROS-CTD (Clitoral Therapy Device)

- Approved by the FDA (May 2000) to treat female sexual arousal disorder
- Battery operated vacuum pump (Rx only - $360) that provides “gentle suction” directly to the clitoris
  - increase blood flow
  - engorgement of the clitoris
- Need to use q week for weeks to months for optimal efficacy
- Supply >> demand…patients do not find the device helpful!
Conjugated Estrogen Vaginal Cream

- Approved by the FDA (May 2008) to treat:
  - Moderate to severe vaginal dryness due to menopause
  - Moderate to severe dyspareunia due to menopause
- Apply 0.5 gm intravaginally twice weekly or cyclic regimen of 21 days of therapy followed by 7 days off of therapy. Each gram contains 0.625 mg conjugated estrogens
- Clinical trial results: dyspareunia baseline mean 2.43 vs. 2.28 placebo to 0.88 vs. 1.63 (after 12 weeks)
- Endometrial and breast cancer, cardiovascular disorders associated with estrogen therapies

Osphena (Ospemifene) 60 mg/day

- Osphena is an estrogen agonist/antagonist with tissue selective effects, with estrogen agonistic effects in the endometrium. There is an ↑ risk of endometrial cancer in women with uterus using unopposed estrogens
- Estrogen-alone therapy also has ↑ risk of stroke and DVT
- ADRs: Hot flashes, vaginal discharge, muscle spasms
- Clinical trial results: dyspareunia baseline mean score of 2.7 to 1.31 vs. 1.81 placebo on the 1st trial (p 12 weeks); 2.7 to 1.15 vs. 1.41 placebo on the 2nd trial (p 12 weeks)

Which of the following are contraindications with the use of flibanserin (Addyi)?

A. Alcohol
B. Moderate or strong CYP3A4 inhibitors
C. Hepatic impairment
D. All of the above
Which of the following statements is true regarding flibanserin (Addyi)?

A. Recommended dose is 100 mg prn 4 hours before sexual activities
B. Should be avoided at night due to insomnia
C. Discontinue treatment after 8 weeks if there are no improvement with sexual desire

Contraindications with the use of flibanserin (Addyi)

A. The use of ADDYI and alcohol increases the risk of severe hypotension and syncope
B. The concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope
C. The use of ADDYI in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope

ADDYI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) - ADDYI REMS Program

A. Recommended dosage is 100 mg po qhs
B. ADDYI is dosed at bedtime - administration during waking hours increases risks of hypotension, syncope, accidental injury, and CNS depression
C. Discontinue treatment after 8 weeks if no improvement

Boehringer Ingelheim withdraws libido drug for women (BMJ 2010)

• The German drug company Boehringer Ingelheim announced in 2010 that it was withdrawing from developing flibanserin to increase female sexual desire, after negative reviews by an advisory panel of the US Food and Drug Administration in June 2010. Sold to Sprout Pharmaceuticals in 2012

• FDA previously rejected new drug applications for the HSDD treatment in September 2013 and February 2014. Sprout returned with additional data and political support from women’s groups -> FDA approval in August 2015!

• Sold to Valeant Pharmaceuticals for $1B! Stock dropped 87%
Fugh-Berman A. Advise Against Flibanserin

- FDA requested that Sprout Pharmaceuticals perform an alcohol interaction study. The study included 23 men and 2 women, an absurdity for a drug intended only for use by women, who are more susceptible to alcohol’s effects than men.

- Four (17%) of the participants who mixed the 100 mg dose of flibanserin with the equivalent of 2 drinks experienced hypotension or syncope. Their systolic blood pressure levels dropped by 28-54 mmHg; diastolic blood pressure levels dropped by up to 24-46 mmHg. A quarter of the subjects (6 out of 24) who took 100 mg of flibanserin with the equivalent of four drinks experienced orthostatic hypotension.

- Even without alcohol, flibanserin can cause severe drops in blood pressure levels and sudden prolonged unconsciousness.

JAMA Internal Medicine Feb 2016 Review on Addyi

- Laan et al. reviewed eight clinical trials conducted with Addyi, including 5 published and 3 unpublished studies involving almost 6,000 women. Addyi provides marginal benefit for women who are suffering hypoactive sexual desire disorder.

- Addyi (flibanserin) quadruples the risk of dizziness and sleepiness, more than doubles the chances of nausea, and increases the risk of fatigue by more than half.

- For all those risks, a woman taking Addyi can expect to gain an average of 0.5-1.0 additional satisfying sexual event per month only.

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Would you recommend Addyi 100 mg PO QHS for your patients with HSDD?

