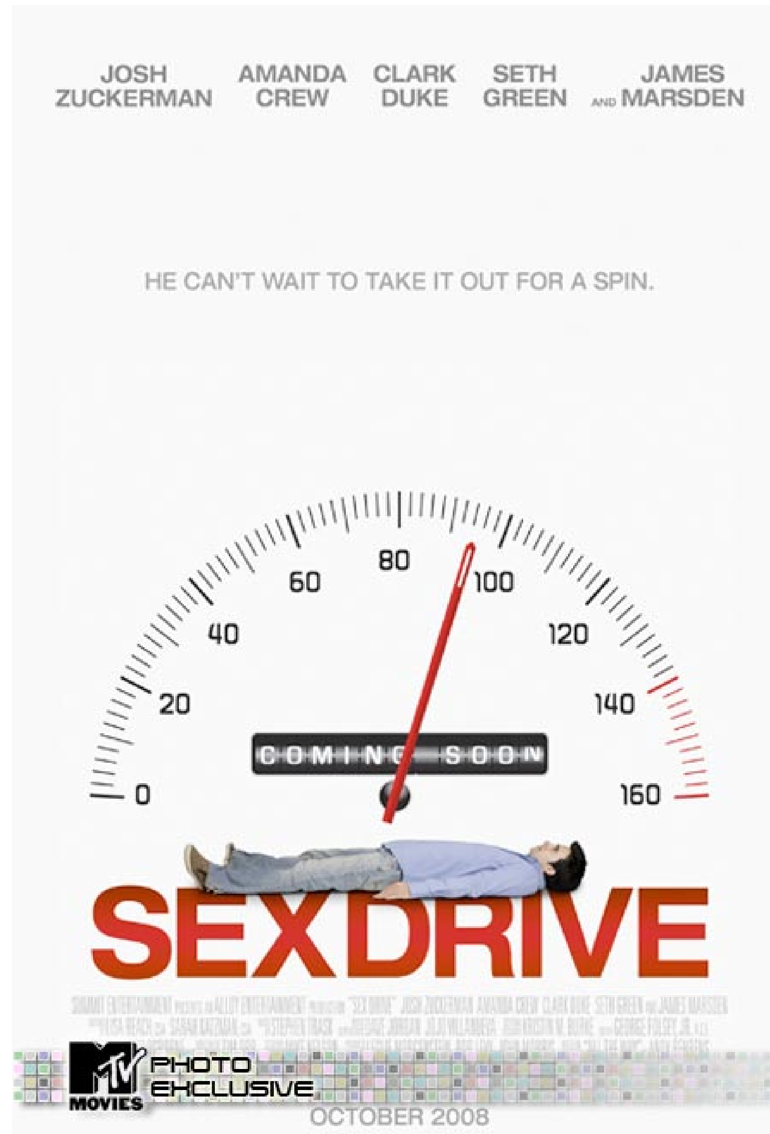
Antiandrogen Treatment of Sex Offenders

Howard E. Gilman, MD
Roger M. Harris, MD

Learning Objectives

- Gain a basic understanding of biology of sexual drive
- Gain a basic understanding of effects and side-effects of antiandrogens
- Gain practical advice on setting up antiandrogen treatment clinic

Biology of Male Sexual Drive



Definition - Sexual Drive

A complex physiological and psychological reaction to certain stimuli resulting in some or all of the following:

