Gender-Affirming Hormone Therapy

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Faculty/Presenter Disclosure

- **Faculty: Dr. Ryan Herriot**

- **Relationships with financial sponsors:**
  - The Victoria Division of Family Practice paid me to give this talk

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Disclosure of Financial Support

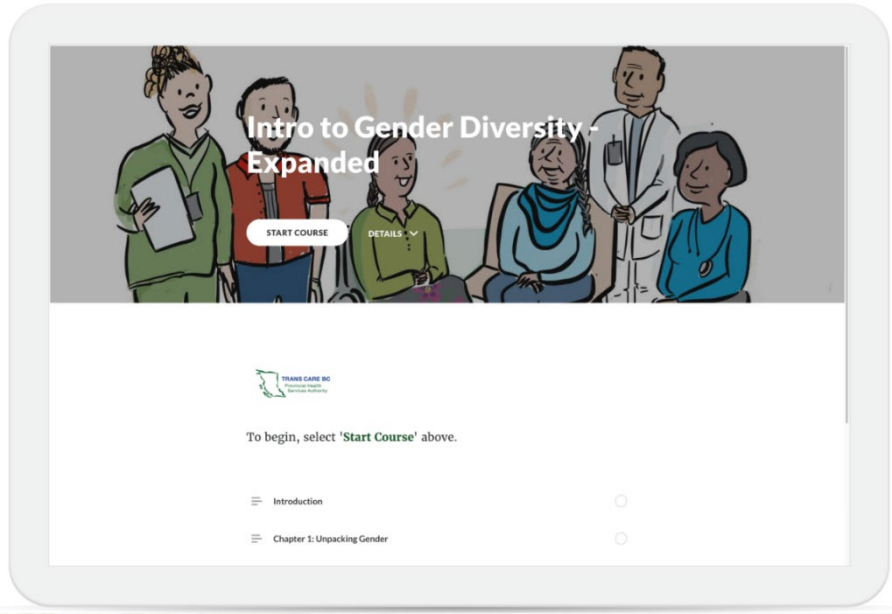
- **<u>Potential for conflict(s) of interest</u>:**
  - Nothing else

Mitigating Potential Bias

- N/A

Trans Health 101 (and 201)

- Intro to Gender Diversity https://learninghub.phsa.ca/Courses/8141/
- Gender-Affirming Primary Care https://ubccpd.ca/course/gender-affirming-care
- Advanced gender-affirming primary care http://www.phsa.ca/transcarebc/health-professionals/education/training



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Impact of gender-affirming treatment

- Access to gender affirming interventions can improve the overall well-being of transgender people
- No studies showed transition harms well-being
- Positive outcomes include:
  - Improved quality of life
  - Greater relationship satisfaction
  - Higher self-esteem and confidence
  - Reductions in anxiety, depression, suicidality and substance use
- The positive impacts are growing and regret rates lowering as surgical techniques and social supports improve (Regret rate = 0.3%)

(The Effect of Transition on Well-Being – systematic review of 73 studies
Public Policy Research Portal, Cornell University, 2018)

