

Pharmacist's Role in Transgender and Gender Non-Conforming Care

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Disclosure

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Pharmacist Objectives

- Define current terminology with regards to transgender and gender non-conforming (TGNC) patients
- Discuss monitoring parameters for TGNC patients taking hormone replacement therapy
- Design proper medication therapies for TGNC patients undergoing medical transition
- Investigate the role of pharmacists' in TGNC care

Pharmacy Technician Objectives

- Describe correct gender pronouns
- Recognize barriers to healthcare faced by TGNC patients
- Examine different medication therapies for TGNC patients

Introduction

- The transgender and gender non-conforming community face considerable barriers to quality of healthcare
- Report inability to find healthcare providers properly trained to treat them
- 41.6% worry about discrimination by pharmacists
- 52.5% felt pharmacists had very little or no competency in transgender health
- Pharmacist require education on the unique needs for TGNC patients



Prevalence of TGNC

	United States	New York State
Total TGNC (No., %)	1,397,150 (0.58)	78,600 (0.51)
TGNC: Age 18-24 yo (No., %)	205,850 (0.66)	11,150 (0.56)
TGNC: Age 25-64 yo (No., %)	967,100 (0.58)	54,150 (0.51)
TGNC: Age 65+ yo (No., %)	217,050 (0.50)	12,850 (0.47)

Definitions

Gender assigned at birth, based on external genitalia

Assigned Gender

Individual's gender identity ——— Affirmed Gender

Expression of their gender — Gender Behavior

Behaviors, attitudes, and personality tracts designating by societal standards

Gender Role





Cisgender

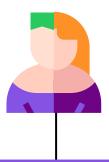
Individuals who identify with their assigned gender

Gender Spectrum



Transgender

Individuals who identify as a different gender than their assigned gender



Gender nonconforming

Individual who does not express their gender in cultural or socio-typical ways

Transgender male

Assigned female at birth, but identifies as a male (FTM)

Transgender female

Assigned male at birth, but identifies as a female (MTF)

Gender Spectrum

Agender

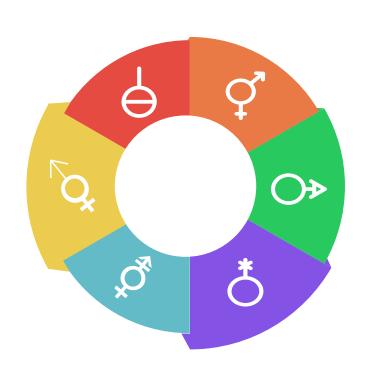
Does not identify with any gender (neutral gender, null-gender, genderless)

Genderfluid

Has a gender identity that shifts between societal expectation of gender

Androgyne

Identifies as a gender that is both masculine and feminine or between



Intersex

Discrepancy between internal and external genital

Aliagender

Does not fit into existing gender schemas or constructs

Non-binary

Does not experience gender within societal limitations

Gender Pronouns

- Pronouns: use based on patient preference
- Patient's may identify as one gender, but not ready to use pronoun
- Gender identity varies at different stages of life
- Ask and check each visit
- Normalize interaction
 - "Hi my name is Tony; I'm a pharmacist and I use he/him pronouns. Can you tell me about of yourself?"
 - Last time we spoke you were using she/her */
 pronouns. What pronouns are you using
 currently?"



Gender Pronouns

He/Him/His

She/Her/Hers

They/Them/Theirs

Ze/Hir/Hirs



Take time to learn and use people's correct pronouns



Sexual Vs. Gender Identity

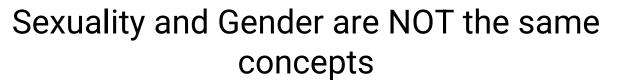
- Straight
- Bisexual
- Gay
- Lesbian
- Asexual
- Pansexual

