



Medical
Management of
Gender
Transition

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Disclosures

I have nothing to disclose or conflicts of interest

Objectives

- Understand criteria for puberty blockers and gender affirming hormones
- Differentiate between options for puberty blockers
- Identify medication options for the treatment of gender incongruence
- Explain risks and expected outcomes associated with gender affirming hormone treatment



Why Transition?

- Gender Dysphoria- Persistent physical, emotional, and/or psychological distress due to discomfort with one's assigned sex
 - Physical characteristics (breasts, genitalia)
 - Clothing (Being forced to wear clothes that don't align with your gender identity)
 - Being mis-gendered (especially in public and school)
 - Physical exams
 - Puberty

T r a n s i t i o n i n g

Reversible

- Social transition
- Clothing
- Hair style
- Pronouns
- GnRH agonist (leuprorelin, histrelin)

Partially Reversible

- Testosterone
- Estradiol
- Spironolactone
- 5- Alpha reductase inhibitors
- Progestins

Permanent

- Vaginoplasty
- Phalloplasty
- Orchiectomy
- Metoidioplasty
- Chest surgery, breast augmentation
- Hysterectomy, oophorectomy
- Facial feminization

DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

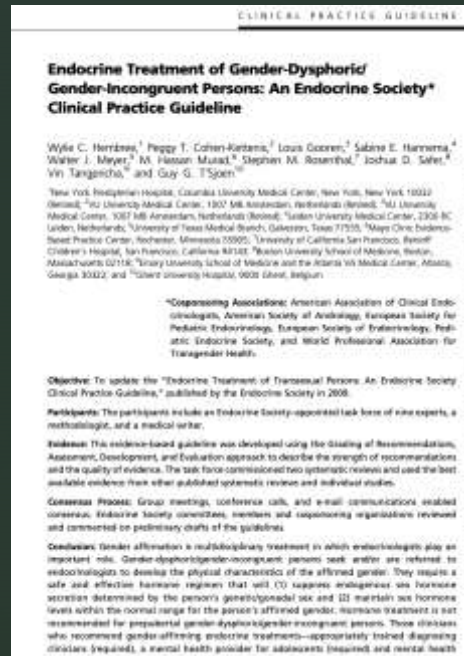
Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

- A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender
 4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
 5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)
- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Specify if:
1. The condition exists with a disorder of sex development.
 2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Guidelines

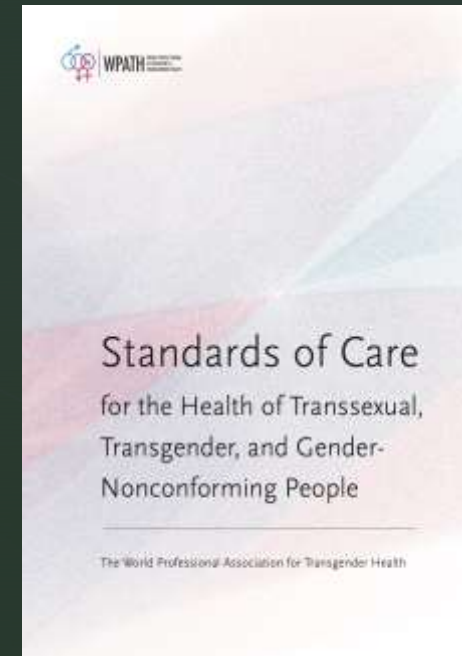
Endocrine Society

- Published 2017, updated guidelines from 2009



Standards of Care 7 (SOC7)

- Published in 2011, World Professional Association for Transgender Health



Goals of Hormone Therapy



- Reduce endogenous sex hormone levels, and thus reduce the secondary sex characteristics
- Replace with exogenous sex hormone levels consistent with the individual's gender identity
- Acquire secondary sexual characteristics that align with the individual's gender identity

Children and Adolescents

Adolescent Risk Behaviors

- Risk behaviors higher in trans vs cis

Protective factors:

- Family connectedness
- Student-teacher relationships
- Feel safe in community

Health Risk Behavior	Trans/Gender-Diverse Youth	Cis Youth
Alcohol use	23%	17%
No condom at last sex	51%	38%
No birth control at last sex	41%	25%
Depressive symptoms	58%	21%
Self-harm past year	54%	14%
Suicidal Ideation	61%	20%
Physical bullying	25%	12%
Relational bullying	52%	32%
Prejudice-based reason: gender	35%	5%
Prejudice-based reason: gender expression	47%	15%

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:

- the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
- gender dysphoria worsened with the onset of puberty,
- any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
- the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,

2. And the adolescent:

- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment

- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent (Tanner stage \geq G2/B2),
- has confirmed that there are no medical contraindications to GnRH agonist treatment.