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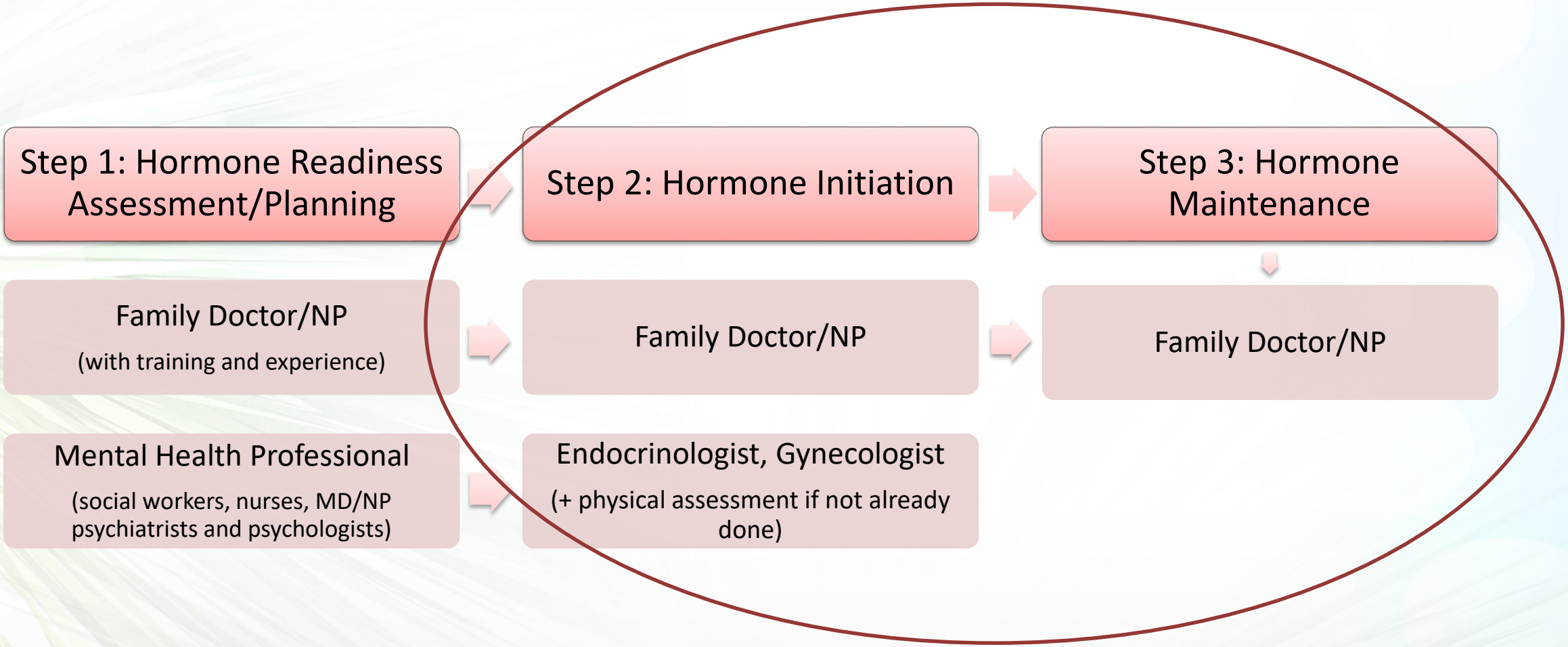
Pathway to Hormone Management



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Care Planning for interventions

- This session does not cover care planning for interventions (readiness assessment)
- It assumes that the treating clinician has either completed care planning directly with the patient or is prepared to treat based on another practitioner's recommendation

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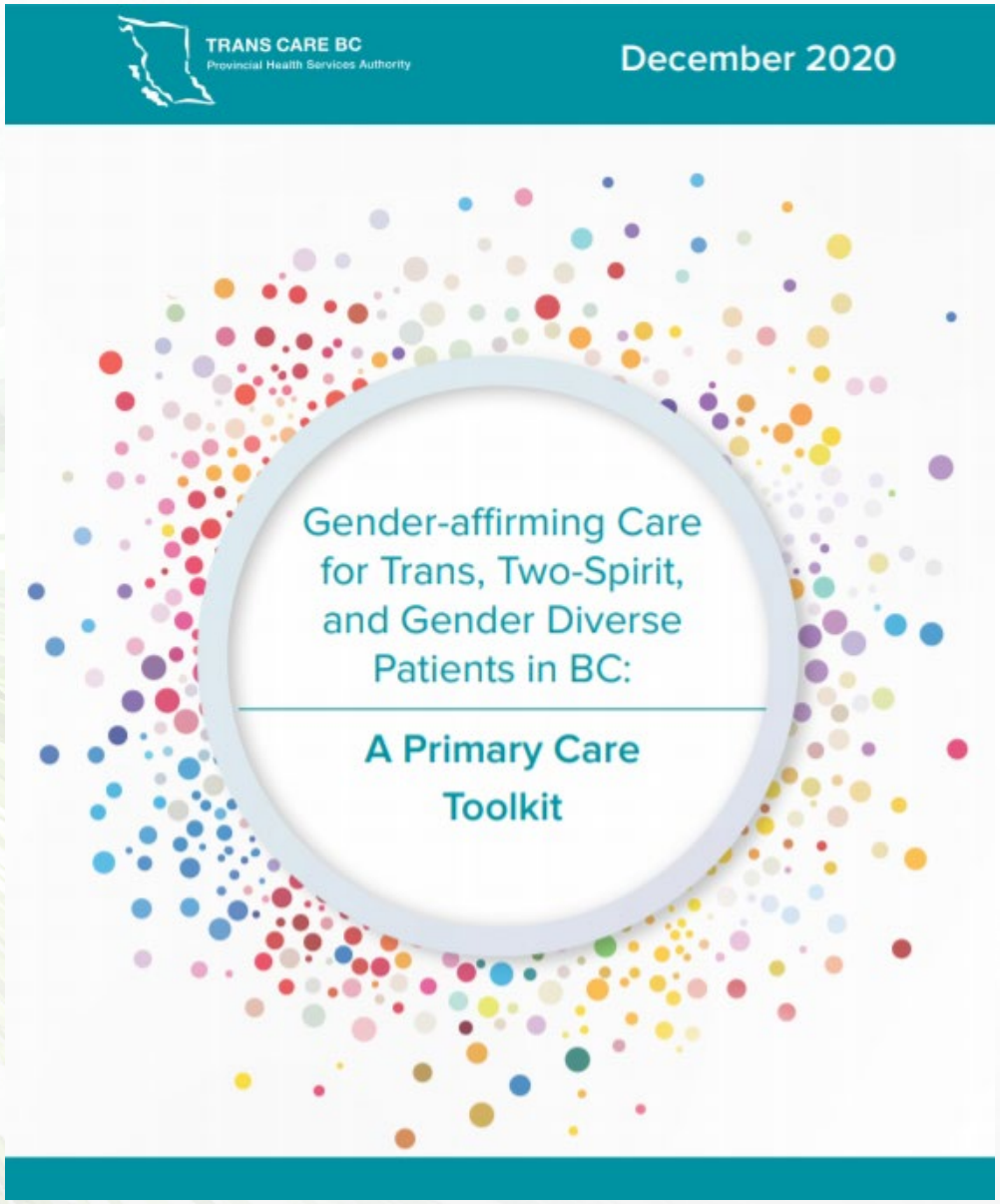