A. Yes
B. No

A woman taking Addyi 100 mg/day can expect to gain 0.5-1.0 additional satisfying sexual event per month, on average.
Mechanism of Action for HSDD?...Unknown?

- Flibanserin demonstrated high affinity for the following serotonin (5HT) receptors:
  - agonist activity at 5HT-1A
  - antagonist activity at 5HT-2A
- Increases DA and NE...like bupropion?
- Is NOT effective as an antidepressant!

Metabolism and Hepatic Impairment

- Flibanserin is primarily metabolized by CYP3A4 and by CYP2C19 to a lesser extent
- AUC increased 4.5-fold in patients with mild hepatic impairment, compared to subjects with normal hepatic function, and t1/2 was longer (26 hours compared to 10 hours in matching healthy controls)
- In women who were CYP2C19 PM, Cmax increased 49% and AUC of flibanserin 100 mg once daily increased 34%, compared to exposures among CYP2C19 EM. The frequencies of poor metabolizers of CYP2C19 are approximately 2–5% among Caucasians and Africans and approximately 2–15% (more like 18–23%) among Asians.... Note: Only a small # of Asian patients were in these trials!

Flibanserin Drug Interactions

- In a study of 15 healthy female subjects, fluconazole increased flibanserin 100 mg single dose exposure (AUC) 7-fold and Cmax 2.2-fold compared to flibanserin 100 mg alone. Three of 15 subjects (20%) experienced hypotension or syncope...the study was stopped early
- In a study of 26 healthy female subjects, grapefruit juice (240 mL) increased flibanserin 100 mg single dose exposure (AUC) by 1.4-fold and Cmax 1.1-fold compared to flibanserin 100 mg alone
- Oral contraceptives are weak CYP34A inhibitors ➔ increase flibanserin by 40% ➔ increased ADRs
Addyi (Flibanserin) Patient-Provider Agreement

**Patient-Provider Agreement: Patient Information**

Patients taking Addyi® must express an understanding of the following:

- I understand I must not drink alcohol while taking Addyi (Flibanserin).
- Drinking alcohol during treatment with Addyi has been shown to increase the risk of severe low blood pressure and fainting (loss of consciousness).
- If I feel lightheaded or dizzy, I will lie down right away and seek medical help if these symptoms do not go away.
- If I faint (loss of consciousness), I will tell my healthcare provider as soon as possible.
- I understand that I should only take Addyi at bedtime.

**Addyi REMS Program Certification Process**
(required for prescribers and pharmacies)

Complete the Addyi REMS Program Prescriber and Pharmacy Training in 3 easy steps:

**READ**
Read the Addyi REMS Program Prescriber and Pharmacy Training and Prescription Information

**REVIEW**
Review your knowledge by answering Knowledge Assessment questions

**ENROLL**
Enroll by completing the enrollment process online or by faxing the appropriate enrollment form

*For online enrollment first sign-up by creating an account and providing all requested contact information*
Viagra inhibits the PDE5 enzyme → increased cGMP → promotes erection

Which of the following PDE-5 inhibitors can be affected by high fatty meals?

1. Viagra
2. Levitra
3. Cialis
4. All of the above
“Viagra Does Not Work!”

Reasons why Viagra may not work optimally:
– When taken with a high fatty meal, rate of absorption is delayed with mean reduction of Cmax by 29%
– Absence of sexual stimulation/libido \( \rightarrow \) no nitric oxide release \( \rightarrow \) low cGMP \( \rightarrow \) no effect with PDE5 inhibitors
– Timing: average onset of action at 30 mins post PRN dose, and \( 1\frac{1}{2} \) of parent & active metabolite (4 hours)
– Doses too low (starting doses 50 vs. 100 mg max)
– Severe arterial insufficiency or loss of corpus cavernosa smooth muscle
– Concurrent use of enzyme inducers (e.g., carbamazepine, phenytoin, St. John’s Wort) \( \rightarrow \) decreased Viagra conc

Which of the following PDE-5 inhibitors can cause back pain and muscle aches?
1. Viagra
2. Levitra
3. Cialis
4. All of the above

Cialis
- Similar ADRs as Viagra & Levitra (e.g., HA, dyspepsia). No visual changes (less PDE-6 than Viagra or Levitra)
- Has PDE-11 in muscles \( \rightarrow \) 5-6% back pain/muscle aches (vs. 3% placebo). Usual onset of back pain is 12-24 hrs after dose lasting NMT 2 days
Cialis QD Dosing
"When The Moment Is Right, Will You Be Ready?" (Cialis Ad)

Cialis for qday use (3 FDA-approved indications):

**ED:** 2.5 mg taken once daily, without regard to timing of sexual activity. May increase to 5 mg based upon efficacy and tolerability

**BPH:** 5 mg, taken at approximately the same time every day

**ED and BPH:** 5 mg, taken at approximately the same time every day

Cialis may be taken without regard to food

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Which of the following can increase the conc of the PDE-5 inhibitors?

