

Testosterone and Aging

Clinical Research Directions

Committee on Assessing the Need for Clinical Trials
of Testosterone Replacement Therapy

Board on Health Sciences Policy

Catharyn T. Liverman, Dan G. Blazer, *Editors*

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Willing is not enough; we must do.”*
—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Robert B. Wallace**, Professor of Epidemiology and Internal Medicine, College of Public Health, University of Iowa. Appointed by the National Research Council and Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

In the popular literature, testosterone has been linked with youth, vitality, and strength. These perceptions seem to fuel interest in the use of testosterone as a means of delaying or averting the effects of aging, as is evident by the growing numbers of middle-aged and older men using testosterone products.

In November 2002, the National Institute on Aging and the National Cancer Institute requested that the Institute of Medicine conduct a study to provide an independent assessment of clinical research on testosterone therapy and make recommendations on future research directions for this field.

As the committee examined the state of research on testosterone therapy, it was struck by the paucity of randomized controlled clinical trials, particularly in middle-aged or older men. Those clinical trials that have been conducted are generally of short duration and involved small numbers of participants. In some ways this is not surprising, as testosterone products have been approved by the Food and Drug Administration primarily to treat hypogonadism, a medical condition that can occur in younger men and involves markedly low levels of testosterone and other symptoms. Many of the studies of testosterone therapy to date have thus been in young hypogonadal males. Further, conducting clinical trials of testosterone therapy in older men is fraught with complexities, particularly considerations regarding the potential effects of testosterone on the prostate gland and other potential adverse health outcomes.

The committee's task was to identify the research needed to determine if testosterone is an efficacious treatment option for older men. This approach does not directly address the research needed to determine whether current off-label use, particularly by middle-aged men, is either efficacious or safe. The committee has concerns about the growing use of testosterone by men who do not meet the clinical definition of hypogonadism in the absence of controlled trials needed to determine efficacy and safety.

This is an opportune time for examining the efficacy of testosterone therapy in aging men while carefully monitoring for safety. The use of testosterone continues to escalate at a rapid rate, and more data are needed for informed

decisions. This is also a time when women's postmenopausal hormone therapy is at the forefront of health issues, and the public is in the midst of sorting out new research results and realizing the complexities of hormone therapy issues in general.

It was a privilege to chair this Institute of Medicine committee whose members brought their breadth and depth of knowledge to bear on this important topic. The committee's work greatly benefited from the input it received from researchers in the field who made presentations at the committee's scientific workshop and committee meetings, and from the staff members of the sponsoring federal agencies. The committee truly appreciates the work of IOM staff members Ben Hamlin and Judy Estep who provided outstanding research and organizational support for the committee's work. Last, but certainly not least, it has been a true pleasure to work on this project with Cathy Liverman. I could not have asked, nor could have the committee, for more assistance. In addition, she made important substantive contributions to our deliberations.

The committee hopes that this report will provide useful guidance to the National Institute on Aging, the National Cancer Institute, and other interested parties as they consider next steps for research on testosterone therapy. The report may also be informative for men considering this therapy as they, along with their health professionals, become aware of the extant research available to date on potential long-term benefits and harms of testosterone therapy in aging men. Research opportunities abound, and randomized clinical trials are critical to provide the data for informed clinical decisions.

Dan G. Blazer

Chair

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ES-1 Key Conclusions and Considerations

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2-1 Major Cohort Studies Examining Endogenous Testosterone Levels and Health Outcomes

3-1 Key Conclusions and Considerations

3-2 Recommendations

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Executive Summary

Testosterone is often equated in the popular culture with the macho male physique and virility. Viewed by some as an *anti-aging tonic*, the growth in testosterone's reputation and increased use by men of all ages in the United States has outpaced the scientific evidence about its potential benefits and risks. In recent years there has been growing concern about an increase in the use of testosterone by middle-aged and older men who have borderline testosterone levels—or even normal testosterone levels—in the absence of adequate scientific information about its risks and benefits.

In 2002, the National Institute on Aging (NIA) and the National Cancer Institute (NCI) of the National Institutes of Health (NIH) asked the Institute of Medicine (IOM) to conduct a 12-month study to review and assess the current state of knowledge related to the potential beneficial and adverse health effects of testosterone therapy in older men, and to make recommendations regarding clinical trials of testosterone therapy, including the parameters that should be considered in study design and conduct.

