

APPENDIX 3

Hormone Options: Anti-Androgen Therapy

For many, androgen blockers are needed or desired to drive down one's own production and response to testosterone, and allow the effects of estrogen to be more apparent. Estrogen alone can suppress testosterone, but for some estrogen alone may not be enough to suppress testosterone sufficiently.

ORAL	
Medication name	Aldactone (spironolactone)
Frequency	By mouth once or twice daily
Additional comments	A potassium-sparing diuretic that can directly inhibit testosterone production and its effects, as well as potentially having its own small estrogenic effect. Those who are smaller and thinner, have lower blood pressure, are on certain blood pressure medications, and/or have underlying kidney disease may be at increased risk of experiencing adverse side effects. This is currently the anti-androgen of choice in the United States.
Medication names	Propecia, Proscar (finasteride), Avodart (dutasteride)
Frequency	By mouth once daily
Additional comments	Blocks the conversion of testosterone to its more potent form, DHT. It does not inhibit the production of testosterone and therefore will not lower blood testosterone levels. May be most effective for those with hair loss/baldness, significant facial hair, or those who are unable to tolerate higher doses of spironolactone.

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ORAL (continued)	
Medication name	bicalutamide
Frequency	By mouth once daily
Additional comments	<p>A nonsteroidal androgen blocker that works by blocking the androgen receptor. Bicalutamide does not suppress testosterone itself, but blocks its ability to bind to the receptor. Bicalutamide can also have indirect estrogenic effects, such as increased breast growth. This occurs when testosterone levels increase as a result of blocked receptors, and the body then converts this excess testosterone to estrogen.</p> <p>Bicalutamide has a rare, but severe potential side effect of liver toxicity (fulminant hepatitis). There are only several documented cases worldwide. Though uncommon, fulminant hepatitis can result in death</p> <p>Bicalutamide can be used for GAHT, but there are very few studies examining its use and the relative risk/benefit for this purpose. Because of reported cases of fulminant hepatitis, consensus is that its use in gender affirming hormonal regimen should be carefully considered, used only after alternative options have been trialed or offered, and an in-depth discussion of these potential risks have been had.</p>
INJECTABLES	
Medication name	Lupron (leuprolide)
Frequency	Injected monthly or every 3 months, depending on the formulation. This injection is done by a medical provider.
Additional comments	<p>Decreases one's own production of sex hormones, and is used for the purpose of blocking gonadal (testicular or ovarian) function. In youth, this can also reversibly block pubertal development prior to starting on gender-affirming hormone therapy.</p> <p>Lupron can be an option for some adults as part of a hormone therapy regimen, but it may be cost prohibitive and is not first-line use.</p>

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Hormone Options: Estrogen Therapy

17 β -estradiol, more commonly known as estradiol, is the bioidentical formulation of estrogen and the most effective form with the lowest risk profile when used for gender affirming therapy. There are several options for administration, and the choice is typically based on patient preference, accessibility, effectiveness, cost, and individual safety considerations.

Oral Estrogen Formulations

Oral estradiol is dosed daily and therefore provides steady levels of estrogen in the body. This formulation is relatively cheap, accessible, and easy to administer.

ORAL	
Medication name	Estradiol tablets
Frequency	By mouth daily
Additional comments	Some dissolve these tablets under the tongue, called sublingual (SL) dosing. The theory is that SL dosing may decrease the potential for estradiol affecting the liver (and the liver affecting the medication). However, this is not evidence-based and there is no data to support that SL dosing is any safer or more beneficial than swallowing the tablets. The amount absorbed under the tongue is likely to be variable and unpredictable. The benefits versus risks of this dosing method are largely unknown.

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Topical Estrogen Formulations

Topical estradiol appears to be the safest formulation from a cardiovascular standpoint, showing little impact on lipids (cholesterol) and decreased risk of thromboembolic events (blood clots, strokes) when compared to other formulations. This makes topical formulations ideal for those with higher than average cardiovascular risk, such as patients who are hypertensive, diabetic, or smokers. Topical formulations are also dosed daily, thereby providing the benefit of steady levels, as well as ease of use.

