guidelines for gender-affirming primary care with trans and non-binary patients

A QUICK REFERENCE GUIDE FOR PRIMARY CARE PROVIDERS (PCPs)

This quick reference guide was derived from Sherbourne's *Guidelines for Gender-Affirming Primary Care with Trans and Non-Binary Patients* and is designed to be used in conjunction with the full Guidelines.

Please click here to read the 2023 medication updates at the end of this document.

Key messages

- Prescribing hormone therapy for trans patients is well-situated in primary care.
- The risks of witholding hormone therapy are often more substantial than the risks of treatment.

AN INDIVIDUALIZED APPROACH

Given the spectrum of gender identity and the variation in each person's expression, there is no single pathway for a trans person to follow in order to actualize the presentation of their authentic self. Non-binary patients may also seek hormone therapy to modify their secondary sex characteristics.

When hormones are chosen as part of transition, some patients may seek maximum feminization/masculinization, while others may seek a more androgynous appearance.

DECISION TO INITIATE HORMONE THERAPY

The decision to initiate hormone therapy is a collaborative patient-centered process that focuses on both psychosocial preparation and informed consent. The PCP (with or without the support of a multi-disciplinary team) can facilitate a decision-making process that informs, educates and supports patients. For each patient seeking hormone therapy, it is important to not only consider the possible risks of treatment but to consider the often substantial risks of witholding treatment.

TERMINOLOGY

CIS: Refers to a state of alignment of one's gender identity with the gender assigned at birth. You may also sometimes see "cissexual" or "cisgender." Thus, non-trans men are "cis men" and non-trans women are "cis women." It is preferable (and more accurate) to use "cis" than to use terms such as "bio", "genetic" or "real." It is also preferable to use "cis" rather than only using "woman" or "man" to describe non-trans persons. If cis is not used as a descriptor for non-trans persons, then such persons may be presumed to be the more "normal" or "valid" instantiation of that particular gender, thus contributing to cissexism.

TRANS: Umbrella term for people who are not cis, includes persons who are (or identify as) non-binary as well as transmasculine and transfeminine individuals.

NON-BINARY: Umbrella term for anyone who does not identify with static, binary gender identities. Includes persons who may identify as having an intermediary gender (e.g. genderqueer), as being multiple genders (e.g. bigender, polygender, etc.), as having a shifting gender (gender fluid), or as not having a gender altogether (agender).

DISCLAIMER:

These guidelines reflect the current practice at Sherbourne Health in the management of trans patients. We do not present it as a 'Standard of Care' but instead as a guide to help clinicians in their day-to-day practice. Adaptions may be considered relating to each patient's unique circumstances. Clinicians must use their own expertise and decision-making skills within each clinical encounter.

Feminizing hormone therapy

The goal of hormone therapy in transfeminine patients is to reduce the endogenous effects of testosterone and to induce feminine secondary sex characteristics. Physiologically, this requires a suppression of endogenous androgens and the addition of estrogen. This treatment results in both reversible and irreversible feminization.[1]

ANTI-ANDROGENS

The anti-androgens typically used at Sherbourne Health are spironolactone and cyproterone, with the former historically chosen preferentially as it was believed to have a superior safety profile. This practice has changed over time, as adequate anti-androgen effects and testosterone suppression into the female range are achievable at lower doses of cyproterone (i.e. 12.5 – 25mg daily) at which adverse effects are less likely.[2] Thus the choice of anti-androgen should be made individually for each patient based on their medical history and preference regarding risk and side effect profiles. Following orchiectomy (+/- vaginoplasty), most transfeminine patients will not require androgen suppression. The androgen-blocker can be stopped immediately after surgery or tapered over the course of 4-6 weeks or more depending on individual factors (e.g., patients with hypertension or renal dysfunction on spironolactone should be tapered).

ESTROGENS

Estrogen acts directly on estrogen receptors to initiate feminization. Several forms and routes of estrogen have been used for feminization. At Sherbourne Health, the most common form used is oral 17-β estradiol (Estrace), which is covered by the ODB program. While conjugated estrogens (e.g. Premarin) have historically been used due to their accessibility/affordability, they are no longer recommended.[3] There is a lack of consensus on the preferred timing of the initiation of estrogens in relation to an anti-androgen. Common approaches have included both the initiation of an anti-androgen (usually 1-3 months) prior to the addition of estrogen, or alternatively, the simultaneous introduction and subsequent titration of both components. In patients over 50 years old who have been on estrogen for several years, doses may be reduced to those administered to post-menopausal cis women (e.g. starting/low dose topical formulations).

