West London Mental Health NHS Trust

SHARED CARE PRESCRIBING GUIDANCE FOR

Treatment of Gender Dysphoria in Transwomen (Male to Female Transsexuals)

Applicable to:	GPs referring patients to the Charing Cross Gender Identity Clinic
Date Approved:	14 March 2017
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INTRODUCTION

This document has been prepared by Dr Leighton Seal, Consultant Endocrinologist, and the GIC's Clinical Team together with WLMHT's Chief Pharmacist.

The information contained in this document has been compiled in order to support GPs and other medical practitioners in safe prescribing and monitoring arrangements. The document outlines the roles and responsibilities of the Gender Specialists, General Practitioners and Patients and contains both a **Shared care agreement** and a patient **letter of consent** for the initiation of hormones. It is imperative that patients who take the preparations, as listed, do so under medical supervision, and are monitored as recommended.

Please ensure that the latest updates on the medications and interactions, as listed, are obtained from the BNF.

LETTER FROM LEAD CLINICIAN
and
CONSULTANT ENDOCRINOLOGIST

Dear Colleague

We have created this Shared Care protocol in order to ensure that patients who attend the Charing Cross Gender Identity Clinic receive a partnership of care from both their Gender Clinicians and their General Practitioners.

The medicine recommended by the GIC is usually an oestrogen (e.g. estradiol valerate) to cause feminisation, and which will be continued indefinitely after surgery. In some cases additional or alternative medicines are used, as outlined in the shared care protocol. Sometimes there is a need for a GNRH analogue (e.g. decapeptyl or zoladex) to suppress testosterone prior to surgery.

In view of the fact that the patients will be having long-term maintenance treatment, it is in their best interests for their GP to prescribe and monitor their treatment, with support from our clinic as necessary. The standardised mortality rate for transsexuals is 1.0, demonstrating that longer term oestrogen therapy is not detrimental or harmful. That is to say, patients are no more likely to die as a result of taking this treatment than if the GP did not prescribe at all.

Although not all these medicines are licensed for the treatment of gender dysphoria (nor are they likely to be), they are medicines with which, in our experience, GPs will be familiar. The doses of oestrogen are often slightly higher than would usually be prescribed, as a born male tends to have a larger frame and needs a bigger dose to reach the normal physiological range for a woman.

There is a comprehensive programme for assessment and evaluation of patients referred to this clinic, into which GPs and any relevant secondary care clinicians are routinely copied. When all these assessments have been undertaken, the decision may be taken to recommend medication.

In the event that a written recommendation for hormone therapy is made, we would be grateful if arrangements can be made by the patient's GP to see the patient within 2 weeks in order to initiate the treatment.

We hope that this will give GPs enough information to feel confident to prescribe the maintenance medication for their patients as specified. If you have any questions, or would like more information, you are welcome to contact us.

Yours sincerely

Dr James Barrett
Lead Clinician, Gender Identity Clinic

Dr Leighton Seal
Consultant Endocrinologist

SUPPORTING CLINICAL INFORMATION

Indication(s):	Treatment of gender identity disorder following psychiatric/psychological assessment at Gender Identity Clinic.
Place in Therapy:	Hormonal therapy will usually be recommended after the initial assessment is complete. Commencement of hormonal therapy should generally be recommended following commencement of a change of social gender role. Clinical practice in the GIC follows a modified version of the WPATH vers.7 Standards of Care. The use of hormonal manipulation in the treatment of transsexual individuals is hampered by a lack of any randomised controlled trials to assist in our therapeutic decisions. There has however been a significant amount of experience in the treatment of this condition over the last 30 years, using several well-established hormonal protocols , and the totality of the available evidence is demonstrates that, for carefully selected patients, hormone therapy is a safe and effective means of alleviating the potentially debilitating condition of gender dysphoria.[1.2]
Dose & route of administration:	**<u>Oestrogen to cause feminisation:</u>** Estradiol valerate Initiated at a dose of 2mg o.d. orally and used in a range of 2-10mg daily, dose titrated three monthly to give a plasma estradiol level of 400-600pmol/l **Alternatives (if estradiol valerate not tolerated or inadequate levels achieved)**: Gels often achieve better levels than patches Topical oestrogen gel (Sandrena 1-5mg/day) Dose titrated three monthly to give a plasma estradiol level of 400-600pmol/l 4-6 hours after the gel is applied to the skin Estradiol patches 50 –200mcg twice a week dose titrated three monthly to give a plasma estradiol level of 400-600pmol/l 48 hours after the patch is applied to the skin POST surgery oestrogen dose stays the same **Third line**: Treatment rarely used in exceptional circumstances where levels have not been reached by alternatives above, or they have not been tolerated Ethinyloestradiol 50-150 micrograms daily orally. (Note Oestradiol levels cannot be used to monitor treatment) **<u>Gonadotrophin analogue to suppress testosterone (in addition to treatments to increase levels of oestradiol</u>):** If oral oestrogen at 4mg p.o. (or equivalent topical dose) does not suppress the plasma testosterone into the female range of 1-3 nmol/l Decapeptyl 11.25mg (IM)every 12 weeks is the most cost-effective option Goserelin (s.c) 10.8mg every 12 weeks **Alternatives:** Goserelin 3.75mg monthly subcutaneously