Blocking Puberty

- Ideally around Tanner 2
 - Maintain prepubertal status
- Can use Tanner 3-5
 - Halt continued puberty changes
 - Prevent continued secondary sex characteristics



Blocking Puberty

GOALS

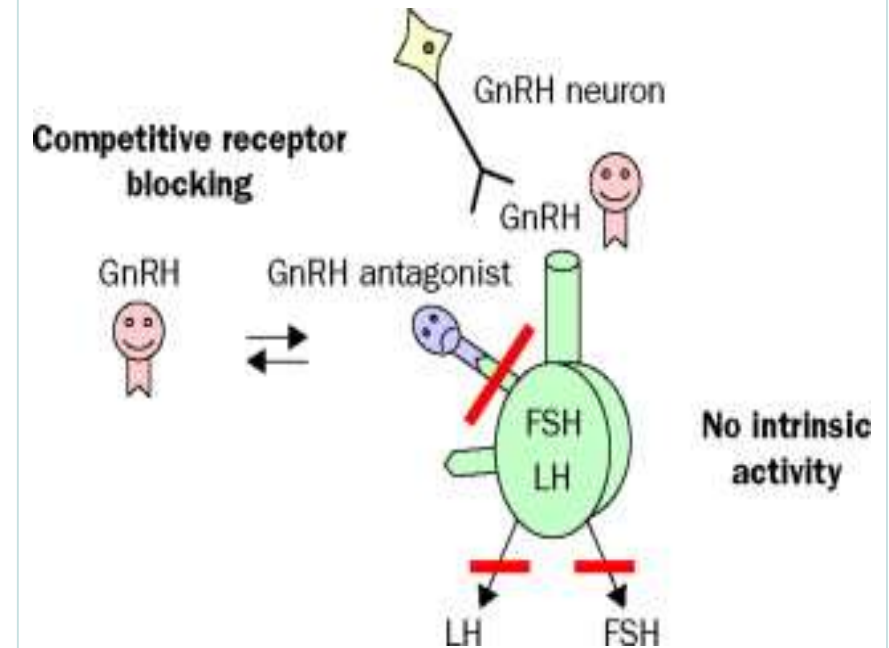
- Delay irreversible secondary sex characteristics
- Allow time for teen to mature and make decision
- Allow time for parent and social support to develop
- Allow provider reluctance for irreversible effects in minor

BLOCKERS

- Gonadotropin-Releasing Hormone (GnRH) agonists
 - First-line option
 - Leuprolide (Lupron)
 - Histrelin (Supprelin LA)
- Progestins
- Anti-androgens
 - Spironolactone
 - Bicalutamide

GnRH Agonists

- Continuous GnRH secretion
 - Suppresses FSH, LH
 - Initial ↑ LH, FSH followed by desensitized pituitary
 - LH, FSH secretion suppressed
- May have increase in pubertal changes 1-2 months before suppression occurs



Types of GnRH agonists

Leuprolide

- Depot IM or Sub Q:
 - 3.75mg monthly
 - 11.25mg q 3 months
 - 22.5mg IM q 3 months
- Depot administered IM
- Eligard administered SubQ
- Brand names: Lupron, Eligard

Histrelin acetate

- Implant
- Need procedure consult to discuss risks and benefits of placement
- SQ implant placed every 1-2 years
- Vantas vs Supprelin LA
 - Vantas is \$5K but not approved for pediatrics
 - Supprelin LA is \$25K approved for precocious puberty

