Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Policy Review: Leuprolide (Lupron®)

Reason for Review: Puberty suppression in adolescents with gender dysphoria is now a funded condition on the Oregon Health Plan (OHP) Prioritized List. The goal of this review is to summarize current evidence of leuprolide for puberty suppression in adolescents with Gender Dysphoria to inform policy options.

Key Questions:

1) What are the current recommendations for using puberty suppression agents to treat gender dysphoria?
2) What is the evidence of efficacy and safety of leuprolide when used to suppress puberty?

Conclusions:

- Gender dysphoria falls on line 412 on the OHP List Prioritized Services and treatment is currently funded.[1]
- GnRH analogues are recommended to suppress puberty in adolescents with gender dysphoria. Therapy should be initiated at the first signs of physical changes of puberty, confirmed by pubertal levels of hormone, but no earlier than Tanner stages 2-3.

Recommendations:

- GnRH analogues appear to be safe and effective in reversibly suppressing puberty.
- Modify PA criteria presented at the end of this review to allow approval of leuprolide in adolescents with documented gender dysphoria at the beginning of puberty, confirmed by pubertal levels of hormone but no earlier than Tanner stages 2-3.

Background:

Gender dysphoria or gender identity disorder (GID) is recognized in the Diagnostic and Statistical Manual of Mental Disorders. Individuals with GID have a persistent and profound discomfort with their biological sex and a strong identification with the gender of the opposite sex. The diagnosis is made when this is manifested by unrelenting cross-gender thought and behavior. Children as young as 3 years of age may experience GID and cross-gender behavior. However, only 16% of children will continue to have persistent gender dysphoria into adolescence and adulthood. [2] Childhood GID without treatment leads to a minority of these children identifying as transsexual or transgender in adulthood; the majority will become comfortable with their natural gender over time.[3] GID that persists into adolescence is more likely to persist into adulthood.[3]

Children do not have the legal ability to provide informed consent and must rely on parents or legal guardians to make treatment decisions on their behalf. There is a lack of randomized controlled studies regarding treatment of GID in children and adolescence, so treatment decisions must rely on expert opinion. It is not currently possible to differentiate between preadolescent children in whom GID will persist and those who it will not.[3] Indeed, no long-term data has demonstrated a statistically significant effect on gender identity in adulthood.[3]

Author: Amanda Meeker

Date: May 2015

Ongoing psychological support of children and adolescents with GID should be offered. In addition, peripubertal adolescents with persistent GID may be treated with a gonadotropin-releasing hormone (GnRH) analogue to suppress puberty once it has commenced, followed later by cross-hormone therapy to promote physical development in the affirmed gender. This is done to reduce the psychological distress associated with unwanted pubertal development which can result in hormonal self-medication, self-harm or suicide. Current evidence suggests that hormone treatment to suspend the development of puberty is associated with good outcomes and a low level of regret.[2] Giving adolescents the time for continued psychological support during the process of either resolving GID or coping with its persistence may help adjustment in adulthood.[4]

In January 2015, the Oregon Health Evidence Review Committee (HERC) published a new OHP Prioritized List, with gender dysphoria placed on Line 412 (above the Funding Line). Guideline Note 127 provides guidance on the treatment of Gender Dysphoria. Hormone treatment is included on this line for the express purpose of delaying the onset of puberty and/or continued pubertal development with GnRH analogues for gender questioning children and adults. The guideline note states that therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of hormone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression.

Tanner proposed a scale to describe the onset and progression of pubertal changes that is uniformly accepted. Children are rated on a scale of 1-5 with 1 being preadolescent and 5 being fully developed. Males are rated for genital development and pubic hair growth. Girls are rated for breast development and pubic hair growth. Stage 2 is where sparse, long, pigmented, downy hair which is straight or only slightly curled appears, mainly along labia and at the base of the penis. [5] Stage 3 is where considerably darker, coarser, and curlier sexual hair appears, usually spread over the junction of the pubes. [5] GnRH analogues have been used to suppress puberty for treating central precocious puberty since the 1980s; however, the use of these agents to treat GID is relatively new.

Several preparations of GnRH are available, including leuprolide, goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas). Leuprolide is available as a daily subcutaneous injection, and a monthly and every 3 months IM depot injection. Histrelin and goserelin are available as implants. Triptorelin is available as an IM depot injection. Histrelin, goserelin and triptorelin are covered under the OHP medical benefit. GnRH analogues have demonstrated to be safe and effective in treating precocious puberty.[6–14] Administration of these agents results in initial stimulation of pituitary gonadotropin secretion, followed by complete but reversible suppression of the pituitary-gonadal axis and suppression of puberty. GnRH therapy does not appear to induce polycystic ovarian syndrome or have negative long-term repercussions on either bone mineral density or body composition.[15] Evidence is insufficient to identify agent-specific differences in outcomes, reproductive function, and health of offspring.[15]

Systematic Reviews:
None identified.

Guidelines:
The American Psychiatric Association released guidelines in 2012 on GID.[3] They make specific recommendations surrounding psychotherapeutic treatment of GID in childhood and adolescence. In cases where children's cross-gender identification is affirmed by mental health professionals and family members, children are supported in transitioning to a cross-gendered role with the option of endocrine treatment to suspend puberty in order to suppress the development of unwanted secondary sex characteristics. The guideline recommends that adolescents with GID have the option to suspend puberty medically in order to prevent or minimize development of unwanted secondary sex characteristics. Sexual reassignment surgery is not performed prior to the age of 18 years in the United States. There is insufficient evidence to support the development of a practice guideline for treatment of GID in either childhood or adolescence.