- sexual desire
- sexual arousal
- orgasm
- resolution

Sexual Drive

7th Avenue and 42nd Street

New York City, NY

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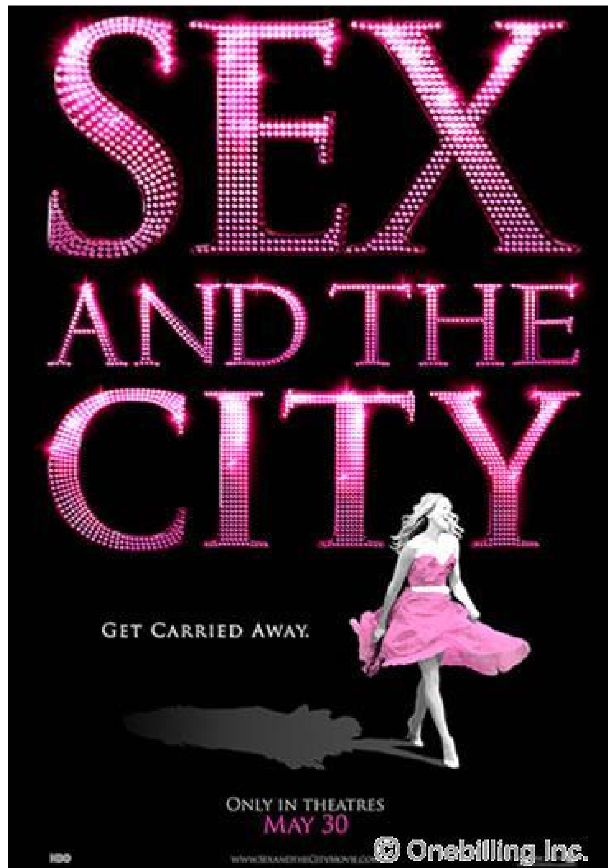
Sexual Drive

Influenced by a variety of factors including:

- **Biological**
- Cognitive
- Motivational
- Relational
- Affective

Cast List



- Testosterone
- Other Androgens
- Binding Proteins
- Hypothalamic and Pituitary Hormones
- Estrogens
- Spinal Cord Innervation

Testosterone

- 95% secreted by Leydig cells
- Linked to sexual interest and nocturnal tumescence
- Level needed for sexual interest/arousal is lower than normal levels

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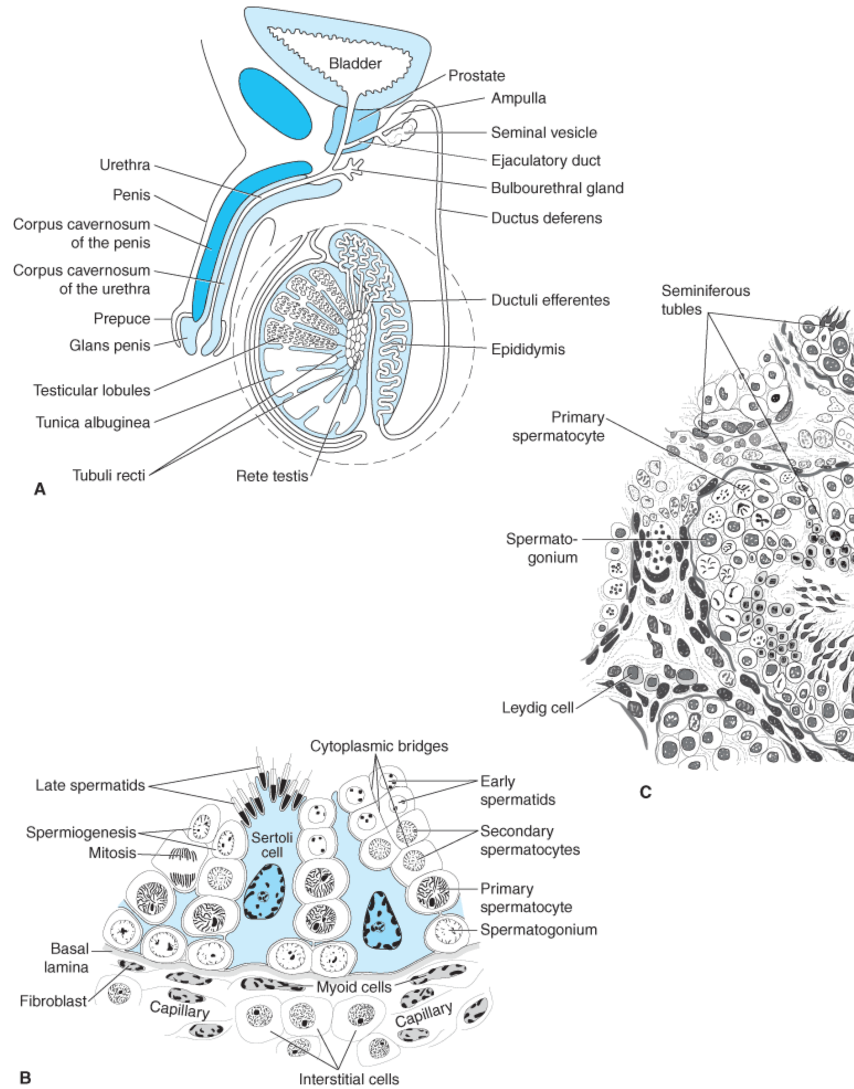

