NHS
Sunderland
Clinical Commissioning Group

GUIDELINES FOR THE USE OF FEMINISING HORMONE THERAPY IN GENDER DYSPHORIA

Information for Primary Care
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Further information on this guideline can be obtained from:

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1. Introduction and Background

Gender dysphoria is a condition in which there is a psychological experience of oneself as a man or woman, which is incongruent with the individual's external sexual characteristics of the body. The individual's physical sex is not aligned to their gender identity.

Sometimes, the distress/discomfort is sufficiently intense that people undergo transition from one point on a notional gender continuum to another – from Male-to-Female or Female-to-Male. This typically involves changes to social role and presentation, and may necessitate treatment with cross-sex hormones and/or having gender related surgery. In order to achieve this, hormones of the opposite biological sex are administered, sometimes in conjunction with medication to suppress endogenous sex hormone production. Gonadotrophin Releasing Hormone (GnRH) analogues are generally used in order to achieve this.

The aim of endocrine treatment is a physiological end organ response. This is based on the management of circulating hormone levels to allow accurate and individual dose titration to achieve suppression of hormone effects associated with the undesired gender. Treatment is flexible and patient-led according to the individuals needs as far as is consistent with clinical safety and the agreement of the prescriber.

2. Transfer of Prescribing Responsibilities from Secondary to Primary Care

In March 2014 NHS England Specialist Services Circular SSC1417 was issued which described Primary Care responsibilities in relation to prescribing and monitoring of hormone therapy for patients undergoing or having undergone Gender Dysphoria treatments. Those responsibilities include prescribing hormone therapy, patient safety monitoring, provision of physical health examinations and blood tests under the guidance of a specialist Gender Dysphoria service.

The specialist Gender Dysphoria service will assist primary care by providing specific, relevant information and support for prescribing and monitoring, including the interpretation of blood test results. Once a patient has completed the care pathway and has been discharged by the
Specialist service, GPs should offer them the usual range of primary healthcare services that are available to other patients.

3. Formulary Approved Indications

The listed drugs (see table 1 below) are approved for use in Gender Dysphoria in the NoT APC Formulary section 6.4.4. Although theses medicines may not be licensed for use specifically in Gender Dysphoria , they are widely used medicines for other indications which are managed in primary care. Hormone therapy here is based on traditional patterns of treatment. In the Northern Region

Gender Dysphoria Service support is provided by a multidisciplinary team that includes advice from a specialist clinical endocrinologist.

Table 1 – Medicines Included in the NoT APC Formulary Section 6.4.4 for use in gender Dysphoria (Trans women)

Drug	Formulation
Goserelin	3.6mg injection & 10.8mg injection
Leuprorelin	3.75mg and 11.25mg injection
Estradiol Valerate (Oestradiol)	1mg & 2mg tablets
Estradiol patches	Twice weekly matrix patches releasing approximately 50, 75 & 100 microgram/24 hours
Estradiol gel	0.1% gel (Sandrena®)
Finasteride	5mg tablets
Cyproterone Acetate	50mg & 100mg tablets
Spironolactone	25mg & 100mg tablets

4. Treatments for Gender Dysphoria

The choice of hormone preparation, formulation and dosage is in line with current understanding of minimum health risks and maximum efficacy. Where an individual has a medical condition that may impact on hormone treatment or vice versa, the specialist clinician may request that the GP refers the patient to the regional specialist endocrinology service (see contact details available a). Tables 2,3 and 4 below list the treatment options available.

Table 2 – Estradiol

Drug	Route/ Formulation	Dose	Comments
Estradiol	Oral	1-6mg daily	
Estradiol	0.1% gel	1-2mg daily	Particularly patients over 40 years, smokers or those with liver disease due to lower risk of thrombosis and liver dysfunction.
Estradiol	Transdermal patches	50 – 200 microgrammes twice /week	
• Dosage of estradiol therapy depends on circulating serum estradiol levels • Gradually increase dose to achieve a maximum degree of feminisation. This is particularly relevant for breast development. • Estradiol levels should be in the upper half – third of the normal follicular range (300–600 pmol/l depending on the laboratory) • Prolactin should be less than 400 mU/l. • LH + FSH can be used to help determine whether to increase or decrease dosage			

Table 3 - GnRH Analogues

Drug	Route/ Formulation	Dose	Comments
Goserelin	implant	3.6mg every 4 weeks, increasing to 10.8mg every 12 weeks if tolerated	Alternatives include Tripterolin and Leuproelin, as per BNF doses