The Endocrine Society guidelines on the endocrine treatment of transsexual persons (2009)[16] recommends that adolescents who fulfill eligibility and readiness criteria for gender reassignment undergo treatment to suppress puberty in those who first exhibit physical changes of puberty, confirmed by hormone levels, but no earlier than Tanner stages 2-3. They recommend GnRH analogs be used to suppress puberty and hormones of cross-sex gender be used starting at age 16 years for pubertal development of the desired opposite sex. They also recommend that hormone-treated adolescents be referred for gender reassignment surgery when the real-life experience has resulted in a satisfactory social role change, the individual is satisfied with the hormonal effects, and the individual desires definitive surgical changes. They suggest deferring surgery until the individual is 18 years old.

References:

1. PRIORITIZED LIST OF HEALTH SERVICES. Oregon Health Authority. 201AD. http://www.oregon.gov/oha/herc/PrioritizedList/1-1-2015%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed April 15, 2015.
2. Steensma, T. D., Biemond, R., de Boer, F. & Cohen-Kettenis, P. T. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry* **16,** 499–516 (2011).
3. Byne, W. *et al.* Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* **41,** 759–796 (2012).
4. Hewitt, J. K. *et al.* Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med. J. Aust.* **196,** (2012).
5. Feingold, David. 'Pediatric Endocrinology' In Atlas of Pediatric Physical Diagnosis, Second Edition, Philadelphia. W.B. Saunders, 1992, 9.16-19.
6. Tanaka, T. *et al.* Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J. Clin. Endocrinol. Metab.* **90,** 1371–1376 (2005).
7. Walvoord, E. C. & Pescovitz, O. H. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* **104,** 1010–1014 (1999).
8. Pasquino, A. M. *et al.* Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. *J. Clin. Endocrinol. Metab.* **84,** 449–452 (1999).
9. Rosenfield, R. L. Selection of children with precocious puberty for treatment with gonadotropin releasing hormone analogs. *J. Pediatr.* **124,** 989–991 (1994).
10. Comite, F. *et al.* Luteinizing hormone releasing hormone analogue therapy for central precocious puberty. Long-term effect on somatic growth, bone maturation, and predicted height. *JAMA* **255,** 2613–2616 (1986).
11. Crowley, W. F. *et al.* Therapeutic use of pituitary desensitization with a long-acting lhrh agonist: a potential new treatment for idiopathic precocious puberty. *J. Clin. Endocrinol. Metab.* **52,** 370–372 (1981).
12. Comite, F. *et al.* Short-term treatment of idiopathic precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. A preliminary report. *N. Engl. J. Med.* **305,** 1546–1550 (1981).
13. Klein, K. O., Barnes, K. M., Jones, J. V., Feuillan, P. P. & Cutler, G. B. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J. Clin. Endocrinol. Metab.* **86,** 4711–4716 (2001).
14. Lazar, L., Pertzelan, A., Weintrob, N., Phillip, M. & Kauli, R. Sexual precocity in boys: accelerated versus slowly progressive puberty gonadotropin-suppressive therapy and final height. *J. Clin. Endocrinol. Metab.* **86,** 4127–4132 (2001).
15. Thornton, P. *et al.* Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev* **11,** 306–317 (2014).
16. Hembree, W. C. *et al.* Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **94,** 3132–3154 (2009).

Leuprolide Hormone Therapy

Goal:

- Approve for OHP-funded conditions in children and adolescents up to 16 years of age.

Length of Authorization:

Precocious puberty: through age 12 years in females, age 13 years in males.
Gender dysphoria: through age 16 years.

Requires PA:

- Leuprolide in children and adolescents through 16 years of age.

Approval Criteria		
1. What diagnosis is being treated and what is the age and gender of the patient?	Record ICD9 code and age/gender.	
2. Is the patient female and aged <13 years or male and aged <14 years?	Yes: Go to #3	No: Go to #4
3. Is the diagnosis central precocious puberty (CPP)? [precocious sexual development and puberty, ICD-9 259.1] • Note CPP is often associated with hydrocephalus, cranial irradiation, Silver-Russell syndrome, hypothalamic tumor, or hamartoma. • All above diagnoses and conditions are rare in children and adolescents.	Yes: Approve through: • Age 12 years for females • Age 13 years for males	No: Go to #4
4. Is the diagnosis gender dysphoria (ICD-9 302.6, 302.85)?	Yes: Go to #5	No: Pass to RPH; deny for medical appropriateness

Approval Criteria		
5. Does the request meet all of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience treating gender dysphoria? • At least 6 months of counseling and psychometric testing for gender dysphoria? • Prescriber is trained in puberty suppression using a gonadotropin releasing hormone agonist • Confirmation of puberty (physical changes and hormone levels) no earlier than Tanner Stages 2-3 (bilateral breast budding or doubling to tripling testicular volume)	Yes: Approve through • Age 16 years	No: Pass to RPH; deny for medical appropriateness
RPH only: All other indications need to be evaluated as to whether it is an OHP-funded condition. Refer unique situations to Medical Director of DMAP.		

P&T / DUR Action: *5/15 (AM); 9/07*
Revision(s): *5/15 (AM)*
Initiated: *Via Retro DUR 11/07, 7/1/09 via PA*