As an FDA-approved treatment for male hypogonadism, testosterone therapy has been found to be effective in ameliorating a number of symptoms in markedly hypogonadal males. Researchers have carefully explored the benefits of testosterone therapy in this population. However, there have been fewer studies, particularly placebo-controlled randomized trials, in populations of middle-aged or older men who do not meet all the clinical diagnostic criteria for hypogonadism but who may have testosterone levels in the low range for young adult males and show one or more symptoms that are common to both aging and hypogonadism. Further, studies of testosterone therapy in older men generally have been of short duration, involving small numbers of participants, and often lacking adequate controls. In its review of the literature the committee identified only 31 placebo-controlled trials of testosterone therapy in older men. The placebo-controlled trial with the largest sample size involved 108 participants and the duration of therapy in 25 of the 31 trials was 6 months or less. Only one placebo-controlled trial lasted longer than a year. Therefore, assessments of risks

and benefits have been limited, and uncertainties remain about the value of this therapy for older men.

CLINICAL TRIALS OF TESTOSTERONE THERAPY IN OLDER MEN

Before weighing the options for future research directions, the committee reached several general conclusions that serve as the rationale for its recommendations (Box ES-1). The committee felt that the first and most immediate goal is to establish whether treatment with testosterone results in clear benefits in aging men. In the committee's determination this could be accomplished in a set of efficacy trials with a study population of older men (65 years and older) who have clinically low testosterone levels and at least one symptom that might be related to low testosterone.

Secondly, given the potential risks of testosterone therapy and the availability of other safe and effective therapeutic intervention options for some of the diseases and conditions it is intended to treat (e.g., bisphosphonates for osteoporosis), the committee felt that testosterone should be considered a therapeutic, not a preventive, measure. Thus, trials of testosterone therapy should be conducted in men with symptoms or conditions that might benefit from a therapeutic intervention.

A third consideration focused on using resources most effectively. A fundamental challenge in assessing the possible benefits and risks of testosterone therapy is that the sample size and follow-up time needed to assess efficacy for potential benefits such as improvements in strength, cognition, mood, and sexual function are substantially less than those needed to assess the risks of prostate cancer and cardiovascular disease. For example, studies to assess the potential benefit of testosterone therapy in elderly men who are frail and testosterone-deficient would likely require fewer than 500 persons followed for one year. In contrast, a study that would provide the information needed to assess a

BOX ES-1

Key Conclusions and Considerations

- Focus on the population most likely to benefit.
- Use testosterone as a therapeutic intervention, not as a preventive measure.
- Establish a clear benefit before assessing long-term risks.
- Focus on clinical outcomes in which there is a preliminary suggestion of efficacy and for which safe and effective therapeutic options are not currently available.
- Ensure safety of the research participants.

moderate increase in the risk of prostate cancer might require 5,000 men followed for 3 to 5 years. In the committee's opinion, it is important to firmly establish benefit in the target population before expending the time and effort necessary to study the potential for long-term risks and benefits of testosterone therapy. Trials of efficacy can be accomplished in smaller populations and in shorter time frames. Although the research to date shows suggestions of outcomes in which testosterone may show efficacy, the benefits of testosterone therapy in older men have not been clearly established. If clear efficacy cannot be demonstrated, then large scale trials are not indicated.

Fourthly, the committee determined that clinical trials should focus on those health outcomes and conditions among older men for which there is preliminary evidence of the efficacy of testosterone therapy and for which safe and effective therapeutic options are not currently available. The most promising potential benefits of testosterone therapy, in the opinion of the committee, are improvement in weakness, frailty, and disability; sexual dysfunction; cognitive dysfunction; and vitality, well-being, and quality of life among older men with low testosterone levels. Lower priority should be placed on establishing benefit for conditions in which there is already effective pharmacotherapy, such as fracture prevention.

Finally, and most importantly, in any clinical trial, the utmost consideration is minimizing risks to research participants. The committee believes that it is possible to ethically and safely conduct clinical trials of testosterone therapy in older men as long as strict exclusion criteria are developed and implemented and monitoring practices are carefully followed.

Overview of Recommended Clinical Trials

In implementing the general conclusions and rationale discussed above, the committee encourages clinical research efforts to initially focus on determining the benefits of testosterone therapy in older men as compared with placebo controls, and then, contingent on finding benefit(s), focus on assessing long-term risks and benefits. This rationale will determine that testosterone is a viable therapeutic option in older men before expending the time and resources to determine long-term risks. The committee recommends that the initial short-term efficacy trials focus on examining whether testosterone improves one or more of the following clinical outcomes: strength/frailty/disability; cognitive function; sexual function; or vitality/well-being/quality of life. The initial efficacy effort could be designed as a coordinated set of trials structured through a cooperative agreement or other similar mechanism. Such a coordinated approach would provide for standardization of data collection methods across study sites to ensure that the results on common study endpoints can be analyzed in aggregate. In this way, all participants would contribute to the short-term assessment of risk, and more information would be gathered on potential benefits as well. If adequate benefits are observed in the initial trials, the next effort would involve a larger

scale and longer-term study that would require careful planning to most effectively protect research participants.