Sexual Identity

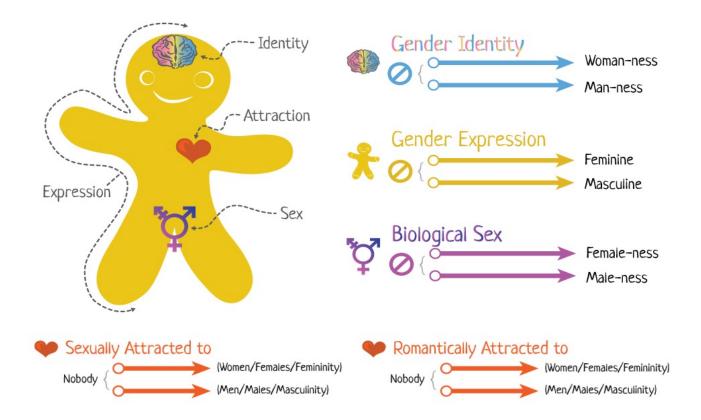


- Female
- Male
- Non-binary
- Agender
- Gender fluid

Gender Identity



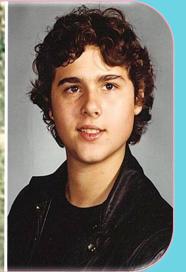
The Genderbread Person v3.2 by its pronounced METROSEXUAL COM



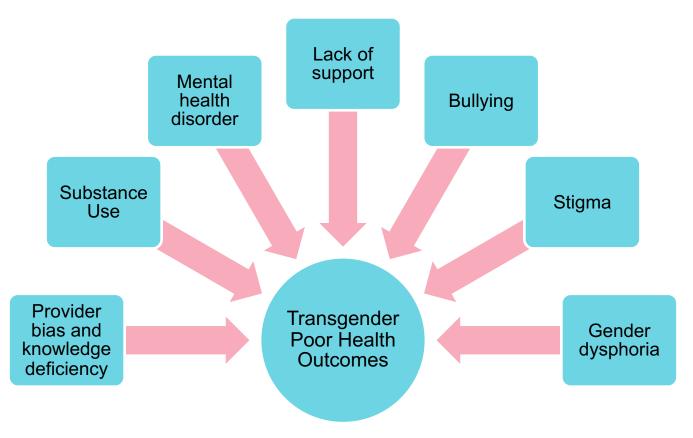
Neurobiological Factors

- Gonadal hormones can influence gender identity and sexual orientation during prenatal and early neonatal development
- Genes, hormones, neuroanatomy suggestively influence gender identity
 - Most data from the case of David Reimer
 - Inconsistent data





Risk Factors



Substance Use in TGNC Individuals

- 2.5-4 times higher substance use
 - Hazardous alcohol use
 - 2-2.5 times more likely to use illicit drugs in lifetime
 - 2 times likely to report recent 30-day prescription pain medication use
 - More than 3 times likely to smoke cigarettes
- Higher rates of depression, suicidality, self-harm and eating disorders than other sexual minority groups or cisgender individuals

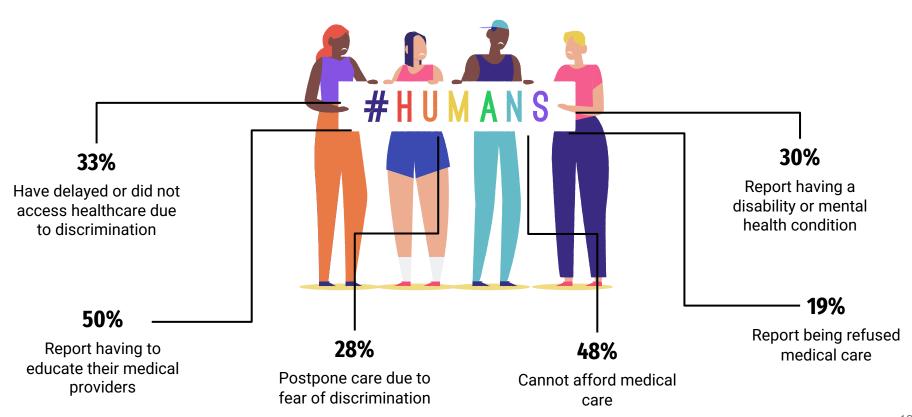


Discrimination of TGNC Individuals

- In 2011, the National LGBTQ Task Force and the National Center for Transgender Equality surveyed 6,450 TGNC individuals.
 - 90% reported harassment or mistreatment on the job
 - 26% lost a job due to being transgender
 - 53% had been verbally harassed in a place of public accommodation