- GnRH analogues usually required to achieve maximum suppression of the secondary male sexual characteristics.
- They are usually introduced after Estradiol
- Treatment goal – achieve equivalent female levels of testosterone.
- Allows patients electing for gonadectomy to experience a post surgical hormonal milieu.
- Inhibit the secretion of pituitary gonadotrophins leading to low circulating levels of testosterone
- Effective, well tolerated and generally not associated with significant side effects
- Many listed side effects i.e. feminising effects such as gynaecomastia and erectile dysfunction, are treatment goals in trans women
- Co-administration of estradiol avoids hypogonadism and reduces risk of other side effects, such as hot flushes, depression and oesteoporosis

Table 4. Adjunctive anti-androgen treatments if clinically indicated

Drug	Route/ Formulation	Dose	Comments
Finasteride	oral	5mg daily	Blocks conversion of testosterone to dihydrotestosterone. Discourages male pattern hair loss and testosterone-dependent body hair growth. Recommended for a time limited period only, prior to introduction of GnRH analogues to reduce male pattern hair loss.
Cyproterone	oral	50-100mg daily	Recommended for a brief period on initiation of GnRH analogues to prevent a testosterone surge.
Spironolactone	oral	100–200 mg daily	Occasionally used. Causes hyperkalaemia + hyponatraemia. Long-term use associated with liver dysfunction + possible hepatoma risk. May inhibit breast development.
• Cyproterone and spironolactone are not recommended for long-term therapy unless there are no good alternatives, as side-effects may occur			

5. Monitoring Requirements

Close liaison between the specialist clinician and GP is essential, as are physical assessment and ongoing haematological, endocrinological and biochemical monitoring. The monitoring parameters and frequencies are shown below in table 5:

Table 5 – Recommended Monitoring

Test	Frequency – monitor ahead of initiating treatment then at least 6 monthly for 3 years and then a minimum of yearly according to clinical need
Body mass index	√
Blood pressure	√
Full blood count	√
Urea and electrolytes	√
Liver function tests *	√
Fasting blood glucose or HbA1C	√
Lipid profile	√
Thyroid function	√
Serum testosterone*	√
Serum estradiol *	√
Serum prolactin *	√
LH *	√
FSH*	√

Nb. Endocrine normal ranges differ between laboratories therefore use local laboratory ranges when interpreting results as reported. Levels quoted here are indicative only.

A combination of those marked * may be requested depending on the needs and stage of treatment of the service user.
When patients are prescribed estradiol, tests should be taken 24 h after a tablet, 48 h after a patch has been applied or 4-6 hours after application of a gel.

All patients receiving hormone therapies are regularly reviewed to ensure that clinical well-being is maintained. The service aims to see patients every 4 months in the first year of treatment, 6 monthly for 3 years and then yearly depending on clinical assessment and results

Monitoring is designed to detect major side effects of hormonal treatment and guide dosage of treatment. The risks of estradiol exposure appear to be related to the duration of treatment in genetic females.

6. Treatment Outcomes

The effects of feminising hormones and the time to realise the desired outcomes are shown below in table 6:

Table 6. Effects and expected time course of feminising hormones

Effect	Expected onset	Expected maximum effect
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/ strength	3–6 months	1–2 years
Softening of skin/ decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed growth of body and facial hair	6–12 months	> 3 years
Male pattern baldness	Loss stops 1–3 months, no regrowth	1–2 years

Note: This is a general guide and the timing of introduction of GnRH analogues may influence timescales

7. Adverse Effects due to treatment for gender dysphoria

Table 7 below shows the adverse effects that can be experienced by patients prescribed treatments for gender dysphoria and the level of risk associated with them.

Table 7: Risk level of feminizing hormones

Risk Level	Condition
Likely increased risk	Venous thromboembolic disease* Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia
Likely increased risk with presence of additional risk factors (including age)	Cardiovascular disease
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma
Possible increased risk with presence of additional risk factors (including age)	Type 2 diabetes*
No increased risk or inconclusive	Breast Cancer

*Risk is greater with oral estradiol than with transdermal preparations

Additional information on risks is shown in table 8 below.