Source: Gardner DG, Shoback D: *Greenspan's Basic and Clinical Endocrinology*, 8th Edition: http://www.accessmedicine.com

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Relative Contributions (Approximate Percentages) of the Testes, Adrenals, and Peripheral Tissues to Circulating Levels of Sex Steroids in Men

	Testicular Secretion	Adrenal Secretion	Peripheral
Testosterone	95%	<1%	<5%
Dihydrotestosterone	<20%	<1%	80%

Protein Binders of Testosterone

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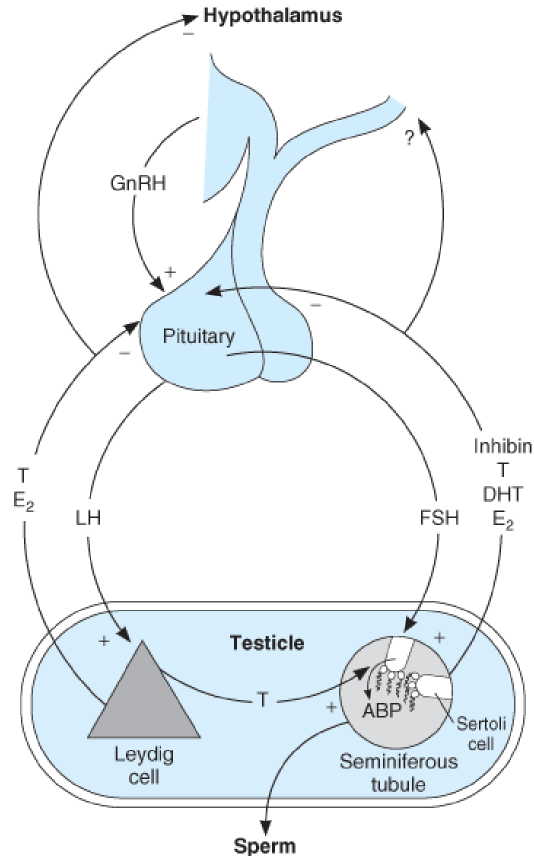
- Albumin, Sex Hormone-Binding Globule, Androgen Binding Protein
- Pick up androgens and keep them from being free for action
- 98% testosterone is protein bound

Normal Ranges for Gonadal Steroids, Pituitary Gonadotropins, and Prolactin in Men.

Testosterone, total	260–1000 ng/dL (9.0–34.7 nmol/L)
Testosterone, free	50–210 pg/mL (173–729 pmol/L)
Dihydrotestosterone	27–75 ng/dL (0.9–2.6 nmol/L)
Androstenedione	50–250 ng/dL (1.7–8.5 nmol/L)
Estradiol	10–50 pg/mL (3.67–18.35 pmol/L)
Estrone	15–65 pg/mL (55.5–240 pmol/L)
FSH	1.6–8 mIU/mL (1.6–8 IU/L)
LH	1.5–9.3 mIU/mL (1.5–9.3 IU/L)

Pituitary Hormones



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- Follicle Stimulating Hormone(FSH)
  - Stimulates production of androgen binding protein
- Luteinizing Hormone (LH)
  - Stimulates production of testosterone by Leydig cell
- LH and FSH production is stimulated by release of Gonadotropin Releasing Hormone (GnRH)

Estrogens

- Estradiol
- Estrone
- Produced primarily in peripheral tissues
- Produces a negative feedback on gonadatropin production

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Spinal Nerve Innervation

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- Synergy between sympathetic and parasympathetic neurons
- May be mediated by nitric oxide on a cellular level
- Sildenafil (Viagra)