Discrimination of TGNC in Healthcare



Gender Dysphoria

- Added to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 2013
- Clinical Symptom
 - "Discomfort, distress, or functional impairment caused by incongruence between assigned gender and affirmed gender"
- DSM-4 diagnosis of gender identity disorder no longer acceptable by TGNC community



Assessment Question #1

True or False: All TGNC patients experience gender dysphoria?

a. True

b. False



Gender Dysphoria

- Not everyone who identifies as a different gender has gender dysphoria
- Must be a level of distress and impairment to diagnose
- Symptoms: persistent for six months

Marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics

A strong desire to be rid of one's primary and/or secondary sex characteristics

A strong desire for the primary and/or secondary sex characteristics of the other gender

A strong desire to be of the other gender

A strong desire to be treated as the other gender

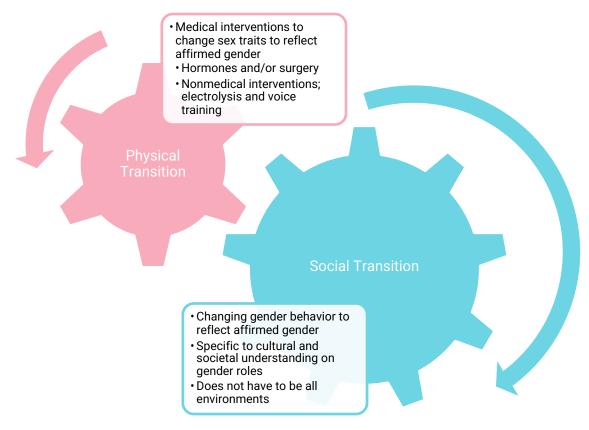
A strong conviction that one has the typical feelings and reactions of the other gender

Diagnosis: Gender Dysphoria

- Diagnosis often facilitates access to health care
 - ICD-10 code of F64.9 (gender identity disorder) needed for insurances to pay for gender-affirming therapy
 - Not required for starting hormone replacement therapy
- Goal of gender affirming therapy is not always to fully transition to the opposite of assigned gender

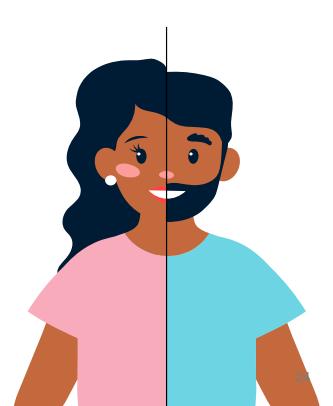


Types of "Transitions"



Goal of Pharmacologic Interventions

- Induce physical change that is more congruent with gender identity
- Individualize based on patient's goal
 - Maximum masculinization/feminization
 - Minimal masculinization/feminization for a more androgynous presentation
- Feminizing Hormone Therapy: Estrogen + androgen blocker
- Masculinizing Hormone Therapy: Testosterone monotherapy



Guidelines for Transgender Medicine

- No major medical societies that publish standard of transgender care
- Treatment regimens are mostly anecdotal
 - Published recommendations are from observations
 - Recommendations created by white/cisgender men
- Hormone therapy often dosed by older transgender people in the community with little to no formal medical education for new generations
 - Patients often know what their dose of hormone therapy should be
- Available guidelines
 - World Professional Association for Transgender Health (WPATH) Standards of Care
 - University of California, San Francisco (UCSF) Transgender Care and Treatment Guidelines
 - Transline Gender Affirming Hormone Therapy Guidelines