	Leuprorelin i.m. 11.25mg every 3 months

	Leuprorelin i.m. 3.75mg monthly To prevent the testosterone flare that can occur with GnRH analogues Cyproterone Acetate 100mg p.o. is co-administered for 2 weeks with the first implant but **not** thereafter. **Rarely:** **Antiandrogens may be used to counteract hirsutism.** Finasteride 5mg orally daily Cyproterone acetate 50mg-150mg orally daily
Duration of treatment	Life-Long Oestrogen Treatment GnRH analogues until gender reassignment surgery or orchidectomy
Criteria for stopping treatment	**Preoperative:** Significant side effects / lack of response at adequate doses / client self discharges from the GIC Review dosage if patient starts smoking **Postoperative**: Development of significant contraindication to oestrogen use
Monitoring Requirements before Starting Treatment:	**Gender Clinicians:** Psychological / psychiatric assessment of patient's suitability for treatment. Baseline blood screening. Measurement of LH, FSH, Testosterone, Estradiol, SHBG, Prolactin, Dihydrotestosterone, PSA, Weight/height/BMI, Blood pressure, Lipid profile, LFTs, Glucose, and renal function if indicated
Monitoring requirements once stable, including frequency:	**Gender Clinicians:** To advise GP on dose alterations required based on hormone and other monitoring information provided. **GP:** Measure the following every 3–6 months initially, annually thereafter: Testosterone levels until stable (range 0-3 nmol/l) Estradiol blood level (if taking estrogen valerate) (range 400-600pmol/l) LFTs, Blood pressure, prolactin, lipids, glucose, Weight/height/BMI
Follow up arrangements	**Gender Clinicians:** The Gender specialist nurse will provide training, support and advice for General Practitioners, Community Pharmacists, District Nurses on request. Patients will be reviewed by the GIC at regular intervals. **GP:** The primary care team will be responsible for the ongoing prescribing of oestrogens and anti-androgens and will continue to act as the primary contact for general healthcare. To refer to specialist team if any significant developments or deterioration occur, such as occurrence of side-effects, worsening of symptoms or complications of feminising hormone therapy.

Prescribing Responsibilities: As above	**Gender Identity Clinic:** The specialist team will take responsibility for the recommendation of treatment, counselling about risks and benefits of therapy and ongoing responsibility for recommending alterations to therapy until patient is stabilised

	• To oversee the whole programme of assessment and treatment, including dose adjustment as necessary to reach a maintenance level • To liaise with the GP on arrangements for stopping medication prior to genital reconstructive surgery, and restarting it afterwards To advise GP on any problems arising from this treatment which may need a dose adjustment or a change in medication **GP:** The GP will take on prescribing responsibility. Further details are outlined in the Shared Care Prescribing Agreement.
Other	The safety monitoring for this ongoing treatment has been out lined. This monitoring is designed to detect the major side effects of hormonal treatment. The risks of oestrogen exposure appear to be related to the duration of oestrogen treatment in genetic females. For this reason the long term monitoring of transsexual individuals should include health screening for breast cancer and monitoring of bone health in any individuals who have had a significant break from sex steroid treatment (>6 months). **Thromboembolic disease** The incidence of deep venous thrombosis (DVT) in transsexual patients is approximately 2.6% (80% of reported cases are in the first 2 years of treatment but no increased risk with lifelong treatment); however in this young population this represents a risk that is 20 times that of the untreated population. The majority of these incidents occur during the first 2 years of treatment. There is however an ongoing risk of 0.4% per year which continues[3]. The type of estrogen may be important. It has been demonstrated that ethinylestradiol alters the levels of plasma protein S, C and prothombin, which results in a procoagulant haemostatic profile in transsexual subjects[4]. In our own clinic we have moved away from using ethinylestradiol to estrogen valerate, however we have demonstrated a **DVT risk of 0.4% over 5 years in our patients**. **Breast cancer** The incidence of breast cancer with standard HRT in genetic females is estimated at an excess of 3.2/1000 aged 50–59 years and 4/1000 aged 60–69.[5] This is based on large population-based studies. We know from both the Heart and Estrogen/Progestin Replacement Study (HERS) [6]and Women's Health Initiative trial [;7] that the inclusion of progesterone in the HRT regimen increases this risk. There are no similar studies available in the transsexual population. There have only been four case reports of breast tumours occurring in treated transsexual patients, suggesting that **the risk of breast cancer secondary to feminising hormone therapy is very low**. **Hyperprolactinaemia** The lactotroph is sensitive to the ambient oestrogen levels in the serum. Oestrogen not only causes increased prolactin release from these cells, but also causes proliferation of them which can result in hyperprolactinaemia and pituitary hypertrophy. The incidence of significant hyperprolactinaemia has been reported to be up to 15%[8]. There have only been two case reports of prolactinomas in tranwomen and none have needed withdrawal of oestrogen treatment [9;10]. **Abnormal liver function** Abnormalities of liver function are, rarely, associated with the use of oestrogen therapy. The risk of abnormal liver function tests is approximately 3% in transwomen
	[3;8]. In half of these, the abnormalities persist for more than 3 months. However the increases are mild and only rarely require discontinuation of treatment **Prostate cancer** Prostate cancer has only been reported in two transgendered women in the world

