MODULE 1

FEMINIZING

MODULE 1
MEDICAL TRANSITION - FEMINIZING

Objectives:

- Describe the basic science underpinning feminizing gender hormonal transition
- List the pharmacologic options including dosing and routes of administration
- Describe an approach to prescribing cross sex hormones in the context of various medial co-morbidities

HORMONAL THERAPY: FEMINIZING

VANESSA

Requesting to be a new patient in your practice

- 31 year old, Accountant
- Marital status: separated

Past Medical History:

- Major depression / generalized anxiety
- Personality disorder (narcissistic)
- Substance abuse

MEDS: Zoplicone 7.5mg at hs
Sertraline 150mg OD

HORMONAL THERAPY: FEMINIZING

VANESSA

Hormonal therapy

- Estradiol 2 mg
- Spironolactone 200mg

HORMONAL THERAPY: FEMINIZING

VANESSA

LAB REPORT (brought in by patient)

- Estradiol 188 pmol/L (female range follicular: 77 – 921, midcycle 139- 2382)
- Testosterone 5.7 nmol/L (female range < 1.8)

Q&A

1. Thoughts about this patient?
   Any additional questions you would like to ask?
2. Have you ever dealt with a patient like this?
3. Would you accept her as a new patient?

Q&A

How do people transition?

SOCIAL TRANSITION

GENDER ROLE EXPERIENCE

(older term is RLE or “real life experience”)

- “Coming out”
- Carry letters
- Washrooms
- Transition at work, school, social media
- Peer support groups
- Gender marker (M or F) changes on legal documents

OPTIONS FOR MEDICAL TRANSITION

	Feminizing	Masculinizing
Hormonal Blockade	Leuprolide (GnRH agonist)	Leuprolide (GnRH agonist)
	Spironolactone	
	Cyproterone	
	Finasteride	
Hormonal	Estradiol	Testosterone
	? Progesterone	
Surgical	Augmentation	Breast reduction / Male chest contouring
	Tracheal shaving	Hysterectomy +/- BSO
	Facial feminization	
	Vaginoplasty	Phalloplasty
	Orchiectomy	Metoidioplasty

Q&A

Who decides when / if a patient is ready for a gender transition?