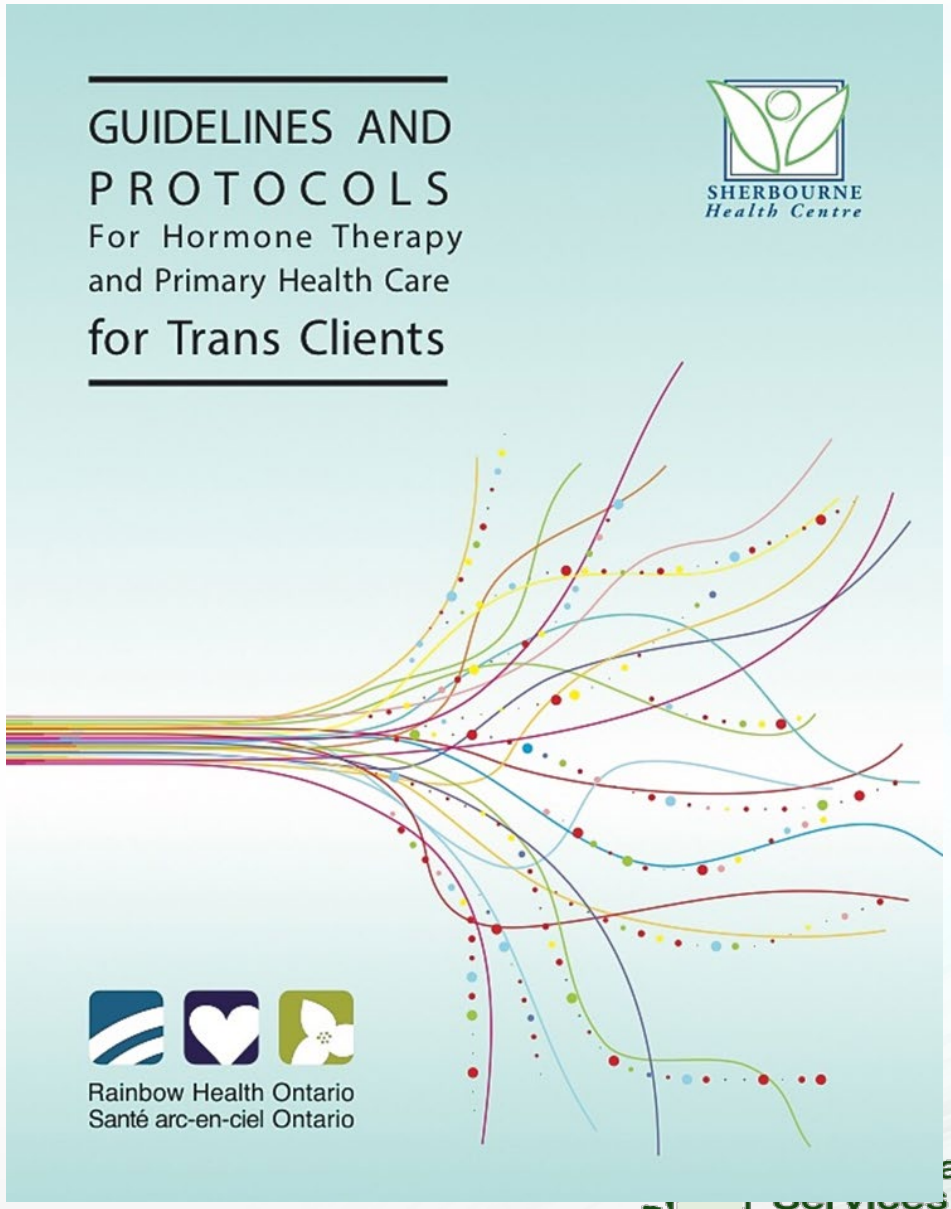

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Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People

