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General

Testosterone Replacement Therapy in the Treatment of Depression

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Background

Depression is a common disorder that affects millions globally and is linked to reduced quality of life and mortality. Its pathophysiology is complex and there are several forms of treatment proposed in the literature with differing side effect profiles. Many patients do not respond to treatment which warrants augmentation with other treatments and the investigation of novel treatments. One of these treatments includes testosterone therapy which evidence suggests might improve depressed mood in older patients with low levels of testosterone and helps restore physical impairments caused by age-related hormonal changes.

Objective

The objective of this review is to synthesize information regarding clinical depression, its treatment options, and the efficacy and safety of testosterone treatment for the treatment of depression.

Methods

This review utilized comprehensive secondary and tertiary data analysis across many academic databases and published work pertaining to the topic of interest.

Results

Within some subpopulations such as men with dysthymic disorder, treatment resistant depression, or low testosterone levels, testosterone administration yielded positive results in the treatment of depression. Additionally, rodent models have shown that administering testosterone to gonadectomized male animals reduces symptoms of depression. Conversely, some studies have found no difference in depressive symptoms after treatment with testosterone when compared with placebo. It was also noted that over administration of testosterone is associated with multiple adverse effects and complications.

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Conclusion

The current evidence provides mixed conclusions on the effectiveness of testosterone therapy for treating depression. More research is needed in adult men to see if declining testosterone levels directly influence the development of depression.

INTRODUCTION

The first interest in studying the effects of testosterone on mood was documented in 1889 by Dr. Charles Brown-Sequard when he injected himself with testosterone filled fluid from the testicles of animals and noted a heightened sense of mood.[1] Since then, there have been a variety of studies investigating the effects of testosterone. It has been documented that testosterone has neurobehavioral, somatic, and metabolic actions throughout the boy.[1,2]

The idea that adequate testosterone levels correlate with depression stems from a 1969 study that concluded that hypogonadism is associated with more depressive symptoms.[3,4] Rodent models have further shown that that administering testosterone to gonadectomized male animals reduces symptoms of depression due to an increase in serotonin in the dorsal raphe nuclei that facilitates neuroplasticity.[5-8]

Over the years, levels of testosterone have been found to be lower in patients who report depression than non-depressed individuals.[1,9-11] However, clinical trials have failed to distinguish the role of testosterone on depressive symptoms versus depressive disorders.[12] Therefore, the role of testosterone on the treatment of depressive disorders remains a controversy.[3,5,11,12] It is unknown whether symptoms of depression are brought about by a deficiency of testosterone in men or if testosterone treatment is effective in treating men with depressive symptoms and disorders.[1,12]

It is important to note that there are several forms of clinical depressive disorders such as Unipolar major depression (Major Depressive Disorder), Severe Major Depression, and Persistent Depressive Disorder (Dysthymia). Only a small number of controlled clinical trials have been on men that meet the criteria for Major Depressive Disorder (MDD) as diagnosed by the DSM-5.[12] The association between testosterone and MDD have yielded conflicting results with some studies suggesting an association between testosterone and MDD and others suggesting little to no association.[3,5,11,12] Yet, epidemiologic and clinical studies have found a more consistent association between low testosterone levels and Persistent Depressive Disorder, specifically in elderly men who have lower testosterone levels than non-depressed men of the general population[2,5,12-16]

EPIDEMIOLOGY

According to the World Health Organization (WHO), depression is a common mental disorder that affects approximately 280 million people globally.[17] The WHO categorizes major depressive disorder as the 11th greatest cause of disability and mortality in the world.[18] Additionally, depression accounts for 10 percent of the total non-fatal disease burden in the world.[19] Depression is linked to reduced quality of life, medical comorbidities, and mortality.[20-24] However, there exists a major health disparity as it disproportionally affects men and women.[19] In the 1970s, it was revealed that twice as many females experience depression than males among adults.[19] Since then, most epidemiological reports have continued to reveal higher rates of major depression in women than in men, staying consistent with the approximate 2:1 ratio.[19,25] However, the 2:1 ratio varies across countries.[19] Studies have shown no gender differences in depression during childhood.[19,26] The discrepancy between men and women seems to appear during adolescence, when the incidence of depressive symptoms and MDD sharply increases.[19,27,28] The high incidence of MDD in adolescence puts them at an increased risk for self-harm and suicide behaviors.[29] The incidence of suicide in adolescence has been documented to be 14.2 per 100,000 making it the 2nd highest cause of death amongst this age group.[29] Symptoms of depression in adolescents has been attributed to diminished neural reward processing.[29] In addition to adolescents, depression is prevalent among old age as elderly individuals are faced with functional decline, disability, an overall decreased quality of life, and a higher mortality rate from comorbid conditions.[30]