	literature despite many years of data collected about these treatments [11;12]. As this is such a common malignancy the male population with an incidence of up to 50% by the eight decade, this suggested that the incidence of prostate cancer is reduced in transwomen compared with the natal male population. **Fertility** Oestrogen therapy leads to a suppression of gonadotrophin production and subsequent reduction in spermatogenesis. Patients should be counselled that treatment will reduce their fertility, and offered the chance of sperm storage if desired. **Myocardial Infarction**. The rate of myocardial infarction in the transfemale population is reduced by two thirds compared to a natal male population. **Cerebrovascular Disease** There does not appear to be an increased risk of stroke in the transfemale population[3]. To attempt to minimise the cumulative exposure to oestrogen it is advisable to use the lowest oestrogen dose tolerated by the patient and when a preparation that can be monitored is used use plasma levels of oestrogen to guide replacement therapy. Gonadotrophin level measurements are unhelpful. For the same reason GnRH analogues are used preoperatively to reduce the dose of oestrogen used. In this situation these medicines are extremely effective and safe as the majority of the side effects of GnRH analogues ie hot flushes depression and oesteoporosis do not occur as the client is co administered oestrogen. When the patient reaches 40years old then consideration of transdermal oestrogen preparation has been recommended by one group, in our practice however there does not appear to be an increase risk of thromboembolic events after age possibly reflecting the fact that we insist on patients stopping smoking which is not the case in the Liège series. When the individual reaches 55 years old then the discontinuation of HRT should be discussed. It is known that prolonged HRT use beyond 5 years after the menopause is associated with an increased risk of breast cancer in born females. Although this is the best evidence available on the long term effects of oestrogen therapy we do know that breast cancer is rare in transwomen with only 4 cases in the world literature. Which means that oestrogen use beyond 55 years old in Transwomen appears safe from the point of view of breast health The current data suggest that long-term treatment with oestrogen in male to female transitioners is associated with a slight increase in the standard mortality ratio. The increase in mortality appears to be associated with an increase in the risk of suicide in vulnerable individuals [HR 5.7[14] 19 [15] and also an increase in cardiovascular deaths RR1.46[14] 2.5[15]]. The increase in suicide deaths appears to be historical when comparing the cohort treated in 1972-180 vs those treated 1983-2010, this may reflect improvements in the availability and quality of care or alternative improvement in the status of transpeople in society leading to a reduction in their psychological stress but it is important that the psychological health of people treated for gender dysphoria should be assessed. The increase in vascular disease however appears to be associated with the use of Ethinyloestradiol but not other oestrogen types and so this oestrogen type should be avoided[15]. Breast cancer is extremely rare in Transwomen and equates to the background breast cancer risk in males, therefore hormone treatment can continue life-long.
Information provided	Patients are given a copy of the Clinic's Management Booklet which is also available for GPs www.wlmht.nhs.uk/gi/gender-identity-clinic . It is based on The Practical Management of Hormonal Treatment in Adults with Gender Dysphoria[13]**.**