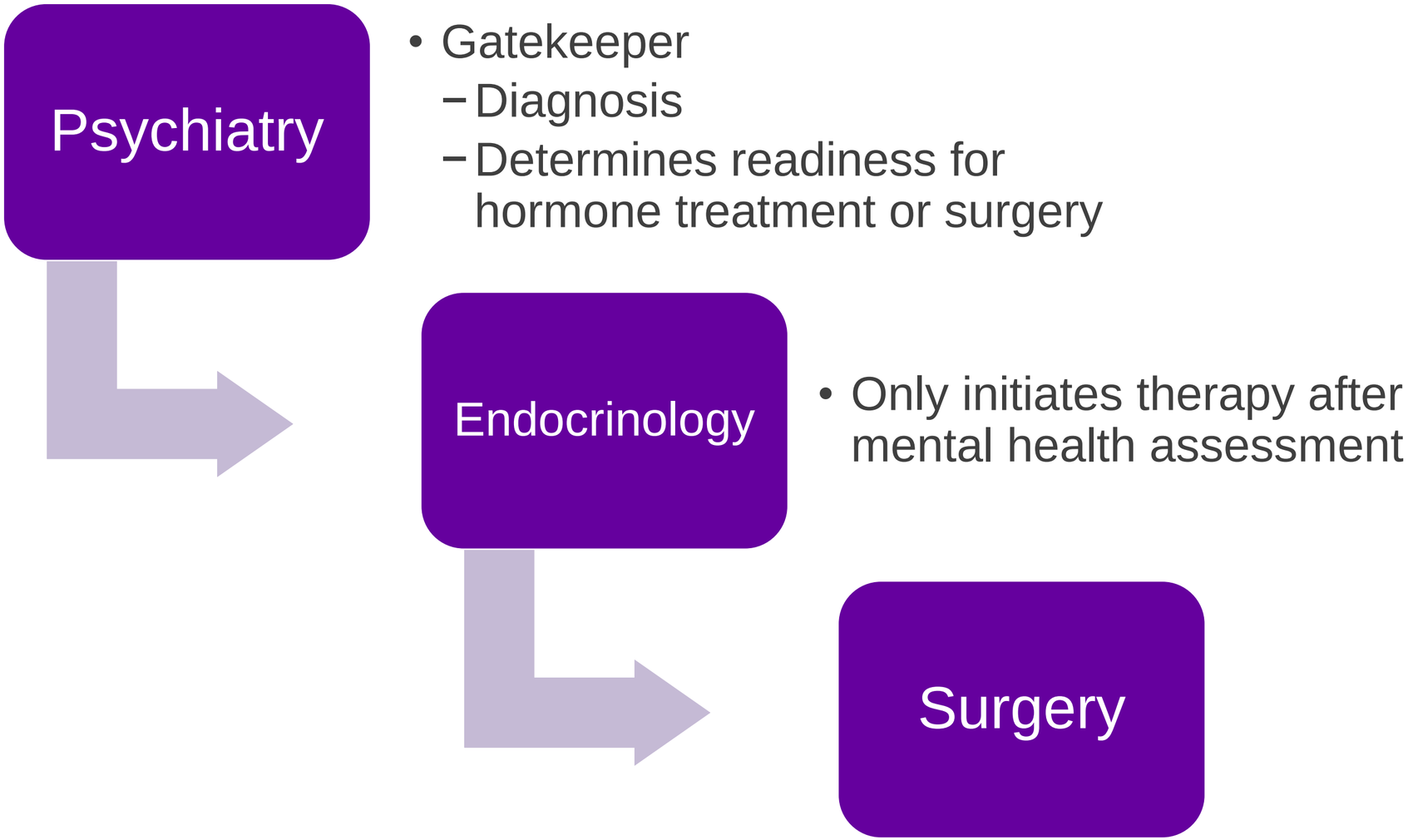
READINESS FOR HORMONES

- FP / any primary care practitioner – what would you need to make this determination?
- Psychologist – when is their involvement preferred / crucial?
  - access, expertise, cost (private)
- Psychiatrist – when is their involvement preferred / crucial?
  - access, expertise

BEFORE STARTING HORMONES…

- Ask if they know if anyone who has transitioned and if they had any challenges?
- Assess if patient has adequate social supports? Who have they disclosed to? How do they plan on disclosing?
- Need help with connecting patient to community resources, support groups, etc.
- Counsel patient about anticipated hormone effects and risks of hormones
- Assess and counsel on fertility preservation options – if patient is interested

SPECIALIST-BASED MODEL OF CARE

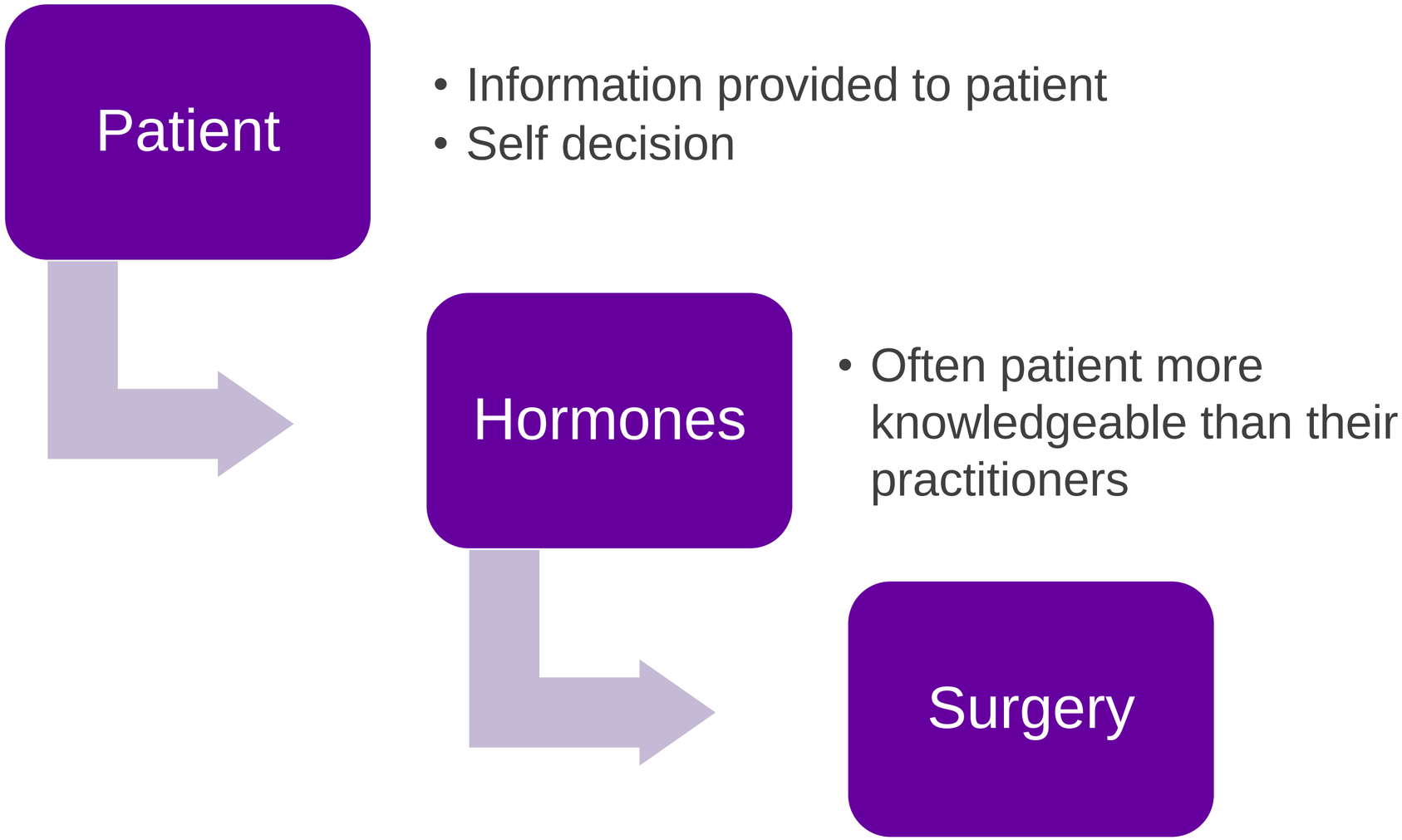


- Gatekeeper
  - Diagnosis
  - Determines readiness for hormone treatment or surgery