Table 8 Hormone therapies and associated adverse effects

Adverse Effect	Comments
Thromboembolic disease	The incidence of deep venous thrombosis (DVT) in trans women is raised at approximately 2.6%. The majority occur during the first 2 years of treatment. An ongoing risk of 0.4% per year continues. The type of estradiol may be a factor Ethinylestradiol results in a procoagulant haemostatic profile in transsexual subjects and is not recommended.
Breast cancer	The incidence of breast cancer with standard HRT in genetic females is increased. Only 4 case reports of breast tumours in treated trans women, risk of breast cancer secondary to feminising hormone therapy likely to be low.
Hyperprolactinaemia	Estradiol therapy can result in hyperprolactinaemia and pituitary hypertrophy. The incidence of significant hyperprolactinaemia reported to be up to 15% but there have only been two case reports

	of prolactinomas in trans women and none have needed withdrawal of estradiol treatment.
Prostate cancer	Prostate cancer has only been reported in two trans women in the world literature. This suggests the incidence of prostate cancer is reduced in trans women compared with the natal male population.
Fertility	Estradiol therapy leads to a suppression of gonadotrophin production and subsequent reduction in spermatogenesis. Service users are counselled that treatment will reduce or remove their fertility, and gamete storage is discussed.
Abnormal liver function	Abnormalities of liver function are, rarely, associated with the use of estradiol therapy. The risk of abnormal liver function tests is approximately 3% in trans women. In half of these, the abnormalities persist for more than 3 months. However, the increases are mild + only rarely require discontinuation of treatment.
Age and mortality	When the patient reaches 40years old consider transdermal estradiol preparations . Prolonged HRT use beyond 5 years after the menopause is associated with an increased risk of breast cancer in natal females. Although this is the best evidence available on the long term effects of estradiol therapy, breast cancer is rare in trans women. Estradiol use beyond 55 years old in trans women appears safe from the point of view of breast health The current data suggests long-term treatment with estradiol in trans women is associated with a slight increase in the standard mortality ratio, possibly due to an increase in cardiovascular deaths or suicide in vulnerable individuals. However, the increased suicide data is historical and improvements in service provision in recent decades mean this may no longer be relevant. Meanwhile, increased cardiovascular mortality may be related to the use of Ethinylestradiol rather than current recommended estradiol therapy. Ethinylestradiol is no longer recommended. Life long treatment is considered safe, in the absence of serious but rare conditions, although breast screening should continue beyond the age of 70, if estradiol is continued.

8. Managing treatments pre and post planned surgery

Due to an increased risk of venous thromboembolism, it is recommended that:

- Estradiol is stopped around 4-6 weeks before surgery resulting in immobility (including genital reconstructive surgery).
- GnRH analogues do not need to be stopped.
- Estradiol can be resumed 4 weeks post-operatively if there are no complications.
- After gonadectomy GnRH analogues are no longer required. However, rarely androgens may still be significantly derived from adrenal glands. If so Finasteride can be prescribed.

9. Other Information

See the manufacturer's SPC or BNF for more detailed prescribing information

10. Follow up and Discharge Arrangements

When service users are discharged from the service, detailed information is sent to the GP and service user. Guidance includes:

- Breast screening
- Prostrate screening (prostatectomy is not part of genital reconstructive surgery)
- Monitoring of bone health in individuals who have had a significant break from sex steroid treatment (>6 months).
- Ongoing treatment - Estradiol is usually life long, in the absence of serious complications, although lower doses and circulating levels are acceptable in older trans women
- Long term goals and monitoring of hormone treatment, including target ranges for hormone levels
- Monitoring tests are needed for life on 6 monthly basis for 3 years, then yearly thereafter if the patient remains well
- Action to take in response to common disorders and serious complications, including cessation of treatment
- When and where to seek specialist advice
- How to refer back or contact the Northern Region Gender Dysphoria Service.

11. Relevant guidance

- Standards of Care for the Health of Transsexual, Transgender and Gender-Nonconforming People, Version 7, World Professional Association of Transgender Health, 2012

- Good practice guidelines for the assessment and treatment of adults with gender dysphoria, College Report 181, The Royal College of Psychiatrists, 2013
- Interim Gender Dysphoria Protocol and Service Guideline2013/14, NHS England, 2013
- Primary Care responsibilities in relation to the prescribing and monitoring of hormone therapy for patients undergoing or having undergone Gender Dysphoria treatments Specialist Services Circular SSC1417 NHS England March 2014
- North of Tyne Area Prescribing Committee Formulary May 2014

The information included has been adapted from the above documents, with additional information from the shared care protocol used at the Gender Identity Clinic, West London Mental Health NHS Trust, with their permission and our thanks.

12. Communication + Contacts

Northern Region Gender Dysphoria Service
Walkergate Park, Benfield Road, Newcastle Upon Tyne, NE6 4QD
Lead Clinician – Dr Helen Greener
Telephone: 0191 287 6130

Regional Specialist Endocrinology Service
Refer to:
Dr Richard Quinton
Endocrinology Department, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP
Telephone: 0191 282 4635