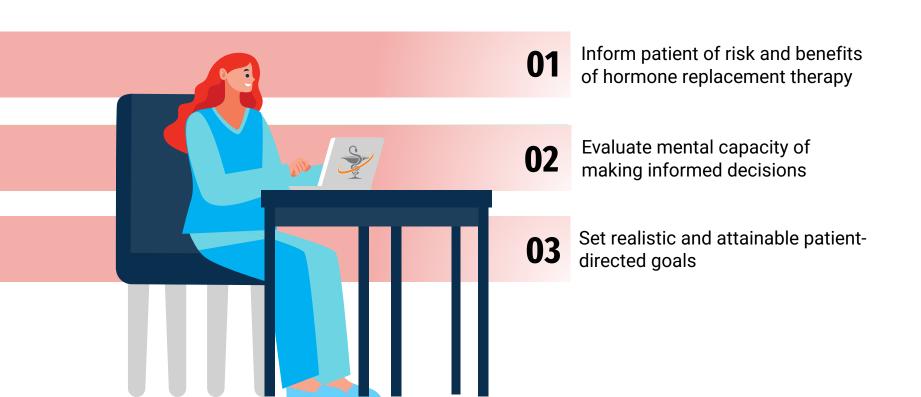
Initiation of Hormone Replacement Therapy

- Historically letters from > 2 providers needed to start hormone replacement therapy
 - Wanting to start hormones for a full calendar year
 - Assessment of readiness completed

Readiness

- 1. Persistent, well-documented gender dysphoria
- Capacity to make a fully informed decision and to consent for treatment
- 3. Age of majority in a given state
- 4. If significant medical or mental concerns are present, they must be reasonably well-controlled.

Informed Consent



Feminizing Therapies

Estrogen

 Suppress/minimize male secondary sex characteristics, develop female secondary sex characteristics

Anti-androgen (T-Blockers)

 Directly inhibit testosterone secretion and androgen binding to the androgen receptor

GnRH agonists (Puberty Blockers)

 Block the release of follicle stimulating hormone and luteinizing hormone

Estrogen

- Three natural occurring human estrogens
 - Estrone (E1)
 - Estradiol (E2)
 - Estriol (E3)
- E2 principle intracellular human estrogen; more potent than estrone and estriol at receptor level
- E1 levels higher in early development of cisgender females; breast bud formation
- Exogenous oral estradiol results in higher serum levels of E1 due to first pass hepatic metabolism:

Estrogen Therapies

Medication	Initial - Low dose	Typical Max Dose	Frequency	
Estradiol Valerate	5 – 10 mg IM	20 mg	Weekly	
Estradiol Cypionate	1.25 -2.5 mg IM	5 mg	Weekly or Bi-weekly	
Estradiol Transdermal	0.1 - 0.2 mg	0.4 mg	Bi-weekly	
Estradiol Oral	2 mg - 6 mg PO or SL	8 mg	Daily	

Estrogen Therapies

Medication	Pros	Cons
Estradiol Valerate	 Less frequent administration Avoids first pass metabolism 	Fluctuation in levels
Estradiol Cypionate	May help better suppress endogenous hormone production	• Injection
Estradiol Transdermal	Less fluctuation in levelsNo first pass metabolism	CostMax single patch dose of 0.1 mg
Estradiol Oral	Oral option Less fluctuation in levels	First pass metabolismDaily administrationSL TID dosing

Feminizing Therapies: Onset of Effect

Effect	Expected Onset	Maximal Effect
Decreased libido	1-3 months	1-2 years
Decreased spontaneous erections	1-3 months	3-6 years
Body fat redistribution	3-6 months	2-5 years
Decreased muscle mass/strength	3-6 months	1-2 years
Softening of skin	3-6 months	unknown
Breast growth	3-6 months	2-3 years
Male sexual dysfunction	Variable	Variable
Male pattern baldness	No regrowth, loss stops 1-3 months	1-2 years

Monitoring Estrogen Therapy

- Estradiol Reference Range: 100 to 300 ng/mL
 - Based on female follicular/pre-ovulatory phase reference range
 - In patients who can't achieve targeted estradiol (E2) levels, check E1:E2 ratio
 - Case series support ratio up to 3:1 (Ideal ratio 1:1)
 - Can switch to IM to shift ratio in favor of E2; no first pass metabolism
- Testosterone Reference Range: <50-75 ng/dL
- Prolactin Reference Range: < 20 ng/dL
 - >40 ng/dL consider decreasing dose of estrogen

