Low Serum Testosterone in Outpatient Psychiatry Clinics: Addressing Challenges to the Screening and Treatment of Hypogonadism

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ABSTRACT

Introduction: The symptoms of low testosterone frequently overlap with psychiatric complaints including depression and fatigue. Testosterone repletion has been shown to improve mood symptoms in men with low testosterone, although this finding has not been consistent across all studies. Despite the potential importance of low testosterone for psychiatry, the prevalence of low testosterone in men who present to psychiatric clinics with mental health complaints is unknown.

Aim: To provide an overview of the current state of knowledge of the psychiatric complications of male hypogonadism, the challenges of screening for hypogonadism in a psychiatric population, and the potential mental health treatment implications of hypogonadism.

Methods: A literature review was conducted using PubMed.

Main Outcome Measures: Publications pertaining to the epidemiology, psychiatric symptomatology, and impact of treatment of male hypogonadism on psychiatric outcomes.

Results: A review of the literature suggests a lack of information on the prevalence of low testosterone in patients presenting with psychiatric complaints despite an overlap in clinical symptoms. The identification of low testosterone could have a significant impact on treatment through urologic referral for testosterone repletion or the use of treatments that spare the gonadal axis.

Conclusion: We hope our results will help those who care for patients in psychiatric settings to better assess for the presence of hypogonadism and its potential contribution to depressive illness. **Smith JB, Rosen J, Colbert A. Low Serum Testosterone in Outpatient Psychiatry Clinics: Addressing Challenges to the Screening and Treatment of Hypogonadism. Sex Med Rev 2018;6:69–76.**

Key Words: Depression; Male; Hypogonadism; Testosterone

INTRODUCTION

According to the Endocrine Society guidelines, the clinical manifestations of low testosterone in men are separated into specific signs and symptoms (incomplete sexual development, loss of body hair, small testes, low sperm count) and non-specific signs and symptoms.[1] These latter non-specific signs are indistinguishable from those of mood and anxiety disorders typically treated in outpatient psychiatric settings (Table 1). However, routine screening for low testosterone is not performed in psychiatric outpatient clinics, and therefore the approach to these patients rarely involves testosterone repletion or otherwise restoring the gonadal axis. In fact, many treatments for mood and anxiety disorders include medications such as selective serotonin reuptake inhibitors (SSRIs), which lower testosterone and often cause sexual dysfunction.[3,4]

There is an urgent and unmet need to improve outcomes in psychiatric illness. The largest trial of antidepressant efficacy in a diverse outpatient clinical population (STAR*D) found that nearly 1 third of patients with major depressive disorder, the most common major mood disorder, did not achieve remission after 4 treatment trials. With each subsequent medication trial, the chance of remission decreased.[5] Despite the overlap of symptoms, it is not known to what extent occult hypogonadism plays a role in treatment-resistant and treatment-refractory depressive and anxiety disorders in the outpatient psychiatric population.

FUNCTIONAL HYPOGONADISM AND AGING

In men, testosterone decreases by 1% to 2% per year after 40 years of age. Despite this average decrease in testosterone over

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Table 1. Comparison of non-specific signs of hypogonadism with DSM-V criteria for major depressive disorder

Non-specific signs of hypogonadism[1]	DSM-V criteria for major depressive disorder[2]
Sadness	Depressed mood
Decreased motivation	Markedly diminished interest or pleasure in activities
Decreased confidence	Fatigue or loss of energy
Decreased energy	Insomnia or hypersomnia
Sleep disturbances	Diminished ability to think or concentrate
Poor concentration	Psychomotor agitation or retardation
Memory disturbances	Feelings of worthlessness or inappropriate guilt
Decreased work and physical performance	Recurrent thoughts of death
	Significant weight loss or weight gain