1. Grapefruit juice
2. Paroxetine
3. Buspirone
4. All of the above

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Metabolism of PDE-5 Inhibitors

PDE-5 inhibitors are metabolized mainly by the CYP3A4 enzymes. Viagra, Levitra, and Cialis levels can be increased with the following CYP3A4 inhibitors:

- Grapefruit juice, cimetidine, macrolides (clarithromycin, erythromycin) calcium channel blockers (non-DHP: verapamil, diltiazem), fluoxetine, fluvoxamine, ketoconazole, itraconazole

[http://medicine.iupui.edu/clinpharm/ddis/clinical-table/](http://medicine.iupui.edu/clinpharm/ddis/clinical-table/)
Orgasm (Sympathetic Nervous System)

- SNS stimulation → releases NE → contract/propel seminal fluid into the bulbar urethra (emission)
- Sacral spinal reflex, also SNS stimulation → clonic contraction/relaxation of striated muscle surrounding bulbar urethra (ejaculation) releasing the semen in spurts

SNS stimulation → released NE → wave of contractions at 0.8 sec intervals about 4-15 secs. The vagina lengthens and dilates → rhythmic muscle contractions of the uterus, vagina, anus, and pelvic muscles

* Skene’s gland – 8% of women are "female ejaculators"

Detumescence

Loss of erection dependent on:

- Sympathetic activity (α-adrenergic) → contracts arterial smooth muscle → pushes blood out => decompresses the veins

- Potent α-adrenergic blockers without anticholinergic effects (e.g., trazodone, prazosin, cocaine, PDE5 inhibitors) can prevent detumescence → priapism (sustained, painful erection without sexual desire)

Which of the following medications has shown efficacy with PRN use in the treatment of premature ejaculation?

1. Paxil
2. Zoloft
3. Anafranil
4. Cymbalta
Anafranil (Clomipramine)

- PRN dose 4-6 hrs prior to sex → prolonged ejaculatory latency by average of 500%:
  - baseline → 81 seconds; 25 mg → >3 mins;
  - 50 mg → 7 mins

  (Althof et al. 1995)

- 22 pts, double-blind placebo controlled crossover design – 25 mg PRN 12 - 24 hours prior to sex
  → average of 2 min increased to 8 minutes
* Ineffective if pt had PE and ED
  Mild dry mouth, fatigue, dizziness in 33% of pts
  (Haensel 1996)

Which of the following SSRIs has shown most efficacy in the treatment of premature ejaculation?

1. Paxil
2. Prozac
3. Zoloft
4. Luvox
Dapoxetine

- Dapoxetine has been specifically designed to treat premature ejaculation
- Approved in 2013, dapoxetine (Priligy) became the first medication to be licensed for premature ejaculation in the UK. Available in many countries, but not in the U.S.
- Dapoxetine acts faster than the other SSRIs; can be used PRN 1-3 hours before having sex; NMT 1/day
- For men with an average baseline Inter-vaginal latency time (IELT) of 0.9 minutes, the average IELT improved to 3.1 minutes for a 30 mg dose and 3.6 minutes for a 60 mg dose. Patients taking the placebo improved to 1.9 minutes
- Common side effects of dapoxetine include nausea, headaches, and dizziness

Premature Ejaculation

- Careful evaluation is indicated before medication is recommended…Occasional vs. always? Situational problem? Performance anxiety with heightened sympathetic system? On daily sympathomimetics?
- Management – stop start, squeeze techniques, topical numbing agents, SSRIs (slow onset, daily dosing), clomipramine (prn use, ADRs – highly anticholinergic → can worsen ED, high sedation)
Topical Treatments for PE
Local anesthetics
Lidocaine, prilocaine or benzocaine creams, gel, or spray
Goal is to reduce sensitivity of glans penis
Apply to the head and shaft of the penis before intercourse
* Wash product off after intercourse
Local irritation (burning pain)
Transvaginal absorption
Vaginal numbness
Female anorgasmia
* Prevented with condom use

Viagra for Females?
• 1996: Pfizer Viagra studies for FSD
• 1998: Introduction of Viagra for ED
• Viagra studies for FSD → mixed results
• 2000: UCLA Female Sex Medicine Clinic → good results for women with low clitoral blood flow
• 2/28/04: Pfizer announced termination of Viagra studies for women after 8 years/>3000 pt studies

Viagra Studies for FSD
➢ Kaplan (1999)
  Open-label (50 mg PRN; 12 wk), postmenopausal, n=33 Safe, no clear evidence of efficacy (Sexual Function Questionnaire [SFQ])
➢ Berman et al (2001)
  DB (100 mg), PC, crossover, posthysterectomy/ postmenopausal, n=19 → Sildenafil increased genital blood flow [57% vs 44% Pl (p=0.017)] & subjective response [69% vs 41% Pl (p=0.0004)]
Which of the following herbal products does NOT have any phosphodiesterase-5 inhibitor property?