PATHOPHYSIOLOGY/RISK FACTORS

The pathophysiology of depression is a complex process that involves the interplay of several factors including neurotransmitter deficiency, neurogenesis, inflammatory, genetic, environmental, and endocrinal influences.[31] Several studies have investigated the etiology of depression starting with the monoamine hypothesis, which proposes that a reduction in the monoamine neurotransmitters of serotonin (5HT), norepinephrine (NE), and dopamine (DA) results in decreased cognitive functions that culminate into the depression.[31-35] It has been shown that low NE, 5HT and DA influence a wide spectrum of depressive symptoms including motivation, interest, and suicidal ideation.[31] Studies on individuals with MDD have revealed reduced serotonin receptor binding in comparison to healthy subjects in brain regions such as the anterior cingulate cortex, prefrontal cortex, and hippocampus; PET scan studies have also shown reduced NE transmission in patients with MDD.[31,36-39]

Additional studies have revealed a reduction in the density and size of glial cells in patients with MDD and proposed that this lack of neurogenesis causes depression.[31,40] Postmortem studies of patients with MDD have revealed the density of GABAergic neurons in the occipital cortex to be reduced by 28 percent and 50 percent in the prefrontal cortex in comparison to controls.[41,42] Evidence suggests that disrupting GABA neurotransmission contributes to the

onset of MDD.[43] Studies report decreased GABA in the cerebral spinal fluid as well as in cortical brain regions of patients experiencing depression.[43] Functional neuroimaging studies on patients with MDD has shown abnormal activity between different brain areas within the frontolimbic and frontoparietal networks involved with emotional regulation and processing, respectively.[44-47] Neuroimaging on patients with MDD has revealed a lack of communication, or hypoconnectivity, between brain regions within the frontoparietal network as well as between the frontoparietal network and the dorsal attention network involved with attention.[44] Additional neuroimaging studies on patients with MDD have revealed abnormal cerebral blood flow and glucose metabolism in multiple limbic and prefrontal cortical structures involved with emotional behavior.[48]

The inflammatory theory of depression suggests that depression is due to excessive inflammation as studies have shown elevated levels of C reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin 1 (IL-1) receptor antagonist in people with depression compared to controls.[49] This is supplemented with further evidence that the infusion of interferon-α and cytokines can induce depressive symptoms.[49]

There have been studies to determine the genetic influence of depression, however the heritability of depression does not follow a classical Mendelian pattern and cannot be attributed to a single gene locus.[31,50-53] Only a few studies have found significant relationships between genetic polymorphisms and MDD including the apolipoprotein E (APOE), particularly APOEε2 and APOEε4, guanine-nucleotide-binding protein (GNB3), methylenetetrahydrofolate reductase (MTHFR 677T), dopamine transporter (SLC6A3), serotonin transporter (SLC6A4) and the dopamine receptor D4 gene.[31,50,53] MDD is likely due to the interplay between individual genetic and environmental influences as the environment may alter gene expression, especially in response to stress.[31,54-56]

Studies on monozygotic twins have revealed the influence of environmental stressors on the onset of depression.[31,57,58] Early life adversities and traumatic events in one's environment can predispose individuals to MDD by altering their sensitivity to aversive stimuli.[59,60] Patients with MDD have been shown to have increased corticotrophin-releasing factor (CRF) and cortisol secretion which increases their physiological stress response.[31,61-63] Studies have shown that HPA axis dysfunction not only suppresses neurogenesis and causes hippocampal atrophy, but also results in depressive symptoms such as hopelessness, weight loss, diminished appetite, and psychomotor activity.[31,61-63]

Other risk factors for depression include quality of social relationships, comorbidities, and internal factors. Lack of social support from others and social isolation have been shown to increase the onset of depression.[64-66] Important medical history to note is prior psychotic experiences which are known to increase the onset of MDD in comparison to people with no history of psychotic episodes.[67] Finally, personality traits can play a role in the onset of depression as maladaptive beliefs and attitudes can lead to more frequent negative thoughts that can leave people vulnerable to depressive outcomes.[68,69]

STANDARD TREATMENTS FOR DEPRESSION

Clinical depression is treated with pharmacotherapy as well as psychotherapy. The combination of the two has proven to be more efficacious than either treatment alone.[20,70-72] However, there is no evidence to suggest that there is a significant difference in clinical outcomes between medication and psychotherapy as well as between specific medication/psychotherapy combinations in comparison to other combinations.[20,70,73,74] While medication and therapy have comparable effects, there is evidence to suggest that psychotherapy is more effective in the long term (1 year and over) as relapse is common in remitted patients who discontinue their medication; the benefits of psychotherapy often persist.[20,75-77]

