Table 8.
Precautions with testosterone therapy and suggested measures to minimize associated risks

Precaution to Testosterone Therapy	Suggested Measures to Minimize Associated Risks
Stable ischemic cardiovascular disease	Consider referral to cardiology, ensure optimal medical (including prophylactic anticoagulation) and/or surgical management as indicated, aggressive risk factor optimization, consider transdermal route of administration +/- lower dose
Uncontrolled high blood pressure	Identify and address barriers to optimal BP control, initiate antihypertensive(s) as needed, consider cardiac stress test, encourage deferral of testosterone until adequately controlled
Uncontrolled diabetes	Identify and address barriers to optimal glycemic control, refer to dietician, encourage lifestyle modification, initiate antiglycemic agent(s), consider cardiac stress test, encourage deferral of testosterone until adequately controlled
Uncontrolled dyslipidemia	Identify and address barriers to optimal lipid control, refer to dietician, initiate antilipemic pharmacologic therapy, consider endocrinology referral, consider cardiac stress test, encourage deferral of testosterone until addressed
Hepatic dysfunction	Dependent on etiology, e.g. minimize alcohol consumption, weight loss in NAFLD, consider referral to hepatology/GI
Polycythemia	Refer to hematology, identify etiology and address contributing factors, consider low-dose ASA, strongly encourage deferral until adequately managed, consider transdermal route of administration, monitor RBCs/Hct closely
History of DVT/PE or hypercolaguable state	Identify and minimize co-existent risk factors, monitor RBCs/Hct closely, consider transdermal route of administration
Chronic respiratory disease that may be worsened by erythrocytosis/ polycythemia	Consider referral to respirology, monitor RBCs/Hct closely, consider transdermal route of administration
Severe/ uncontrolled sleep apnea	Initiate CPAP or oral device, encourage weight loss if overweight, consider uvulopalatoplasty, monitor for changes in CPAP pressure requirements
Androgen-sensitive epilepsy	Refer to neurology
Smoker	Encourage and support smoking cessation, offer NRT and/or bupropion/varenacline, or negotiate a decrease in smoking, consider cardiac stress test especially in the presence of additional risk factors, consider transdermal route of administration
Migraines	Consider referral to neurology, consider daily migraine prophylaxis, consider transdermal route of administration
Inter-menstrual bleeding	Consider pelvic ultrasound (transvaginal if possible), consider gyne referral - especially if significant risk factors for endometrial cancer
Oligo-/ Amenorrhea	Consider pelvic ultrasound (transvaginal if possible), consider progesterone-induced menstrual bleed prior to testosterone initiation

Metabolic Effects and Cardiovascular Disease

The prevalence of polycystic ovarian disease (PCOS) is higher in transgender men prior to use of testosterone when compared to cis women. This prevalence is estimated to be as high as 40%.[64] Administration of testosterone has been found independently to increase insulin resistance.[21] Additionally, long-term treatment of testosterone is associated with increased deposition of visceral fat.[29] These facts taken together suggest that transgender men may be at higher risk of metabolic problems before and after the administration of testosterone.

A review of the data in trans men in 2009 led Feldman and Safer[40] to conclude that testosterone therapy does not appear to increase the risk of diabetes mellitus type II (DMII) among trans men overall, but may further increase the risk in clients with other risk factors such as significant weight gain, family history, and PCOS. A subsequent case control study of 138 trans men did reveal a statistically significant increase in the incidence of DMII with testosterone.[47]

The risk of hypertension among trans men using testosterone is unclear, as data have been inconclusive. Cis women with PCOS (a hyperandrogenic condition) are known to be at an increased risk of hypertension.[64] It appears that testosterone therapy likely leads to a small increase blood pressure that is statistically significant but may not be clinically significant.[40] For example, a recent meta-analysis revealed an average increase in systolic blood pressure of 1.74 mmHg.[48] We agree with the UCSF Centre for Excellence in Transgender Health recommendation to maintain systolic BP ≤130 mmHg and diastolic BP ≤90 mmHg.[18]

Testosterone therapy appears to decrease HDL but variably affects LDL and triglycerides. Adverse effects may be worse with supraphysiologic doses. Clients with risk factors such as PCOS or existing dyslipidemia may be at increased risk of further abnormalities with testosterone administration. Again, while found to be statistically significant, it remains unclear whether changes are of clinical significance.[48] Transdermal formulations appear to be lipid-neutral,[40] and should be used preferentially in those with dyslipidemia and/or other significant risk factors for or pre-existing cardiovascular disease. In some cases, statins may be needed.