Center of Excellence for Transgender Health

Department of Family & Community Medicine

University of California, San Francisco

2nd Edition – Published June 17, 2016

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UCSF

center of excellence for TRANSGENDER health

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FEATURING...

Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree, Peggy T. Cohen-Kettenis ... Guy G. T'Sjoen

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WPATH Criteria for Hormone Therapy in Adults

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

Treating Youth Under 19

- In BC, Infant's Act allows us to provide treatment at any age to a person who has the **capacity to consent** to this treatment
- Treatment must also be in the youth's **Best Interest**

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Hormone Therapy Overview

- Goals: to reduce secondary sex characteristics of the assigned sex, induce affirming secondary sex characteristics, reduce gender dysphoria, increase alignment.

Estrogen + Testosterone blocker (+/- Progesterone), or Testosterone

Start low and titrate ~ q 4-6 weeks

- Base dose changes on lab values, patient goals, response, side effects
- Maintain blood levels in typical affirmed gender ranges (may vary depending on client goals)

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ESTROGEN BASED THERAPY

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Estrogen/testosterone-blockers related changes may include:	Expected onset	Expected maximum effect
* Breast growth	3-6 months	2-3 years
* Smaller genitals (testes)	3-6 months	2-3 years
Decreased fertility	Variable	Variable
Fat redistribution and potentially weight gain or loss	3-6 months	2-5 years
Decreased muscle mass	3-6 months	1-2 years
Mood changes	Variable	Variable
Decreased spontaneous genital arousal (erections)	1-3 months	3-6 months
Changes to sex drive, sexual interests or sexual function	Variable	Variable
Skin changes including softening & decreased oiliness	1-6 months	Unknown
Decreased growth of body & facial hair	6-12 months	3 years
Decreased scalp hair loss (balding)	No regrowth, loss stops 1-3 months	1-2 years

From the World Professional Association of Transgender Health's Standards of Care, Version 7

*Change is permanent and will remain even if hormone therapy is stopped

Effects & expected time course of Estrogen Therapy

Potential Risks	
Increased risk of blood clots, pulmonary embolism (blood clot in the lung), stroke or heart attack Gall stones	Likely increased risk Oral estrogen: 5.5/1000 vs 1.2/1000
Changes to cholesterol which may increase risk for pancreatitis, heart attack or stroke Liver inflammation Nausea Headaches	Possible increased risk
Diabetes Heart and circulation problems (cardiovascular disease) Changes to kidney function (if using spironolactone) Increased potassium which can lead to heart arrhythmias (irregular heart beat) if using spironolactone Increased blood pressure Breast cancer Increased prolactin and possibility of benign pituitary tumours	Possible increased risk if you have additional risk factors

Risks of Hormone Therapy: Estrogen Based

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Risk Considerations

- Contraindications to estrogen therapy may include unstable cardiovascular disease, active hormone-sensitive cancer, end-stage liver disease and allergy.
  - Many patients choose to begin or continue hormone therapy in spite of higher risk
  - In such cases, care providers should do a careful informed consent process that takes into consideration the capacity of the patient to make an informed decision and the significant harm that can come from withholding treatment

