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

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

"neuro-steroids" are produced from steroid and sex hormone precursors.[16] In addition, lipophilic peripherally produced steroids can cross the blood-brain barrier to exert central effects.

Testosterone has the potential to enact rapid effects (eg, through interaction with membrane-bound receptors and ion channels), more classic slower effects (through genomic interactions with intracellular hormone receptors and subsequent interaction with DNA hormone response elements), and a combination of rapid and slow effects through intracellular signaling cascades such as the MAPK-ERK-CREB pathway.[17,18]

From a neuroanatomic perspective, the machinery for neuro-steroidogenesis has been localized to areas of the cortex, amygdala, and hippocampus.[16] In addition, functional magnetic resonance imaging studies have identified the hippocampus and amygdala as key areas of testosterone functionality during affective and social stimulation.[19] These 2 locations are central in proposed pathophysiologic mechanisms of anxiety, stress response, and depression.

Testosterone and its metabolites have been shown to exert central nervous system effects through modulation of neuronal firing, typically through its effects on neurotransmitter release or receptor interactions.[20] Serotonergic pathways specifically have been implicated in depressive disorders and are modulated by testosterone. Administration of testosterone has been shown to increase neuronal firing rate in the dorsal raphe nucleus, leading to an increase in synaptic serotonin.[21] A recent study has further shown that testosterone administration increases serotonin transporter expression in the amygdala, caudate, putamen, and raphe nucleus, possibly due to upregulation secondary to this synaptic serotonin increase.[22] Peripheral testosterone concentration also has been associated with increased central serotonergic tone, as evidenced by its inverse correlation with $5HT_4$ receptor density.[23,24] The administration of testosterone intranasally has been shown to enhance dopamine and serotonin release in the neostriatum (caudate, putamen) and nucleus accumbens of male rats, which could have implications in reward pathways associated with depressive anhedonia.[25]

Hypothalamic-pituitary-adrenal axis dysregulation also has been implicated in the pathogenesis of some mood disorders. In rat models, testosterone administration has been shown to dampen the hypothalamic-pituitary-adrenal stress response to typical chemical activators,[26] specifically through interactions in the medial preoptic area of the hypothalamus.[27] Dihydrotestosterone and 3β-diol, 2 downstream testosterone metabolites, also have been shown to exert an inhibitory effect on hypothalamic-pituitary-adrenal axis stress reactivity, the latter likely through interaction with estrogen receptor-β.[28]

Different testosterone and estrogen metabolites can function as a positive allosteric modulator of the γ-aminobutyric acid A receptor, which can result in rapid anxiolysis in a similar mechanism to the benzodiazepines, although through a different γ-aminobutyric acid receptor binding site.[29]

ASSOCIATION BETWEEN LOW MOOD AND TESTOSTERONE LEVELS

Many studies have identified an association between low testosterone and depressed mood. In 2017 Giltay et al[30] published the results of a cross-sectional prospective 2-year study of testosterone levels in men and women with major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th Revision* (DSM-IV) compared with age-matched healthy controls. The study sample (N = 469) consisted of 350 depressed and 119 non-depressed older persons; the mean age ± SD was 70.5 ± 7.3 years (range = 60−93) and 166 were men (35.4%). They found that subjects with major depressive disorder had lower average testosterone levels than non-depressed controls after controlling for age, level of education, BMI, physical activity, smoking status, alcohol use, number of chronic diseases, and androgen-affecting medication. A small percentage of subjects (5.4%) had a total testosterone level lower than 230 ng/dL, but interestingly 90% of these subjects met criteria for major depressive disorder.

Giltay et al concluded that testosterone levels are associated with major depressive disorder in older patients, and that for men with the lowest testosterone levels, the risk of major depressive disorder appears to be even higher.[30]

A similar conclusion was drawn by McIntyre et al[31] in 2006 when they evaluated 44 depressed men and 50 non-depressed controls 40 to 65 years old. They found that the depressed cohort (as defined by DSM-IV criteria for major depressive disorder) had significantly lower total and bioavailable testosterone levels than controls. This observation remained after controlling for age, BMI, comorbid medical conditions, and psychotropic medications.