Recent data has shown a significant increase in cardiovascular disease (CVD) and cardiovascular (CV) events in older cis men prescribed hormonal therapy for testosterone deficiency.[66] It is important to note however that transgender men generally initiate exogenous

testosterone at a younger age and with significantly less medical comorbidity than the population in this study. Following a review of the available data in trans men in 2009, Feldman and Safer[40] concluded that masculinizing hormone therapy does not appear to increase the risk of CV events among healthy clients at normal physiologic doses, but may increase the risk of CVD in clients with underlying risk factors. A subsequent case control study of 138 trans men on testosterone for an average of 7.4 years revealed no increase in CVD or CV events.[47]

Data suggest that, as with estrogen treatment, risk stratification can be a highly useful concept to apply when assessing individual clients. Risk factor modification should be emphasized. Smoking cessation should be strongly encouraged, as well as a regular exercise schedule, healthy food choices, and the maintenance of healthy body weight. Unfortunately, Framingham calculations are less reliable with exogenous hormone use. It is reasonable to consider using high-risk category lipid targets in trans men who have any significant risk factors for cardiac disease. Individuals at high risk for developing cardiovascular disease should be offered aspirin as primary prevention.

Hepatic Dysfunction

Elevation of liver enzymes may occur with testosterone therapy. These elevations are generally transient if no other cause of hepatic dysfunction is present.[67] Baseline elevation in liver enzymes should be investigated and any existing hepatic disease optimized prior to the initiation of testosterone therapy.

Polycythemia

Testosterone increases renal erythropoietin production, which in turn induces increased marrow production of red blood cells. In trans men, high levels of serum testosterone may cause polycythemia (an increase in red cell mass) and erythrocytosis (an increase in red cell concentration). Higher blood viscosity may lead to increased risk of adverse vascular events in those with predisposing risk factors. The transdermal route of testosterone administration may decrease the risk of developing clinically significant erythrocytosis by virtue of steady delivery and avoidance of serum peaks.[68] Transdermal formulations should be used preferentially in those with a history of or risk factors for this problem.

Obstructive Sleep Apnea

Sleep apnea may be worsened or unmasked by testosterone therapy.[69,70] Those with risk factors and/or suggestive signs or symptoms of sleep apnea should be screened via sleep study. CPAP should be initiated prior to testosterone in those with clinically significant sleep apnea. As CPAP pressure requirements may change with masculinizing therapy, they should be reassessed periodically via sleep study following testosterone initiation.

Psychiatric effects

Mood changes can occur with testosterone; many clients describe a feeling of wellbeing associated with testosterone administration and a decrease in this wellbeing as it wears off. Typically, this is the reason clients prefer a 7-10 day injection schedule when using intramuscular formulations. The half-life of testosterone is 8-9 days, which corresponds to the timing of mood change in these clients. There have also been concerns about other mood changes with testosterone use. A small number of case reports and observational studies note psychiatric effects including hypomania, mania, increased aggression and psychosis with the use of testosterone and testosterone precursors.[40] These adverse events seem to be associated with higher doses or supraphysiologic serum levels of testosterone. Caution should be exercised in clients with uncontrolled bipolar disorder, a history of psychosis, or a strong family history of these problems. Transdermal preparations result in a steady serum testosterone level and may be preferred in clients prone to mood or other psychiatric disturbances.

Endometrial cancer

There is some debate regarding the impact of testosterone on the endometrium. PCOS, which is associated with higher levels of circulating endogenous androgens, has been associated with an increased risk of endometrial cancer.[71] Data seem to suggest that exogenous testosterone has one of two effects on the endometrial lining: in some individuals it may become atrophic and non-proliferating,[72,40] while in others it may lead to endometrial hyperplasia.[73,40] This may be due to individual differences in the degree of aromatization of testosterone to estrogen in the uterine tissues. The proliferative pathway theoretically confers an increased risk of endometrial cancer, however no cases in trans men have been reported in the literature to date.

Unexplained intermenstrual bleeding should be investigated in those considering testosterone, especially in the presence of other risk factors for endometrial hyperplasia and cancer. Clients who may have a thickened lining at baseline (eg. due to oligo- or amenorrhea) may also warrant investigation. A pelvic ultrasound may reveal previously unknown PCOS and can provide an estimate of the endometrial thickness. Some gynecologists advocate for the induction of a menstrual period for such clients prior to starting testosterone, with the rationale that it is preferable to start out with a thinner lining. This may be emotionally difficult for some trans men, however,
anecdotally, it may have the added benefit of decreasing the length of time to achieving complete cessation of menses in oligomenorrheic clients initiating testosterone.