Table 4. Laboratory monitoring for feminizing hormone therapy

Table 4. Laboratory monitoring for feminizing normone dierapy							
Test	Comments	Baseline	3 months*	6 months*	12 months*	Yearly	PRN
BUN/Cr/K+	Only if spiro used	X	X	X	Х	X	Х
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			Х	Х			x
Total Testosterone			х	х	Х		Х
Sex Hormone Binding Globulin (SHBG)**			X	X	X		X
Albumin**			х	X	X		X
Prolactin	Only if symptoms of prolactinoma						X

Estrogen Dose Equivalence

Estradiol Valerate	Estradiol Cypionate	Estradiol Transdermal	Estradiol Oral
5mg weekly	1.25mg weekly	0.1mg	2mg
10mg weekly	2.5mg weekly	0.2mg	4mg
20mg weekly	5mg weekly	0.4mg	8mg

Thromboembolic Risk of Estrogen Therapy



- Transgender females taking estrogen at high risk for venous thromboembolism (VTE)
- Risk depends on formulation and dose of estrogen and presence of other risk factors
 - Tobacco use, history of VTE, comorbidities
- Padua risk assessment accounts for ongoing hormone treatment
- Unclear if additional point for female should be given in CHADS₂-VASc scoring
 - Clinical decision based on risk factors

Antiandrogen (T – Blockers)

Anti-Androgen	Starting Dose	Max Dose	Notes
Spironolactone	100 mg PO daily	400 mg PO daily	 Risk of hyperkalemia Diuretic effect Can contribute to breast development
Finasteride	5 mg PO daily	5 mg PO daily	 Slows and prevents balding due to androgen alopecia Used as adjunct therapy for patients who can't use
Dutasteride	0.5 mg PO daily	0.5 mg PO daily	spironolactone • Dutasteride can be used every 3 days with finasteride for additive effect

GnRH Agonists (Puberty Blockers)

- Used in the care of peripubertal transgender youth who require pubertal delay
- Guideline recommendation initiation when first signs of puberty are seen; with cessation when cross-sex hormones are initiated
- Can be used in adults who are not achieving goal with hormone therapy
- Significant bone density loss with prolonged use

Medication	Starting Dose	Typical Max Dose	Frequency
Leuprolide Acetate	11.25 mg	22.5 mg	Every 3 months
Histrelin Pellets	50 mg	50 mg	Once yearly

Nonpharmacologic Approaches in MTF



Tucking Voice Therapy Surgery Evaluation Feminizing Used to and support surgery obtain provided by a (vaginoplasty, feminine trained penectomy) genital speech and Breast surgery appearance recommended language before or pathologist to after 2 years instead of of hormone achieve surgery feminine voice therapy

MJ is a 56 YO transgender female with a PMH of HTN and tobacco use. She has been on 1 year of hormone replacement therapy and comes into your clinic today for a follow up

Medications
Aspirin 81 mg PO daily
Spironolactone 300 mg PO daily
Chlorthalidone 25 mg PO daily
Estradiol 4 mg PO daily

Labs		
Estrone (ng/mL)	500	
Estradiol (ng/mL)	50	
Testosterone (ng/mL)	40	
Prolactin (ng/mL)	10	



MJ is concerned she is not getting the results she expected. Based on MJ's labs and goals of therapy what is the best option for MJ at this time

- a) Discontinue PO estradiol and initiate IM estradiol valerate
- b) Discontinue PO estradiol and initiate IM leuprolide acetate
 - c) Increase the dose of PO estradiol
 - d) Continue current medication regimen