- Only initiates therapy after mental health assessment

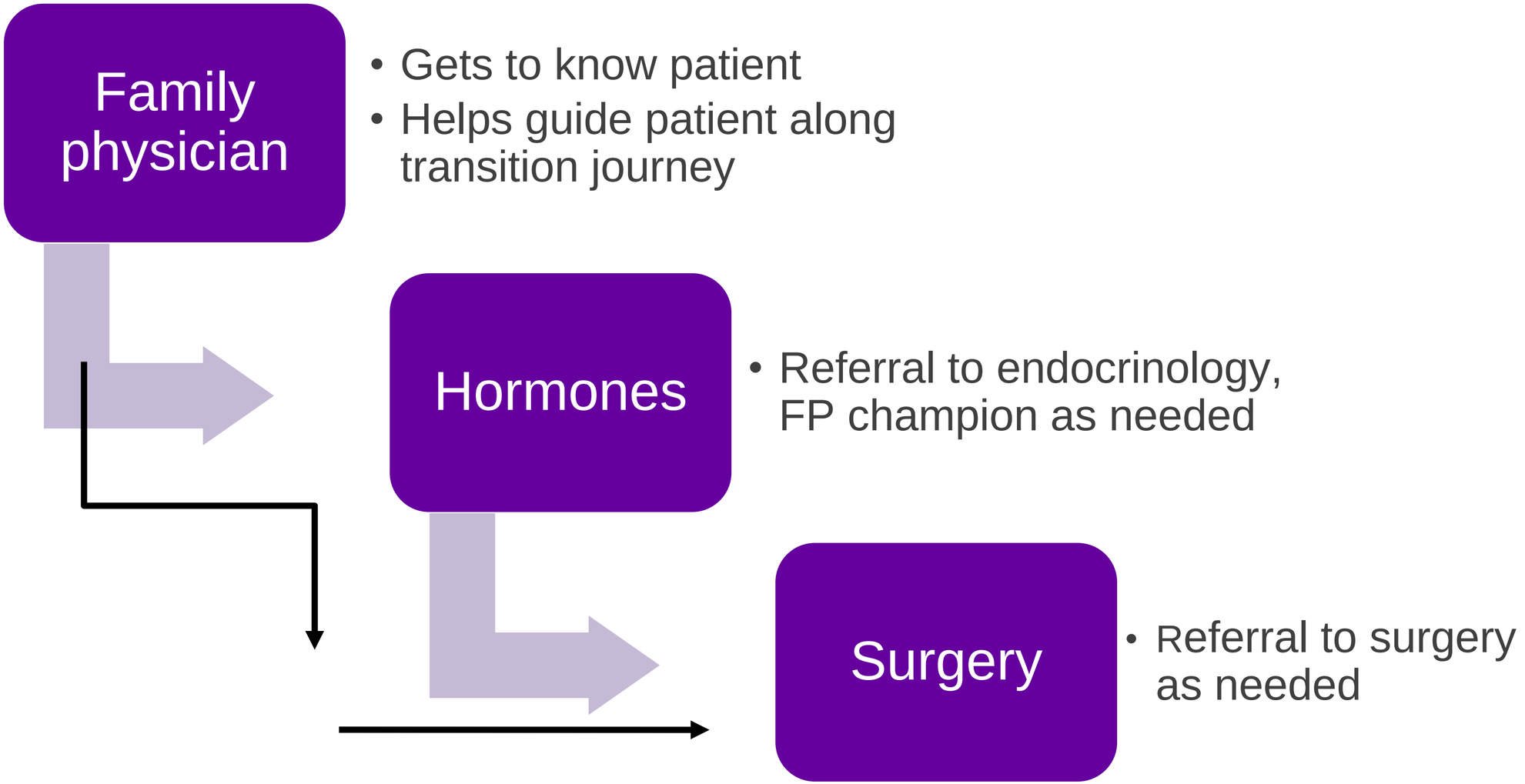
It should be noted that not all patients transition using hormones and/or surgery

“INFORMED CONSENT" MODEL OF CARE



It should be noted that not all patients transition using hormones and/or surgery

PRIMARY CARE MODEL



It should be noted that not all patients transition using hormones and/or surgery

WHEN PSYCHIATRY/MENTAL HEALTH INVOLVEMENT WOULD BE HELPFUL / CRITICAL

- For surgical readiness assessments *
- Severe and persistent mental illness
  - e.g. schizophrenia, schizoaffective disorder, bipolar I disorder
- Severe personality disorders
- Autism / developmental delay
- Need to exclude a possible differential diagnosis
  - e.g. transvestic fetishism (sexual arousal to cross-dressing), psychosis, malingering, etc.
- Patients questioning their gender identity who request therapy to support/explore this

Q&A

What are the criteria for hormonal transition?

CRITERIA FOR HORMONE THERAPY

- Longstanding pattern of gender non-conformity or dysphoria
- No confounding psychological, medical, or social problems that would affect treatment
- Informed consent
- Age of majority in given country
- If significant medical or mental health concerns, they must be reasonably well controlled

For adolescents

- Gender dysphoria emerged or worsened with puberty

Coleman, E. *et al.* Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. *International Journal of Transgenderism* **13,** 165–232 (2012)

Q&A

What are the key concepts to HORMONAL TRANSITION ?

