INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Male Hypogonadism***
-November 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a therapeutic overview of male hypogonadism at the Fall 2022 NPTC meeting. Following clinical review and analysis, the NPTC **made no modifications** to the National Core Formulary (NCF) as testosterone, any formulation, is already listed on the NCF.

Male hypogonadism (MH) refers to a decrease in one or both of the major functions of the male reproductive organs, the testes: sperm production and or testosterone production. Primary hypogonadism refers to the failure of the testes while secondary hypogonadism refers to failure of the central hypothalamic/pituitary axis. Signs and symptoms of MH depend on the organ of failure as well as timing relative to the onset of puberty. Causes of primary hypogonadism include Klinefelter syndrome (most common congenital form), testicular torsion (most common in men ages 1-25 years) and viral orchitis which can occur in up to 25% of post pubertal males with mumps.[1] Secondary MH has a wide variety of causes, including Kallmann syndrome, a congenital condition affecting 1-10 in every 100,000 live births.[1] While population screening for MH is not recommended, patients whose prevalence of MH is higher should be evaluated. These groups include but are not limited to: those with sexual dysfunction concerns (low libido), low energy or mood, infertility, gynecomastia, diseases of the sellar region, medications that affect testosterone production, prolonged high-dose glucocorticoids, sustained-release opioids, HIV-associated weight loss, end-stage kidney disease (on maintenance hemodialysis), moderate to severe COPD, osteoporosis or low-trauma fracture especially in youth, and type 2 diabetes mellitus.[2] Patients who warrant testing should have an early morning total testosterone level drawn between 0800 and 1000. If the level is below 280 ng/dL on two separate mornings, the diagnosis of MH is likely. At that point, measurement of LH and FSH should be measured to determine primary versus secondary disease. Early morning testosterone can vary up to 21% daily and concentrations of sex hormone binding globulin may affect measurement highlighting the importance of repeated testing to verify low values for the diagnosis. A study examining U.S. claims data demonstrated that only 74.7% of men $\geq$ 40 years had testosterone levels measured prior to prescription of testosterone replacement therapy.[3] The importance of correct diagnosis in addition to appropriate treatment cannot be underemphasized.

Discussion:

A drug evaluation for the following drugs was provided: testosterone (all formulations), gonadotrophin-releasing hormones (GnRH), aromatase inhibitors (AIs, specifically anastrazole), and clomiphene citrate. Testosterone replacement therapy (TRT) is the mainstay of treatment for both primary and secondary MH, however there are specific clinical situations in which an alternative non-testosterone therapy might be indicated. These include but are not limited to infertility with active conception attempts, fertility preservation (without active conception attempts), high risk of prostate cancer, history of breast cancer, polycythemia, thrombophilia, or severe cardiovascular disease.[4] Specialist consultation is recommended for treatment of MH in these clinical situations. Generally, data for use of GnRH in treatment of MH is lacking, however a small retrospective trial showed improvement in symptoms, normalization of testosterone levels, and no discontinuations for serious adverse effects.[5] The role of AIs is also uncertain, the mechanism of which is to prevent conversion of androgens to estrogens. Data on AIs is limited however; a meta-analysis of all AI's for treatment of MH showed an overall mean increase of testosterone level 48.5% and improvement in T:E2 ratios, however data were very heterogeneous and no conclusive recommendations were made.[4] Clomiphene citrate (CC) is a selective estrogen receptor modulator with the most data for use in MH. In a meta-analysis, CC showed normalization of testosterone, LH and FSH levels as well as significant improvement in symptoms of MH as measured by the ADAM scale.[6] Several trials included in the meta-analysis examined reduction in body mass index (BMI), however only one showed significant reduction in BMI and improvement in lipid profile with CC treatment.[6] Lastly, safety analysis indicated no increased prostate-specific antigen levels, changes in bone density, or elevations in hematocrit in treatment with CC.[6] Thus, alternatives to testosterone may be considered with endocrinology consultation in limited clinical settings.