Keep in mind: In adolescent patients, the initiation of estrogen therapy prior to the completion of skeletal growth may lead to an earlier cessation of long bone growth and thus shorter adult height, an effect which would be irreversible. This may be a desired effect. Complete epiphyseal fusion can occur as early as age 14 and as late as age 19 in AMAB individuals.[4]

PRECAUTIONS

Evidence compiled by the Endocrine Society suggests that feminizing hormone therapy is "**safe without a large risk of adverse events when followed carefully for a few well-documented medical concerns.**"[5]
Available measures to reduce risks associated with feminizing hormone therapy should be considered and discussed with patients and if possible, undertaken prior to or concurrently with hormone therapy.[6] Suggested measures to minimize risks associated with precautions may be found in the full Guidelines.

Contraindications

- Unstable ischemic cardiovascular disease
- Estrogen-dependent cancer
- End stage chronic liver disease
- Psychiatric conditions which limit the ability to provide informed consent
- Hypersensitivity to one of the components of the formulation

FORMULATIONS AND RECOMMENDED DOSES OF ANTI-ANDROGENS AND ESTROGEN

Formulations	Starting Dose	Usual Dose	Maximum Dose	Cost* (4 weeks)
Spironolactone (oral)	50 mg daily - BID	100 mg BID	150 mg bid[a]	$15–$41
Cyproterone (oral)	12.5 mg (1/4 50 mg tab) q2d - daily	12.5 mg (1/4 50 mg tab) – 25 mg (1/2 50 mg tab) daily	50 mg daily[a]	$16–$56
Estradiol (oral)*	1–2mg daily	4mg daily or 2mg bid	6 mg daily or 3 mg BID	$18–$54
Estradiol (transdermal, patch)*[b]	50 mcg daily/apply patch 2x/ week	Variable[c]	200 mcg daily/ apply patch 2x/ week	$39–$76[d]
Estradiol (transdermal, gel)*[e]	2.5 g daily (2 pumps, contains 150 mcg estradiol)	Variable[c]	6.25 g OD (5 pumps, contains 375 mcg estradiol), may be limited by surface area requirements for gel application	$58–$154
Estradiol valerate** Injectable (IM)[f]	3–4 mg q weekly or 6–8 mg q 2 weeks	Variable[c]	10mg q weekly	$36–$46

** Price quotes are provided by www.pharmacy.ca. The above prices are accurate as of May 2018 and represent the price for a 4-weeks supply of a generic brand of medication unless indicated otherwise (ranging from low dose to maximum dose). Prices include a usual and customary dispensing fee of $9.99, which may vary from pharmacy to pharmacy.* **Note: For patients on ODB, spironolactone, cyproterone, and oral estradiol are covered without the submission of an EAP form.**
*** Estradiol valerate IM must be prepared by a compounding pharmacy, price quote provided by Pace Pharmacy (including $10.99 dispensing fee)*
a) *rarely required or used. Maximal effect does not necessarily require maximal dosing. Use clinical judgement in selecting optimal individual dosing;* ***b)*** *Estradot® brand;* ***c)*** *Usual doses vary significantly between individuals. Use starting doses and titrate up based on patient response. Maximum doses are not often needed. Use clinical judgement in selecting optimal individual dosing;* ***d)*** *200 mcg daily given as 2x100 mcg patches applied twice weekly (4 patches/week);* ***e)*** *Estragel® brand* ***f)*** *Estradiol valerate IM must be prepared by a compounding pharmacy, commonly at the minimum concentration of 10mg/mL. Per updated Ontario guidelines, opened multi-use vials must be discarded after 28 days.*

SAFETY

Transdermal estradiol seems to be less thrombogenic than oral estradiol with fewer hepatic side effects and is thus recommended for patients over 40 or with risk factors for cardiovascular, thromboembolic, or liver disease.[7]

