EDITORIAL

Testosterone Treatment of Depressive Disorders in Men
Too Much Smoke, Not Enough High-Quality Evidence

Shalender Bhasin, MB, BS; Stuart Seidman, MD

The role of testosterone in the pathophysiology and treatment of depressive disorders in men has remained shrouded in controversy. We do not know whether depressive symptoms are a part of the syndrome of testosterone deficiency in men, and if so, whether testosterone replacement relieves such symptoms, whether low testosterone levels contribute to the pathophysiology of depressive disorders in men, and whether testosterone treatment is efficacious in treating men with depressive disorders. A well-performed meta-analysis by Walther et al in this issue of *JAMA Psychiatry*[1] attempts to synthesize data from randomized, placebo-controlled clinical trials to assess the association of testosterone treatment with depressive symptoms in men. Although this meta-analysis adds to the body of data that testosterone administration may be associated with small improvements in depressive symptoms, we do not know whether these improvements are clinically meaningful. These data should not be extrapolated to imply that testosterone treatment induces remission of major depressive disorder (MDD) or that it augments response to antidepressant therapy in such patients. Furthermore, neither the long-term safety nor the efficacy of testosterone therapy has been established in any depressive disorder. Because some of the adverse effects of testosterone are associated with its dose and on-treatment concentrations, the use of supraphysiologic doses of testosterone could be associated with increased risk of adverse effects and is currently not recommended.[2]

Related article

In evaluating the efficacy of any intervention, it is important to be specific about the condition for which the treatment is being tested. A major problem in evaluating this and other meta-analyses of randomized trials of the effects of testosterone on depressive disorders is that the trials included in these meta-analyses recruited heterogeneous populations of participants with diverse medical conditions; importantly, most of the trials failed to distinguish between depressive symptoms, such as dysphoric mood, anhedonia, and anergia, and depressive disorders, such as MDD and dysthymic disorder (DD, now termed *persistent depressive disorder*, with pure dysthymic syndrome in *DSM-5*).

The testosterone-depression literature can be considered from 2 different perspectives: the endocrine literature, in which mood effects have been assessed by self-report in randomized clinical trials of testosterone therapy, and the psychiatric literature, in which hypothalamic-pituitary-testicular axis function and exogenous testosterone treatment have been studied in men with interview-diagnosed MDD. Most of the randomized clinical trials of testosterone therapy have recruited androgen-deficient men who did not have any depressive disorder. For instance, in the Testosterone Trials, a set of 7 coordinated placebo-controlled trials in older men with unequivocally low testosterone levels and sexual dysfunction, impaired mobility, and/or low vitality, assignment to the testosterone arm of the trial was associated with small but statistically significantly greater improvements in mood and depressive symptoms than in those assigned to placebo.[3] However, the participants of the Testosterone Trials were not selected based on a diagnosis of a depressive disorder or even on the presence of depressive symptoms. The modest improvements in mood and depressive symptoms that were observed in the Testosterone Trials and in this meta-analysis might suggest that a poorly defined hypogonadal-type depressive condition, not necessarily overlapping with MDD, can be improved with testosterone therapy. However, the extant testosterone therapy randomized clinical trial literature, clarified by this meta-analysis, does not support the extrapolation that testosterone is efficacious in treating MDD.

Multiple large, population-based epidemiologic studies have failed to find a consistent association between circulating endogenous testosterone levels and depression.[4] In neuroendocrine studies of men with MDD, the early-morning luteinizing hormone and testosterone release is blunted in men with melancholic depression[5]; however, such studies have not shown consistently lower testosterone levels in men with MDD compared with healthy control individuals. Parenthetically, no study has reported higher testosterone levels in the depressed men than in control individuals. Finally, only a small number of rigorous randomized clinical trials have been performed in men who met *DSM-5* criteria for MDD[6,7]; these trials have failed to demonstrate consistent superiority of testosterone over placebo. Similarly, placebo-controlled trials of testosterone therapy in men with refractory depression have not consistently shown a beneficial effect of testosterone.[7] The cumulative evidence suggests that testosterone, whether administered alone or as an adjunctive therapy with traditional antidepressant therapy, tends to be ineffective in men with MDD.

In contrast to MDD and early-onset DD, late-life–onset DD has a male preponderance, is typically not associated with comorbid MDD or a family history of depressive illness, and is resistant to treatment with the usual antidepressant therapy.[8] It has been hypothesized that this distinct subgroup of late-life–onset DD is associated with age-related decline in testosterone levels and is responsive to testosterone therapy. Indeed, epidemiologic and clinical studies have found a more

consistent association between low testosterone levels and DD. Elderly men with DD have lower testosterone levels than age-matched, nondepressed men in the general population.[9-11] Further, among older dysthymic men with low testosterone levels, 2 small placebo-controlled trials have reported a mood-enhancing effect of testosterone replacement.[12,13] Such observations suggest that the age-related testosterone decline in middle-aged and older men may be associated with dysthymia, and that testosterone replacement may exert an antidepressant effect in such men.

