



Sexual Medicine Society of North America (SMSNA)
Consensus Statement and White Paper¹ Executive Summary:
Adult Onset Hypogonadism (AOH)

In August 2015, a colloquium of experts commissioned by the Sexual Medicine Society of North America (SMSNA) convened in Washington, DC, to discuss the common clinical scenario of men who present with low testosterone (T) and associated signs and symptoms accompanied by low or normal gonadotropin levels. **This syndrome is not classical primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism because low T may be the result of both testicular and pituitary-hypothalamic failure. The Panel designated this syndrome Adult Onset Hypogonadism (AOH) because it occurs commonly in men of middle-age and older.**

The Panel consisted of 17 experts in men's health, sexual medicine, urology, endocrinology, and methodology. All colloquium participants declared potential conflicts of interest; participants were both members and non-members in the SMSNA. The Panel deliberated regarding a rigorous diagnostic process to document signs and symptoms of AOH, the rationale for treatment with T, and a monitoring protocol for T-treated patients.

The SMSNA recognizes that the evaluation and management of hypogonadal syndromes have been addressed in recent publications (i.e., the Endocrine Society, Bhasin et al., 2010; the American Urological Association, Paduch et al., 2013; the International Society for Sexual Medicine, Dean et al., 2015). **The primary purpose of this document is to support health care professionals in the development of a deeper understanding of AOH, particularly in how it differs from classical primary and secondary hypogonadism, and to provide a conceptual framework to guide its diagnosis, treatment, and follow-up.**

Consensus statement: AOH is a measurable syndrome characterized by low T, associated symptoms, and low or normal gonadotropin levels. Men with AOH who are candidates for treatment with T should be counseled regarding the benefits and risks of treatment. Patients who are treated should be monitored regularly.

Section 1: Conceptualization of AOH.

AOH is a clinical and biochemical syndrome characterized by a deficiency of T with symptoms and signs that can be caused by testicular and/or hypothalamic-pituitary (HP) dysfunction; AOH is therefore clinically distinct from classical primary and secondary hypogonadism. This syndrome is characterized by T deficiency and the failure to mount an adequate compensatory pituitary response to low T levels; gonadotropin levels are low or in the normal range.



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AOH is well-illustrated by hypogonadal men in the European Male Ageing Study (EMAS) (Tajar et al., 2010; see Figure 1). Approximately 2.0% of men had primary hypogonadism (low T, high LH), 9.5% had “compensated” hypogonadism (normal T, high LH), and 11.8% of men were classified as having secondary hypogonadism with low T accompanied by low or normal LH – a presentation consistent with AOH.