1. Horny goat weed
2. Yohimbe
3. Rize2
4. Viapro

Horny Goat Weed (Epimedium)
- Horny goat weed – derives its layman names from goats and sheep who were more sexually active after consuming HGW that grew in the fields
- Epimedium species have been utilized for the treatment of erectile dysfunction in traditional Chinese medicine for many years
- Icariin (ICA) is the active moiety of epimedium. ICA may have neurotrophic effects in addition to known phosphodiesterase type 5 inhibiting effects.
- ADRs: insomnia, anxiety, palpitations

FDA Warning: OTC Products with PDE-5 Inhibition
- Since 2008 to present – lab analysis by FDA found thiomethisosildenafil, an analog of sildenafil (Viagra) in multiple OTC sexual enhancement products (e.g., “Rize 2 The Occasion” & “Rose for Her”)
- Contraindications – harmful interactions with nitrates! → lower blood pressure to dangerous levels
- One brand had 41 mg vardenafil (Levitra), >2X the recommended daily dose. Another brand had 189 mg of sildenafil (Viagra), which is normally prescribed in 50 mg doses up to a maximum of 100 mg
Caution with OTC Sexual Enhancement Products

Not regulated
No studies on efficacy and safety
May contain various ingredients:
- Yohimbine
- L-arginine
- DHEA
- Gingko biloba
- Korean Ginseng
SAFE? Not for people with HTN, other heart conditions or anxiety problems

Yohimbe (Yohimbine)

- In various OTC sexual enhancement products
- Presynaptic alpha₂-adrenergic blocker
  → inc’d NE → inc’d BP & HR
  and decrease 5HT-1A → anxiety
- Questionable efficacy
- Risks >> benefits → NOT recommended
  by the American Urology Association!

Sad but true: Tiger penis wine and rhino horns are used as sexual performance medicines! Education needed
Smokers/Alcoholics → Sexual Dysfunction

- "Marlboro man" or "Impotent man"?
- Smoking → impaired testosterone synthesis
- Nicotine → vasoconstriction & penile venous leakage
- Chronic heavy drinking is a leading cause of ED → decreased production of testosterone; destroys the neurogenic reflex necessary for erection

Zestra

**Internet Ad** → “unique topically applied feminine massage oil.”

**Contents** → “starflower oil, evening primrose oil, special extract of angelica & coleus, vitamin C, vitamin E, natural fragrances.”

**Instructions for use** → “Apply between 14 drops (0.5ml) to 28 drops (1.0ml) with gentle massage to the external female genitalia (clitoris, labia & vaginal opening) for 5 minutes prior to vaginal intercourse.”

**Published studies** → Zestra™ is the only topically applied product for women that has been published in highly respected medical journals (The Journal of Sex and Marital Therapy 2003, Drugs 2003; 63 (14): 1445-1457).


<table>
<thead>
<tr>
<th>Drug mechanism of action</th>
<th>Indication</th>
<th>Product Name</th>
<th>Developing company (phase of development)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine receptor agonist</td>
<td>Arousal</td>
<td>Intranasal apomorphine</td>
<td>Nastoic/Pharmacia (phase II)</td>
</tr>
<tr>
<td>Selective 1- and 2-adrenoceptor antagonist</td>
<td>Arousal</td>
<td>Oral phentolamine</td>
<td>Zonagen (phase I)</td>
</tr>
<tr>
<td>Nitric oxide system</td>
<td>Arousal</td>
<td>Sildenafil</td>
<td>Pfizer (phase II)</td>
</tr>
<tr>
<td>Phosphodiesterase IV inhibitor</td>
<td>Arousal</td>
<td>Tadalafil</td>
<td>LillyICOS (phase II)</td>
</tr>
<tr>
<td>Other nitric oxide donors</td>
<td>Arousal</td>
<td>Arginine + yohimbine</td>
<td>NitrolMED</td>
</tr>
<tr>
<td>Alpha-melanocyte stimulating hormone analogue</td>
<td>Arousal and Arousal</td>
<td>PT-141</td>
<td>Palatin (phase I)</td>
</tr>
<tr>
<td>Prostaglandins (smooth muscle relaxant)</td>
<td>Arousal</td>
<td>Alprostadil topical gel</td>
<td>Vivus (phase II)</td>
</tr>
<tr>
<td>Androgens - Testosterone</td>
<td>Desire</td>
<td>Transdermal testosterone gels</td>
<td>Proctor &amp; Gamble (phase III)</td>
</tr>
<tr>
<td>Estrogen/androgen combo</td>
<td>Desire</td>
<td>Esterified estrogen/methyltestosterone</td>
<td>Solvay</td>
</tr>
<tr>
<td>Androgenic dietary suppl</td>
<td>NNR</td>
<td>Multiple androgen substances</td>
<td>Multiple sources</td>
</tr>
<tr>
<td>Natural Products</td>
<td>NNR</td>
<td>Zestra for Women</td>
<td>QualLife</td>
</tr>
</tbody>
</table>