HORMONAL THERAPY – KEY CONCEPTS

- Annihilation (muting) of sexual characteristics of the gender assigned at birth
- Induction of secondary sexual characteristics of the gender desired
- Maintenance of these characteristics

Q&A

What are the hormonal options available to FEMINIZE a patient?

HORMONAL THERAPY: FEMINIZING

Suppress:

Anti-androgen

- Androgen receptor blocker
- GnRH agonists
  - Decrease testosterone production by suppressing GnRH-LH-testosterone axis

No prospective randomized controlled trials on effectiveness of different regimens

Enhance:

Estrogen

- (Progesterone)

Hembree, Wylie et al, Endocrine treatment of Transsexual Persons: An Endocrine Society Clinical practice guideline. Journal Clin Endocrinology and metabolism; 94:3132-3154, 2009.

Medications: Anti-Androgens

Common:

- Spironolactone (Aldactone)
- Cyproterone (Androcur)

Less common:

- GnRH Analogs (Leuprolide, or Lupron, Buserelin / Suprefact)
- Non-Steroidal Anti-Androgens

FEMINIZING HORMONES

Formulations	Starting Dose	Maximum Dose	Cost* (4 weeks)
Spironolactone	50 - 100 mg OD	200 mg BID	$16.56[a] - $40.58[b]
Cyproterone	12.5 - 25 mg OD	50 mg OD	$32.98[c] - $101.92[d]
Conjugated Estrogen*	0.625 mg OD	1.25 mg OD	$20.01[e]
Estradiol (oral)*	1 - 2mg OD	4 mg OD	$18.53 - $40.14[f] **Covered by ODB with EAP request**
Estradiol Patch (transdermal) *[g]	0.1 mg OD / apply path 2x/week	0.2 mg OD / apply path 2x/week	$39.97 - $69.95[h]
Estradiol valerate** injectable (IM)[i]	10mg q 2/52	10mg q 1/52	$14.20 - $28.40

* Price quotes provided by www.pharmacy.ca. represent the price for 4 weeks' supply of a generic brand of medication where available (unless indicated otherwise). Prices include a usual and customary dispensing fee of $9.99 ($10.99 for Pace), which may vary from pharmacy to pharmacy. Accurate as of February 4th, 2015.
**estradiol valerate IM must be prepared by a compounding pharmacy, price quote provided by Pace Pharmacy

a) 50 mg OD given as 2x25 mg tablets OD;
b) 200 mg BID given as 2x100 mg tablets BID;
c) 25mg OD given as 1/2 x 50mg tablet OD;
d) 100mg OD given as 2x50 mg tablets OD;
e) The cost of 28 tablets of Premarin® 0.625 mg or 1.25 mg is the same
f) 4mg OD given as 2 x 2mg tablets
g) Estradot® brand
h) 0.2mg OD given as 2x100 mcg patches applied twice weekly(4 patches/week)
i) given as 1mL of 10mg/mL Estradiol valerate

http://www.rainbowhealthontario.ca/TransHealthGuide/img/fem-ht-doses.png

Q&A

1

What are the anti-androgren products and how do you pick between the options available?

Medications: Anti-Androgens

Spironolactone

- Acts in the kidneys to block aldosterone
- An androgen receptor blocker
- May not totally suppress blood levels because testosterone still produced
- Effective, affordable

Cyproterone

- Blocks androgen receptors
- Suppresses LH, reduces testosterone conversion to DHT
- May affect mood
- Effective, but more expensive

ANTI ANDROGEN

- Used in conjunction with estrogen to diminish effects of remaining testosterone and augment feminization effects
- Spironolactone 100 to 400mg
  - Androgen Rx antagonist
  - Minor effect: inhibit 17B dehydrogenase, production of testosterone, will not decrease LH
  - hyperkalemia

ANTI ANDROGEN

- Cyproterone Acetate (Androcur®)
  - Androgen Receptor antagonist
  - Progesterone activity: inhibit LH and therefore testosterone production
  - Rare cases of severe liver toxicity reported
  - May increase depression (common in TG population)
  - Ethinyl estradiol / cyproterone (Diane 35®) -?more thrombogenic
  - 25 to 100mg, but 25mg is adequate in most situations to achieve testosterone suppression

ANTI ANDROGEN

Spironolactone	Cyproterone
Used in US	Used in Europe
High K, Cr (ACE/ARB)	Liver toxicity, depression, ?thrombosis
Testosterone decreases less	Effective testosterone suppression
May be weaker anti androgen	May be stronger anti androgen
HDL increases	HDL decreases
Prolactin increases less	Prolactin increases more
100-200mg, up to 400mg	25*-100mg

OTHER OPTIONS ANTI-ANDROGEN

GnRH agonist

- Suppresses LH/FSH → testosterone axis
- Luprorelin (Lupron®) –monthly, 3 monthly injections
- Buserelin (Suprefact®) –nasal spray
- Expensive options

Q&A

1

What are the estrogen products and how do you pick between the options available?