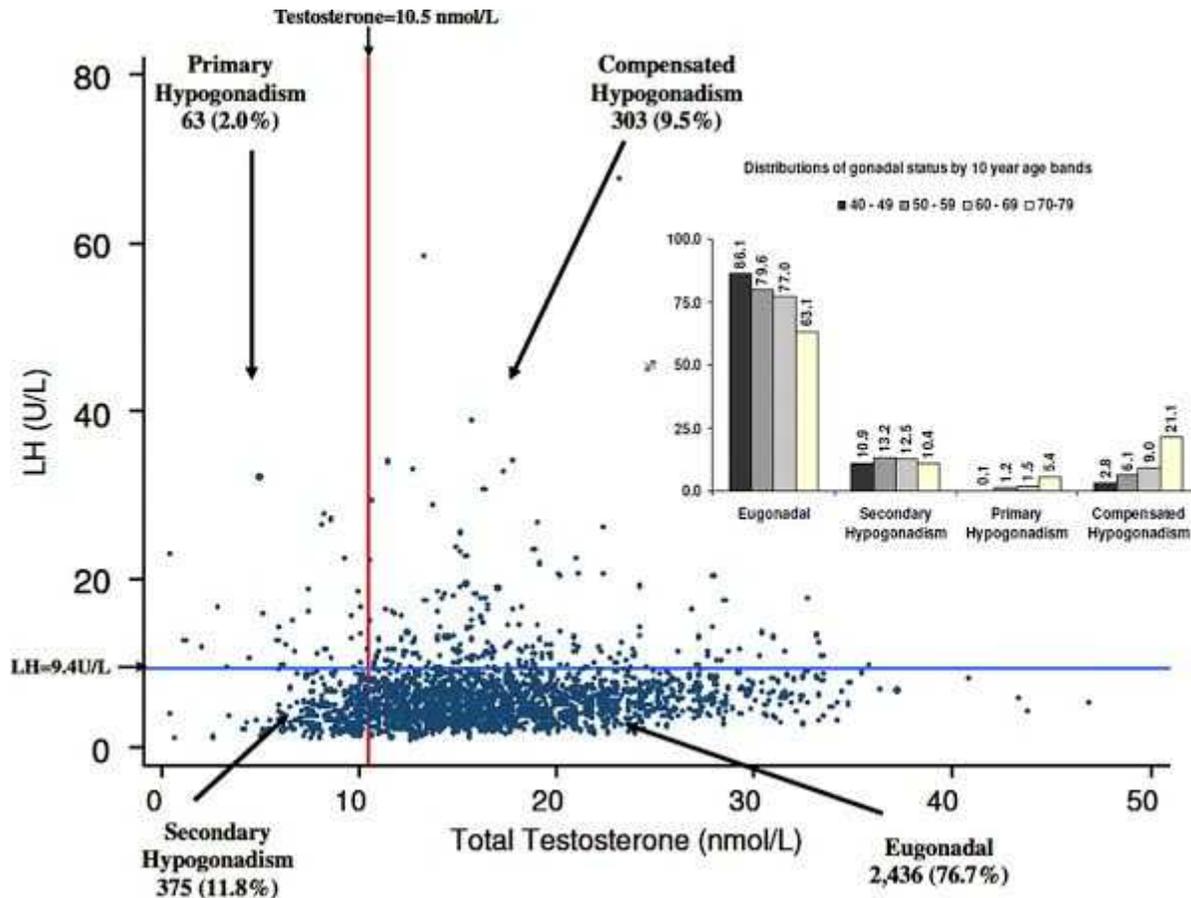


Figure 1. Subgroups of men by gonadal status and by decade of age from the European Male Ageing Study (EMAS) (Tajar et al., 2010).

In the EMAS study, the prevalence of hypogonadism was 13.8%; of these men, 85.5% were classified as having secondary hypogonadism (Tajar et al., 2010). Similar prevalences of secondary hypogonadism have been reported among men seeking care for sexual dysfunction (Guay et al., 2010; Maseroli et al., 2015).



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Importantly, among men with secondary hypogonadism in the EMAS sample, only 11% had a specific medical condition (e.g., genetics, surgery, radiotherapy, trauma) that could account for the hypogonadism; the etiology in the remaining 89% was unknown (Corona & Maggi, 2015). The term AOH could be applied to the overwhelming majority of these men, many of whom also had concomitant metabolic disease (i.e., obesity, type 2 diabetes, or metabolic syndrome).

Hypogonadism prevalence in general may increase with age (e.g., the Baltimore Longitudinal Study of Aging, BLSA, Harman et al., 2001). The prevalence may be higher among men 65 years of age although prevalence rates by decade up to age 84 have been reported as statistically indistinguishable (range 34% to 45.5%) (Mulligan et al., 2006). Patterns are similar when symptoms are considered. In the Massachusetts Male Aging Study (MMAS), symptomatic AD prevalence was similar for men aged 40 to 49 years (4.1%) and 50 to 59 years (4.5%) but was increased among men aged 60 to 70 years (9.4%) (Araujo et al., 2004). In the Boston Area Community Health (BACH) study prevalence rates of symptomatic AD by decade among men aged 30 to 69 years ranged from 3.1% to 7.0% and were statistically indistinguishable; the prevalence rate for men aged 70 to 79 years, however, was 18.1% (Araujo et al., 2007). Some studies suggest that AOH, unlike overall hypogonadism, is less likely to be influenced by age. **In the EMAS study, the prevalence of men with primary hypogonadism increased significantly with age but not among men with low T and normal LH levels – men likely to have AOH (Tajar et al., 2010).**

Pathophysiology.