*This product has been deemed as 'generally recognized as safe' and is available via the internet.

NRR = no regulatory review
Good Sexual Function Needs Good Interplay of...

- **Hormonal:**
  - Proper balance of hormones, such as testosterone & progesterone

- **Vascular:**
  - Proper balance of blood in/outflow
  - Adequate blood flow to genitalia

- **Neurological:**
  - Proper balance of neurotransmitters and the autonomic nervous system

- **Psychological:**
  - Good attitudes & experiences with sexual activities

A delicate chain of events that is too easily broken => sexual dysfunction

---

**Psychological Factors**

- *Unpleasant prior experiences*
  - unsatisfying/unpleasant sexual experiences => SD
  - fear of sex => adrenaline response
  - decreases sexual arousal => worsen SD

- *Negatively-shaped sexual attitudes*
  - sex is sinful, dirty, evil, etc.

- *Myths & misconceptions*
  - ever ready penis
  - mutual climax
Psychological Factors

• Intrapsychic conflicts
  – major depression => no libido => SD
  – anxiety => high NE => arousal problem or premature ejaculation
  – sexual victimization or traumatic sexual acts => long-lasting SD effects

• Interpersonal issues
  – can be partner specific
  – loss of attraction & affection
  – interpersonal conflicts

Psychological Factors

• Situational stress
  – stress => chronic high cortisol levels => decreased libido
  – deadlines & obligations at work or home => no interest or time!

• Altered body image
  – 40% of people (esp. females) are unhappy with their bodies or images => avoid physical contact

Evaluation of Sexual Dysfunction

• A detailed medical, medication, sexual history with a thorough physical examination

• Hormonal (e.g., unbound testosterone, prolactin) and labs (e.g., FBS, TFT, lipids) screening, presence or absence of nocturnal erections (during REM sleep)

• Time correlation of onset of SD with various factors. Ask specific questions to determine the type of SD, and if the SD is a “true” dysfunction vs. incorrect assumptions. Use layman terms to ask questions
Incorrect Assumptions of Sexual Functioning

- C/O premature ejaculation after “only 15 minutes!”
- C/O erectile dysfunction after failure to achieve another erection soon after an orgasm “like before!”
- C/O abnormal ejaculation or retrograde ejaculation because of “too less than a teaspoon!” of ejaculate… “not like in those movies!”

Help Improve Sexual Function

- R/O if patients’ SD may be drug-induced; recommend alternatives with less potential for SD
- R/O disease state-induced SD; recommend optimal treatment for improved sx and sexual functioning
- R/O psychological factors; refer patient to appropriate professional help
- Encourage decrease in risk factors, e.g., smoking, excessive alcohol consumption, “couch potatoes”
- Treat SD; patient monitoring and education

Psychopharm PK/PD Clinical Pearls (Part 2)

- Address questions and cases on psychotropic drugs’ pharmacokinetics and pharmacodynamics differences with gender and age.
- Recognize and minimize clinically significant psychotropic drug interactions.
Which of the following psychotropic medications had a requirement from FDA in 2013 to lower its maximum dose for women?

1. Ambien (zolpidem)
2. Xanax (alprazolam)
3. Zoloft (sertraline)
4. Zyprexa (olanzapine)

Zolpidem Dose Changes

- FDA 2013 - required the manufacturers of Ambien, Ambien CR, Edluar, Zolpimist, generic zolpidem, to lower current recommended doses
- Zolpidem clearance is lower in women than in men. Recommended dose for women of zolpidem (Ambien) is 5 mg/day, 6.25 mg/day of Ambien CR for women
- Evaluation of 14 studies showed that women are more affected than men in driving after taking zolpidem 10 mg the previous night
- Multiple cases of sleep driving, walking, talking, eating, and sex…with amnesia of these events the next day!