Blocker's Continued

- Progesterone
 - Medroxyprogesterone (Depo-Provera): IM 150mg q 3 months
 - Micronized progesterone (Prometrium): 100-200mg q HS
 - Not as effective in lowering endogenous sex hormones
- Antiandrogens (transfeminine)
 - Spironolactone 25-50mg PO, QD-BID (less potent)
 - Bicalutamide 50mg PO, QD (blocks testosterone receptors)

Side Effects

GnRH Agonists

- Adverse effects on bone mineralization
- Compromised fertility
- Unknown effects on brain development
- Injection site infection

Progesterone

- Acne
- Headache
- Menses cessation
- Metrorrhagia
- Fatigue
- Weight gain
- Depression

Side Effects

Spironolactone

- Hyperkalemia
- Increased urinary frequency
- Hypotension
- Renal insufficiency

Bicalutamide (Neyman, Fuqua, & Eugster, 2019)

- Hepatotoxicity (<1%)
- Gynecomastia
- Breast pain
- Fatigue

Follow Up

- Every 3-6 months
 - Height, weight, sitting height, blood pressure, Tanner Stages
- Every 6-12 months
 - Labs: LH, FSH, E2/T, Vit d
- Every 1-2 years
 - Bone density scan using DXA
 - Bone Age on X-ray of left hand (baseline)

When to Start Gender-Affirming Hormones?

- Endocrine Society recommends starting at age 16
- Decision to start earlier should be individually determined
 - Length of time on GnRH analogues (risk for impacting bone density) if started at earlier stage of puberty
 - Experiencing puberty in late high school/early college can have negative social impacts
- Youth who reach adolescence with gender dysphoria are unlikely to revert to a gender identity that is congruent with their assigned sex at birth (de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT, 2011)

Criteria for Gender-Affirming Hormone Therapy for Adolescents

Endocrine Society

- Persistent, well-documented gender dysphoria/gender incongruence
- The capacity to make a fully informed decision and to consent to treatment
- The age of majority in a given country
- Mental health concerns, if present, must be reasonably well-controlled

SOC 7

- Adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria
- Gender dysphoria emerged or worsened with onset of puberty
- Coexisting psychological, medical or social problems that could interfere with treatment are addressed
- Adolescent has given informed consent and parents/caregivers have consented to treatment

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
 - the persistence of gender dysphoria,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
 - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
 2. And the adolescent:
 - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
 3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
 - agrees with the indication for sex hormone treatment,
 - has confirmed that there are no medical contraindications to sex hormone treatment.
-

Initiating Hormone Therapy

- Assess readiness
 - Referral letter from mental health professional?
 - Informed Consent
 - Assess and diagnose gender dysphoria/incongruence
 - Assess for capacity to provide informed consent (able to understand risks, benefits, alternative, limitations, risks of no treatment)
 - Many adolescents ages 15-16 have reasonable level of competence
- Continue GnRH agonists?
 - GnRHa continued until serum estradiol > 40 or serum testosterone > 100 ng/dL

Puberty Inducing Hormones

Transfeminine

- Continue blocker?
- Start antiandrogen?
- Add low dose estradiol

Transmasculine

- Continue blocker?
- Start low dose testosterone

Protocol Induction of Puberty

Induction of female puberty with oral 17β -estradiol, increasing the dose every 6 mo:

5 $\mu\text{g}/\text{kg}/\text{d}$

10 $\mu\text{g}/\text{kg}/\text{d}$

15 $\mu\text{g}/\text{kg}/\text{d}$

20 $\mu\text{g}/\text{kg}/\text{d}$

Adult dose = 2–6 mg/d

In postpubertal transgender female adolescents, the dose of 17β -estradiol can be increased more rapidly:

1 mg/d for 6 mo

2 mg/d

Induction of female puberty with transdermal 17β -estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):

6.25–12.5 $\mu\text{g}/24\text{ h}$ (cut 25- μg patch into quarters, then halves)

25 $\mu\text{g}/24\text{ h}$

37.5 $\mu\text{g}/24\text{ h}$

Adult dose = 50–200 $\mu\text{g}/24\text{ h}$

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):

25 $\text{mg}/\text{m}^2/2\text{ wk}$ (or alternatively, half this dose weekly, or double the dose every 4 wk)

50 $\text{mg}/\text{m}^2/2\text{ wk}$

75 $\text{mg}/\text{m}^2/2\text{ wk}$

100 $\text{mg}/\text{m}^2/2\text{ wk}$

Adult dose = 100–200 mg every 2 wk

In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:

75 mg/2 wk for 6 mo

125 mg/2 wk

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).