Among healthy aging men, hypothalamic-pituitary-gonadal function may be maintained (i.e., Nieschlag et al., 1982; Yeap et al., 2009; Sartorius et al., 2012). In a broader population of men, however, beginning at 20-30 years of age T levels decline by 0.3% to 1.4% per year (Wu et al., 2008). It is believed that declining T levels are partly the result of primary testis failure – the Leydig cells become less responsive to exogenous gonadotropin stimulation (Rubens et al., 1974) and the number of Leydig cells declines (Neaves et al., 1984).

The relationship between secondary hypogonadism and aging is complex. Production of GnRH decreases with age and GnRH/LH pulse amplitude diminishes (Araujo et al., 2011; Takahashi et al., 2005). In addition, androgen negative feedback suppression of LH secretion may be increased (Winters & Atkinson, 1997). Sex hormone binding globulin (SHBG) levels tend to rise in older men, causing free T levels to decline (Feldman et al., 2002). T levels are higher in the morning than in the evening and there is a dampening of this diurnal rhythm as men grow older (Zumoff et al., 1982).



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Section 2: AOH and Common Comorbidities

AOH more often occurs in men who have chronic disease states that are more common as men age, making it difficult to separate the influence of comorbidities from the influence of aging. High BMI, central adiposity, and the metabolic syndrome are associated with low serum total T and low free T levels (Wang et al., 2011; Allan & McLachlan, 2010; MacDonald et al., 2010; Brand et al., 2011; Laaksonen et al., 2004, 2005). Low total and free T levels are associated with an increased risk of developing metabolic syndrome, independent of age and obesity (Wang et al., 2011; Allan & McLachlan, 2010; MacDonald et al., 2010; Brand et al., 2011). In the EMAS study, BMI was significantly associated with risk for secondary hypogonadism and the risk for secondary hypogonadism increased as a man's number of comorbidities increased (Tajar et al., 2010).

Section 3: Clinical Signs and Symptoms of AOH

AOH is often overlooked because hypogonadal men ignore their symptoms (Dandona & Rosenberg, 2010). T influences all the steps of the male sexual response; sexual dysfunctions are a prominent symptom of AOH and are often the presenting symptom. These symptoms may include: hypoactive sexual desire (HSD), reduced nocturnal and morning erections, reduced sex-induced erections, delayed ejaculation and reduced semen volume (Buvat et al., 2013; Mulligan et al., 2006). The Endocrine Society and the American Association of Clinical Endocrinologists (AACE) suggest that physicians should measure the T levels of men with any of the symptoms and signs in Table 1.

Infertility
Osteoporosis, low trauma fracture
Type 2 diabetes
Glucocorticoids, ketoconazole, opioid or other medications that affect T metabolism or production
Moderate to severe COPD
Sellar mass, radiation to the sellar region, or other diseases of the sellar region
End-stage renal disease, maintenance hemodialysis
HIV-associated weight loss

Section 4: Diagnosis and Monitoring

Men presenting with possible signs and symptoms of AOH must be systematically evaluated, accurately diagnosed, carefully counseled regarding the risks and benefits of treatment, and followed regularly if T replacement is initiated. The process recommended by the panel is summarized in Figures 2 and 3.



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Risks and Safety of T. There are two challenges to understanding the risks of T replacement in appropriately selected men. The first challenge is the lack of definitive evidence derived from properly-designed prospective studies. The second challenge is the existence of mixed evidence that is not definitive from the literature that is available. In the absence of definitive evidence regarding risks, patients must be monitored regularly for adverse events.