History of Zolpidem Dose Changes

- FDA approval for Ambien (zolpidem) was in 1992. Until 1993, women of childbearing age were routinely excluded from trials of new drugs. Most drug studies were done in men! 1992-2013 – 21 yrs of same dose for men & women
- Nov 2011 – Intermezzo (zolpidem sublingual tabs) PK studies showed that women’s metabolism is slower than men’s. FDA approved a lower dose for women (1.75 mg) than men (3.5 mg) for insomnia characterized by middle of the night waking with difficulty returning to sleep
- 2013 – FDA decreased the recommended doses of zolpidem based on new data showing 45% higher Cmax and AUC for females vs. males on the same dose
Gender Differences for Drug Levels and ADRs

- Dr. Janine Clayton, director for the Office of Research on Women’s Health at NIH quoted – “This is not just about Ambien, that’s just the tip of the iceberg. There are a lot of sex differences for a lot of drugs, some of which are well known and some that are not well recognized.”

- Drugs with gender differences in concentrations/effects: F>M – beta-blockers (propranolol, metoprolol), clozapine, olanzapine, zolpidem

- First pass metabolism of ethanol is higher in men than in women → higher blood alcohol concentrations in women than men

In geriatric population, zolpidem showed no differences in pharmacokinetics and concentrations between men and women (True or False?)

A. True
B. False

Mechanism of Zolpidem Gender PK Differences?

- Unknown…but some literature suggested that there may be an induction of CYP3A4 protein expression by testosterone

- A small study with 16 men showed free serum testosterone concentrations were lower in the elderly and significantly correlated with zolpidem clearance → suggests that reduced free serum testosterone may have a modulatory role in age-dependent changes in zolpidem PK in men.
Oral contraceptives, containing ethinyl estradiol, can decrease the concentrations of which of the following psychotropic medications?

1. Lamictal (lamotrigine)
2. Ativan (lorazepam)
3. Restoril (temazepam)
4. All of the above

Drug Interactions with Oral Contraceptives

• OCs with ethinyl estradiol induce hepatic glucuronidation
• In most studies, women taking OCs have lamotrigine conc about 40–50% lower than those not taking OCs
• Should not be given to using contraceptives with a pill-free week to avoid fluctuations in lamotrigine concentrations
• Can consider using progestin-only contraception, or nonhormonal methods of contraception may also be used to avoid the interaction if necessary
• Same DDIs for BZDs with hepatic glucuronidation pathway \( \rightarrow \) decreased (lorazepam, oxazepam, temazepam)

Horn JR, Hansten PD. Oral Contraceptives and Reduced Lamotrigine Efficacy. US Pharm 2012.


Lamotrigine doses have to be significantly decreased when used concurrently with valproic acid (Depakene) or Depakote (divalproex sodium). Which of the following statements is false?

1. VPA is an inhibitor of hepatic glucuronidation
2. VPA is an inducer of hepatic glucuronidation
3. VPA increases the risk of Stevens Johnson syndrome with lamotrigine
Dosing Precautions: VPA + Lamotrigine

Which of the following drug classes can increase the concentrations and ADRs of amphetamines?

A. Antacids (e.g., TUMS, Mylanta)
B. H2 blockers (e.g., Tagamet, Zantac)
C. Proton pump inhibitors (e.g., Prilosec, Prevacid)
D. All of the above

Psychostimulants – weak basic drugs

Vitamin C

Acidic Urine (pH 4.9-5.3)

Vita

Non-pH Control

B. H2 blockers, pH
Valium (diazepam) can accumulate in the body with increased half-life of up to 100 hours in the elderly. Which of the following is the most likely reason for the significant increase in its half-life for the elderly?

1. Decreased cytochrome enzymes
2. Increased body fat
3. Decreased renal function
4. Increased gastric pH

**Effects of Physiological Changes on pharmacokinetics In Elderly Subjects**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Increased gastric pH</td>
<td>- Decreased hepatic mass</td>
</tr>
<tr>
<td>- Delayed gastric emptying</td>
<td>- Decreased hepatic blood flow</td>
</tr>
<tr>
<td>- Decreased splanchnic blood flow</td>
<td>- Decreased Phase I metabolism (Oxidative)</td>
</tr>
<tr>
<td>- Decreased intestinal mobility</td>
<td>- Unaltered phase II metabolism (Conjugation &amp; Acetylation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Increased body fat</td>
<td>- Decreased Creatinine Clarence</td>
</tr>
<tr>
<td>- Decreased total body water</td>
<td>- Decreased GFR</td>
</tr>
<tr>
<td>- Decreased Serum albumin</td>
<td>- Decreased tubular filtration</td>
</tr>
<tr>
<td>- Increased X-acidic glycoprotein</td>
<td>- Creatinine</td>
</tr>
<tr>
<td>- Cerebral flow</td>
<td></td>
</tr>
</tbody>
</table>