Follow Up

- Every 3-6 months
 - Height, weight, sitting height, blood pressure, Tanner Stages
- Every 6-12 months
 - Labs
 - In transmasculine: Hgb/Hct, lipids, testosterone, vit d
 - In transfeminine: prolactin, estradiol, vit d
- Every 1-2 years
 - BMD using DXA
 - Bone Age Study

Adults

Criteria for Gender-Affirming Hormone Therapy for Adults

Endocrine Society and SOC 7

- Persistent, well-documented gender-dysphoria
- Capacity to make a fully informed decision and to consent to treatment
- Age of majority in a given country
- If significant medical or mental health concerns present, they must be reasonably well controlled

Feminizing Hormones

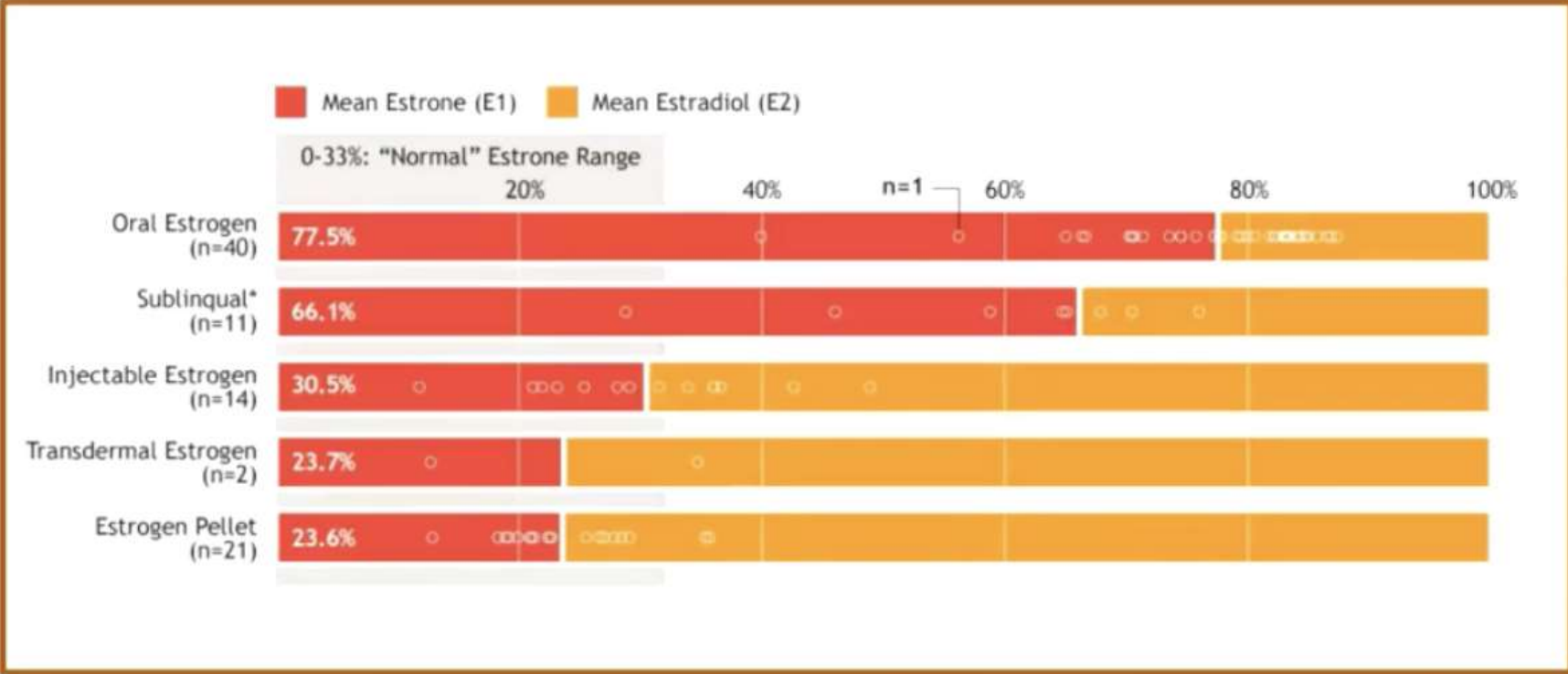
- Estradiol
 - Average female levels 100-200
 - Avoiding side effects, adverse effects
 - Base dosing on desired effects
- Antiandrogens
 - Spironolactone
 - Bicalutamide
- 5-Alpha Reductase Inhibitors
 - Finasteride
 - Prevent conversion of testosterone to dihydrotestosterone
 - Build-up of testosterone converts to estradiol
 - Not endorsed by Endo, but is recommended by WPATH
- Progestins
 - Unclear if benefit or harm
 - If used, micronized progesterone is preferred