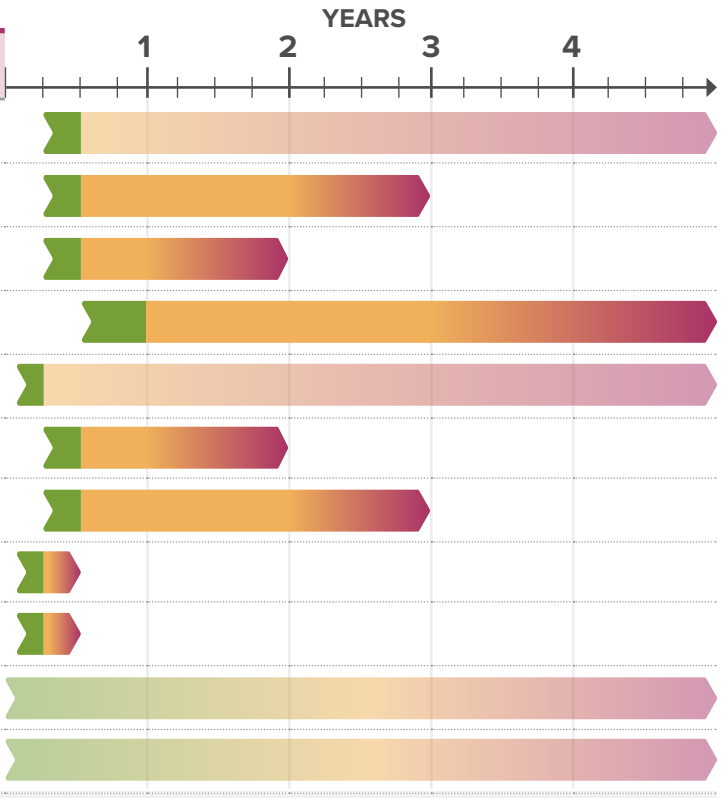
PREVENTIVE CARE

Transfeminine patients maintained on feminizing hormone therapy have unique preventive care needs and recommendations. An adapted ***Preventive Care Checklist*** for transfeminine patients that can be used at the point of care can be found in the full Guidelines.

EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES

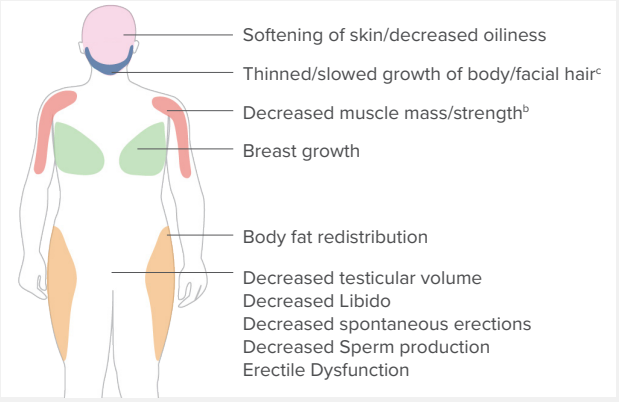
The degree and rate of physical effects are largely dependent on patient-specific factors such as age, genetics, body habitus and lifestyle, and to some extent the dose and route used (selected in accordance with a patient's specific goals and risk profile).[8]

Physical Effects	Reversibility	Onset[a]	Expected maximal effect[a]
Softening of skin/ decreased oiliness	Reversible	3-6 months	Unknown
Body fat redistribution	Reversible/ Variable	3-6 months	2-3 years
Decreased muscle mass/strength[b]	Reversible	3-6 months	1-2 years
Thinned/slowed growth of body/facial hair[c]	Reversible	6-12 months	>3 years
Scalp hair loss (loss stops, no regrowth)	Reversible	1-3 months	Variable
Breast growth	Irreversible	3-6 months	1-2 years
Decreased testicular volume	Variable	3-6 months	2-3 years
Decreased libido	Variable	1-3 months	3-6 months
Decreased spontaneous erections	Variable	1-3 months	3-6 months
Decreased sperm production	Variable	Variable	Variable
Reduced erectile function	Variable	Variable	Variable



Keep in mind: Use patient preferred terminology. "Testicular" and "erections" may be upsetting to some but not all. Physical changes related to androgen blockade and estrogen may take months to appear and are generally considered to be complete after 2-3 years on hormone therapy. Breast growth is an aspect of feminization to which many transfeminine patients assign great importance. The degree of breast development is dependent on many factors, but most transfeminine patients experience modest breast development (average cup size <A, at a developmental Tanner stage of 2-3).[9, 10] Feminizing therapy does not affect the pitch of the voice in transfeminine patients.