Psychology

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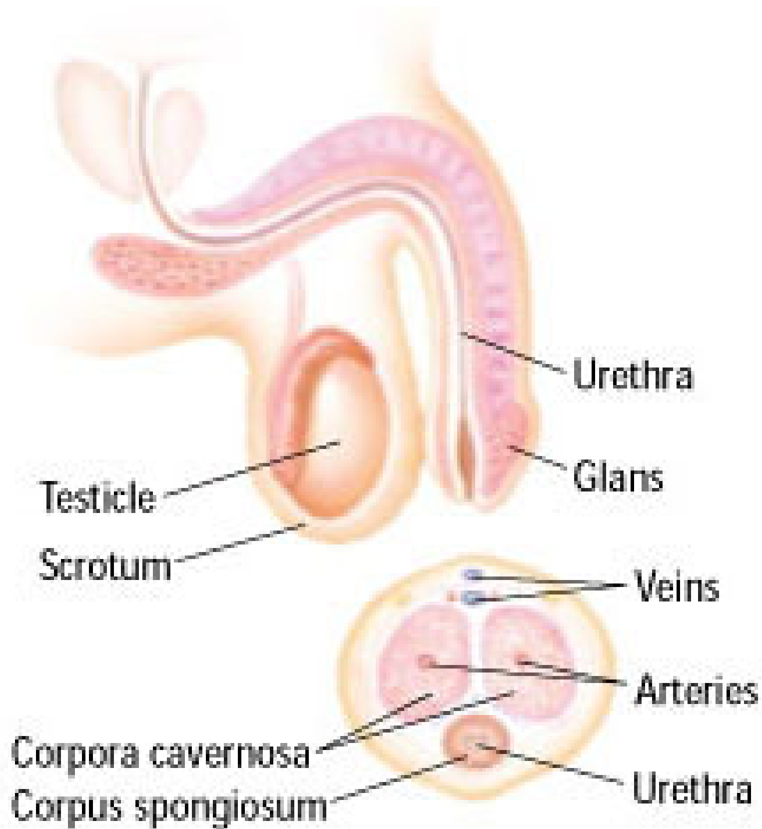
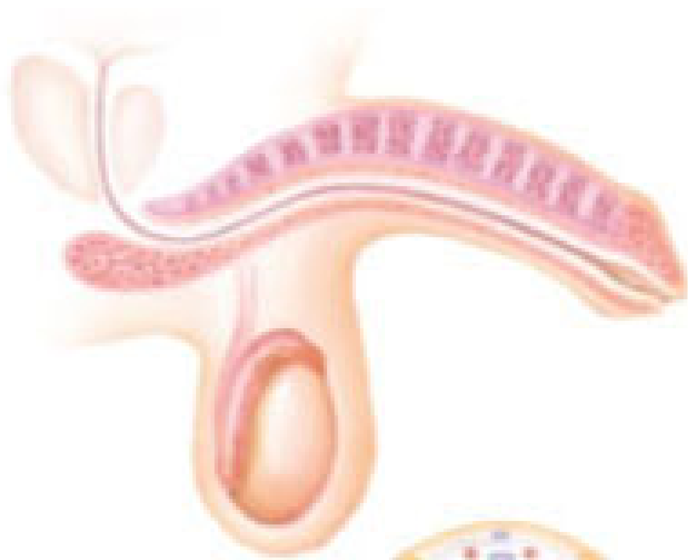
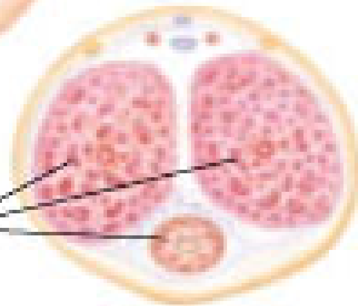
Summary of Influence on Sexual Drive