There are many types of antidepressant medications composed of different drug classes with Monoamine oxidase inhibitors (MAOIs) and Tricyclic antidepressants (TCAs) among the oldest class of medications introduced in the 1950s.[78,79] Monoamine oxidase inhibitors (MAOIs) which prevent the breakdown of monoamines, were the first well documented medication used to treat depression[81]. These drugs include isocarboxazid, phenelzine, and tranylcypromine. However, the use of this drug class is considered last line treatment due to its side effects.[78,80-83] Tricyclic antidepressants (TCAs), such as amitriptyline and imipramine, inhibit the reuptake of neurotransmitters, particularly serotonin and norepinephrine.[78,84] Like MAOIs, TCAs also have a large side effect profile which has led to their diminished use.[78] Currently, the Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake inhibitors (SNRIs) are considered the first line pharmacological treatment for clinical depression and are the most widely prescribed class of antidepressants due to their lower side effect profiles.[78,85-87] However, SSRIs and SNRIs may have sexual side effects as well as weight gain which deters patients from continued use.[78,88,89] SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram prevent the reuptake of serotonin while SNRIs such as duloxetine, venlafaxine, and desvenlafaxine prevent the reuptake of both serotonin and norepinephrine.[78] Finally, another antidepressant used to treat clinical depression is Mirtazapine, an antagonist of alpha 2-adrenergic autonomic receptors as well as serotonin 5-hydroxytryptamine-2 (5H2) and 5-hydroxytryptamine-3 (5-HT3) receptors.[78,90] The mechanism of action Mirtazapine ultimately enhances norepinephrine release as well as increase serotonin.[78,90]

It is important to note that pharmacologic treatments are ineffective in a subset of patents.[91,92] It has been reported in the literature that approximately 60 percent of patients experiencing clinical depression do not benefit from their first antidepressant.[91,92] Little is known about what causes resistance to antidepressants and the pathophysiology remains largely obscure as resistance depends

on an individual basis.[92] In order to help clinicians prescribe the right antidepressant, several guidelines have been published.[91] Yet, the process of matching the correct antidepressant to meet the needs of an individual patient often involves trial and error.[91] Clinicians have resorted to prescribing antidepressants through predictive models as studies have shown that thorough medical histories can anticipate which patients will experience remission and ultimately influence prescription patterns.[91]

The range of therapies to treat clinical depression includes but is not limited to, Cognitive Behavioral Therapy (CBT), Interpersonal psychotherapy (IPT), Acceptance and Commitment Therapy (ACT), and Electroconvulsive Shock Therapy (ECT). CBT is among the most widely studied form of therapy and focuses on the thoughts, feelings, and behavior of patients in order to address psychological distress.[77,78,93-95] It may involve patients re-engaging in previously enjoyed activities and reassessing negative thoughts and feelings.[78] ACT differs from CBT in that rather than try to minimize distress by altering the way of thinking, it focuses on getting patients to actively choose to remain in contact with experiences that they previously tried to avoid or escape, but in the context of more behavioral freedom than their previous encounters with these private experiences.[78,96] IBT focuses on the reciprocal relationship between mood and interpersonal events and aims to target interpersonal problems to alleviate depressive symptoms.[78,97] Finally, the use of ECT, which involves electrical stimulation of the brain, has been shown to be promising for patients with severe and unremitting depression who are unresponsive to medication.[78]

NON-STANDARD TREATMENTS FOR DEPRESSION

There are several other treatments that have shown promising outcomes on the treatment of depression but are not the standard practice for the treatment of clinical depression. Some of these treatments are FDA approved alternatives for the treatment of depression while other treatments are used off-label to treat depression. These treatments include atypical or second-generation antipsychotics, NMDA antagonists, neuroactive steroid GABA-A receptor positive modulators, lamotrigine, psychostimulants, statins, and scopolamine.

Atypical antipsychotics are currently FDA approved as adjunctive treatment to SSRIs in individuals with severe treatment resistant depression (TRD).[78,98-101] Several studies have shown that atypical antipsychotics are associated with improvement of depression symptoms.[78,102] One specific second-generation antipsychotic in particular, quetiapine, has been extensively studied for this purpose and is known to resemble several anti-depressant compounds in its chemical nature.[98] The use of quetiapine has been demonstrated in patients suffering not only from TRD, but also from depression associated with psychosis, bipolar disorder 1 and 2, and anxiety.[98]

In 2019, intranasal esketamine was approved by the FDA for TRD in patients that have failed to respond to two or more antidepressants.[103-105] It is the S-enantiomer of ketamine and is a more potent NMDA receptor antagonist than R-ketamine.[103-105] However, there remains disagreement in the literature regarding the safety and efficacy of esketamine for the treatment of TRD.[103-105] Because of its potential risks, the FDA currently limits eskatmine to be administered through a restricted program called the Spravato REMS.[105,106] Also, in 2019, the FDA approved the use of brexanolone, a neuroactive steroid GABA-A receptor positive modulator for the treatment of post-partum depression.[107] Neuro-steroids, which are naturally made from cholesterol in the brain, have been reported to be potent modulators of GABA.[108] Studies have shown that the neuro-steroid allopregnanolone is a positive allosteric modulator of synaptic GABA-A receptors; reduced levels of allopreganoline in the cerebrospinal fluid have been reported to normalize after treatment of depression with antidepressants.[108] Although the mechanism of brexanolone is not fully known, it consists of the aqueous formulation of allopregnanolone.[109] Like eskatmine, brexanolone is also only available through a restricted program called Zulresso REMS.[110] While brexanolone is FDA approved for the treatment post-partum depression specifically, additional studies have been done to investigate the effects of neurosteroid positive allosteric modulators of GABA-A receptors on MDD. One promising treatment has been reported to be the neuro-steroid SAGE-217 which has shown a reduction in depressive symptoms in patients with MDD.[108]