HORMONAL THERAPY : FEMINIZING

ESTROGENS

- Oral
- Transdermal
- Injectable

ESTROGEN

MAINLY USE

- 17B-Estradiol
- Oral Estradiol (Estrace®) 2-6mg/d (up to 8) (1-2$ per tab)
- Transdermal Estradiol 100 to 400ug (Estradot®) patch 2x/wk/ or Estradiol gel (Estrogel®)

Other lesser used options:

- Conjugated Equine Estrogen (Premarin®)
  - 0.625mg to 10mg (7 groups) (1.25-3.75mg)
- Ethinyl Estradiol (not used anymore)
  - 50 to 100ug (3 groups)
- Estradiol valerate (injectable)
  - 5-20mg IM q2wks

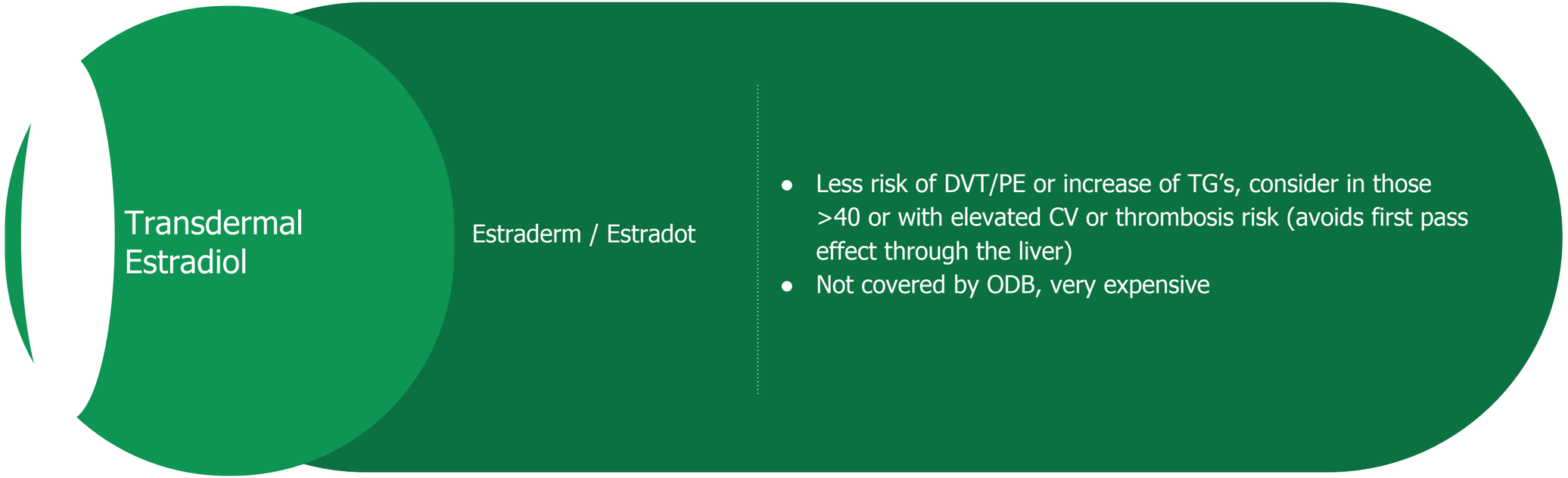
Medications: Estrogens

Oral

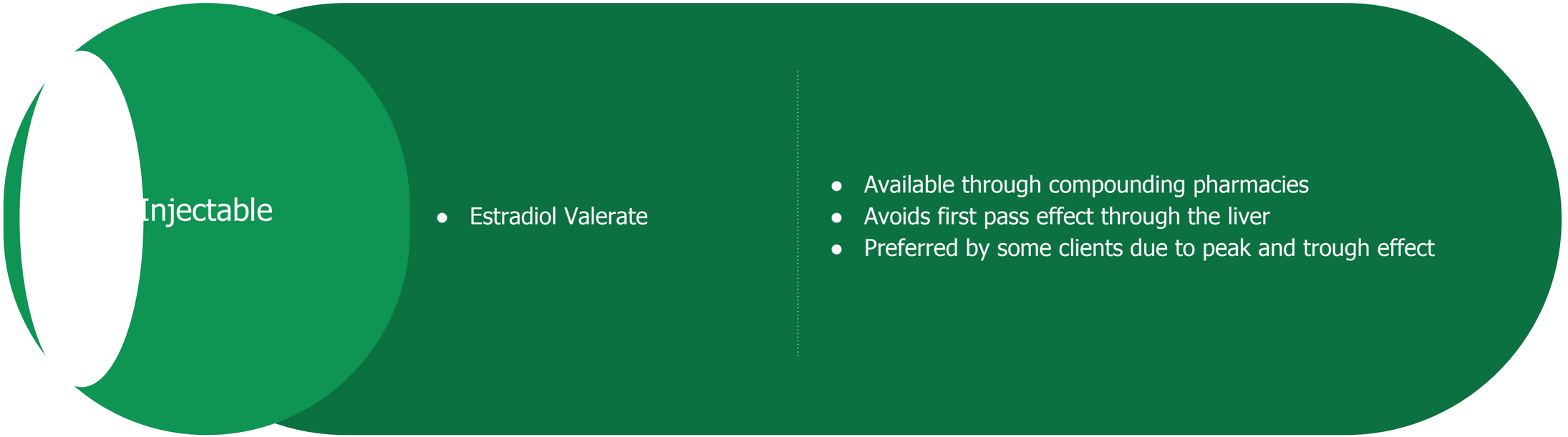
Estradiol / Estrace: Most common formulation due to cost, relative risks, and adherence