a) Estimates represent unpublished clinical and published observations[11,12,13]
b) Significantly dependent on amount of exercise;
c) Complete removal of facial hair requires electrolysis, laser treatment, or both



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Visual reference: Tetzlaff K.Patient's guide to transgender, trans, & gender diverse health. 2015. https://ktetzlaffdotcom.files.wordpress.com/2015/01/ tetzlaff_transhealthbooklet1.pdf

MONITORING STRATEGIES & DOSE ADJUSTMENTS

- Standard monitoring of a feminizing hormone regimen should be employed at baseline, 3, 6, and 12 months; and yearly thereafter (creatinine and electrolytes should be checked 4-6 weeks after the initiation or dose increase of spironolactone).
- Some providers prefer to see patients monthly until an effective dose is established. Follow up visits should include a functional inquiry, targeted physical exam, bloodwork, and health promotion/disease prevention counselling as indicated.
- Dose titration of an anti-androgen and estrogen may be performed over the course of 3-6 months or more and will depend on patient goals, physical response, measured serum hormone levels, and other lab results.
- For many transfeminine patients, the goal will be to achieve the suppression of testosterone into the female range. Hormone levels for those seeking a more androgynous appearance may intentionally be mid-range between male and female norms.
- Measurement of total testosterone is adequate to assess the degree of androgen suppression, without the routine need for free testosterone levels. Be mindful that patients may have clinically relevant results without complete suppression of testosterone because of androgen blockade, which is not measurable.
- Serum estradiol levels should also be monitored. Most patients attain considerable feminization at estradiol levels between 200-500 pmol/L.

Keep in mind:
Clinical effects are the goal of therapy, not specific lab values. If the sex marker associated with the patient's health card has not been changed, the reported reference ranges will refer to the sex assigned at birth. Reference ranges vary between laboratories - refer to reference ranges from the specific laboratory (often available online or by request from the lab).

HORMONE MONITORING SUMMARY FOR TRANSFEMININE PATIENTS

In this table, smaller and lighter grey checkmarks indicate parameters that are measured under particular circumstances.
NB: Individual parameters should be considered more frequently if concerns identified or existing risk factors are present.

Non-hormone labs:

- **Hemoglobin/Hematocrit** - use female reference for lower limit of normal and male reference for upper limit of normal
- **Creatinine** - use male reference for upper limit of normal.

	Baseline	Month 3	Month 6	Month 12[e]	Yearly	According to guidelines for cis patients, or provider discretion
Exam/ Investigations	Focused Physical Exam. Include: height, weight, BP, +/- breast inspection/ measurement(s)*	BP, weight, +/- breast inspection/ measurement(s) at 12 months*			See Preventive care checklist for transfeminine patients and Accompanying Explanations in the full Guidelines.	
BLOODWORK						
CBC[a]	✓	✓	✓	✓	✓	
ALT[b]	✓	✓	✓	✓	✓	✓
Creatinine/Lytes[c]	✓	✓	✓	✓	✓	
HbA1c or Fasting Glucose	✓			✓		✓
Lipid profile	✓			✓		✓
Total Testosterone	✓	✓	✓	✓	✓	
Estradiol	✓	✓	✓	✓	✓	
Prolactin[d]	✓			✓	✓	✓
Other	Hep B and C					
	Consider: HIV, syphilis, and other STI screening as indicated, frequency depending on risk					

** for patients who may have interest in OHIP-covered breast augmentation surgery, perform breast inspection at baseline and 12 months with particular attention to Tanner stage. Chest circumference at fullest part of the breast and areolar diameter may be helpful in determining the presence or absence of breast growth*
a) at baseline for all, and regularly with cyproterone
b) at baseline for all and regularly with cyproterone, otherwise repeat once at 6-12 months then as needed
c) Cr and lytes should be monitored at each visit with spironolactone (including 2-6 weeks after starting), but is only required at baseline and then once between 6-12 months with cyproterone unless risk factors or concerns re: renal disease are present
d) Prolactin should be monitored at least yearly with the use of cyproterone, and more frequently if elevation is noted
e) during first year of treatment only

This Quick Reference Guide for pimary care providers was authored by Dr. Amy Bourns and produced by Rainbow Health Ontario, a program of Sherbourne Health, to accompany the ***Guidelines for Gender-Affirming Primary Care with Trans and Non-Binary Patients, 4th edition.***

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Masculinizing hormone therapy

The cornerstone of hormone therapy for transmasculine patients is testosterone. The goal of treatment is virilization – the development of masculine secondary sex characteristics. This treatment results in both reversible and irreversible masculinization.