**CASE: DIFFERENT RESPONSES TO DRUGS AMONG INDIVIDUALS**

Mr. A and Mr. B (with similar physical build, medical status, and on no other medications) were both given the same drug at the same dose and schedule. A week later, Mr. A responded to the drug with no adverse effects while Mr. B ended up in the ER with severe toxic effects. A STAT drug level in Mr. B showed an excessive amt of drug leading to the toxicity.

- What are some of the most important reasons for the differences in their responses to the drug?
Reasons Why People Differ In Their Responses to Drugs

1. Genetics – poor/extensive (normal)/rapid metabolizers; differences can be >10,000 fold!
2. Disease – renal or hepatic disease, endocrine problems
3. Age – decrease in some hepatic enzymes, and blood flow; higher body fat; weaker blood-brain-barrier
4. Drug interactions – enzyme inhibition; enzyme induction; competitive metabolism; protein-binding displacement; altered rate or extent of absorption/excretion; additive, synergistic, or antagonist effects
5. Environmental factors – diet, smoking, storage of drugs

P450 ISOENZYMES POLYMORPHISM

• Genetic polymorphism = monogenic trait that exists in the population in at least two phenotypes/genotypes, neither of which is < 1%

• 1A2  12% Poor metabolizers (PM)  40% Rapid metabolizers (RM) for the general population
• 2C19  2-5% Caucasians & Blacks are PM  18-23% Asians are PM
• 2D6  7-10% Caucasians, 2-5% Blacks, 1-5% Asians are PM
• 3A4  No polymorphism, but still has high variability among individuals

CASE: CYP1A2

• Two average-sized males were started on clozapine for schizophrenia.
• Mr. X had severe adverse effects at subtherapeutic doses. When a plasma level was taken, he had a level above the therapeutic range.
• Mr. Y was titrated to the max high dose but showed a subtherapeutic level. Noncompliance, other disease states, drug and food interactions, and smoking were ruled out.
CYP1A2 ENZYMES

- P450 1A2 enzyme deficiency in 12% of the population
  => poor metabolizers => high drug levels
  => possible adverse/toxic effects with normal therapeutic doses
- 40% of the population are rapid metabolizers
  => subtherapeutic levels => therapeutic failure
  with normal therapeutic doses; usually need higher than normal doses for efficacy

CYP1A2

- Metabolizes clozapine, olanzapine, fluvoxamine, duloxetine, caffeine
- Inhibited by fluvoxamine, fluoxetine, ciprofloxacin, cimetidine
- Inducible by drugs, food, and smoking
- 12% poor / 40% rapid metabolizers

CYP2C19 - Case

A 24 y/o Asian male was started on a small dose of diazepam for his anxiety disorder. Within days, the patient was ataxic and confused. The patient was compliant, and there were no drug interactions or other disease states.
**CYPC19 ENZYME**

- 18 to 23% East Asians may be very sensitive to drugs metabolized by the 2C19 isoenzyme; risk is much higher than Blacks and Caucasians (2-5% PM)
- Dose precaution with benzodiazepines and other drugs metabolized by CYP2C19

**CYP2C19**

- Metabolize N-desmethyldiazepam, omeprazole, phenytoin, S-warfarin
- Inhibited by omeprazole, fluoxetine, cimetidine
- Inducible by drugs; not food or smoking
- Can also decrease with age

**CYP2D6 - Case**

A 35 y/o Caucasian male was titrated on risperidone to 4 mg/d. He refused to take any more medications b/c of excessive sedation and EPS. He remembered having intolerable SEs from a small dose of another antipsychotic in the past. Patient was compliant, and there were no drug interactions or other disease states.
CYP2D6 ENZYMES
- 7-10% Caucasians, 2-5% Blacks, 1-5% Asians are poor metabolizers → high drug levels → adverse/toxic effects on normal therapeutic doses
- levels/responses on normal therapeutic doses
- Substrates – most cardiovascular drugs, many antidepressants and antipsychotics, codeine

CYP2D6 - Case
A 28 y/o Caucasian female was given Tylenol with codeine for pain after her dental surgery. She called her dentist a day later complaining of severe pain despite the use of the Tylenol #3. She informed her dentist that the analgesic effect is no better than that of plain Tylenol.