- Premarin / CES: not generally used due to risk profile

Medications: Estrogens



Medications: Estrogens



EFFECTS AND EXPECTED TIME COURSE OF A REGIMEN CONSISTING OF AN ANTI-ANDROGEN AND ESTROGEN

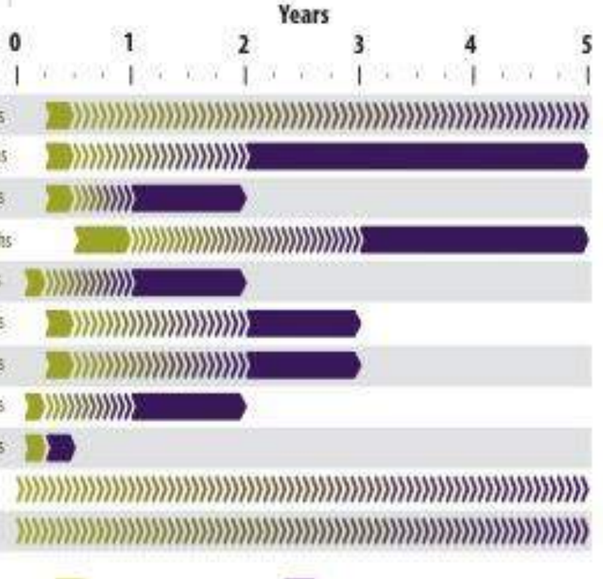
IRREVERSIBLE
Chest growth

REVERSIBLE
Skin softening/Decreased oiliness
Thinned/slowed terminal hair growth
Decreased muscle mass/strength

VARIABLE
Decreased spontaneous arousals
Decreased libido
Decreased testicular volume
Decreased sperm production
Erectile Dysfunction

VARIABLE
Fat redistribution

PHYSICAL EFFECTS	REVERSIBILITY	ONSET
Softening of skin/decreased oiliness	Reversible	3 - 6 months
Body fat redistribution	Reversible/Variable	3 - 6 months
Decreased muscle mass/strength[b]	Reversible	3 - 6 months
Thinned/slowed growth of body/facial hair[c]	Reversible	6 - 12 months
Male Pattern Baldness[d]	Reversible	1 - 3 months
Breast growth	Irreversible	3 - 6 months
Decreased testicular volume	Variable	3 - 6 months
Decreased libido	Variable	1 - 3 months
Decreased spontaneous erections	Variable	1 - 3 months
Decreased sperm production	Variable	variable
Erectile Dysfunction	Variable	variable



a) Estimates represent published and unpublished clinical observations
b) Significantly dependent on amount of exercise
c) Complete removal of male facial and body hair requires electrolysis, laser treatment, or both
d) No regrowth, loss stops

http://www.rainbowhealthontario.ca/TransHealthGuide/pdf/fem-ht-expectedeffectsguide.pdf

Q&A

1

When do you consider adding progesterone therapy and is it appropriate?

HORMONAL THERAPY : FEMINIZING

PROGESTERONE – oral /transdermal

Use remains controversial

- overall not recommended because there is no good evidence for benefit
- no effective transdermal progesterone available

PROS / CONS –potential side effects for limited additional efficacy

PRODUCTS – Prometrium®

DOSING 100- 200mg OD

CONTRAINDICATIONS/ CAUTION – active liver dysfunction, estrogen/progestin dependent cancer, CAD, MI, stroke, migraine with aura

ADVERSE REACTIONS – HTN, liver inflammation, migraine headaches, weight gain, bloating fluid retention, worsening lipids/blood glucose, acne, body hair, depression

Q&A

1. What should be monitored?

2. Are there appropriate therapeutic “targets” for estrogen and testosterone?

[Trans Health Guide]
[Point of Care Guides]

Type to enter a caption.

Q&A

What are the most common challenges with feminization?

CHALLENGES

- Perceived lack of efficacy
- Decreased libido
- Decreased erectile function (if penis intact)
- Increased risk with increasing age

VANESSA (REVISITED)

You have taken her into your practice, hormones have been titrated and you have started referral for gender transition related surgery

HORMONES

- Estradiol titrated to 4mg
- Spironolactone titrated to 300mg

LAB

- Estradiol 302 pmol/L (female follicular: 77–921, midcycle 139-2382)
- Testosterone 0.9 nmol/L (female < 1.8)

HAVE WE ACHIEVED OUR OBJECTIVES?

Objectives:

- Describe the basic science underpinning feminizing hormonal gender transition
- List the pharmacologic options including dosing and routes of administration
- Describe approaches to using cross sex hormones with various medical co-morbidities

DISCUSSION

MODULE 2

MASCULINIZING

MODULE 2
MEDICAL TRANSITION - MASCULINIZING

Objectives:

- Describe the basic science underpinning masculinizing hormonal gender transition
- List the pharmacologic options including dosing and routes of administration
- Describe approaches to using cross sex hormones with various medial co-morbidities

SAM

24 year old Transman healthy, construction worker in relationship

Past Medical History

- Smoker, just quit
- MDD / GAD in past

MEDS

- Started TESTOSTERONE (bought at gym)
- OTC bodybuilding supplements

Q&A

Your patient has already started hormonal transition on his own ….