The European Male Aging Study is a large multinational European project with the goal of identifying and measuring the symptoms, disabilities, and biochemical changes associated with aging (http://www.emas.man.ac.uk/). In this study, the investigators sampled a random population of 3,369 men 40 to 79 years old at 8 European centers. Using questionnaires, they evaluated subjects' general, sexual, physical, and psychological health. They found that depression, poor morning erection, low sexual desire, erectile dysfunction, inability to perform vigorous activity, and fatigue were significantly related to testosterone levels. Free testosterone levels lower than 160 pmol/L, but not total testosterone, were associated with sadness and fatigue, whereas the physical symptoms listed earlier were significantly associated with low total testosterone.

Despite the association, in their analysis, sadness and fatigue were not considered useful for defining the syndrome of late-onset hypogonadism. The investigators proposed that late-onset hypogonadism be defined by 3 sexual symptoms combined with a total testosterone level lower than 317 ng/dl and a free testosterone level lower than 220 pmol/L.[7]

Westley et al[32] in 2015 found that 56% of men referred for borderline testosterone levels had significant depressive

symptoms as defined by a Patient Health Questionnaire (PHQ-9) score higher than 10. This represents a significant increase compared with the general population with the same PHQ-9 score (6–23%).

Barrett-Connor et al[33] in the Rancho Bernardo Study evaluated testosterone levels and depressive symptoms in 856 community-dwelling adults. In that study the Beck Depression Inventory (BDI) score was inversely associated with free testosterone levels after controlling for age, weight, and physical activity. Free testosterone levels were 17% lower for those with a categorically defined major depressive episode.

LOW TESTOSTERONE PREDICTS THE ONSET OF DEPRESSION

In 2016 Ford et al[34] published a large prospective trial of older men with the goal of studying the association between testosterone and depression over 9 years of follow-up. The goal was to identify new depressive episodes, so men with current or previous depression were excluded. They found that the risk of developing depression over the course of the study was nearly double in men with lower baseline testosterone levels even after adjusting for age, lifestyle factors, and medical comorbidities.

Similarly, Shores et al[35] retrospectively analyzed veterans affairs records for 278 men older than 45 years without prior diagnosed depressive illness over the course of 2 years. For all testosterone levels lower than 280 ng/dL, hypogonadal men showed a significant increase in incident depression compared with eugonadal men. The risk of developing depression increased with decreasing testosterone levels, with the 2-year incidence of depression in men with a total testosterone level lower than 150 ng/dL being nearly 30%. This relation remained after controlling for prostate cancer, medical comorbidity, sexual functioning, and ethnicity. These data support the presence of a graded risk of depression based on testosterone levels strengthening the association between low testosterone and depression.

ANDROGEN DEPRIVATION LEADS TO DEPRESSIVE SYMPTOMS

Further evidence for the association between depression and testosterone comes from studies of iatrogenic androgen deprivation therapy (ADT) for prostate cancer. 2 recent large epidemiologic studies reviewing insurance databases found an increased risk for receiving the diagnosis of a depressive disorder, depressive symptoms, and depression treatment in patients who received ADT compared with controls with prostate cancer who did not receive ADT. These studies quantified the risk using hazard ratios of 1.23 and 1.93, respectively.[36,37] This increased risk remained after controlling for age, comorbidity, and severity of prostate cancer. Smaller prospective trials have been inconsistent, with some finding an association between depression and ADT and others not finding an association. These studies might have been limited by the shorter duration because they followed

patients for only 6 months, whereas the larger retrospective trials observed patients for 3 years.[38]

IMPACT OF TESTOSTERONE REPLACEMENT ON DEPRESSIVE SYMPTOMS

Although the impact that low testosterone can have on mood in some patients is clear, the benefit of restoring testosterone levels for depressive symptoms is more controversial.

In 2016 Snyder et al[39] published the results of a large multicenter trial evaluating the benefit of testosterone supplementation in men older than 65 years with hypogonadism defined by testosterone levels lower than 275 ng/dL. They found a statistically significant benefit for mood as measured by the PHQ-9, although it was well below what is considered a clinically important difference. Conversely, baseline values for depressive severity were low (PHQ-9 = 6.6 in the 2 groups), which would make it difficult to show a large change.

In 2016 Jung and Shin[40] published a randomized placebo-controlled trial evaluating the effect of testosterone replacement on depressive and cognitive symptoms in 106 men older than 40 years (average = 56). The baseline values for depression as measured by the BDI were in the moderately depressed range. The average baseline value for total testosterone in the testosterone-replacement arm was 250 ng/dL and that in the placebo arm was 260 ng/dL ($P = .841$). There was a clinically meaningful and significant decrease in BDI score in the testosterone compared with the placebo group at the 8-month end point.

