

# Long-term outcome studies of testosterone therapy in older hypogonadal men: waiting for Godot?

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As men age, a gradual decline in serum testosterone levels occurs that is accompanied by reductions in muscle and bone mass, sexual function, vitality and cognitive function and increases in fat mass. Similar alterations occur in young men with severe androgen deficiency and improve with testosterone therapy. It seems logical to assume, then, that androgen deficiency in older men will also respond to testosterone therapy. Hypogonadism in this population is clinically challenging, however, as comorbidities and medications can cause nonspecific manifestations similar to androgen deficiency and alterations in total testosterone measurements that can confound the diagnosis. In addition, there is some concern that testosterone therapy in older men might increase the risk of prostate cancer and cardiovascular disease.

Firm data on the benefits of testosterone therapy in older hypogonadal men are currently lacking. Short-term, randomized trials in small numbers of older men with low or low-to-normal testosterone levels have demonstrated consistent increases in lean mass (mainly muscle mass) and decreases in fat mass. Some, but not all, of these studies have also demonstrated improvements in parameters, such as physical, sexual and cognitive function. Nevertheless, a large randomized trial designed to assess the long-term effects of testosterone therapy was halted after approval and partial funding, in large part because of the potential increased risk of prostate cancer.

After reviewing the published studies, an Institute of Medicine committee concluded in 2004 that there was insufficient evidence for the overall efficacy of testosterone therapy in older hypogonadal men. The committee recommended additional studies to assess the effect of testosterone therapy on physical, sexual and cognitive function, and vitality in this population.

**...failure to conduct such a study will leave the aging man, as well as his family and physician, in a state of uncertainty**

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## Competing interests

AM Matsumoto declared associations with the following companies: Amgen, Ascend, Auxilium, GlaxoSmithKline, GTx, and Solvay. WJ Bremner declared an association with the following companies: Clarus and GlaxoSmithKline. See the article online for full details of the relationships.

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Inconsistent results from previous studies might reflect a number of factors: small study cohorts; inclusion of eugonadal men and men without symptoms or signs of androgen deficiency; failure to achieve consistently normal testosterone levels; short duration of therapy; and use of insensitive outcome measures. The National Institute on Aging (NIA) and an industry partner have recently funded a study (The Testosterone Trial) to address these limitations. The NIA study will be a short-term, randomized, double-blind, placebo-controlled trial of testosterone therapy in men with unequivocally low serum testosterone concentrations, and symptoms and impairments in one or more of four key areas. Unfortunately, the results will probably not be available for at least 6 years.

Some recent epidemiological studies have found that low testosterone levels are associated with important adverse clinical outcomes, such as type 2 diabetes mellitus, fractures, depression, dementia, cardiovascular disease, and mortality. Although the NIA study represents a valuable addition, and should provide more definitive results about the short-term efficacy of testosterone therapy in older hypogonadal men, it will not address the long-term clinical benefits and risks. An adequately powered, randomized, placebo-controlled clinical trial of testosterone treatment on clinically important outcomes—fundamentally a ‘Men’s Health Initiative’—is needed to provide the evidence base to guide clinical practice. This study should include adequate numbers (at least 6,000 men) and be of sufficient duration (at least 6–8 years) to determine whether there are positive effects on clinically relevant end points, as well as negative effects on prostate disease. Just like the characters in Beckett’s play, failure to conduct such a study will leave the aging man, as well as his family and physician, in a state of uncertainty.