Hormone Preparations and Dosing

Hormone	Initial-low	Initial	Maximum	Comments
Estrogen				
Estradiol oral/sublingual	1mg/day	2-4mg/day	8mg/day	if >2mg recommend divided bid dosing
Estradiol transdermal	50mcg	100mcg	100-400 mcg	Max single patch dose available is 100mcg. Frequency of change is brand/product dependent. More than 2 patches at a time may be cumbersome for patients
Estradiol valerate IM ^a	<20mg IM q 2 wk	20mg IM q 2 wk	40mg IM q 2wk	May divide dose into weekly injections for cyclical symptoms
Estradiol cypionate IM	<2mg q 2wk	2mg IM q 2 wk	5mg IM q 2 wk	May divide dose into weekly injections for cyclical symptoms
Progestagen				
Medroxyprogesterone acetate (Provera)	2.5mg qhs		5-10mg qhs	
Micronized progesterone			100-200mg qhs	
Androgen blocker				
Spironolactone	25mg qd	50mg bid	200mg bid	
Finasteride	1mg qd		5mg qd	
Dutasteride			0.5mg qd	

Results

Comparison of mean E1 and E2 in fractionated estrogen labs (n=88) between oral (n=40), sublingual (n=11), injectable (n=14), transdermal (n=2), and implantable pellets (n=21) for feminizing cross-sex hormone therapy



Robert Francis Mijares, MSN. Retrospective Chart Review for Assessment of Risks of Estrogen Therapy for Transgender Females. Repository Posting Date 2019-07-26T18:52:05Z

Risks of Feminizing Hormones

- **Venous thrombosis/ thromboembolism**
- Increased risk of cardiovascular disease
- Weight gain
- Decreased libido
- Hypertriglyceridemia
- Elevated blood pressure
- Decreased glucose tolerance
- Gallbladder disease
- **Benign pituitary prolactinoma**
- Mental health effects
- ? Breast cancer (lower risk than cisgender females)
- Infertility
- Increased urinary frequency
- Hyperkalemia
- Hypotension
- Renal insufficiency

Effects of Feminizing Hormones

Action	Onset	Max
Breast growth	3-6 months	2-3 yrs
Body fat, muscle changes	3-6 months	2-3 yrs
Softening skin	3-6 months	
Softer, less male pattern terminal hair	6-12 months	> 3 years
Emotional changes	1-3 months	
Change in libido, erectile dysfunction	1-3 months	3-6 months
Decrease testicular volume	25% see change in 1 yr	50% see change by 2-3 yrs
Decrease sperm production	?	?

Follow Up/Monitoring

- Evaluate patient every 3 in first year, then 1-2 times annually
 - Assess for appropriate signs of feminization and development of adverse reactions.
- Measure serum testosterone and estradiol every 3 mo.
 - Serum testosterone levels should be less than 50 ng/dL.
 - Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
- If taking spironolactone check electrolytes (K+) every 3 months and then annually thereafter
- Routine cancer screening is recommended per the guidelines
 - Colonoscopy
 - Prostate Exam
 - Mammograms
- Consider BMD testing at baseline and in individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