In 2014 Hackett et al[41] evaluated the impact of testosterone replacement in diabetic hypogonadal men with and without comorbid depression. Their primary outcome was a decrease in hemoglobin A_{1C} (HgbA$_{1c}$) with secondary outcomes including a change in the Hospital Anxiety and Depression Rating Scale (HADS). They found no significant change in the depressed or non-depressed cohort for the HADS during the placebo-controlled 30-week study period. Interestingly, they found that comorbid depression significantly affected the response of HgbA$_{1c}$ to testosterone repletion. Patients with comorbid depression did not have an improvement in HgA$_{1c}$, whereas those without comorbid depression did have an improvement in HgA$_{1c}$. This suggests that depression might decrease the metabolic benefit of testosterone repletion.

Before the studies cited earlier, 2 systematic reviews and meta-analyses were performed evaluating the efficacy of testosterone replacement for depressive symptoms.

In 2009 Zarrouf et al[42] evaluated 7 randomized placebo-controlled trials of testosterone replacement in those with DSM-IV–defined depressive disorders. They found a significant positive effect of testosterone replacement on Hamilton Depression Rating Scale (HAM-D) scores in depressed patients compared with placebo.

In 2014 Amanatkar et al[43] performed a systematic review and meta-analysis of 16 studies (944 subjects). Their inclusion criteria were broader, including all randomized controlled trials evaluating the effect of testosterone repletion on mood as measured by common depression rating scales. They found a large effect size in hypogonadal men younger than 60 years but a non-statistically significant change in eugonadal men and men older than 60 years. They found that oral testosterone was not as effective as parenteral testosterone. The effect size was larger for subjects with subthreshold depressive symptoms than for those who met criteria for major depressive disorder.

LOW TESTOSTERONE AND TREATMENT RESISTANT MAJOR DEPRESSIVE DISORDER

The data to date looking at the efficacy of testosterone in the subpopulation of hypogonadal men with treatment-resistant depression are much more limited.

In 2010 Pope et al[44] published a randomized controlled trial of testosterone gel vs placebo for men with depression resistant to an SSRI antidepressant. At the 6-week end point the testosterone-replacement group did not separate from placebo on the HAM-D. In this trial, the mean total testosterone levels were borderline low (335 ng/dL in the testosterone group and 331 ng/dL in the placebo group) before treatment. Based on the guidelines proposed by the European Aging Male Study, these levels would not meet the criteria for hypogonadism.

In an earlier study by Pope et al,[45] the baseline total testosterone levels were 293 and 267 ng/dL for the testosterone and placebo groups, respectively. These lower levels might be responsible for the finding in this study that 1% testosterone gel 10 g/day was significantly more effective than placebo as measured by the HAM-D and the Clinical Global Impression scores.

Orengo et al[46] also looked at the efficacy of testosterone 1% gel augmentation in treatment-resistant depressed men with hypogonadism. They did not find a statistically significant difference between the testosterone treatment and placebo conditions. However, they noted that during the placebo condition, the average total testosterone level increased to 350 ng/dL (considered low normal). Given the variability of serum testosterone over time in individuals, it is likely that some of their subjects were not in fact hypogonadal. In addition, the number of subjects in the study (N = 12) included in the final analysis was too small to detect a significant treatment difference especially given the limitations noted earlier.

These data in combination with the meta-analyses cited earlier suggest that the effect of testosterone on eugonadal men with depressive symptoms is less robust and that there is likely a threshold above which testosterone does not significantly improve mood. Subthreshold depressive symptoms also might be more responsive to testosterone replacement than those in major depressive disorder.

PSYCHIATRIC SAFETY OF TESTOSTERONE REPLACEMENT

A few older studies using physiologic doses of testosterone found a subjective increase in aggression, irritability, and hostility, although these changes were not observed on rating scales for mood and hostility.[47,48] Naturalistic studies following athletes who abuse steroids have shown significant increases in irritability, aggressiveness, and euphoria and manic symptoms. Steroid withdrawal also has been demonstrated to induce depressive symptoms in some users.[49] There also is some evidence in the literature to suggest that steroids can lead to dependence or addiction.[50,51] In general, steroid use and certainly steroid withdrawal are believed to have the potential to produce adverse psychiatric effects, although these seem to be subtle in physiologic dosing and more prominent with markedly supraphysiologic doses.[49]

A significant relation has not been established between suicide and testosterone levels in a broad population.[52] There are a few studies that have reported on a trend toward lower testosterone levels after suicide attempts, although these tend to be small and measure testosterone after the attempt once the patient has arrived at the hospital, which might not accurately reflect their level just before the attempt.[53] Another study with 130 participants focused on levels of dehydroepiandrosterone, androstenedione, testosterone, and estradiol in men with post-traumatic stress disorder who had attempted suicide in the past 6 months and found no connection between testosterone levels and suicide.[54] One recent study showed no significant difference in testosterone levels between men who attempted suicide that day and healthy controls.[55]

One older study found that the addition of oral methyltestosterone to standing antidepressant treatment led to 4 of 5 men developing paranoid delusions.[56] However, increased paranoia has not been reported in more recent treatment trials including those listed in the preceding sections.