Meta-analyses can be useful in pooling data from studies of variable sizes, some of which may not have been adequately powered, and in establishing whether the treatment effects are consistent across studies. However, this meta-analysis,[1] similar to other meta-analyses of the effects of testosterone on depressive symptoms, contains some inherent problems. The studies included in the meta-analysis were heterogeneous in their study populations, eligibility criteria, testosterone doses and formulations, intervention durations, and in the quality of outcome ascertainment. Most of the trials were not conducted in men with a rigorously established diagnosis of MDD or even in men with depressive symptoms. Only a handful of trials were conducted in men with MDD or DD diagnosed using interview-elicited, standardized diagnostic criteria. Some trials included men who met the definition of hypogonadism; however, many trials included men with normal testosterone levels. Thus, meta-analyses of such heterogeneous populations of men with diverse conditions, many of whom did not have a depressive disorder or even depressive symptoms, do not permit strong inferences about the efficacy of testosterone treatment in inducing remission of depression.

In summary, this meta-analysis suggests that among nondepressed hypogonadal men, testosterone replacement may enhance mood. Overall, some epidemiologic evidence and a limited amount of clinical trials' evidence suggests that a late-life–onset DD may be associated with late-onset hypogonadism; randomized trials of the efficacy of testosterone replacement as a specific antidepressant therapy in such men are warranted. A large placebo-controlled, randomized, double-blind, multicenter study of topical testosterone replacement therapy in 6000 symptomatic hypogonadal men at increased risk for cardiovascular disease is currently being conducted in the United States (the TRAVERSE trial). One substudy of the TRAVERSE trial will determine the efficacy of testosterone replacement therapy in inducing remission of depression in middle-aged and older hypogonadal men with late-onset DD. Until then, the clinicians should follow the Endocrine Society guideline for testosterone replacement therapy of androgen-deficient men[2]; the available data do not support the use of testosterone treatment, especially in supraphysiologic doses, for the treatment of depressive disorders in men.

ARTICLE INFORMATION

Author Affiliations: Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts (Bhasin); Research Program in Men's Health: Aging and Metabolism, Brigham and Women's Hospital, Boston, Massachusetts (Bhasin); Boston Claude D. Pepper Older Americans Independence Center, Brigham and Women's Hospital, Boston, Massachusetts (Bhasin); Columbia University, New York, New York (Seidman).

Corresponding Author: Shalender Bhasin, MB, BS, Brigham and Women's Hospital, 221 Longwood Ave, Boston, MA 02115 (sbhasin@bwh.harvard.edu).

Published Online: November 14, 2018. doi:10.1001/jamapsychiatry.2018.2661

Conflict of Interest Disclosures: Dr Bhasin reports receiving research grants from the National Institute on Aging, the National Institute of Nursing Research, the National Center for Medical Rehabilitation Research of the Eunice Kennedy National Institute of Child Health and Human Development, the Foundation of the National Institute of Health, the Patient Centered Outcome Research Institute, AbbVie, Transition Therapeutics, Alivegen, and Metro International Biotechnology; receiving consulting fees from AbbVie and OPKO; and having equity interest in FPT Information System, LLC. No other disclosures were reported.

REFERENCES

1. Walther A, Breidenstein J, Miller R. Association of testosterone treatment with alleviation of depressive symptoms in men: a systematic review and meta-analysis [published online November 14, 2018]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2018.2734.

2. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744. doi:10.1210/jc.2018-00229

3. Snyder PJ, Bhasin S, Cunningham GR, et al; Testosterone Trials Investigators. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;374(7):611-624. doi:10.1056/NEJMoa1506119

4. Seidman SN, Araujo AB, Roose SP, McKinlay JB. Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. *Biol Psychiatry*. 2001;50(5):371-376. doi:10.1016/S0006-3223(01)01148-9

5. Schweiger U, Deuschle M, Weber B, et al. Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. *Psychosom Med*. 1999;61(3):292-296. doi:10.1097/00006842-199905000-00007

6. Seidman SN, Spatz E, Rizzo C, Roose SP. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry*. 2001;62(6):406-412. doi:10.4088/JCP.v62n0602

7. Pope HG Jr, Amiaz R, Brennan BP, et al. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. *J Clin Psychopharmacol*. 2010;30(2):126-134. doi:10.1097/JCP.0b013e3181d207ca

8. Devanand DP, Nobler MS, Singer T, et al. Is dysthymia a different disorder in the elderly? *Am J Psychiatry*. 1994;151(11):1592-1599. doi:10.1176/ajp.151.11.1592

9. Seidman SN, Araujo AB, Roose SP, et al. Low testosterone levels in elderly men with dysthymic disorder. *Am J Psychiatry*. 2002;159(3):456-459. doi:10.1176/appi.ajp.159.3.456

10. Markianos M, Tripodianakis J, Sarantidis D, Hatzimanolis J. Plasma testosterone and dehydroepiandrosterone sulfate in male and female patients with dysthymic disorder. *J Affect Disord*. 2007;101(1-3):255-258. doi:10.1016/j.jad.2006.11.013

11. Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry*. 2004;61(2):162-167. doi:10.1001/archpsyc.61.2.162

12. Shores MM, Kivlahan DR, Sadak TI, Li EJ, Matsumoto AM. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J Clin Psychiatry*. 2009;70(7):1009-1016. doi:10.4088/JCP.08m04478

13. Seidman SN, Orr G, Raviv G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. *J Clin Psychopharmacol*. 2009;29(3):216-221. doi:10.1097/JCP.0b013e3181a39137