Recommendation 1. Conduct Clinical Trials in Older Men. The committee recommends that the National Institute on Aging and other research agencies and institutions conduct clinical trials of testosterone therapy in older men with low testosterone levels. Initial trials should be designed to assess efficacy. Studies to assess long-term risks and benefits should be conducted only if clinically significant benefit is documented in the initial trials.

Recommendation 2. Begin with Short-Term Efficacy Trials to Determine Benefit. The committee recommends an initial focus on conducting short-term randomized double-blind, placebo-controlled efficacy trials of testosterone therapy in older men to determine potential health benefits and risks.

Recommendation 3. Conduct Longer-Term Studies if Short-Term Efficacy is Established. The committee recommends that if clinically significant benefits of testosterone therapy are seen in the initial studies of older men, then larger-scale clinical trials should be conducted to assess the potential for long-term risks and benefits. The targeted population for these studies, their duration, and the long-term risks and benefits to be assessed would vary depending on the findings of the initial studies.

PROTECTION OF RESEARCH PARTICIPANTS

It is an axiom of research ethics that risks to research participants be minimized and that risks are reasonable in proportion to the potential benefits of participating in the study. Any clinical study designed to determine the efficacy of testosterone therapy in the aging male must manage the risk of prostate diseases, specifically benign prostatic hyperplasia and prostate cancer. There remain many unknowns regarding the extent or mechanisms by which testosterone or its metabolite, dihydrotestosterone, may be involved in modifying the risk of adverse prostate outcomes. Nevertheless, concerns about possible adverse effects necessitate careful attention to exclusion criteria and adverse event monitoring to minimize risks to research participants. The committee acknowledges the concerns about potential adverse effects and the unique dilemmas posed by detecting prostate cancer in populations of older men in which subclinical cancers may otherwise go undetected and not become a health concern. This area is made exceedingly complex by controversies and trade-offs about when and how to intervene. After carefully examining the issues and weighing the ethical considerations, the committee determined that older men participating in clinical

trials of testosterone therapy can be fully informed, provide voluntary consent to participate, and be adequately protected against potential adverse effects.

All of these considerations are, of course, integral to the ethical norms for the standard conduct of clinical trials, as regulated by human research protection regulations and applied by institutional review boards. However, the committee felt it was important to emphasize these practices and provide detailed discussion, as testosterone therapy in older men is an area of research that is made complex, and at times controversial, by ethical considerations regarding the safety of research participants.

Recommendation 4. Ensure Safety of Research Participants.

The committee recommends a system for minimizing risk and protecting participants in clinical trials of testosterone therapy.

The committee recommends:

- **Strict exclusion criteria, such as for men who are at high risk for developing prostate cancer or for requiring an intervention to treat benign prostatic hyperplasia (BPH);**
- **Careful participant monitoring for changes in prostate specific antigen (PSA) levels or in the digital rectal examination (DRE) and for other adverse effects;**
- **Incorporating into the trial design the interim monitoring of trial results, stopping guidelines, and other measures deemed appropriate, particularly for long-term studies;**
- **Careful planning to address prostate risk issues. In long-term clinical trials, the primary safety endpoint will be increased incidence of prostate cancer. Ascertaining such an increase could be complicated by prevalent occult prostate cancer and detection bias associated with testosterone-induced PSA elevation leading to an increased number of biopsies. There should be careful consideration of these issues in the planning of long-term trials of testosterone therapy.**
- **Attention to communicating risks and benefits to study participants, particularly in light of multiple outcomes and the potential for long-term risks. This will be especially important for long-term clinical trials.**

RESEARCH ISSUES

There is still much to be learned about changes in endogenous testosterone levels associated with aging and the impact of those changes on health outcomes. Research has shown that testosterone levels in men decline with age, but more research is needed to determine how declining endogenous testosterone levels are associated with health outcomes during aging. It is unclear whether low testosterone levels are a marker of poor health, a contributing factor, or both. There are many research challenges in sorting out the role of testosterone and how testosterone interrelates with other hormones and with the myriad of other genetic, environmental, and biologic factors occurring during aging. Additionally, there are many unknowns regarding exogenous testosterone administration. Therefore, the committee believes that further investigator-initiated research should be pursued on a range of areas regarding endogenous and exogenous testosterone.

Recommendation 5. Conduct Further Research. In addition to the research strategy for clinical trials recommended above, the committee recommends further investigator-initiated research on such issues as physiologic regulation of endogenous testosterone levels, mechanism of action of testosterone, and age-related changes in testosterone levels.

CONCLUDING REMARKS

Despite the increasing popularity of testosterone treatment, there is not a large body of data to suggest the efficacy of testosterone therapy in older men who do not meet the clinical definition of hypogonadism. Moreover, the effects of testosterone on the prostate and its implications for cancer warrant caution in extensive nontherapeutic use.