Cardiovascular risks. Definitive evidence regarding the short- and long-term cardiovascular risks of T replacement is not yet available because the published prospective trials were not designed or powered to examine cardiovascular endpoints. The available trials and meta-analyses report mixed findings, with some finding no risks associated with T replacement and others reporting risks associated with T replacement. The need for definitive trials that can yield unambiguous findings is underscored by several recent publications using retrospective data that report possible risks of T replacement (i.e., Layton et al., 2015; Finkle et al., 2014; Vigen et al., 2013). **The clinical utility of these data is unclear because of the inherent limitations of these studies** (e.g., lack of assessment of whether men met criteria for T replacement, failure to compare event rates to those in non-T-using men, and statistical limitations). **Therefore, it is critically important that men administered T be monitored regularly.**

Prostate cancer risks. No appropriately designed and powered study has been conducted to assess prostate cancer-related risks of T replacement. The available evidence has yielded mixed findings although most studies have found no risk associated with T replacement (e.g., Hsing et al., 2001; EHPCCG, 2008; Calof et al., 2005). **Given the absence of definitive evidence, men administered T should be monitored regularly.**

Erythrocytosis. During TRT, levels of hemoglobin (Hb) and hematocrit (Hct) rise for the first 5-6 months, then tend to plateau (Swerdloff & Wang, 2003; Wang et al., 2004). Injectable T formulations are associated with the greatest treatment-induced increases in Hb and Hct (Dobs et al., 1999; Rhoden & Morgentaler, 2004; Vorkas et al., 2012; Jick & Hagberg 2013). Although it has been hypothesized that enhanced blood viscosity poses a threat for ischemic sequela, the direct relationship between TRT-induced erythrocytosis and subsequent risk for cardiovascular (CV) events has not been demonstrated through prospective randomized controlled trials (Schreijer et al., 2010; Braekkan et al., 2010; Vaya & Suescun 2013; De Stef et al., 2008; Glueck et al. 2014). **Therefore, in the absence of sufficient information regarding risk, men administered T should be monitored regularly.**



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Benign Prostatic Hypertrophy (BPH)/Lower Urinary Tract Symptoms (LUTS). The preponderance of evidence indicates that T replacement has no effect on BPH and LUTS symptoms or improves symptoms (Amano et al., 2010; Francomano et al., 2014; Haider et al., 2009; Kalinchenko et al., 2008; Karazindiyanogly & Cayan, 2008; Pearl et al., 2013; Shigehara et al., 2011).

Section 5: Conclusion

AOH is a diagnosable clinical syndrome in which men experience signs and symptoms associated with low T levels and low or normal gonadotropin levels. Its etiology appears to include failure at the testicular and hypothalamic-pituitary levels, making it distinct from classical primary and secondary hypogonadism. The AOH presentation is more common among men with prevalent comorbidities such as obesity, metabolic syndrome, and diabetes. AOH is a more accurate diagnosis for the group of adult men most frequently diagnosed with hypogonadism. Men with AOH who are candidates for treatment with T should be counseled regarding the risks and benefits of treatment. Men who are treated with T should be monitored regularly given that definitive evidence regarding potential short-term and long-term risks of T is not yet available.