Off-label treatments of depression include psychostimulants, lamotrigine, statins, and scopolamine. Psychostimulants are known to increase synaptic activity of monoamine neurotransmitters and have been reported to have a fast onset of action with some patients reporting improved outcomes within 24 hours.[111] Studies have shown that methylphenidate, a dopamine reuptake inhibitor, in combination with citalopram shows significant improvement in depression severity in the elderly population.[111] Additionally, studies have demonstrated that lamotrigine (LTG) is beneficial for treating the depressive symptoms of bipolar disorder.[112] The mechanism of action of LTG on bipolar depression is thought to be due to inhibition of the release of glutamate by blocking voltage-gated sodium channels.[112] Statins have been considered as a potential treatment for depression due to their anti-inflammatory properties that have been documented to reduce C-reactive protein levels and inhibit monocyte expression of pro-inflammatory cytokines.[49,113] The use of statins as adjunctive treatment to SSRIs have shown stronger antidepressant effects than the use of SSRIs alone.[113] Finally, in the 1970s, Janowsky and colleagues showed that increasing cholinergic function worsened depressive symptoms in patients with MDD as well as in patients with bipolar disorder.[114] Since then, studies have been done to investigate antimuscarinics on the treatment of depression.[114] Scopolamine has been documented to produce antidepressant effects with a fast onset of action.[114] The findings behind these alternative medications, both FDA approved alternatives for the treatment of depression as well as the novel off label uses, highlight the

possibility of nontraditional therapies in the treatment of mood disorders.

WHY IS TESTOSTERONE USED TO TREAT DEPRESSION?

The current literature that explores the effectiveness of testosterone administration for the treatment of major depression disorder and depressive symptoms is inconsistent. Testosterone can affect neurobehavioral, somatic, and metabolic pathways in humans. This androgen's modulation of neurobehavior may play a role in the development of depression. In the central nervous system, testosterone has been shown to influence male arousal, behavior, energy, and mood.[20] Because of this, exogenous testosterone administration is being investigated as a potential independent or adjunctive treatment of depression.

The cause of major depressive disorder is multifactorial. It is well-known that levels of testosterone decline as males age.[115] Shores et al. showed an increase incidence of depressive symptoms in hypogonadal males when compared to eugonadal males.[116] Additionally, Gould et al. reported a correlation between decreased testosterone levels and an increased predisposition for depression and suicide attempts.[7] More research is needed to see if declining testosterone levels in adult men directly influence the development of depression.

The current evidence provides mixed conclusions on the effectiveness of testosterone therapy for treating depression. Wang et al. showed testosterone replacement resulting in an improved mood and sense of well-being and decreased fatigue and irritability in patients with a hypogonadal baseline. However, Wang et al. did not compare the results to a placebo control group.[117] In addition, Carrier et al. demonstrated that both testosterone and estradiol exerted an antidepressant and anxiolytic effect in male rats after removal of the gonads.[6] A 2018 systematic review and meta-analysis of randomized controlled trials studying testosterone administration do not support its efficacy in the treatment of depression. However, within some subpopulations such as men with dysthymic disorder, HIV, treatment resistant depression, or low testosterone levels, testosterone administration yielded positive results in the treatment of depression. This meta-analysis also showed promising results for improvement of depressive symptoms in eugonadal or older men with administration of higher testosterone doses.[5] There is a need for larger, unbiased randomized controlled trials to determine the true effectiveness of testosterone supplementation for treatment of depression.

WHO CAN BENEFIT FROM TESTOSTERONE REPLACEMENT THERAPY FOR DEPRESSION TREATMENT?

As we age, our susceptibility to physical and mental disease increases, which will lead to a rise in health care costs. Successful aging with less disease burden has become a major health care goal. Over the past few decades, research has focused on successful aging in men and associated age-related hormonal changes with testosterone (T) starting to decline around age 40. Other steroid hormones including dehydroepiandrosterone (DHEA), estradiol (E2), progesterone (P) also show an age-dependent reduction at around the same age.[118,119] Moreover, the subsequent principal component combining these four sex steroid hormones (T, DHEA, E2 and P) extracted the component of declining steroid hormones (DSH). It was further shown that the association between age and DSH revealed significant moderation effects for psychosocial factors including depression, chronic stress, and perceived general health.[119] Late-onset hypogonadism (ages 40-79) can be defined by the presence of at least three sexual symptoms (poor morning erection, low sexual desire, or erectile dysfunction). The association between male age-related testosterone deficiency and late-onset hypogonadism were related with decreased testosterone levels.[120] It was found that longitudinal age trends in middle-aged men were significant compared to cross-sectional trends suggesting that poor health (presence of chronic illness, prescription medication, obesity, or excessive drinking) may accelerate the age-related decline in androgen levels.[121] Another longitudinal study discovered inverse associations between sex hormones and depressive symptoms; however, none of the observed associations remained after multivariable adjustment suggesting relevant confounders such as body mass index, smoking and physical inactivity may be present.[122]