DSM-V = *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.*

time, there remains a wide variation in testosterone levels in the aging male population. 95% of men 19 to 39 years old have testosterone levels of 264 to 916 ng/dL.[6] The European Male Aging Study found that 17% of men older than 40 years have biochemical testosterone deficiency, which they defined as a total testosterone level lower than 317 ng/dL. However, only 2.1% of men in their sample had 3 sexual symptoms and thus met their criteria for hypogonadism. Therefore, many men have levels of testosterone that are in the lower range of normal or even below the normal range, but remain asymptomatic.[7]

Grossman and Matsumoto[8] use the term *functional hypogonadism* to refer to the syndrome of symptomatic androgen deficiency and low serum testosterone in the absence of intrinsic structural, destructive, or congenital hypothalamic-pituitary axis pathology known as *classic hypogonadism*. Functional hypogonadism occurs more often in older men and those with various lifestyle factors and medical comorbidities that are common in psychiatric settings.

PATHOPHYSIOLOGY OF FUNCTIONAL HYPOGONADISM

The cause of this gradual decrease in testosterone involves morphologic changes to the testes over time including a decrease of germinal epithelium and a concomitant increase in connective tissue. There is a total decrease of Sertoli and Leydig cells in aging to half that of the young testis. Testosterone is largely protein bound to SHBG and albumin, leaving a small fraction (0.5−3%) as the biologically active form. The concentration of SHBG tends to increase with aging; therefore, in aging men the proportion of free testosterone decreases even further than the decrease of total testosterone.[9]

In addition to the independent effects of aging on testosterone levels, testosterone is decreased in a number of age-related conditions including weight gain, diabetes, hypertension, renal and hepatic failure, and chronic obstructive pulmonary disease. An increased body mass index (BMI) has an even greater testosterone-lowering effect than age. For example, men with a BMI higher than 30 kg/m^2 have on average 30% less serum testosterone than men with a BMI lower than 25 kg/m^2.[9]

Several commonly prescribed medications also cause a decrease in testosterone levels, including opioids and many antidepressants. All 6 of the most commonly used SSRIs, the most prescribed class of antidepressants, have testosterone-lowering effects. In a 2017 study by Hansen et al,[10] in vitro administration of these antidepressants to an adrenocortical cell line resulted in decreased testosterone production, ranging from 30% to 80% depending on the drug, through interactions with several different enzymes in the steroidogenesis pathway. In addition, there was a relative increase in the ratio of estrogen to androgen, likely due to stimulation of the aromatase enzyme by the SSRIs. Several in vivo studies in rats and humans have found similar results of the effects of antidepressants on steroid levels, although data have been sparse and at times conflicting. For example, in a study by Muller et al,[11] rats administered fluoxetine were found to have an increase in estrogen-dependent organ weights (specifically the uterus), which was believed to be due to an increase in estrogen action secondary to the SSRI. In a 2010 prospective study by Tanikrut et al,[12] 35 men were treated with paroxetine in escalating doses and were found to have a significant decrease in testosterone and β-estradiol levels, although the levels stayed within the normal range. These 2 studies are in line with the aforementioned in vitro studies, at antidepressant doses similar to what could be administered in clinical practice.

Studies have confirmed that long-term opioid use lowers testosterone levels.[13] Rubinstein et al[14] reported in a retrospective cohort study of 81 men 26 to 79 years old that 53% of men on daily opioids had a total testosterone level lower than 250 ng/dL. The opioid buprenorphine, which is a partial μ-opioid agonist, could be the exception because it has been shown to have less testosterone suppression than methadone-treated patients and equivalent testosterone levels to normal controls. This is theorized to be due to buprenorphine's unique binding profile, with only partial μ-opioid agonist and κ-opioid antagonist properties counteracting the typical gonadal axis suppression of a full μ-opioid agonist.[15]

PATHOPHYSIOLOGY OF MALE HYPOGONADISM IN THE BRAIN

There are several mechanisms by which testosterone can affect mood. Although the major peripheral sites of synthesis and metabolism of testosterone are the gonads and adrenal glands, several of these reactions also can occur throughout the brain in myelinated glial cells and local neurons, where de novo