Is this safe?

How do you manage this moving forward?

Q&A

1. What are the hormonal options available to MASCULINIZE a transgender patient?

2. How do you chose between options?

TESTOSTERONE

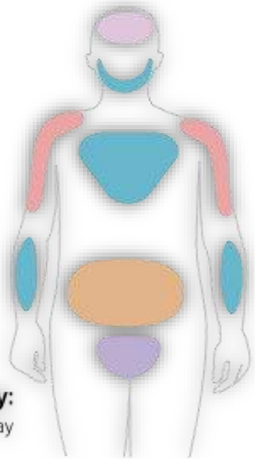
Formulations	Starting Dose	Maximum Dose	Cost Per Unit	Approx. Cost* (4 weeks)
Testosterone enanthate (IM)	50mg q week or 100 mg q 2 weeks	100mg q week or 100 mg q 2 weeks	$69.03 per vial (each vial contains 200mg/mL x 5mL = 1000mg)	$13.81 - $27.60 **Generally approved by ODB with EAP request**
Testosterone cyponiate (IM)	50mg q week or 100 mg q 2 weeks	100mg q week or 100 mg q 2 weeks	$43.31 per vial (each vial contains 100mg/mL x 10mL = 1000mg)	$8.66- $17.32 **Generally approved by ODB with EAP request**
Testosterone Patch (transdermal)	2.5 - 5 mg OD	5 - 10 mg OD	$159.27 / 60 x 2.5mg patches $159.27 / 30 x 5mg patches	$74.33 - $297.30
Testosterone Gel (transdermal)[i]	2.5 - 5g OD (2-4 pumps, equivalent to 25-50 mg testosterone)	5 - 10g OD (4-8 pumps, equivalent to 50-100 mg testosterone)	$85.90 / 30 x 2.5g patches $147.29 / 30 x 5g patches $167.55 / 2 pump bottles[j] **Only gel in packets (not in pump form) covered by ODB**	Sachets $80.17 - $274.94 Bottles $78.19 - 312.76
Testosterone Gel (transdermal, axillary)[k]	1.5 - 3g OD (1-2 pumps, equivalent to 30-60 mg testosterone)	3 - 4.5mL OD (2-3 pumps, equivalent to 60-90 mg testosterone)	$166.89 / pump bottle[l] **Only gel in packets (not in pump form) covered by ODB**	$77.88[a] - $233.65 **Axiron not covered by ODB**

*Price quotes provided by www.pharmacy.ca. The above-mentioned prices are accurate as of February 4th, 2015 and represent the price of the generic brand of medication where available (unless otherwise indicated). Prices include a usual and customary dispensing fee of $9.99, which may vary from pharmacy to pharmacy.

i) Androgel® 1% gel
j) each pump bottle provides 60 doses of 1.25g (=12.5mg testosterone)
k) Axiron™ 2% solution
l) each pump bottle provides 60 doses of 1.5 mL (=30mg testosterone)

http://www.rainbowhealthontario.ca/TransHealthGuide/pdf/rho_transprimarycare_masculinizinghtguide.pdf

EFFECTS AND EXPECTED TIME COURSE OF A REGIMEN CONSISTING OF TESTOSTERONE



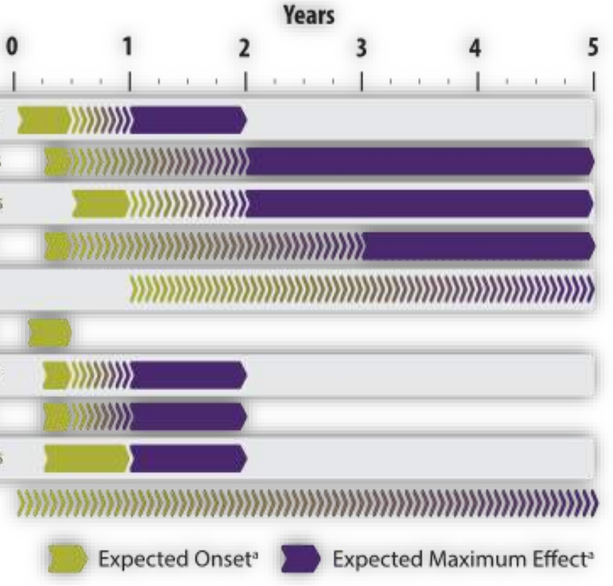
IRREVERSIBLE
- Scalp hair loss
- Deepened voice
- Facial and body hair growth
- Clitoral enlargement

REVERSIBLE
- Skin oiliness/acne
- Increased muscle mass/strength
- Vaginal atrophy

VARIABLE
- Fat redistribution

Use client's preferred terminology:
Terminology such as "clitoral" and "vaginal" may be triggering to some but not all clients.