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Evidence Base for treatment and Key references:	(1) Gooren, L. J., van de Wall, H. A. D. (2007). Hormone treatment of adult and juvenile transsexual patients. In R. Ettner., S. Monstrey and A. E. Tyler (Eds.), Principles of Transgender Medicine and Surgery (pp 73-88). New York: The Haworth Press. (2) Seal, L.J. The practical management of hormonal treatment in adults with gender dysphoria. In: J Barrett, editor. Transsexual and Other Disorders of Gender Identity: a practical guide to management. Oxford: Radcliffe; 2007. 157-190. (3) van Kesteren P.J., Asscheman H., Megens J.A., Gooren L.J. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997; 47(3):337-342. (4) Toorians A.W., Thomassen M.C., Zweegman S., Magdeleyns E.J., Tans G., Gooren L.J., et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 2003; 88(12):5723-5729. (5) Beral V., Banks E., Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet 2002; 360(9337):942-944. (6) Hulley S., Grady D., Bush T., Furberg C., Herrington D., Riggs B., et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280(7):605-613. (7) Rossouw J.E., Anderson G.L., Prentice R.L., LaCroix A.Z., Kooperberg C., Stefanick M.L., et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3):321-333. (8) Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. Arch Sex Behav 1998; 27(2):209-226. (9) Gooren L.J., Assies J., Asscheman H., de Slegte R., van Kessel H. Estrogen-induced prolactinoma in a man. J Clin Endocrinol Metab 1988; 66(2):444-446. (10) Serri O., Noiseux D., Robert F., Hardy J. Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. J Clin Endocrinol Metab 1996; 81(9):3177-3179. (11) Thurston A.V. Carcinoma of the prostate in a transsexual. Br J Urol 1994; 73(2):217. (12) Goodwin W.E., Cummings R.H. Squamous metaplasia of the verumontanum with obstruction due to hypertrophy: long-term effects of estrogen on the prostate in an aging male-to-female transsexual. J Urol 1984; 131(3):553-554. (13) Barrett, J. Transsexual and other disorders of Gender Identity a practical guided to management. 2007 Oxford Press (14) Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L V Johansson, Niklas Lanstrom Mikael Landen Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011 22;6(2):

(15) Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones Eur J Endocrinol. 2011 Apr;164(4):635-42

NB: for full details of adverse effects and drug interactions refer to latest Summary of Product Characteristics emc.medicines.org

SHARED CARE PRESCRIBING AGREEMENT

(Appendix ia)

1. CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- The GP will commence prescribing when the clinicians from the GIC judge the patient's condition as both medically, and psychologically, stable or predictable.

2. AREAS OF RESPONSIBILITY

Specialist Gender Identity Clinic Team/Consultant Responsibilities

- Establish or confirm diagnosis and assess patient suitability for treatment
- Baseline monitoring of bloods by Consultant Endocrinologist:
- Discuss treatment with patient and ensure they have a clear understanding of benefits and side-effects of treatment, including dose adjustments and how to report any unexpected symptoms The specialist team provides the patient with information and advice, supported by written information as required.
- Obtain signed consent for hormonal treatment
- Send a signed shared care guideline with patient details completed together with relevant clinical information to GP for consideration of shared care request
- Monitor treatment according to clinical guidance and advise patient and GP on dose titration of medicines.

Ongoing Care Arrangements: Specialist team to

- Write to GP following clinic contacts
- Inform GP of abnormal monitoring results and any recommended changes in therapy prescribed by the GP, including the need to discontinue if appropriate
- Evaluate adverse events reported by GP or patient and communicate outcome to GP
- Make arrangements for ongoing monitoring and follow up accordingly to shared care guidelines including continued need for therapy.

Consultant/Gender specialist Nurse:
The Gender specialist nurse will provide training, support and advice for General Practitioners, Community Pharmacists, District Nurses, on request.

GP RESPONSIBILITIES

- Prescribe treatment as advised by the Specialist Team and previously discussed with the patient
- Monitor general health of patient and check for adverse effects as appropriate
- Inform specialist consultant of suspected adverse effects
- Stop treatment on advice of Gender Clinician or immediately if urgent need arises
- Check compatibility interactions when prescribing new or stopping existing medication
- Carry out monitoring and follow up according to shared care guideline
- Discuss any abnormal results with Gender Clinician and agree any action required

PATIENT'S RESPONSIBILITIES

- Keep a copy of information provided by Gender Identity Clinic, including consent to treatment, to take along when seeing GP
- Take medicines as agreed and prescribed
- Report any adverse effects to GP or hospital doctor at the earliest opportunity
- Ensure that you attend for tests as requested by your Gender Clinician or GP
- Do not share medicines
- Attend appointments for review as necessary
- Always inform the Specialist team and GP of all medication being taken, whether prescribed or bought

SHARED CARE PRESCRIBING AGREEMENT

(Appendix ib)

GENDER CLINICIAN

I confirm that I have assessed the patient today,

Attach patient addressograph or
Insert patient details
Patient name
Patient ID
Date of Birth

and it is my clinical recommendation that the following treatment is prescribed:

Furthermore, the "Areas of Responsibility" have been covered and I agree to the "ongoing care arrangements".

Signature:

Print Name:

Date:

PATIENT CONSENT LETTER FOR INITIATION OF HORMONES

(Appendix ii)

I, …… …… (print name) met with Dr

…… today, ……..(date)

I can confirm that we have discussed the potential effects, side effects and expectations of Hormone therapy. In addition we have also discussed the potential effects that this therapy will likely have on my fertility.

Furthermore I confirm that I will adhere to the "Patient Responsibilities" as outlined in the shared care agreement.

…… (signature)