Masculinizing Therapies

Androgen	Initial - Low dose	Initial - Typical	Maximum - Typical
Testosterone Cypionate	20 mg/week IM or SQ	50 mg/week IM or SQ	100 mg/week IM or SQ
Testosterone Enthanate	20 mg/week IM or SQ	50 mg/week IM or SQ	100 mg/week IM or SQ
Testosterone topical gel 1%	12.5-25 mg in the morning	50 mg in the morning	100 mg in the morning
Testosterone topical gel 1.62%	20-25 mg in the morning	40.5 - 60.75 mg in the morning	103.25 mg in the morning
Testosterone patch	1-2 mg at bedtime	4 mg at bedtime	8mg at bedtime
Testosterone cream	10 mg	50 mg	100mg
Testosterone Undecanoate	N/A	750 mg IM, repeat in 4 weeks, then Q 10 weeks ongoing	N/A

Masculinizing Therapies

Androgen	Pros	Cons	
Testosterone Cypionate	Less frequent administration	 Peak/trough fluctuation effect Self-injection or frequent in-office injections 	
Testosterone Enthanate	compared with transdermal • Peak concentration may better suppress endogenous hormone production		
Testosterone topical gel 1%		 Slower to stop menses and may not fully stop at lower doses Risk of transferring to others/pets 	
Testosterone topical gel 1.62%			
Testosterone patch	TopicalLess fluctuation in levels	(except patch) • Some products are scented	
Testosterone cream	Good for more gradual effects	Daily application May be expensive if not covered by insurance	
Testosterone Undecanoate	Least frequent dosing		

Masculinizing Therapies: Onset of Effect

Effect	Expected Onset	Maximal Effect
Skin Oiliness/Acne	1-6 months	1-2 years
Cessation of menses	2-6 months	
Clitoral enlargement	3-6 months	1-2 years
Body fat redistribution	3-6 months	2-5 years
Vaginal atrophy	3-6 months	1-2 years
Facial/body hair growth	3-6 months	3-5 years
Increased muscle mass/strength	6-12 months	2-5 years
Deepened voice	3-12 months	1-2 years

Masculinizing Therapies: Monitoring

- Cisgender male testosterone reference ranges used
- Recommended mid-cycle reference ranges vary
 - WPATH/Endocrine Society: 400-700 ng/dL
 - UCSF: 350-1100 ng/dL unless in the setting of undesired effects
- Clinical response can be measured in presence of amenorrhea by month 6



Table 2. Titration and monitoring of 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					х
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			х	х	х		х
Sex Hormone Binding Globulin (SHBG)**			х	х	х		х
Albumin**			×	×	x		x
Hemoglobin & Hematocrit		×	х	x	Х	х	X

^{*} In first year of therapy only

^{**} is optional and may be helpful in complex cases (see text) Used to calculate bioavailable

Monitoring Testosterone Therapy

- Testosterone levels difficult to measure in cis-gender males due to rapid fluctuation in levels
- Recommended mid-cycle reference ranges vary
 - Related to release of gonadotropin
 - Produce more testosterone in the morning
 - Not the same for transgender males
- Mid-cycle levels often sufficient unless patient experiencing cyclic symptoms (migraine, pelvic cramps, mood swings)
 - Obtain peak (1-2 days post injection) and trough to check fluctuations in hormone levels
 - Can consider switching to transdermal preparation or reducing injection interval
- Estradiol levels not routinely monitored unless experiencing cyclic symptoms

Special Considerations and Conditions

Mental Health

No clear association; may experience anxiety and depression

History of Cancer

Active sex hormone -sensitive cancer an absolute contraindication. Refer to oncologist