Exogenous testosterone comes in many formulations; thus, no specific formulation was examined for this report, which focuses instead on the conditions for which TRT may be used. Data for use of TRT in post-pubertal men not desiring fertility who have symptomatic MH is excellent. Long standing data supporting TRT use for symptomatic disease demonstrates good efficacy with all FDA approved formulations.[7] TRT also improved lumbar bone mineral density significantly.[8] Observational studies have noted reduction in metabolic syndrome with TRT, thus the TIMES2 trial published in 2011 sought to understand if TRT might be efficacious treatment for Type 2 Diabetes Mellitus (T2DM) in patients with MH. While it appeared that TRT improves insulin resistance, no significant differences in A1C were shown.[9] In 2022, a meta-analysis examining metabolic effects of TRT on patients with T2DM demonstrated possible trends towards improvement of lipid profiles without any statistically significant outcomes as well as a highly suspicious improvement in all-cause mortality demonstrated by a singular study without transparent methods[10].

Age-related decline in testosterone, also called late-onset hypogonadism (LOH) is a condition of men ≥65 years of age with the presence of at least 3 sexual symptoms and total testosterone less than 320 ng/dL and free testosterone less than 64 pg/mL.[11] While there is an expected decline in testosterone levels as men age, recent studies suggest an association between low testosterone and poor sleep quality, insulin resistance, diabetes, obesity, metabolic syndrome, and unfavorable cardiovascular (CV) risk profile.[11] Severe LOH has been related to a 5.5-fold increase in all-cause mortality irrespective of symptoms and 3 times higher in those with sexual symptoms.[11] RCTs have failed to demonstrate improvement in clinical outcomes (BMD and cognitive function) and had negative impact on lipids and metabolic syndrome.

The safety of TRT was brought into question in 2010, where a study of 209 men (mean age 74 years with high prevalence of HTN, DM, HLD, and obesity) with hypogonadism were randomized to receive TRT versus placebo, however the study was stopped early due to significantly higher rates of CV events in the testosterone group.[12] Shortly thereafter, two observational studies (*Finkle et al. PLoS One, 2014 and Vigen et al. JAMA, 2013*) both demonstrated that use of testosterone in men with MH increased the risk of CV adverse outcomes and death. Given the importance of TRT in treatment for MH, many trials in the last decade have examined the question of CV safety. Most recently, a meta-analysis of TRT versus placebo for long term treatment of MH showed no significant difference in all-cause mortality (82% of studies) between TRT and placebo (OR 0.46; 95% CI: 0.10 to 1.24, p=0.13) and no significant difference in CV events (OR 1.07; 95% CI: 0.81 to 1.42, p=0.62).[13] Post-hoc analysis suggested that CV risk favored TRT when free testosterone was between 180-220 pmol/L (above the upper limit of normal).[13] Safety of TRT use in patients with a history of prostate cancer requires more trials. It is recommended to make patient-centered, informed decisions about risk and monitoring.[14]

Professional guidelines from the European Society of Endocrinology/European Academy of Andrology, the American Urologic Association, the Endocrine Society of Australia, the American Association of Clinical Endocrinologists/American College of Endocrinology, and the Society for Endocrinology were reviewed. Recommendations to appropriately diagnose MH with repeated low testosterone levels and to treat symptomatic MH with TRT (with appropriate counselling for fertility preservation or for patients who have risk factors such as cardiovascular disease, hormone sensitive cancers, or increased risk of venous thromboembolism) are consistent throughout the guidelines[15].

Findings:

Male hypogonadism is a common concern among men with symptoms of fatigue, sexual dysfunction and low energy. The diagnosis of MH is central to utility of treatment and must be demonstrated with two measurements of early morning testosterone that are below the normal range. In patients diagnosed with MH who are trying to conceive, are of child bearing age, or have other risk factors, may be referred to endocrinology for recommendation of alternative non-testosterone therapies for MH. For patients with MH who are interested in treatment and whom are appropriate for TRT, many formulations exist and a patient-centered discussion about administration should be pursued to determine the best treatment method for individuals. Lastly, the safety of TRT is acceptable but should continue to be a part of patient-centered counseling prior to initiation of treatment.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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