Medication	Dose
Androgen Blockers	
Spironolactone First line due to lower cost, effectiveness and tolerability May not significantly lower T levels alone	Starting dose: 50 mg po daily Usual maintenance dose: 200-300 mg daily Can be divided bid
Cyproterone Eligible for special authority if spironolactone is contraindicated, not tolerated or ineffective	Starting dose: 25 mg po daily Usual maintenance dose: 25 – 100 mg daily
Finasteride An anti-androgen with primarily peripheral action Eligible for Special Authority if needed to augment effect of primary anti-androgen	2.5 mg po every other day
Estrogen	
17-beta estradiol (Estrace®) Lowest risk of all estrogens and first choice	Starting dose 1-2 mg po daily Usual maintenance dose 4-8 mg daily Can be divided bid
Estradiol patch (Estradot®/Estraderm®) Eligible for Special Authority for clients >40 years old with additional risk factors	Starting dose 50 mcg patch twice per week. Usual maintenance dose: 100-400 mcg twice per week
Estradiol valerate (injectable) Only available compounded	Start dose at 5 mg IM/SC weekly Usual maintenance dose 10-20 mg IM/SC weekly Weekly dosing is preferred to minimize peak/trough variation Biweekly injection (of 2x the weekly dose) may be tolerated in some individuals
Progesterone	Not routinely recommended but may be included based on patient preference No clear evidence of benefit and possible increased risk Potential role in breast/nipple development (unproven)
Micronized progesterone (Prometrium®) First choice but more expensive	Starting dose 100 mg po daily Usual maintenance dose 100 – 400 mg daily
Medroxyprogesterone (Provera®)	Starting dose 5 mg po bid Usual maintenance dose 10-15 mg bid

Estrogen-based regimens

Estrogen + blocker +/- progesterone (variations exist)

- Choice of estrogen:
  - Typically oral for young healthy patients unless they prefer another option
  - Transdermal indicated if risk factors for CVD: age, nicotine use, HTN, DVT history, etc…
  - Eligible for special authority with clear indication eg. Age > 40 + risk factor

Estrogen

- **Oral** (17 β estradiol):
  - Starting dose 1-2 mg po daily
  - Usual maintenance dose 4-6 mg daily
  - Can be divided bid
- **Sublingual** (same tab as po): dosed bid or tid due to shorter half-life.
- **Patch** (17 β estradiol)
  - Starting dose 50 mcg patch twice per week.
  - Usual maintenance dose: 100-300 mcg twice per week
- **Injectable** (compounded estradiol valerate)**:**
  - Start dose at 5 mg IM/SC weekly
  - Usual maintenance dose 10-20 mg IM/SC weekly
  - Weekly dosing is preferred to minimize peak/trough variation

Testosterone Blockers

Spironolactone (first choice):

- **Potassium Sparing Diuretic (Watch the K+)**
- **Blocks peripheral androgen receptors**.
- May not fully suppress testosterone levels
- Starting dose: 50 mg daily
- Usual maintenance dose: 200-300 mg daily
- Can be divided bid

Testosterone Blockers

Cyproterone:

- **Use if spironolactone ineffective, contraindicated or not tolerated. Use with estrogen only** due to long term risks associated with hypogonadism
- Blocks androgen receptors and inhibits LH
- Can cause severe liver dysfunction and worsening depression (dose-dependent). Increased thrombotic risk
- Requires special authority
- Starting dose: 25 mg po daily
- Usual maintenance dose: 25 – 100 mg daily

Progesterone

- No well-designed studies to guide prescribing in this context
- Not routinely recommended in guidelines (based on data from the WHI)
- Anecdotal reports of increased **breast growth and areolar/nipple development, improved mental health effects**
- Suppresses LH – potentially suppressing testosterone
- Women's Health Initiative: post menopausal women, different formulations e.g., premarin and medroxyprogesterone

UCSF Transgender Protocol Statement on Progestogens

http://transhealth.ucsf.edu/trans?page=guidelines-feminizing-therapy

Considering these differences in demographics and goals of therapy, extremely modest increase in overall risk, and lack of difference in mortality, as well as more recent reassuring data with other forms of estrogen, the risks of using progestogens in transgender women are likely minimal or even absent (Grading: NT O M)

Progesterone

- If a fully informed patient wants to try it, consider a 3-6 month trial
- Micronized progesterone is lower risk and better tolerated than medroxyprogesterone with better effect on lipid profiles.
- Micronized progesterone:
  - Starting dose 100 mg po daily
  - Usual maintenance dose 100 – 400 mg daily
- Medroxyprogesterone:
  - Starting dose 5 mg po bid
  - Usual maintenance dose 10-15 mg bid

Monitoring Estrogen Based Therapy

Baseline and q 6-12 months thereafter	• Total testosterone, CBC, ALT, fasting glucose, lipids, prolactin and if on spironolactone: CR and electrolytes
Following dose changes and 4-6 weeks after gonadectomy	• Total testosterone, estradiol, ALT, and if on spironolactone: CR and electrolytes

Monitoring Estrogen Based Therapy

- Estradiol levels are not correlated with clinical effect and vary widely.
- Testosterone suppression and clinical effects are more important
- Aim for estradiol level in range of ~ 300-800
- Variation in clinical practice and guidelines is common
  - Sherbourne: After gonadectomy add LH – Bone Mineral Density
  - UCSF: No evidence to support lipid or glucose monitoring at any time