TESTOSTERONE

In Ontario, options for testosterone administration include injectable and transdermal preparations (patch or gel). Injectable formulations are most commonly used, due to their superior efficacy and affordability. While intramuscular (IM) injection is the most common means of administering parenteral testosterone, subcutaneous (SC) delivery has also been used with clinical efficacy and is very well-tolerated. A dose reduction of 10-15% can be considered if switching from IM to SC.

PRECAUTIONS

Evidence compiled by the Endocrine Society suggests that masculinizing hormone therapy is "**safe without a large risk of adverse events when followed carefully for a few well-documented medical concerns**".[1] Available measures to reduce associated risks should be considered and discussed with patients and if possible, undertaken prior to or concurrently with the initiation of hormone therapy. Suggested measures to minimize risk associated with known precautions may be found in the full Guidelines.

Contraindications

- Pregnancy or breast feeding
- Active known sex-hormone-sensitive cancer (e.g., breast, endometrial)
- Unstable ischemic cardiovascular disease
- Poorly controlled psychosis or acute homicidality
- Psychiatric conditions which limit the ability to provide informed consent
- Hypersensitivity to one of the components of the formulation

SAFETY

Gel formulations have the risk of inadvertent exposures to others who come into contact with the patient's skin. This is of particular importance for patients with young children and/or with intimate partners who are pregnant or considering pregnancy.

Keep in mind:
Testosterone therapy does not prevent pregnancy even if amenorrhea is achieved. Testosterone is a teratogen thus reliable contraception may be required depending on sexual practices.

PREVENTIVE CARE

Transmasculine patients maintained on masculinizing hormone therapy have unique preventive care needs and recommendations. An adapted *Preventive Care Checklist* for transmasculine patients that can be used at the point of care can be found in the full Guidelines.

FORMULATIONS AND RECOMMENDED DOSES OF TESTOSTERONE

Formulations	Starting Dose	Maximum Dose	Cost per unit*	Approx. Cost* (4 weeks)
Testosterone enanthate (IM/SC)[a]	20–50 mg q weekly or 40–100 mg q 2 weeks	100 mg q weekly or 200 mg q 2 weeks	$73.50 per 5mL vial (each vial contains 200 mg/mL x 5 mL = 1000 mg)	$14–$29 (covered by ODB with EAP request)
Testosterone cypionate (IM/SC)[a]			$64 per 10 mL vial (each vial contains 100 mg/mL x 10 mL = 1000 mg)	$13–$26 (covered by ODB with EAP request)
Testosterone path (transdermal)[b]	2.5–5 mg daily	5–10 mg daily	$164 / 60 x 2.5 mg patches $169 / 30 x 5 mg patches	$76.50–$315
Testosterone Gel 1% (transdermal)	2.5–5 g daily (2–4 pumps, equivalent to 25–50 mg testosterone)	5–10 g daily (4–8 pumps, equivalent to 50–100 mg testosterone)	$67 / 30 x 2.5 g sachets $110 / 30 x 5g sachets $175 / 2 pump bottles[c]	Sachets: $62–$205 Bottles: $81–$327

** Price quotes provided by www.pharmacy.ca. The prices listed above are accurate as of June 2018 and represent the price of the generic brand of medication unless otherwise indicated (ranging from low dose to maximum dose). Prices include a usual and customary dispensing fee of $9 99, which may vary from pharmacy to pharmacy.*
a) Testosterone enanthate is compounded in sesame oil, and testosterone cypionate is compounded in cottonseed oil; patients with allergy to either of these compounds should use the alternative agent
b) Androderm brand, per drug monograph the 12.2 mg patch delivers 2.5 mg/day while the 24.3 mg patch delivers 5 mg per day
c) Each pump bottle provides 60 pumps, 1 pump = 1.25 g of gel, equivalent to 12.5 mg of testosterone

NB: Testosterone (in all forms) is considered a controlled substance in Canada; prescriptions should be written in accordance with provincial requirements for controlled substances.