Lab Monitoring for Feminizing Hormones

Test	Comments	Baseline	3 months*	6 months*	12 months*	Yearly	PRN
BUN/Cr/K+	Only if spiro used	X	X	X	X	X	X
Lipids	No evidence to support monitoring at any time; use clinician discretion	Based on USPSTF guidelines					X
A1c or glucose	No evidence to support monitoring at any time; use clinician discretion	Based on USPSTF guidelines					
Estradiol			X	X			X
Total Testosterone			X	X	X		X
Sex Hormone Binding Globulin (SHBG)** (for calculating bioavailable testosterone)			X	X	X		X
Albumin** (for calculating bioavailable testosterone)			X	X	X		X
Prolactin	Only if symptoms of prolactinoma						X

Masculinizing Hormones

- Testosterone
 - Injectable
 - Transdermal
 - Testopel
 - Subcutaneous pellets
- Progestins may be used for menses cessation and contraception (Depo-provera, Mirena IUD, Nexplanon)

Hormone Preparations and Dosing

Androgen	Initial - low dose	Initial - typical	Maximum - typical	Comment
Testosterone Cypionate^a	20 mg/week IM/SQ	50mg/week IM/SQ	100mg/week IM/SQ	For q 2 wk dosing, double each dose
Testosterone Enthanate^a	20mg/week IM/SQ	50mg/week IM/SQ	100mg/week IM/SQ	"
Testosterone topical gel 1%	12.5-25 mg Q AM	50mg Q AM	100mg Q AM	May come in pump or packet form
Testosterone topical gel 1.62%^d	20.25mg Q AM	40.5 - 60.75mg Q AM	103.25mg Q AM	"
Testosterone patch	1-2mg Q PM	4mg Q PM	8mg Q PM	Patches come in 2mg and 4mg size. For lower doses, may cut patch
Testosterone cream^e	10mg	50mg	100mg	
Testosterone axillary gel 2%	30mg Q AM	60mg Q AM	90-120mg Q AM	Comes in pump only, one pump = 30mg
Testosterone Undecanoate^f	N/A	750mg IM, repeat in 4 weeks, then q 10 weeks ongoing	N/A	Requires participation in manufacturer monitored program

Risks of Testosterone Therapy

- Lower HDL and Elevated triglycerides
- Increased homocysteine levels
- **Polycythemia**
- Possible worsened migraine
- Male pattern baldness
- Variable effects on mood
- ? Increased risk of sleep apnea
- **Chronic pelvic pain**
- Mental health effects
- Liver, renal effects
- Unknown effects on breast, endometrial, ovarian tissues
- **Infertility**

Effects of Masculinizing Hormones

Action	Onset	Max
Male pattern facial/body hair	6–12 mo	4–5 yrs
Acne	1–6 mo	1–2 yrs
Voice deepening	1–3 mo	1–2 yrs
Clitoromegaly	3–6 mo	1–2 yrs
Vaginal atrophy	2–6 mo	1–2 yrs
Amenorrhea	2–6 mo	
Emotional changes/ ↑ libido		
Increased muscle mass	6–12 mo	2–5 yrs
Fat distribution	1–6 mo	2–5 yrs
Tendon weakening		

Lab Monitoring for Masculinizing Hormone Therapy

Therapy	Comments	Baseline	3 months*	6 months*	12 months*	Yearly	PRN
Lipids	No evidence to support lipid monitoring at any time; use clinician discretion	Based on USPSTF guidelines					X
A1c or fasting glucose	No evidence to support lipid monitoring at any time; use clinician discretion	Based on USPSTF guidelines					X
Estradiol							X
Total Testosterone			X	X	X		X
Sex Hormone Binding Globulin (SHBG)**			X	X	X		X
Albumin**			X	X	X		X
Hemoglobin & Hematocrit		X	X	X	X	X	X

Follow Up/Monitoring

- Evaluate patient every 3 months for the first year, then 1-2 times annually
 - Assess for signs of virilization and adverse reactions
- Measure total testosterone every 3 months until in normal range
 - Mid-cycle for injectable, goal is 400-700 ng/dL
 - Can measure trough level to ensure level within male range
 - Measure at least 2 hours and at least 1 week of consistent use for transdermal, goal 700-1000 ng/dL
- Measure Hgb/Hct every 3 months for first year, then 1-2 times annually
- Monitor weight, blood pressure and lipids at regular intervals
- Pap smears and mammograms as recommended by screening guidelines
- Sub and periareolar annual breast exam if status post mastectomy

Questions

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