Since clinical conditions cannot be prevented for every man by maintaining apparent good health, testosterone replacement therapy can offer a chance to overcome undesirable psychological, sexual, cognitive, and physical impairments caused by age-related hormonal changes. Results in studies suggest that testosterone treatment might improve depressed mood in older men who have low levels of physiologically active bioavailable testosterone since low levels correlated with age and increased depression.[123-125] Testosterone's bioactive metabolites (serum dihydrotestosterone and estradiol) were not associated with depression risk.[126] It would be possibly beneficial in the long term to target psychoeducation about these age-related hormonal alterations at a population level to help support men and teach options about treatment.[118]

Additional findings often seen in older men are declines in hypothalamic-pituitary-gonadal (HPG) axis function and dysthymic disorder (DD). Dysphoria, fatigue, and decreased libido are seen in both HPG axis function and dysthymic disorder. Lower total testosterone levels were seen in older men with dysthymic disorder relative to men with major depressive disorder and men without depressive symptoms. Thus, relations between HPG axis hypofunction are seen in depressive men and negatively affecting gonadal function.[13,127] Regarding male and female patients with DD below age 50, results revealed reduced gonadal and adrenal androgen levels with normal-low cortisol levels thus differencing DD from depression. This categorizes the group closer to posttraumatic stress disorder.[14] In contrast to the hypothalamic-pituitary-adrenal cortical and thyroid axis

abnormalities frequently found in endogenously depressed men, the HPG axis function was relatively normal when a study controlled nocturnal and diurnal serum luteinizing hormone (LH), follicle stimulating hormone (FDH), testosterone and estradiol (E2) concentrations and their responses to gonadotropin releasing hormone (LHRH) and dexamethasone administration.[128]

Genetic trait markers of androgen receptor (AR) function such as CAG repeat length may play a role in testosterone levels and depressive symptoms in middle-aged men. Depression was significantly and inversely correlated with total testosterone in men with shorter AR CAG repeat lengths but not with moderate or longer CAG repeat lengths.[129]

Medical and social science research differ on the viewpoints of relationship between testosterone levels and mood symptoms. Medical research suggests positive effects of testosterone on mood versus social science research proposes negative effects of testosterone on mood. On stratification into below average and above average testosterone, it was concluded that men with below average testosterone and depression relationship is inversely and directly related for those with above average testosterone. When controlled for antisocial behavior, risk behavior, unemployment and being unmarried the relationship disappears for those with above average testosterone and unchanged for those with below average testosterone.[130]

Another study concluded that atypical depressive subtypes showed drastically lowered testosterone levels compared with melancholic depressives in men.[131] Decreased muscle mass, bone mineral density, and libido plus anorexia, fatigue, and irritability are common symptoms of age-associated hypogonadism, which occurs in 30% of men after age 55. It was found that hypogonadal men were more likely to suffer from depression and to be diagnosed sooner than others.[116]

High evening saliva testosterone values, reflecting 'free' plasma testosterone, correlated with male depressive syndrome. However, simultaneous testing for evening cortisol and testosterone levels did not increase specificity of detecting depression.[16] When saliva levels along with dexamethasone suppression test were measured in men with major depression with melancholia, pre-dexamethasone levels negatively correlated significantly with depression and anxiety ratings. No significant differences in testosterone levels were seen compared to age-matched control group.[132]

The relative effects of individual testosterone products given for >3 months among hypogonadal men revealed improving quality of life, depression, erectile dysfunction, and libido, but major improvements were not detected with the use of any individual product. In addition, no statistically significant increase in risk of adverse events were observed; however, longer-term high-quality trials are needed to fully evaluate harm risk.[133] Guidelines recommended for T therapy in men with hypogonadism includes creating a diagnosis only in men with symptoms consistent with testosterone deficiency and clear consistent low serum T concentrations. The initial diagnosis recommended to measure fasting morning total T concentrations and confirming the diagnosis by repeating the measurement. It is recommended to treat symptomatic T deficiency with T therapy to induce and maintain secondary sex characteristics and correct symptoms of hypogonadism after going over with the patient the potential benefits/risks and monitoring of therapy. Starting T therapy is discouraged in patients who are planning fertility soon, breast or prostate cancer, palpable prostate nodule/induration, prostate-specific antigen (PSA) level >4 ng/mL, PSA >3 ng/mL with increased risk of prostate cancer (e.g., African Americans and men with a 1st degree relative with diagnosed prostate cancer), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within last six months or thrombophilia. The aim of T therapy is to achieve T concentrations in mid-normal range with patient preference decision making of treatment.[134]

WHAT ARE THE EFFECTS OF TESTOSTERONE?