- Psychological Influences

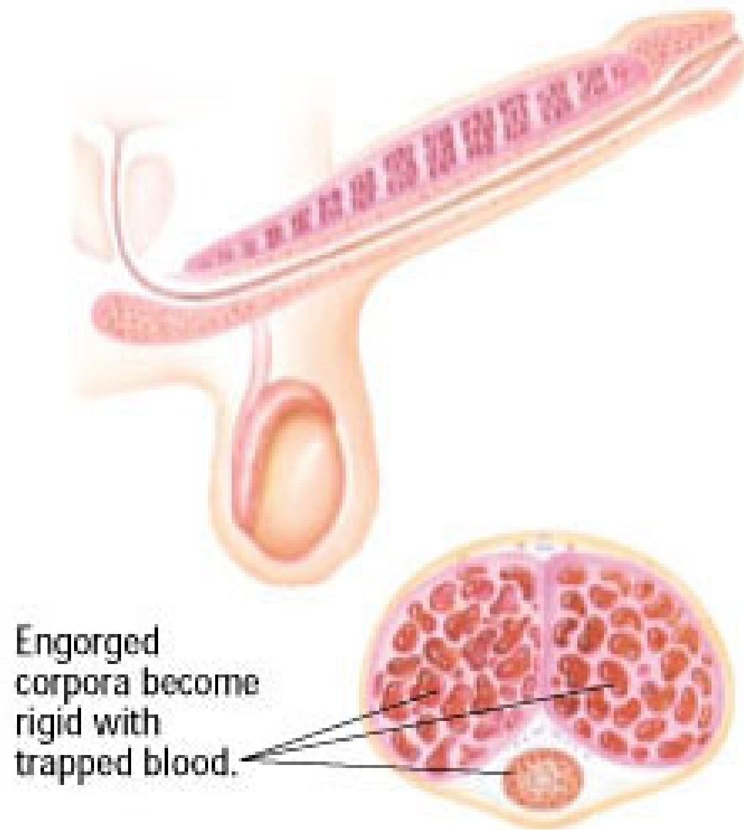
Summary of Influence on Sexual Drive





- Psychological Influences
- Local Spinal Cord Innervation

Summary of Influence on Sexual Drive



- Psychological Influences
- Local Spinal Cord Innervation
- Systemic Biological Factors
  - Androgens (Testosterone)
  - Pituitary/Hypothalamic Hormones (GnRH)

Antiandrogens

- Cyproterone Acetate (CPA)
  - Synthetic steroid similar to progesterone
  - Inhibits intracellular uptake of testosterone by blocking the androgen receptor
  - Inhibits secretion of GnRH with subsequent reduction in testosterone production
  - Not available in the United States

Antiandrogens

- Medroxyprogesterone Acetate (MPA)
  - Suppresses LH and FSH release from pituitary, thus reducing testosterone production in the testes - since it does not bind at the androgen receptor it technically not an antiandrogen
  - Side effects are hypogonadism, weight gain, decreased sperm count, lethargy, cold sweats, hot flashes, diabetes mellitus, headache, deep vein thrombosis, nausea and vomiting, feminization

Antiandrogens

- Gonadotropin Releasing Hormone (GnRH) Agonists
  - Also known as luteinizing hormone-releasing hormone (LHRH) agonist
  - Leuprolide acetate and triptorelin
  - Act like GnRH, causing an initial increase in LH and FSH followed by a depletion of LH and FSH
  - In response there is an initial increase in testosterone production followed by a marked decrease

Antiandrogens

- Gonadotropin Releasing Hormone (GnRH) Agonists - cont
  - Side effects are osteoporosis, hypogonadism, nausea and vomiting, weight gain, hot flashes, cold sweats, facial and body hair loss, sleep disturbances and nightmares, gynecomastia, headaches, dizziness

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General Effects of Antiandrogens

- Reduction in testosterone
  - Virtually all agents, when given in sufficient doses, lead to significant but reversible reductions in testosterone
  - Some evidence in case reports and some studies that GnRH agonists may more effectively reduce testosterone than CPA or MPA

Rosler et al
NEJM 1993

TABLE 2. Effect of Continuous Administration of Triptorelin in Men with Severe Paraphilia.*