CYP2D6 ENZYMES
- Codeine (prodrug with no clinical activity) needs P450 2D6 isoenzyme => morphine (active metabolite)
- Hydrocodone (Vicodin) needs P450 2D6 isoenzyme => hydromorphone (active metabolite)
- Poor metabolizers => no conversion to active metabolite => minimal analgesic effects
- Rapid metabolizers => high conversion to morphine => increased ADRs
CYP2D6 ENZYMES
- Metabolizes many antipsychotics, antidepressants, class 1 antiarrhythmics, cardio-vascular drugs, codeine
- Inhibited by cimetidine, quinidine, bupropion, duloxetine, fluoxetine, paroxetine,
- Not inducible by drugs, food or smoking

CYP3A4 ENZYMES
- Metabolizes carbamazepine, calcium channel blockers, triazolobenzodiazepines (alprazolam, triazolam, midazolam)
- Inhibited by nefazodone, fluvoxamine, verapamil, diltiazem, itraconazole, erythromycin, clarithromycin, cimetidine, grapefruit juice
- Inducible by drugs; not food or smoking
- No polymorphism, but still has high variability

FACTORS TO R/O WHEN UNEXPECTED RESPONSE TO DRUGS IS NOTED
Increased ADRs:
- Poor metabolizers
- Drug interactions
- Hepatic/Renal impairment, CHF
- Advanced age
- Grapefruit juice (3A4)
- Increased bioavailability when taken with meals
  Example: sertraline
- Generic/Brand switch
- Noncompliance (taking too much)
FACTORS TO R/O WHEN UNEXPECTED RESPONSE TO DRUGS IS NOTED

Decreased Effects/Subtherapeutic:

- Rapid metabolizers
- Drug interactions
- Pregnancy - GFR increases 50%
- Hyperthyroidism - increased metabolism
- Charbroiled foods (1A2)
- Smoking (1A2)
- Storage in the heat or humidity
- Generic/Brand switch
- Noncompliance

Selected Current References:


10 Post-Assessment Questions and Answers
1. Which of the following components is essential for good sexual function?
   A. Neurological
   B. Hormonal
   C. Vascular
   D. Psychological
   E. All of the above

2. Which of the following is the most common sexual dysfunction in males and females?
   A. Males – erectile dysfunction, females – anorgasmia
   B. Males – premature ejaculation, females – low libido
   C. Males – erectile dysfunction, females – lack of lubrication
   D. Males – anorgasmia, females – low libido
   E. Males – premature ejaculation, females – lack of lubrication

3. Which of the following OTC/Rx drugs or drugs of abuse can decrease libido?
   A. Cimetidine (Tagamet HB)
   B. Heroin
   C. Hydrocodone (Vicodin)
   D. Oral contraceptives
   E. All of the above
4. Which of the following is an FDA-approved treatment for hypoactive sexual desire disorder in women?

A. Bupropion (Wellbutrin)
B. Flibanserin (Addyi)
C. Testosterone transdermal patch
D. All of the above

5. Which of the following ADRs is most commonly associated with filbanserin (Addyi)?

A. Dizziness
B. Sleepiness
C. Nausea
D. Fatigue
E. All of the above

6. Which of the following are contraindications with the use of filbanserin (Addyi)?

A. Alcohol
B. Moderate or strong CYP3A4 inhibitors
C. Hepatic impairment
D. All of the above
7. Most psychotropic medications are lipophilic and cross the blood-brain-barrier. What are the effects of aging on lipophilic drugs?

A. Increased drug half-life
B. Decreased drug half-life
C. Increased volume of distribution (Vd)
D. Decreased Vd
E. A and C

8. True or False?
As of 2016, zolpidem (Ambien) is the only drug on the market with different recommended doses for men and women.

A. True
B. False

9. Which of the following can increase the concentrations and ADRs of alprazolam (Xanax)?

A. Cimetidine (Tagamet)
B. Clarithromycin (Biaxin)
C. Diltiazem (Cardizem)
D. Grapefruit juice
E. All of the above
10. Which of the following drug classes can increase the concentrations and ADRs of amphetamines?

A. Antacids
   (e.g., TUMS, Mylanta)
B. H2 blockers
   (e.g., Tagamet, Zantac)
C. Proton pump inhibitors
   (e.g., Prilosec, Prevacid)
D. All of the above

Eye Examination Chart
Increase distance from chart until it is readable

Questions/Comments?
Mary Gutierrez, PharmD, BCPP
mgutier@chapman.edu