FIGURE 2: Diagnosis

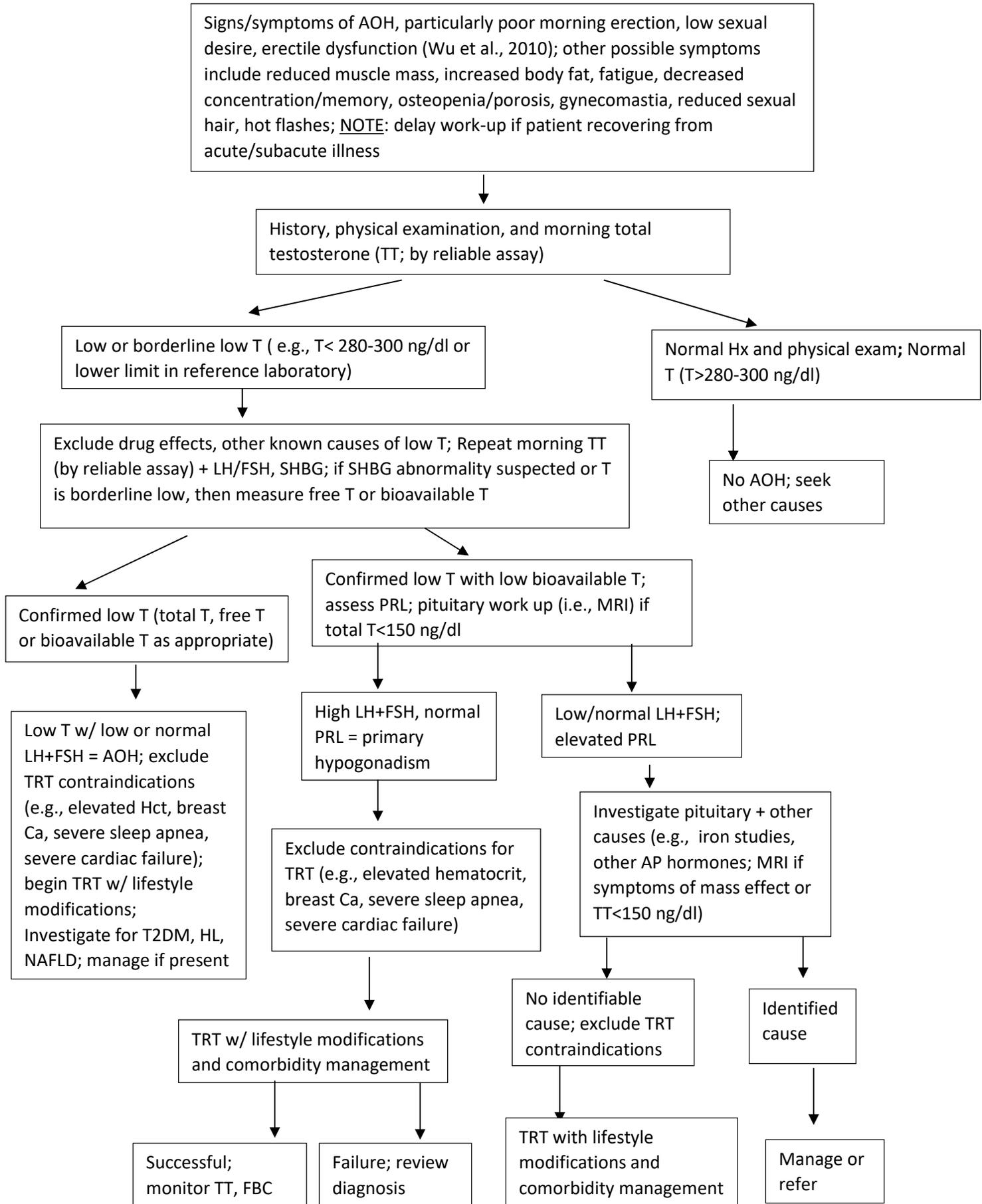
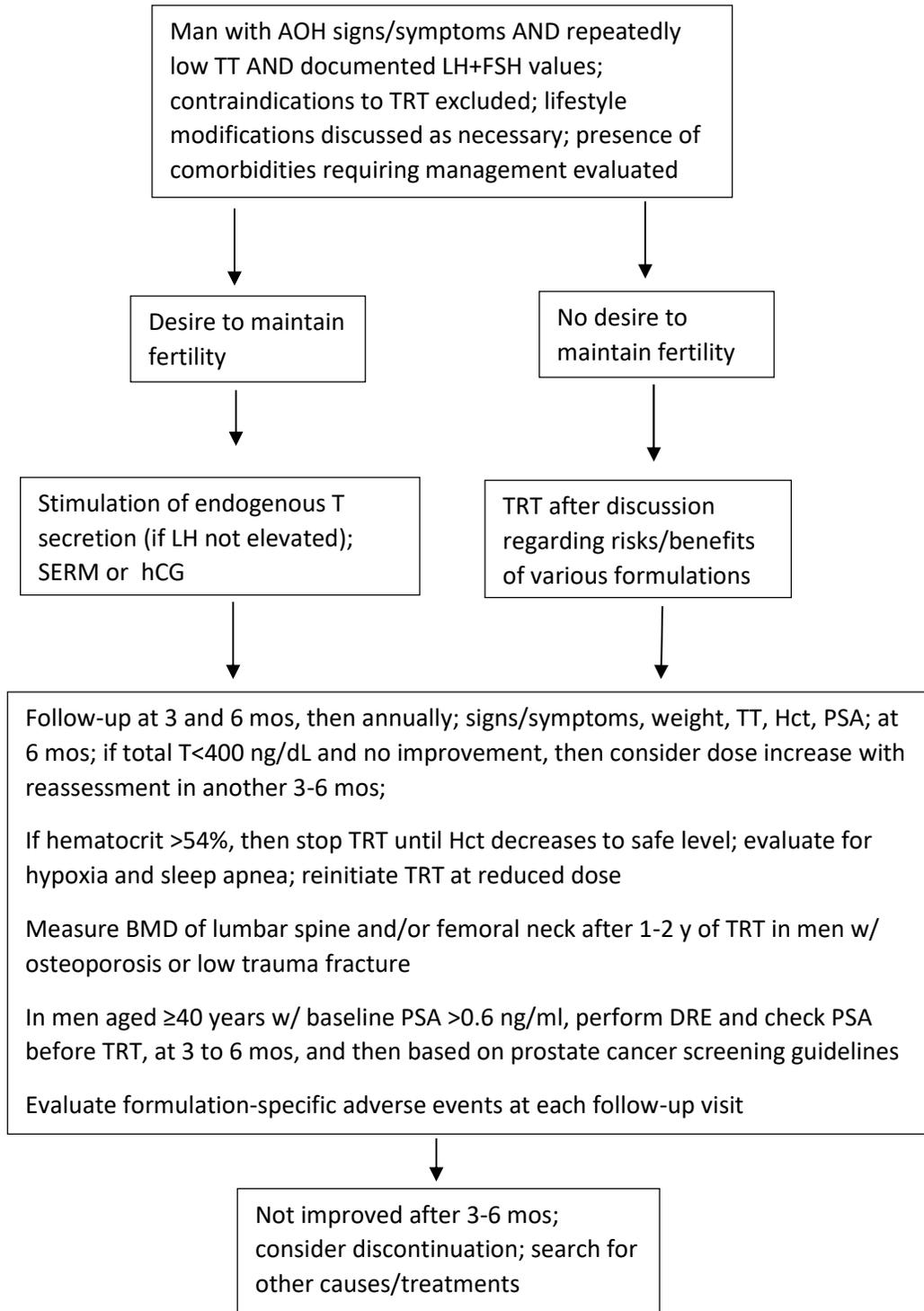


FIGURE 3: Treatment and Follow-Up

(adapted from Bhasin et al., 2010)





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The SMSNA is a not-for-profit society established in 1994 to promote, encourage and support the highest standards of practice, research, education and ethics in the study of the anatomy, physiology, pathophysiology, diagnosis and treatment of human sexual function and dysfunction. The SMSNA strives to support the free exchange and discussion of new ideas, thoughts and concepts in sexual medicine.

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Version 1 – October 31, 2015

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