Variable	Months of Triptorelin Therapy								P Value†	Normal Range
	0	6	12	18	24	30	36	42		
No. of men‡	30	30	24	18	15	11	8	6		
Intensity of Sexual Desire and Symptoms score	8.0±0.2	2.7±2.3§	1.7±0.85	1.6±0.7	1.5±0.5	1.4±0.2	1.3±0.15	1.4±0.15	<0.001	
Serum luteinizing hormone (mIU/ml)	10.6±5.3	4.0±2.4§	2.7±2.7	3.1±2.5	0.8±0.3	0.8±0.5	0.9±0.4	0.8±0.4	<0.001	3–15
Serum follicle-stimulating hormone (mIU/ml)	7.1±6.8	4.6±2.6	3.5±1.9	3.8±1.8	2.2±0.7	2.1±0.4	2.0±0.7	1.9±0.9	0.29	2–10
Serum testosterone (ng/dl)¶	545±196	26±14§	32±14	23±12	26±21	23±12	23±14	23±14	<0.001	280–870
Testicular volume (ml)	26.2±4.6	19.6±4.0§	17.3±4.1§	17.4±5.5	15.6±6.0	14.9±6.2	13.5±9.1	13.8±9.3	<0.001	18–30
Bone mineral density (% of value in age-matched normal men)‖										
Vertebral	92.8±13.0	88.1±12.2§	86.5±10.7§						0.005	
Femoral	84.5±15.7	83.1±14.5	80.4±8.8						0.43	

*Plus–minus values are means ±SD.

†Two-way analysis of variance was used to test the overall homogeneity of the values at all time points. Only the 24 men who completed at least 12 months of therapy were included in the statistical analysis.

‡Values are the number of men who completed the specified number of months of triptorelin therapy.

§P<0.05 for the comparison with the previous months (Wilcoxon matched-pairs signed-rank test).

¶To convert values for serum testosterone to nanomoles per liter, multiply by 0.03467.

‖The analysis included 14 men.

General Effects of Antiandrogens

- Reduction in penile tumescence
  - Penile plethysmography shows reduction of penile tumescence
    - Bradford and Pawlak 1993 noted that this reduction did not occur in treatment with CPA when the stimulus was not pedophilic or coercion tapes
    - Schober et al 2005 noted reduction of penile tumescence on LA but still sufficient enough to register response to pedophilic challenge

General Effects of Antiandrogens

- Self reports of sexual fantasies/behavior decreased
  - Self report suspect in this particular population
  - Schober 2005 used polygraph
    - All respondents answered no to the presence of deviant arousal
    - Deception indicated when on placebo
    - Deception not indicated when on LA

Questions

- Do antiandrogens decrease deviant sexual behavior?
- Do antiandrogens decrease sexual recidivism in sex offenders?
- If either of the above are “yes,” is it predicted by any of the testable factors (i.e., particular medication, dosage, testosterone levels, penile tumescence, self report

Antiandrogens - Do They Work?

- Ideal study would be:
  - Double blind, placebo controlled measuring recidivism
  - Objective measurements of decreased sexual drive
  - Large sample size
    - Reoffense rates are only several % per year
  - Sufficient length of follow-up (years rather than months)
    - Average recidivism rate for sex offenders is 18% at 5 years and 26% at 15 years (Harris et al)

Number of Ideal Studies

0

Recidivism and CPA 1

- Berner 1983 reported on 21 sex offenders given CPA 100 mg daily
  - Over 1 - 2 years 28% were rearrested
  - Few other details
- Prentky 1997 references Bradford 1988 reporting on 7 studies done in the 1970s in which 6 showed recidivism rates of 0 over 1 - 4.5 years

Recidivism and CPA 2

- Bradford 1990 makes reference to 8 European studies from the 1970s in which CPA reduced recidivism from 50% - 100% pretreatment to 0% posttreatment with 1 - 5 year follow-up.
  - In one of the 8 studies (Appfelt 1974) recidivism was 16.7% in 1.5years

Recidivism and MPA 1

- Berlin 1981 follows up a study by Money
  - 20 paraphilic men treated for up to 5 years, 9 months
  - 3/20 relapsed while on IM MPA treatment 150 mg q 2 weeks - 600 mg weekly
  - 11/20 discontinued tx; 10 relapsed

Recidivism and MPA 2

- Meyer 1992 retrospective study of 61 outpatient sex offenders
  - 40 agreed to MPA, 21 declined
  - 12/21 MPA refusers reoffended
  - 7/40 MPA acceptors reoffended
  - 10/29 MPA acceptors, once off MPA, reoffended
  - % reoffending strongly correlated with serum testosterone levels

Recidivism and MPA 3

- Maletzky 2006 retrospective review of 275 male sex offenders (1’ rapists/pedophiles) released from prison referred for psych eval for MPA
  - 134/275 recommended by psych for MPA tx:
  - 79 received MPA
  - 4/79 (5%) MPA vs 17/55 (31%) untx reoffended
  - Rate of reoffense in MD non-recommended (N= 141) sample was 27%