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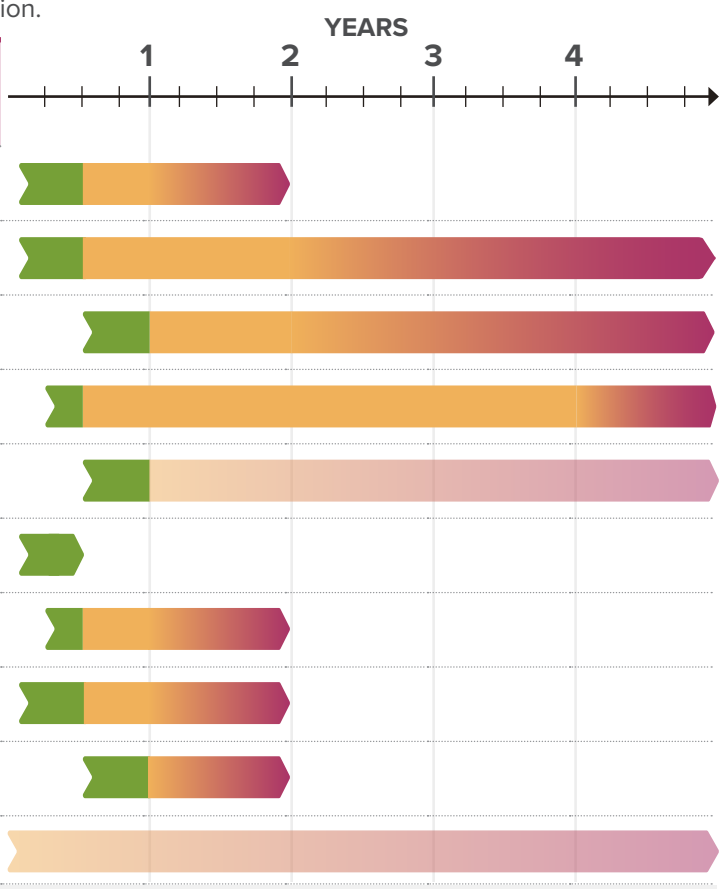
EFFECTS AND EXPECTED TIME COURSE OF TESTOSTERONE

The degree and rate of physical effects is dependent on the dose and route of administration,[2] as well as patient-specific factors such as age, genetics, body habitus and lifestyle. Hormone therapy results in both reversible and irreversible masculinization.

Physical Effects	Reversibility	Onset[a]	Expected maximal effect[a]
Skin oiliness/acne	Reversible	1-6 months	1-2 years
Body fat redistribution	Reversible/ Variable	1-6 months	2-5 years
Increased muscle mass/strength[b]	Reversible	6-12 months	2-5 years
Facial/body hair growth	Irreversible	3-6 months	4-5 years
Scalp hair loss	Irreversible	6-12 months[c]	Variable
Cessation of menses	Reversible	1-6 months	n/a
Clitoral enlargement	Irreversible	3-6 months	1-2 years
Vaginal Atrophy	Reversible	1-6 months	1-2 years
Deepened voice	Irreversible	6-12 months	1-2 years
Infertility	Variable	Variable	Variable

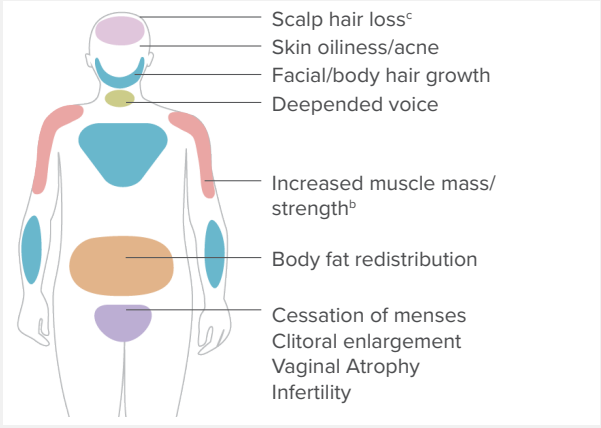


Keep in mind:

Use patient-preferred terminology. Terminology such as “clitoral” and “vaginal” may be upsetting to some but not all.