Testosterone replacement is being researched as a possible treatment of depression. Several studies have been conducted, but the efficacy of testosterone administration for treating depressive symptoms is still up for debate. Shores et al. observed that testosterone deficiency in men was correlated with a higher incidence and earlier onset of depression.[135] In preclinical studies, gonectomized rats were found to have a higher level of depressive behavior than rats with normal gonads. Their depressive behaviors were also reduced after the administration of testosterone or its metabolites.[136] This supports the need to explore testosterone as a potential therapy for depression.

Some studies have shown a significant improvement in depressive symptoms after testosterone supplementation when compared with placebo.[137-142] However, these results must be investigated deeper because the sample population differed significantly across the studies. Some of the significant reductions in depressive symptoms were seen only in subgroups of the samples depending on different factors like age, testosterone levels, comorbidities, etc. For example, Giltay et al. found the beneficial effects of testosterone only in patients with low baseline total testosterone levels.[142] Secondly, Pope et al. found a significant improvement after testosterone therapy only in the Hamilton Depression Rating Scale and not in the Beck Depression Inventory. Pope et al. also only included participants with treatment resistant depression or borderline low serum testosterone levels.[141] Synder et al. only included men over the age of 65.[13] Amanatkar et al. and Zarrouf et al. conducted meta-analyses of 16 trials with 944 subjects and 7 trials with 364 subjects, respectively.[138,139] Amanatkar et al. concluded that testosterone can be used as a monotherapy in dysthymia and minor depression or as an adjunctive treatment for major depression in hypogonadal middle-aged men.[139] Zarrouf et al. showed an enhanced response to testosterone therapy in subpopulations with hypogonadism and with HIV/AIDS. They also showed that the route by which testosterone is administered may influence its effectiveness.[138] A systematic review and meta-analysis

of 27 randomized placebo-controlled clinical trials found a significant reduction of depressive symptoms after treatment with testosterone, but this effect was seen mainly in participants who received higher doses.[5]

Alternatively, some studies have found no difference in depressive symptoms after treatment with testosterone when compared with placebo.[15,16,143-145] Seidman et al. observed an improvement in mood with testosterone injection as an adjunct to selective serotonin reuptake inhibitor (SSRI) therapy. However, this improvement was not significantly different when compared to placebo injection with SSRI.[15] In the study by Shores et al. there was an initial reduction in depressive symptoms and a higher remission rate after testosterone treatment in hypogonadal men with subthreshold depression. However, after the open label phase, there were no differences in any outcome measures between the testosterone treatment and control group.[15] Seidman et al. supports exogenous testosterone as a psychotropic agent, but they suggest that the effects are limited to a subgroup, particularly in hypogonadism. They conclude that testosterones efficacy as an antidepressant is not well supported, even in these hypogonadal men.[16] Investigating further, Pope et al. agreed that testosterone is generally not an effective treatment option for depressed men. Yet, they hypothesize that specific factors (e.g. repeat polymorphisms, prenatal androgenization) might make certain cohorts of men more susceptible to the mood altering effects of testosterone.[144]

The pathogenesis of depression is multifactorial. The development of depression may be due to alterations in genes coding for monoamine regulators, corticotrophin releasing hormones (CRH), and brain derived neurotropic factor (BDNF).[146] Another explanation is atrophy of the hippocampus and prefrontal cortex shown by a decrease in grey matter volume and glial density in postmortem imaging of patients with depression.[147] Additionally, abnormal levels of cortisol, serotonin, and norepinephrine, are implicated in the pathogenesis of depression.[148-150] Another possible etiology of depression is an increased activation of the immune system in the central nervous system resulting in an increased number of vimentin-immunoreactive astrocytes, MCH-II immunoreactive microglia, and GFAP immunoreactive cells.[151,152]

There are a few proposed mechanisms by which testosterone exerts its antidepressant effects. One explanation is through the modulation of serotonin signaling. Testosterone is known to increase the 5-HT (serotonin) transporter mRNA expression and binding in rats and humans.[153,154] Testosterone has also been shown to increase the firing rate of serotonin-secreting neurons in the dorsal raphe nucleus in rats.[155] A serotonin deficit results in long term decreases in hippocampal cells proliferation.[156,157] Raphe grafts that are enriched with serotonin producing neurons restored the proliferation of hippocampal cells.[158] This testosterone mediated increase in serotonin results in preservation of hippocampal volume, thereby exerting antidepressant effects. Another possible mechanism of testosterone antidepressant activity is through the downregulation of the immune system in the central nervous system. For example, Garcia-Estrada et al. found that testosterone treatment significantly decreased the number of reactive astrocytes and microglia around a neuronal wound.[152,159] They concluded that the downregulation of gliosis may be one mechanism of the neuroprotective effect produced by testosterone administration.[159] Lastly, the antidepressant effects of testosterone may result from the direct stimulation of neurogenesis within the dentate gyrus region of the hippocampus.[160] In the adult songbird, testosterone administration was shown to increase vascular endothelial growth factor (VEGF) synthesis. The increase VEGF synthesis induces the formation of new capillaries which in turn increased BDNF synthesis which then increases the migration of new neurons.[161] The androgen dehydroepiandrosterone (DHEA) has been shown to promote neurogenesis in the hippocampus of rats and increase mitosis in fetal neural progenitors.[162,163] More research is needed to determine the reason for the possible antidepressant action of testosterone administration.