PATCHES	
Medication name	multiple brands available (Climara, Vivelle-dot)
Frequency	Patch(es) applied once or twice a week, depending on the brand.
Additional comments	Patches formulated for twice weekly use (change every 3-4 days) may be preferable for patients for whom adhesiveness is an issue.
GELS	
Medication name	Divigel packets, EstroGel actuated pump
Frequency	Applied daily
Additional comments	May be more expensive than other formulations. Less likely to cause a skin reaction (no adhesive as with the patch).

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Injectable Estrogen Formulations

Injectable estradiol is typically dosed intramuscularly(IM) every 2 weeks, though dosing weekly with smaller amounts is possible, with the benefit of decreasing the fluctuations between doses. The peak levels that occur just after dosing can feel affirming for some, and others have felt these may also produce changes more rapidly. However, there is no evidence to suggest that higher levels produce better or quicker results. Some avoid injectable formulations due to needlephobia, the inconvenience and time of injections (whether self-injecting or by a medical professional), and the wider fluctuations in hormone levels from dose to dose.

INJECTABLES	
Medication name	Delestrogen (estradiol valerate)
Frequency	Injected every week or every 2 weeks IM.
Additional comments	Injectable estrogens have few applications outside of their use in gender affirmation, resulting in periodic shortages from the manufacturer and/or difficulty obtaining injectable estradiol. These shortages are likely to continue, and those with concerns about this may consider topical or oral formulations instead.
Medication name	Depo-estradiol (estradiol cypionate)
Frequency	Injected every 2 weeks IM.
Additional comments	<p>If switching from the valerate to the cypionate formulation, there is a dose adjustment needed. The dosing of estradiol cypionate is lower.</p> <p>Estradiol cypionate tends to produce a lower, later, and longer peak level when compared to estradiol valerate, but the average levels in the blood, and effects on the body, should be the same.</p>

APPENDIX 5

Hormone Options: Progesterone Therapy

The benefit of progestins for gender affirmation is not well established. Some patients and medical providers report progesterone may help improve breast development, promote improvement in mood and libido, and have other positive benefits. However, progesterone has also been known to cause weight gain, fatigue, irritability and negative mood changes in other individuals. Progesterone is part of a cisgender female's hormonal makeup, and may be desired on this basis as part of a patient's gender affirming hormone therapy. It is important to weigh the benefits vs potential risks of starting progesterone.

In a few studies progesterone has been shown to play a role in suppressing testosterone production, which supports its use as another, or alternative, anti-androgen when needed. Progesterone may be considered if estrogen alone or estrogen and spironolactone are not effective in adequately suppressing testosterone.

Micronized progesterone (Prometrium) is the bioidentical formulation and appears to be the safest option in terms of cardiovascular health.

ORAL	
Medication name	Prometrium (micronized progesterone), 100 mg, 200mg capsules
Frequency	By mouth once daily, or cyclical dosing (10 days every month)
Additional comments	<p>Some patients may prefer cyclic dosing as its effects may mimic a menstrual cycle, which can be affirming for some. However, others may find the hormonal fluctuations with cyclic dosing troubling, and may prefer to take this medication daily.</p> <p>Progesterone's role in breast development has yet to be proven. Reported increases in breast size seem most likely due to general weight gain and fat deposition in the breasts as caused by progesterone and estrogen, and not the direct effect of progesterone on the breast tissue itself. So far, there is no evidence to show any specific benefit (or lack of benefit) regarding progesterone's effect on breast development.</p>
Medication name	Provera (medroxyprogesterone acetate)
Frequency	By mouth once daily or injected every 3 months (Depo Provera)
Additional comments	<p>Medroxyprogesterone has been shown to have a slightly higher risk of blood clotting than micronized progesterone. In addition, this medication has been associated with bone loss in cisgender women, as well as mood changes (irritability, depression). The benefit may be the 3 month injectable dosing, but the risks may outweigh the benefits in many individuals.</p>