There are very limited data on the impact that testosterone might have on patients with bipolar disorder. One study found that patients with bipolar disorder and higher physiologic testosterone levels had an increased rate of manic episodes and suicide attempts.[52] Although the risk is difficult to quantify given the paucity of data, testosterone's antidepressant effect might produce an increased risk of mania in an analogous way to other available antidepressant treatments.

One study found that Tourette symptoms can worsen with testosterone replacement,[57] and another found that obsessive compulsive disorder symptoms improved with antiandrogen treatment, suggesting a possibility of worsening symptoms with testosterone therapy.[58]

Supraphysiologic doses of anabolic-androgenic steroids (although not exclusively testosterone) have been commonly associated with more severe psychiatric pathology including depression, hypomania, mania, and psychosis. In 1 study that

interviewed athletes who were abusing steroids, 23% met criteria for mood disorders compared with a rate of 6% in athletes who were not using steroids. It also was found that the higher the steroid dose, the more severe the psychopathologic symptoms.[49] In another study, placebo physiologic doses and supraphysiologic doses of testosterone were administered for 3 days each to 2 separate groups of men, with the latter showing modest but significant psychiatric effects and 1 subject developing an acute manic episode.[59]

None of the testosterone-replacement studies for hypogonadism reviewed systematically evaluated for adverse psychiatric events such as irritability, aggression, paranoia, or mania. Depression rating scales such as the HAM-D, PHQ-9, and BDI do not capture these categories of symptoms despite their potential relevance. It would be useful in future testosterone-replacement studies to look systematically at these potential adverse psychiatric events.

CONCLUSION: CLINICAL IMPLICATIONS FOR PSYCHIATRIC OUTPATIENTS

To our knowledge, there have not been any studies designed to determine the prevalence of hypogonadism in treatment-resistant major depressive disorder or the prevalence of hypogonadism in the general outpatient psychiatric population. Because hypogonadism and treatment-resistant depression are common conditions, this is likely a large and relatively undiagnosed population. Evidence for testosterone alleviating depressive symptoms in hypogonadal patients is mixed and further study is warranted. There is sufficient evidence to conclude that in some men repletion of testosterone has the potential to have a significant positive effect on mood.

For screening purposes, commonly used questionnaires for hypogonadism have not been validated in psychiatric populations. Even in non-psychiatric settings, the specificity of questionnaires is poor. Because many screening questions overlap with symptoms of depression and other psychiatric disorders, there is good reason to suspect that they would not be useful. For example, Lee et al[60] found that the prevalence of a positive St Louis Androgen Deficiency in the Aging Male questionnaire in a sample (N = 176) of psychiatric patients was 93%.

We propose that outpatients presenting with psychiatric complaints of depressed mood and associated neurovegetative symptoms be screened for sexual symptoms. Consistent with the European Aging Male Study guidelines, for those with at least 3 sexual symptoms, we recommend that a morning total testosterone level be obtained. If the total testosterone level is lower than 287 ng/dL (11 pmol/L) and the free testosterone level is lower than 0.225 nmol/L, then the patient should be referred to urology for consideration of testosterone replacement.

It is important to keep in mind that testosterone is more likely to be a factor in depressive symptoms when the level is substantially below normal, although some men might have testosterone-responsive depression even in the borderline low range. There also is evidence that subthreshold depressive symptoms (not meeting full criteria for major depressive disorder) might be more responsive to testosterone. If testosterone is initiated, there is more evidence for the effectiveness of parenteral forms than oral forms of testosterone replacement.

We recommend that psychiatrists remain involved in the management of patients' depressive symptoms in collaboration with a urologist or other medical provider experienced in testosterone-replacement therapies. Specifically, management of antidepressant and opioid medication might be of use to optimize the gonadal axis and to monitor for rare adverse psychiatric effects of testosterone.

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