DISADVANTAGES OF TESTOSTERONE USAGE

Androgenic steroids are associated with multiple adverse effects and complications. Most complications include cardiovascular, infection, musculoskeletal, neuropsychiatric, hepatic, male and female reproductive systems.[164] Cardiovascular problems can include coronary heart disease, cardiomyopathy, erythrocytosis, hemostasis/coagulation abnormalities, dyslipidemia, or hypertension. A case report on a 23-year-old body builder who suffered a sudden cardiac death associated with anabolic steroids along with other performance enhancing drugs revealed postmortem cardiac hypertrophy, acute cellular necrosis, and interstitial fibrosis of the myocardium.[165] With limited clinical uses for androgenic-anabolic steroids (AAS), it seems they are widely abused by athletes in attempts to alter lean body mass and strength. For instance, two cases associated with anabolic steroid oxymesterone in healthy footballers aged 18 and 24 sustained fatal cardiac arrests with autopsy findings of normal coronary arteries and no evidence of coronary thrombosis; however, hypertrophic cardiomyopathy in former and myocarditis in the latter were found thus both leading to an arrhythmogenic event.[166] Another cardiac component associated with steroid hormones (AAS in particular) appear to drive left ventricular (LV) hypertrophy through actions on the androgenic receptor (AR) since they are not only found in skeletal muscle cells but also on cardiac myocytes.[167] A study reviewed that short-term administration of AAS up to 16 weeks did not lead to detectable echocardiographic alterations of heart morphology and systolic/diastolic function in athletes probably because echocardiographic evaluations are not sensitive enough to detect alterations at the cellular level of the actual cardiac conditions in ASS users.[168]

Regarding serum lipoprotein levels and routes of AAS administration, one study concluded that oral AAS produce marked reductions in serum concentrations of high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I level with an increase in low-density lipoprotein cholesterol concentration and hepatic triglyceride lipase activity compared

to intramuscular (IM) route. Also, weight gain was similar with both drug routes; however, IM testosterone was more effective in suppressing gonadotropic hormones. Therefore, the study suggested parenteral testosterone would be preferable in clinical situations over oral steroids because of the latter's undesirable lipoprotein effects.[169] Other endocrine responses were reviewed with chronic 100 mg androstenedione (ASD) intake 3 times per day. The study results suggest that ASD intake did not increase serum total testosterone or prostate-specific antigen (PSA) concentrations, but it did produce increases in ASD, free testosterone, estradiol, and dihydrotestosterone with decreases in serum HDL cholesterol concentrations.[170] In support of these findings, other studies showed similar findings along with testosterone dose and concentration dependent changes negatively correlating with HDL-cholesterol and fat mass. Whereas, positive correlations were seen between testosterone concentration and fat-free mass, muscle size, strength and power, hemoglobin, and insulin-like growth factor-I levels.[171,172] Of note, sexual function, visual-spatial cognition plus mood and PSA levels did not change significantly at any dose.[171]

Another cardiac component linked to steroid abuse could be due to thrombosis risk mediated through androgen induced abnormalities of coagulation. Study results showed that steroid users in weightlifters had abnormally high concentrations of thrombin/antithrombin complexes, prothrombin fragment 1 + 1 and D-dimers compared to nonuser weightlifters. In addition, nonusers had elevated levels of tissue plasminogen activator antigen and its inhibitor than steroid users. Whereas the activities of antithrombin III and protein S were more likely to be higher in users than nonuser weightlifters. Furthermore, these changes could reflect the thrombotic predisposition that possibly contribute to vascular occlusion reported in athletes using steroids.[173] A dose-limiting adverse effect of testosterone that was studied showed erythrocytosis. Both young and older men in response to dose-dependent testosterone presented results of significantly increased hemoglobin and hematocrit but with more pronounced findings in older men. However, changes in erythropoietin (EPO) or soluble transferrin receptor (sTfR) levels were not significantly correlated with changes in total or free testosterone levels. Thus, concluding that age-related differences with testosterone-induced rises in hemoglobin and hematocrit may be mediated by factors other than EPO and sTfR.[174] A case supporting cardiac risk factors with supraphysiologic doses of IM testosterone showed that the user suffered an acute ST-segment elevation myocardial infarction along with findings of polycythemia.[175]