Desired androgenic effects of testosterone therapy include deepened voice, cessation of menses, clitoral growth, increased muscle mass, and hair growth in androgen dependent areas including facial hair. Breast tissue may lose glandularity, but generally does not lose mass or hemi circumference. Typically, patients taking testosterone will experience masculinizing changes over a period of months to years. The timeframe of physiologic changes may be slightly slower with the use of transdermal preparations.

a) Estimates represent published and unpublished clinical observations[3-6]
b) Significantly dependent on amount of exercise
c) Highly dependent on age and inheritance; may be minimal



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6. *Wierckx K, Gooren L, T’Sjoen G. Clinical Review: Breast Development in trans feminine patients Receiving Cross-Sex Hormones. The Journal of Sexual Medicine 2014;11(5):1240-1247.*

Visual reference: Tetzlaff K.Patient’s guide to transgender, trans, & gender diverse health. 2015. https://ktetzlaffdotcom.files.wordpress.com/2015/01/tetzlaff_transhealthbooklet1.pdf

MONITORING STRATEGIES & DOSE ADJUSTMENTS

- Standard monitoring of testosterone should be employed at baseline, 3, 6, and 12 months; and yearly thereafter.
- Some clinicians prefer to see patients monthly until an effective dose is established.
- Follow up visits should include a functional inquiry, targeted physical exam, blood work, and health promotion/disease prevention counselling as indicated.
- Titration of doses will generally occur in the early phases of treatment. For example, with injectable testosterone, a starting dose of 30 mg injected weekly could be increased by 10–20 mg every 4–6 weeks. Speed of titration will depend on lab results, patient goals, response, and side effects.
- For those using an injectable route, there may be utility in varying the timing of blood work to gather information regarding serum hormone levels throughout the cycle (peak, mid-cycle, and trough), especially if a patient is reporting cyclic symptoms.
- Hormone levels for those seeking a more androgynous appearance may intentionally be mid-range between male and female norms.
- Supraphysiologic levels should be avoided due to the increased risk of adverse events and side effects, as well the potential for the aromatization of excess testosterone into estrogen. Dose reduction is warranted if supraphysiologic doses are measured at mid-cycle or trough.
- There may be some irregular bleeding or spotting in the first few months of treatment. However, once sustained menstrual cessation is achieved, any vaginal bleeding without explanation (e.g. missed dose(s) or lowered dose of testosterone) warrants a full workup for endometrial hyperplasia/cancer.

Keep in mind:
Clinical effects are the goal of therapy, not specific lab values. If the sex marker associated with the patient's health card has not been changed, the reported reference ranges will refer to the sex assigned at birth. Reference ranges vary between laboratories - refer to reference ranges from the specific laboratory (often available online or by request from the lab).

HORMONE MONITORING SUMMARY FOR TRANSMASCULINE PATIENTS

In this table, smaller and lighter grey checkmarks indicate parameters that are measured under particular circumstances.

Non-hormone labs:
Male reference ranges should be used for Hb/Hct (lower limit of female range can be used if menstruating).

	Baseline	Month 3	Month 6	Month 12[b,c]	Yearly	According to guidelines for cis patients, or provider discretion
Exam/ Investigations	Focused Physical Exam with PAP if indicated. Include: height, weight, BP.	BP, weight			See ***Preventive Care Checklist for Transmasculine Patients*** and accompanying explanations in the ***Guidelines for Gender-Affirming Primary Care with Trans and Non-Binary Patients.***	
BLOODWORK						
CBC	✓	✓	✓	✓	✓	
ALT	✓		✓[c]			✓
HbA1c or Fasting Glucose	✓		✓[c]			✓
Lipid profile	✓		✓[c]			✓
Total Testosterone	✓	✓	✓	✓	✓	
LH[a]	✓			✓	✓	

NB: Individual parameters should be considered more frequently if concerns identified or existing factors are present
a) Post-gonadectomy: Elevated LH may have implications regarding bone mineral density (See full Guidelines)
b) During first year of treatment only
c) Once at either 6- or 12-month mark

This Quick Reference Guide for pimary care providers was authored by Dr. Amy Bourns and produced by Rainbow Health Ontario, a program of Sherbourne Health, to accompany the ***Guidelines for Gender-Affirming Primary Care with Trans and Non-Binary Patients, 4th edition.***

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2023 medication updates to sherbourne's guidelines

FOR GENDER-AFFIRMING PRIMARY CARE WITH TRANS AND NON-BINARY PATIENTS

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CYPROTERONE and risk of meningioma

In addition to the risks and side effects of cyproterone already covered herein, concern is emerging that prolonged use of high-dose cyproterone may be associated with the development of meningiomas.