PCOS

Monitor hyperlipidemia and diabetes

Androgenic Alopecia

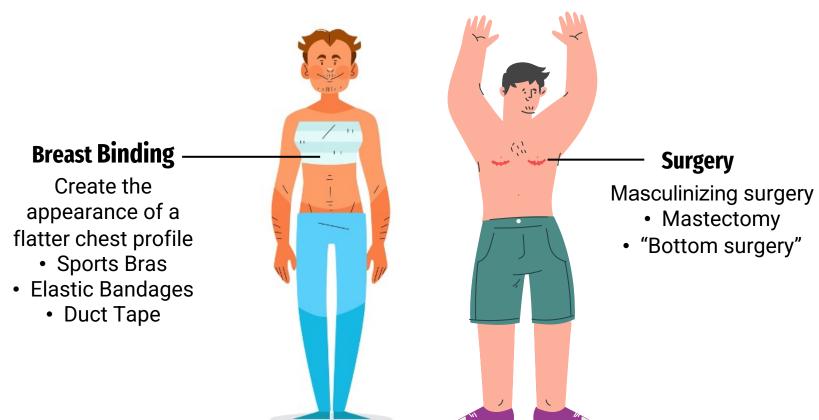
Add finasteride and/or dutasteride

Polycythemia and Testosterone Therapy



- Transgender males taking testosterone at high risk for polycythemia (Hematocrit >55%)
 - Increased risk of hypertension and thrombosis
- Rule out pulmonary disease (asthma, COPD, smoking) or other causes of elevated erythropoietin
- If polycythemia is secondary to testosterone can consider:
 - Changing to a weekly injection schedule
 - Switching to transdermal
 - Therapeutic phlebotomy
- Re-check labs for normalization 1-3 months after changes made

Nonpharmacologic Approaches in FTM



AK is a 52 YO transgender male with a PMH of diabetes, PCOS, and tobacco use. He has been on 6 months of hormone replacement therapy and comes into your clinic today for a follow up

Medications
Metformin 1000 mg PO BID
Testosterone Cypionate 50 mg IM weekly
Atorvastatin 20 mg PO daily
Aspirin 81 mg PO daily

Labs	
Total Testosterone (ng/mL)	1000
Hemoglobin (g/dL)	18
Hematocrit (%)	54

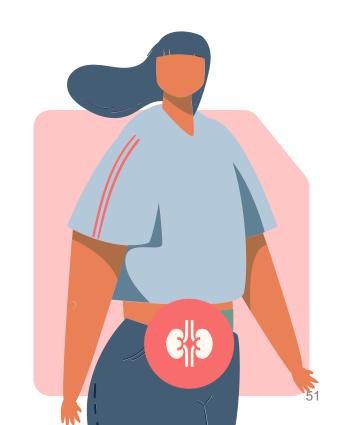


AK reports increased headaches and pelvic cramps since his last visit. Based on AK's clinical presentation what would be the best therapeutic option for him at this time?

- a) Discontinue IM testosterone cypionate and initiate IM testosterone enthanate
 - b) Discontinue IM testosterone cypionate and initiate testosterone patch
 - c) increase dose of livi testosterone cypionate
 - d) Continue current medication regimen

Creatinine Clearance in Transgender Patients

- Effects of gender-affirming hormone therapy on renal function and ideal body weight unknown
 - Differences in fat, muscle, and plasma volume distribution between genders
- Cockcroft-Gault equation for creatinine clearance (CrCl) commonly used to dose various medications
 - Uses Devine formula for ideal body weight (IBW) as part of calculation
- Unclear how to best use these formulas in transgender patients



Lapaw B et al.

Lapaw B, et al. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. Bone. 2008;43(6):1016-1021.		
Methods	 Observation cross-sectional study of transgender women (n=23) and cis-gender men (n=46) Assessed bone composition, lean body mass (LBM), and standard laboratory values including serum creatinine (SCr) 	
Inclusion Criteria	Transgender women must have completed gender affirmation surgery at least 3 years prior and must have taken estrogen therapy for 2 years	
Results	 Median LBM: (51.2 kg vs. 61.8 kg, p<0.001) Median SCr: (0.78 mg/dL vs. 0.94 mg/dL, p<0.001) 	
Author's Conclusion	Biometrics more closely resemble gender identity than assigned gender in transgender women after prolonged hormone therapy	

Giltay EJ et al.