TESTOSTERONE BASED THERAPY

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Testosterone-related changes may include:	Expected onset	Expected maximum effect
*Deeper voice	3-12 months	Years
*Growth of body and facial hair	3-6 months	3-5 years
*Growth of the external genitals (clitoris)	3-6 months	1-2 years
*Scalp hair loss	>12 months	Variable
Decreased fertility	Variable	Variable
Fat redistribution and possible weight gain or loss	3-6 months	2-5 years
Increased muscle	6-12 months	2-5 years
Mood changes	Variable	Variable
Changes to sex drive, sexual interests or sexual function	Variable	Variable
Skin changes including increased oil and acne	1-6 months	1-2 years
Dryness of internal genitals (vagina)	3-6 months	1-2 years
Stopping of monthly bleeding (period)	2-6 months	n/a

From the World Professional Assocation of Transgender Health's Standards of Care, Version 7

*Change is permanent and will remain even if hormone therapy is stopped

Effects & expected time course of Testosterone Therapy

Risks of Testosterone

Potential Risks	
Increased red blood cells (polycythemia) Sleep apnea Scalp hair loss (balding)	Likely increased risk
Changes to cholesterol which may increase risk for heart attack or stroke Liver inflammation	Possible increased risk
Diabetes Heart and circulation problems (cardiovascular disease) Increased blood pressure	Possible increased risk if you have additional risk factors

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Medication	Dose instructions
Testosterone	
Testosterone cypionate 100mg/mL (injectable, suspended in cottonseed oil) **Testosterone enanthate 200mg/mL** (injectable, suspended in sesame oil)	Starting dose: 25 mg IM or SC q weekly Usual maintenance dose: 50-100 mg weekly If local skin reaction occurs, switch oils Weekly dosing is preferred to minimize peak/trough variation Biweekly injection (of 2x the weekly dose) may be tolerated in some individuals
Androderm® (patch)	Starting dose: 2.5 mg patch/24h Usual maintenance dose: 5-10 mg/24h
Androgel® 1% (gel) 12.5 mg/pump or 25mg/2.5g or 50 mg/5g packet	Starting dose: 2 pumps or 1 x 2.5 g packet (25 mg daily) Usual maintenance dose: 4-8 pumps or 1-2 x 5 g packet (50-100 mg daily)
Natesto® (nasal gel) 4.5 w/w	Starting dose: 1 pump daily (1 nostril only) Usual maintenance dose: 2-4 pumps daily (1-2/nostril)
Progestins: May be used for contraception or to assist with suppression of monthly bleeding (menses)	
Medroxyprogesterone IM (Depo-Provera®)	150 mg IM q 12 weeks
Progesterone releasing IUD Higher dose progesterone preferred for suppression of monthly bleeding (menses)	Inserted by MD or NP. Devices effective for 3-5 years

Testosterone

- **Injectable:** testosterone cypionate or enanthate
  - start 25-50 mg q week IM or SC and titrate up based on client's goals (may be between reference ranges or within male range)
- **Patch:** usual maintenance dose of 5-10 mg daily
- **Gel 1%:** usual maintenance dose of 5-10 g of gel daily
- **Nasal:** usual maintenance dose of 5-7.5 mg daily.
- Special authority required
- Maintain testosterone in male range (usually)
- Dose may be reduced post-gonadectomy

Monitoring Testosterone

Baseline and q 6-12 months thereafter	• Testosterone, CBC, ALT, fasting glucose, lipids
Following dose changes and 4-6 weeks after gonadectomy	• Mid-injection cycle testosterone, CBC, ALT • Trough testosterone if amenorrhea is delayed >6 months

Endocrine Society 2017: "Past concerns regarding liver toxicity… have been alleviated.. the risk of serious liver disease is minimal"