Recidivism and MPA 4

- Maletsky 2003 reviewed literature and cites the following:
  - Gottesman 1993 tx 7 offenders with no relapse in 1-1/3 years
  - Federoff 1992 found recidivism over several years in 4/27 tx'd vs 13/19 getting psychotx alone

Recidivism and GnRH Agonists 1

- Rosler 1998
  - 30 outpt paraphilic men (25 pedophiles)
  - triptorelin (TA) 3.75 mg monthly X 8 - 42 mos
  - In follow-up letter they report no recidivism while on meds
- Briken 2001
  - 11 paraphilic men who had been in legal trouble with leuprolide for 6 - 12 mos
  - 1 suicide; no recidivism while in tx

Recidivism and GnRH Agonists 2

- Briken 2003 reviewed 13 articles on GnRH agonists totaling 118 patients
  - Cites studies in which GnRH agonists were associated with no relapse compared with those on CPA/MPA or on no biologic tx

Schober et al
Arch Sex Behav 2005

- 5 convicted outpatient pedophilic males given LA for 1 year followed by placebo (blinded)
- Concomitant cognitive behavioral therapy
- On LA had markedly decreased testosterone levels (<25 ng/dl)
- On LA penile tumescence by plethysmograpy was significantly lower (but sufficient enough to register response to pedophilic challenge)

Schober et al
Arch Sex Behav 2005

- When off LA testosterone levels and penile tumescence returned to baseline
- On polygraph exam all men denied masturbating to and having urges for sex with children under 18; deception was indicated when off LA and no deception was indicated when on LA
- Study weaknesses: short duration, small number of patients

Conclusions

- Significant evidence that antiandrogens can effectively reduce total testosterone and penile tumescence
- Some evidence that antiandrogens can reduce deviant sexual thoughts and behaviors
- Some evidence that antiandrogen treatment may be associated with reduced risk of sexual recidivism in sexual offenders

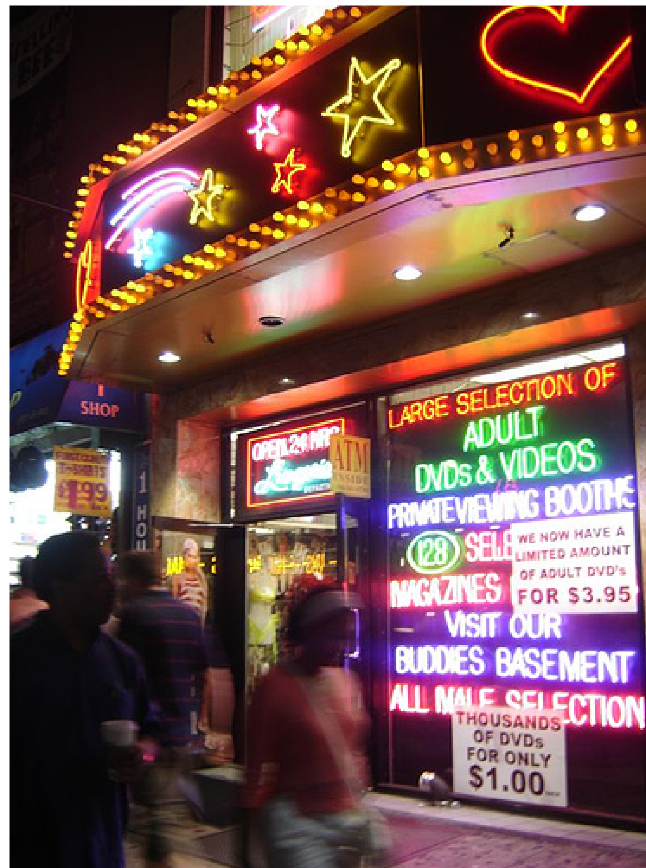
Caveats

- Limited and problematic studies
- Responders may be self-selected
- Side effects

Sexual Drive

7th Ave & 42nd Street

New York, NY



Sexual Drive (after antiandrogens)

7th Ave & 42nd Street

New York, NY

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