Meningiomas are rare, most-often benign, tumours of the meninges (membranes covering the brain and spinal cord). Observations of increased incidence in cis women compared with cis men as well as the histological presence of progesterone (and to a lesser degree estrogen) receptors suggest that these tumours are hormone-sensitive.

Meningiomas may present with singular or multiple lesions which are often extremely slow-growing, and as such can remain asymptomatic for many years. Due to their location they may ultimately cause clinically significant symptoms such as headaches, focal neurologic symptoms, mental status changes and seizures. Symptomatic meningiomas may require neurosurgical resection if feasible.

Nine cases of meningioma(s) in transfeminine individuals have been reported in the literature, in whom eight of nine were using cyproterone and seven of nine were using a high dose (50-100 mg) for at least four years.[1,2]

A retrospective study of 2,555 trans women primarily using high dose (50-100 mg) cyproterone for many years following gonadectomy identified an increased standardized incidence ratio compared with the general population (4.1 compared with cis women and 11.9 compared with cis men).[3]

Based on the available data in cis populations using cyproterone, the European Medicines Agency released a statement in 2020 asserting that the risk of meningioma appears to rise with increasing cumulative doses, primarily occurring at doses >25 mg/day. They recommended that doses >10 mg be restricted to certain uses but did not make any recommendation on dose limits for gender-affirming purposes.[4]

WPATH's updated Standards of Care (SOC-8) acknowledges that there may be some concerns with prolonged use (>2 years) and higher doses (>10 mg daily) of cyproterone. They appear to recommend a maximum dose of 10 mg in Table 4, Appendix C, citing a 2021 prospective cohort study's[5] findings that the 10 mg dose provides comparable efficacy (suppression of serum testosterone into the usual range for cis women) with less adverse effects than higher doses. Importantly, however, they conclude that there is insufficient evidence to recommend the use of one androgen blocker over another.[6]

While further research is needed to demonstrate conclusive evidence of a causative relationship between cyproterone and meningioma, the following recommendations can be considered:

- The possibility of increased risk of meningioma with cyproterone should be included in the informed consent discussion with patients choosing an androgen blocker, as well as reviewed in those who have been on >10 mg for >2 years
- If resources exist to compound medications, a lower initial dose of cyproterone can be considered (eg. 2.5-5 mg), with the use of doses >10 mg limited to those with inadequate response to lower doses
- When compounding is not an option, tablets may be quartered to obtain a 12.5 mg dose [a]
- Those using cyproterone (particularly at doses >10 mg for >2 years) should be aware of and monitored for signs and symptoms of meningioma including: changes in vision, hearing loss or ringing in the ears, loss of smell, headaches, memory loss, seizures or weakness in the arms and legs
- No routine screening for meningioma is recommended for asymptomatic patients, regardless of dose/duration
- In those who present with symptoms concerning for meningioma, MRI or CT of the brain (and spinal cord if spinal meningioma is suspected) is recommended[7]
- As previously noted in these guidelines, personal history of meningioma should be considered a contraindication to cyproterone
- Cyproterone should be discontinued permanently if meningioma is identified
- Any plan for the ongoing use of higher doses of cyproterone following gonadectomy should be reconsidered given that the balance of potential risks and benefits is unlikely to favour its use in this setting

NOTE: Major adverse events remain uncommon even in those using long-term and higher-dose cyproterone.

[a] *Commercially available cyproterone in Canada is available only in a 50 mg tablet. Accounting for medication lost during the splitting process, quartering may in fact result in an average dose closer to 10 mg.*

updates,continued

TESTOSTERONE PATCHES

Testosterone patches were discontinued in 2021 and are no longer available.

ETONOGESTREL SUBDERMAL IMPLANT

The availability of the etonogestrel implant (Nexplanon) offers an additional option for contraception in transmasculine individuals. However, the common side effect of irregular spotting may limit its utility for menstrual cessation, particularly in the absence of exogenous testosterone administration.

FINASTERIDE

The benefit of 5-alpha-reductase inhibitors for the treatment of androgenic alopecia in transmasculine individuals should be balanced with the possibility of impairment of both clitoral growth and the development of facial and body hair.[6]

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