PHYSICAL EFFECT	REVERSIBILITY	ONSET
Skin oiliness/acne	Reversible	1 - 6 months
Body fat redistribution	Reversible/Variable	3 - 6 months
Increased muscle mass/strength[b]	Reversible	6 -12 months
Facial/body hair growth	Irreversible	3 - 6 months
Scalp hair loss	Irreversible	variable
Cessation of menses	Reversible	2 - 6 months
Clitoral enlargement	Irreversible	3 - 6 months
Vaginal atrophy	Reversible	3 - 6 months
Deepened voice	Irreversible	3 - 12 months
Infertility	Irreversible	variable



a) Estimates represent published and unpublished clinical observations
b) Significantly dependent on amount of exercise

http://www.rainbowhealthontario.ca/TransHealthGuide/pdf/masc-ht-expectedeffectsguide.pdf

TESTOSTERONE OPTIONS

- ORAL (rarely used)
- TRANSDERMAL
- INTRANASAL (new / not on protocols)
- INJECTABLE

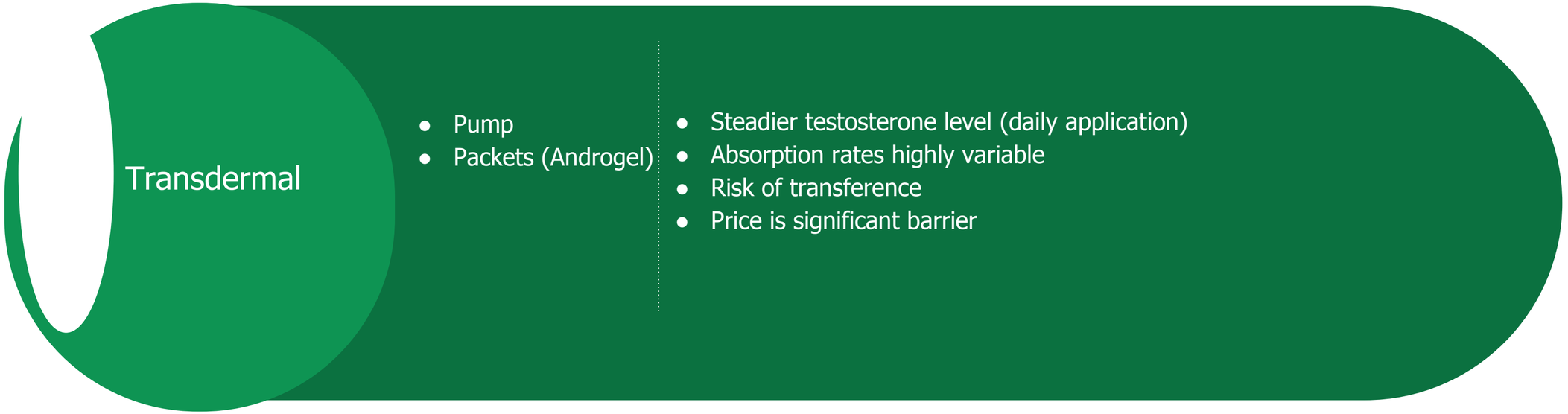
Medications: Testosterone

Injectable

- Testosterone Enanthate (Delatestryl) or
- Testosterone Cypionate (Depo-Testosterone)

- Most common formulation IM or SubQ injection
- Chosen for efficacy, availability, and cost.
- All formulations covered by ODB

Medications: Testosterone



MASCULINIZING HORMONES

INJECTABLE

- Testosterone enanthate (Delatestryl®) or cypionate (Depo-Testosterone®) IM 100 - 200mg IM every 2 wks, 50 - 100mg IM weekly

TRANSDERMAL

- Testosterone gel, 1%
  - ANDROGEL® 2.5-10g/ day; TESTIM® 5g/day; AXIRON® 30-120mg
- Testosterone patch (Androderm®)
  - 2.5-7.5mg/day -changed daily

INTRANASAL

- NATESTO® 5.5 11 mg bid - tid = 1 - 2 pumps in each nostril bid to tid

PHYSICAL/METABOLIC EFFECTS

- Increase in total lean mass, decrease fat mass
- Waist-hip ratio increased, reduced hip circumference
- Hb increased to male range
- Total chol (modest increase), LDL (increase), TG (increase), HDL (decrease)
- Mild acne –majority (can be severe)
- androgenetic alopecia (minority)
- Increase libido, decrease emotionality
- No definite CV risk has been demonstrated

Wierckx et al, Cross Sex Hormone Therapy in Trans Persons is safe and Effective at short-time follow-up:, J Sex Med 2014

Q&A

1. What should be monitored?

2. Are there appropriate therapeutic “targets” for testosterone?

Q&A

What are the most common challenges with hormonal masculinization?

CHALLENGES

- SUPRAPHYSIOLOGIC EFFECTS
- Testosterone side effects
  - ACNE
  - MALE PATTERN BALDNESS
  - MOOD/LIBIDO

SAM (REVISITED)

- Testosterone 100mg IM weekly
- Testosterone trough level 20.5 nmol/L (male range 8 – 29 nmol/L)
- Hematocrit 52% L/L
- HDL dropped approx. 30% - remains just above 1.0 mml/L

[Trans Health Guide]
[Point of Care Guides]

Type to enter a caption.

HAVE WE ACHIEVED OUR OBJECTIVES?

Objectives:

- Describe the basic science underpinning masculinizing hormonal gender transition
- List the pharmacologic options including dosing and routes of administration
- Describe approaches to using cross sex hormones with various medial co-morbidities

DISCUSSION