Giltay EJ, et al. Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. J Clin Endocrinol Metab. 1998;83(2):550-553.				
Methods	 Prospective cohort trial comparing LBM, and laboratory values including SCr, prior to and 4 month after gender-affirming hormone therapy. Transgender women (n=17) and transgender men (n=17) 			
Inclusion Criteria	 Transgender women treated with ethinyl estradiol in combination with cyproterone acetate Transgender men treated with testosterone 			
	Transgender Women	Transgender Men		
Results	 Change in LBM (-0.03 kg; p=0.56) Change in SCr (-0.08 mg/dL; p<0.001) 	 Change in LBM (4.1 kg; p<0.001) Change in SCr (0.09 mg/dL; p<0.001) 		
Author's Conclusion	After 4 months of hormone therapy SCr more closely reflects affirmed gender rather than assigned gender			

Assessing CrCl and IBW in Transgender Patients

Duration of Hormone Gender- Affirming Therapy	Recommendation for IBW Dosing	Recommendation for Estimation of Renal Function
< 1 month	Calculate IBW based on assigned gender	Calculate renal function based on assigned gender
< 6 month	Consider calculating IBW based on assigned gender	Consider calculating renal function based on assigned gender
<u>></u> 6 months	Consider calculating IBW based on gender identity	Consider calculating renal function based on gender identity

BB is a 30 YO transgender female patient who has been on hormone therapy for 12 months. Which version of Cockcroft-Gault formula is most appropriate to use when calculating BB renal function?

a)
$$CrCI = [140-age] \times weight$$

72 x SCr

b) CrCl =
$$[140\text{-age}] \times \text{weight}$$

72 x SCr x 0.85



Preventive Screening for Transgender Patients

Specific issues in screening for transwomen and transmen with past or current hormone use

	Transwomen (MTF)	Transmen (FTM)
Breast cancer	Discuss screening in patients >50 years with additional risk factors for breast cancer*	Intact breasts: Routine screening as for natal females
		Postmastectomy: Yearly chest wall and axillary exams ¶
Cervical cancer	Vaginoplasty: No screening	Cervix intact: Routine screening as for natal females
		No cervix: No screening
Prostate cancer	Routine screening as for natal males	N/A
Cardiovascular disease	Screen for risk factors	Screen for risk factors
Diabetes mellitus	On estrogen: Increased risk	Routine screening $^\Delta$
Hyperlipidemia	On estrogen: Annual lipid screening	On testosterone: Annual lipid screening
Osteoporosis	Testes intact: Routine screening as for natal males	Screen all patients >65 years
	Postorchiectomy: Screen all patients >65 years	Screen patients age 50 to 65 if off hormones for >5 years
	Screen patients age 50 to 65 years if off hormones for >5 years	

^{*} Estrogen/progestin therapy for >5 years, family history, body mass index (BMI) >35.

[¶] While there is no evidence to support clinical breast examinations in this population, we perform yearly chest wall and axillary exams and use this as an opportunity to examine scar tissue, examine any changes, and educate the patient about the small but possible risk of breast cancer.

Δ Transmen with polycystic ovary syndrome (PCOS) should be screened for diabetes as for natal females with PCOS.

Pharmacist's Role

- Be aware of issues TGNC individuals face
- Provide a gender affirming experience
- Troubleshoot how to record assigned gender vs. affirmed gender in electronic medical record (EMR)
- Proper vaccinations
- Proper dosing of medications
- Assist in preventive measures
- Medication education



Resources

- World Professional Association for Transgender Health (WPATH)
- Education/training
 - World Professional Association for Transgender Health (WPATH.org)
 - The Endocrine Society Guidelines
 - Fenway National LGBTQ Health Education Center
 - UCSF Center of Excellence for Transgender Health
 - Genderspectrum.org
 - GLAAD.org
- Consent forms, example letters for insurances, example letters for gender marker changes
 - UCSF CoE for Transgender Health
 - WPATH
 - Fenway Health
 - San Francisco Department of Health, Transgender Health Services

Conclusion

- Important to recognize terminology when caring for TGNC patients
- Understanding physiologic differences between cisgender and transgender individuals can aid in proper medication therapy
- Fundamental to set realistic expectations with regards to gender affirming therapy
- Addressing unique needs TGNC patients is essential in improving lives of this community