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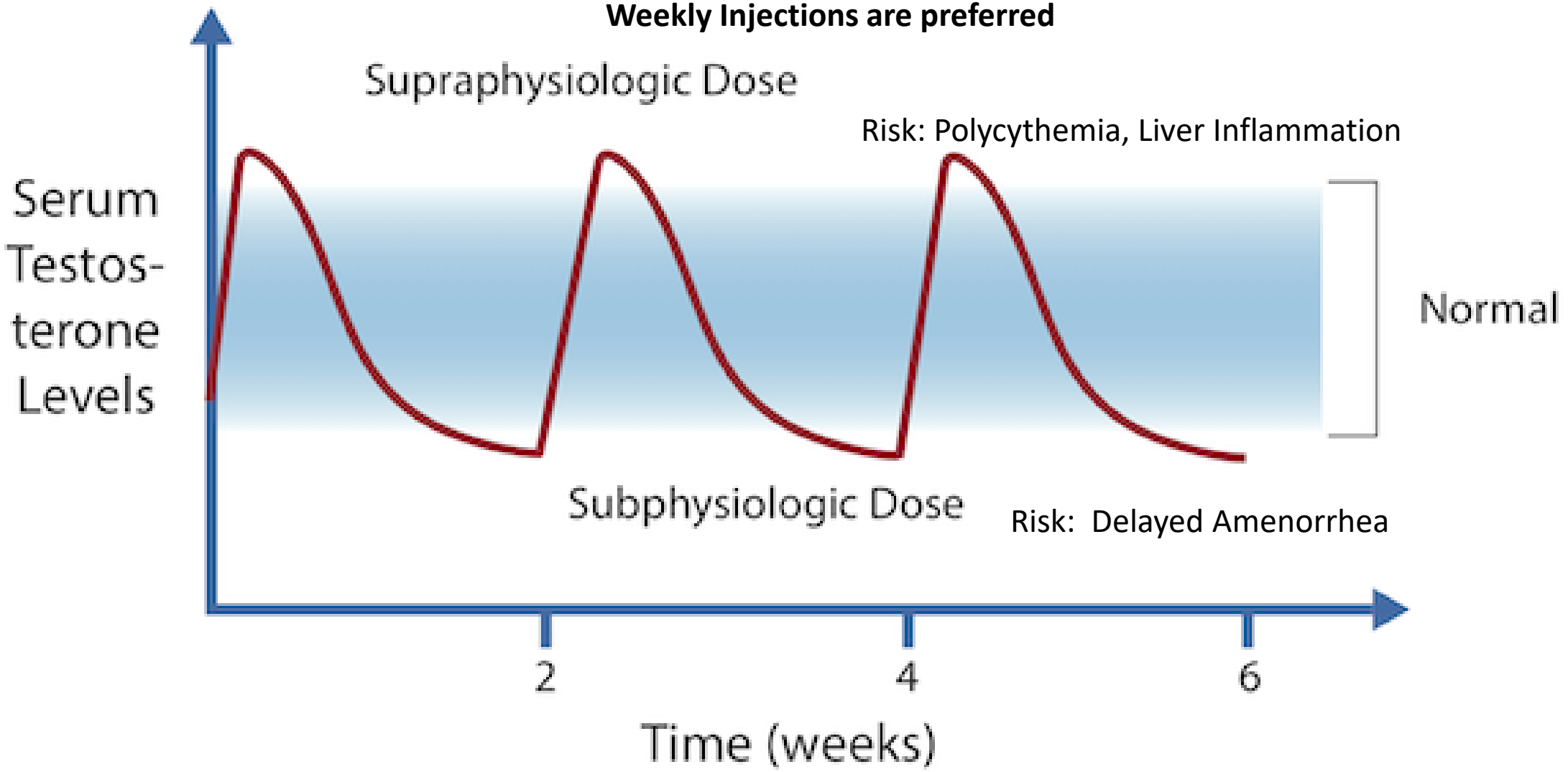
Monitoring Testosterone Therapy

- Must be interpreted based on # of days after injection
- If maximal effects are desired, maintain mid injection cycle hormone levels in the mid-high male range
- Goal is to induce physical changes at expected rate according to the patient's goals and minimize adverse effects
- Order a trough level (day 6 or 7) if cycles haven't stopped by 6 mos
- Order a peak (day 2-3) if polycythemia or liver enzymes elevated

Fluctuating Testosterone Levels

Weekly Injections are preferred



Hormone Therapy Variations

- As always, care should be individualized
- Some possible variations:
  - Lower doses of hormones
  - More gradual titration
  - Temporary use of hormones
  - Using T-blocker without estrogen
  - Using testosterone with finasteride