Infectious disease issues can arise such as HIV, hepatitis B and C, or MRSA via unsafe needle practices and/or contaminated products. In injectors of illicit AAS, exposure to hepatitis B and C viruses were detected; therefore, steroid injectors need not be overlooked in blood-borne virus prevention efforts.[176] The hepatic system could be affected but only with use of oral 17-alpha-alkylated androgens causing possible cholestasis, peliosis hepatitis or hepatic malignancy.[177]

A musculoskeletal adverse effect would include increased risk of tendon ruptures (e.g., triceps, biceps, latissimus dorsi) in AAS abusers.[178] A study reviewed triceps tendon rupture, which is a rare injury, in four weightlifters. Before the injury, two of whom had received local steroid injections in the triceps for pain and all four patients had taken oral AAS.[179] It was shown that steroids, as well as having generalized effects, cause changes in tendon structure and this is intensified by increased exercise. During exercise, the tendon becomes stiffer and absorbs less energy, so it is far more likely to fail during this time.[180]

Neuropsychiatric issues include major mood disorders, aggression/violence, or dependence. One study resulted that 23% of steroid user athletes reported major mood disturbances (mania, hypomania, or major depression) in association with steroid use.[181] Another study investigated the effects of exogenous testosterone in eugonadal group which showed no significant changes in aggression or mood levels. On the other hand, the hypogonadal treated group had significant reductions in negative mood (fatigue, anger, and tension) followed by an increase in vigor.[182] Another study supports testosterone administration (600 mg/wk) increased ratings of manic symptoms in normal men aged 20-50. However, this effect was not uniform across individuals with most showing little psychological change versus a few developed prominent effects. Therefore, the mechanism of these variables remains unclear.[183] Reports of linking illicit substance use (e.g., anabolic steroids and peptide hormones) by college students (especially male student-athletes) to an increased general tendency to engage in more risky health behaviors including increased alcohol, smoking and drug use.[184,185] Moreover, young adult males reported greater involvement in violent behavior with the use of AAS.[186]

Male reproductive problems can arise such as hypogonadism (following withdrawal), gynecomastia, acne, premature epiphyseal closure (when taken before completion of puberty), or potential increased risk for prostate cancer. In a study with men seeking treatment for symptomatic hypogonadism who have used nonprescribed AAS depends on dose, duration, and type of AAS. Treatment with use of testosterone replacement therapy, hCG and selective estrogen receptor modulators depend also on patient specific AAS detailed usage.[187] The most common cause of profound hypogonadism is prior AAS use in young men.[188] With regards to AAS induced azoospermia leading to infertility, semen analysis in bodybuilders with a history of high dose AAS use were compared to normal volunteers without any drug usage. The percentages of motile and normally formed sperm were significantly reduced in bodybuilders. Bodybuilders who ceased consumption of AAS greater than 4 months previously, sperm numbers and density eventually returned to a normal range.[189,190] On the other hand, female reproductive issues like acne, virilization (hirsutism, deepening of voice, clitoromegaly), or irregular periods could be associated with adverse effects and complications of androgenic steroids.[177]

Despite the high media presence of promoting performance-enhancing drugs (PED) in elite athletes illicitly

gaining a competitive advantage in sports, the health risks are minimally looked upon creating a widespread misperception that PED use is safe. When in fact, most PED users are nonathlete weightlifters and adverse health effects including death are greatly underappreciated, thus forming an important public health problem that needs to be further evaluated.[191]

CONCLUSION

Depression is a common disorder that affects millions of people worldwide with a higher incidence in women than men, particularly in adolescents and adults than children. Its pathophysiology is complex and is brought about by many overlapping factors including chemical, morphological, inflammatory, genetic, environmental, and endocrinal processes. There are several drug classes that can be used for the treatment of depression, with SSRIs regarded as the first-line class of drugs due to its relatively lower side effect profile. Due to individual variation, many patients do not respond to treatment which warrants augmentation with either a combination of medications, or with psychotherapy. Many novel treatments are currently being investigated and have shown promising results. One of these treatments includes testosterone therapy due to the widespread effects that testosterone has throughout the body. Studies suggest that testosterone treatment might improve depressed mood in older men who have low levels of physiologically active bioavailable testosterone since lower levels have shown to be correlated with age and increased onset of depressive symptoms. Testosterone therapy may help overcome the undesirable psychological, sexual, cognitive, and physical impairments caused by age-related hormonal changes. However, as an androgenic steroid, testosterone carries a considerable side effect profile associated with cardiovascular, musculoskeletal, neuropsychiatric, hepatic, and reproductive complications. Additionally, it remains unknown whether the symptoms of depression are caused by a deficiency of testosterone in men or if testosterone treatment is effective in treating men with depressive symptoms and disorders. Further research is needed to determine the reason for the possible antidepressant action of testosterone administration and to justify its clinical use.

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