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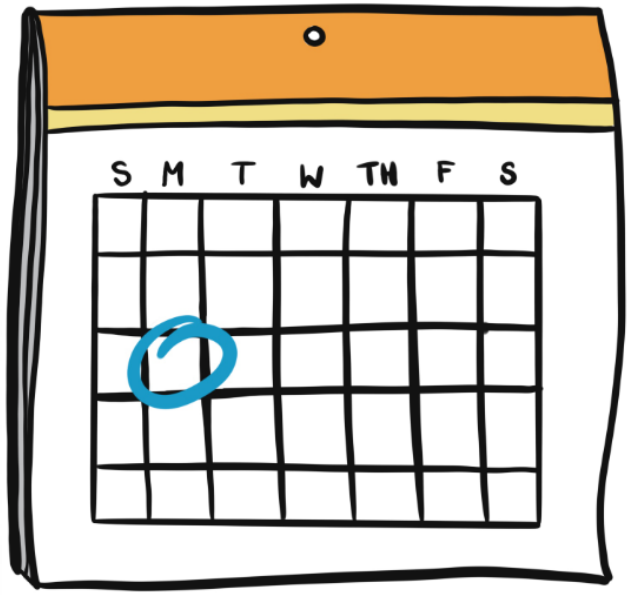
Hormone Therapy Follow Up

- Follow up ~ q 4-6 weeks while titrating and then ~ q 6–12 months
- Review effects of hormones, desire for dose change, side effects, mood, supports, social challenges
- Invite conversation about sexual health, impacts of hormones
- Check BP, other physical exam as indicated
- Review labs
- Adjust dose if indicated



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Tips for Managing Side Effects/Common Concerns

Estrogen/Testosterone blockers

- **Dizziness/postural hypotension** – usually due to spironolactone and resolves. If persistent switch to cyproterone
- **Low libido** – consider maintaining testosterone at a higher level or trial of progesterone
- **Problems with physical arousal (Erectile dysfunction)** – maintain T at higher level or try PDE inhibitors
- **Elevated transaminases** – usually transient and related to other causes. If severe or persistent, consider switching to patch/gel/injection

Tips for Managing Side Effects/Common Concerns

Testosterone

- **Local Injection site reaction** – switch to a different oil
- **Hair loss** – minoxidil (or finasteride depending on patient goals - will inhibit facial hair growth)
- **Polycythemia** – Ensure HB/HCT levels are interpreted based on male range. Reduce dose and duration between doses.
- **Elevated Liver enzymes** – Reference ranges are gender specific. Usually self-limited. If persistent, check for other causes.

Tips for Managing Side Effects/Common Concerns

Testosterone

- **Unexpected Bleeding:**
  - Evaluate for missed/inconsistent/excessive testosterone dosing.
  - Testosterone can convert to estrogen with theoretical risk of endometrial proliferation.
  - Check trough testosterone levels, estradiol, LH, FSH, TSH
  - Consider more frequent dosing (weekly) or dose adjustment
  - Unexplained persistent abnormal bleeding should be evaluated with pelvic ultrasound +/- endometrial biopsy, referral to gyne
- **Acne -** Treat as per usual, isotretinoin may be required, consider reducing testosterone dose

Mental Health

- Often improves with access to care – especially with good social supports
  - Estrogen
    - May worsen depression/anxiety due shifting social status and privilege, transphobia/transmisogyny
  - Testosterone
    - Sometimes causes irritability early in transition
    - May unmask an underlying psychotic disorder or worsen mania (rare)
- Provide education and resources to patients and family, connect to support networks
- Be an ally and an advocate to help clients fight systemic biases

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Clinical Support

RACE — RAPID ACCESS TO CONSULTATIVE EXPERTISE

eCASE — eLECTRONIC CONSULTATIVE ACCESS TO SPECIALIST EXPERTISE

- RACE Line: 604-696-2131 or 1-877-696-2131 & select “Transgender Care” option
- Trans Care BC Care Coordination Team: 1-866-999-1514
- Trans Care BC Primary care mentorship call; every Thursday from 12:10 -1pm

http://www.phsa.ca/transcarebc/health-professionals/clinical-resources/clinical-mentorship-call

- Trans Care BC Quarterly Clinical Speaker Series

http://www.phsa.ca/transcarebc/health-professionals/clinical-resources/clinical-speaker-series

- Email trans.edu@phsa.ca to be added to education distribution list

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Clinical Resources

- Endocrine Therapy for Transgender Adults in British Columbia: Suggested Guidelines – a document with protocols for the prescribing clinician relating to physical assessment, prescription planning, initiation of endocrine therapy, and ongoing maintenance (VCH, 2015)

- Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline (Endocrine Society, 2017)
- Guidelines and Protocols for Hormone Therapy and Primary Health Care for Trans Clients(Sherbourne Health Centre, 2015)

- UCSF Transgender Care, Department of Family and Community Medicine, University of California San Francisco. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People; 2nd edition. Deutsch MB, ed. June 2016. Available at http://transcare.ucsf.edu/guidelines .

- Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People Version 7. (WPATH, 2011). Available for download from WPATH
- Gender-affirming Care for Trans, Two-Spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit (Trans Care BC, 2017)

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