Although the focus of this report is on testosterone therapy in older men, the committee realized that the large and growing population of middle-aged men using testosterone products also raises important public health concerns about the benefits and risks in this age group. Some of the results of trials in older men should shed light on the possible benefits in these areas of testosterone therapy in younger men. However, information about some putative risks—for example, prostate cancer and cardiovascular morbidity—associated with testosterone therapy for older men may not be very informative about the risks in younger men. Relatively small clinical trials of the benefits of testosterone therapy in middle-aged men could readily be fielded as additional arms of the initial efficacy trials recommended above. However, studies of longer-term risks could be much more difficult. Because of the low incidence of morbidity in this population, such trials would likely need to be very large and of long duration. Observational studies may be of only limited value because of their uncontrolled nature and possible selection biases.

Because of the considerable challenges in assessing long-term risk in younger men, it may be prudent to await the results of such studies in older men. At the present time a large-scale clinical trial in middle-aged men does not appear to be the logical next step in testosterone therapy research. It may be feasible and useful to use other research approaches to obtain information on testosterone therapy in middle-aged men. In addition, a new class of compounds—selective androgen receptor modulators (SARMs)—may provide an alternative to the use of testosterone as they appear to have androgenic effects similar to testosterone on muscle mass, sexual function, and bone density in animal models, while apparently causing little or no harm to the prostate.

Experience with the use of postmenopausal hormone therapy in women and the growing body of scientific evidence about its risks and potential benefits provides an apt and timely example of the need for sustained, systematic analysis of short- and long-term effects of new treatments and the caution that must be exercised in widely prescribing drugs as preventive measures. Clearly, empirical evidence about testosterone therapy is needed. Currently testosterone therapy is an attractive option as speculation abounds regarding its potential. What is needed is the research to determine if testosterone therapy is also a rational option for older men.

RECOMMENDATIONS

Summarized in Box ES-2, the recommendations emphasize an approach that the committee believes will most effectively and efficiently determine if testosterone is a therapeutic option for older men, taking into consideration its relative risks and benefits.

BOX ES-2**RECOMMENDATIONS**

Recommendation 1. Conduct Clinical Trials in Older Men. The committee recommends that the National Institute on Aging and other research agencies and institutions conduct clinical trials of testosterone therapy in older men with low testosterone levels. Initial trials should be designed to assess efficacy. Studies to assess long-term risks and benefits should be conducted only if clinically significant benefit is documented in the initial trials.

Recommendation 2. Begin with Short-Term Efficacy Trials to Determine Benefit. The committee recommends an initial focus on conducting short-term randomized double-blind, placebo-controlled efficacy trials of testosterone therapy in older men to determine potential health benefits and risks. Consideration should be given to the following issues in designing the initial trials:

Recommendation 2a. Study Population for Initial Trials. Participants in the initial trials should be men 65 years of age and over with testosterone levels below the physiologic levels of young adult men and with one or more symptoms that might be related to low testosterone.

Recommendation 2b. Testosterone Preparation and Dosages. Routes of testosterone administration and dosages should achieve testosterone levels that do not exceed the physiologic range of a young adult male. When feasible, multiple dose regimens and types of interventions should be compared.

Recommendation 2c. Primary Outcomes. The primary outcomes to be examined in the initial trials should be clinical endpoints for which there have been suggestions of efficacy, particularly where there are not clearly effective and safe alternative pharmacologic therapies. These outcomes include weakness/frailty/disability; sexual dysfunction; cognitive dysfunction; impaired vitality/well-being/quality of life.

Recommendation 2d. Coordination of Clinical Trials. Initial and subsequent trials should be coordinated under a cooperative agreement or similar mechanism to produce a common core data set that would maximize the information obtained from the different studies.

Recommendation 3. Conduct Longer-Term Studies if Short-Term Efficacy is Established. The committee recommends that if clinically significant benefits of testosterone therapy are seen in the initial studies of older men, then larger-scale clinical trials should be conducted to assess the potential for long-term risks and benefits. The targeted population for these studies,

their duration, and the long-term risks and benefits to be assessed would vary depending on the findings of the initial studies.

Recommendation 4. Ensure Safety of Research Participants. The committee recommends a system for minimizing risk and protecting participants in clinical trials of testosterone therapy. The committee recommends:

- Strict exclusion criteria, such as for men who are at high risk for developing prostate cancer or for requiring an intervention to treat BPH;
- Careful participant monitoring for changes in PSA levels or in the DRE and for other adverse effects;
- Incorporating into the trial design the interim monitoring of trial results, stopping guidelines, and other measures deemed appropriate, particularly for long-term studies;
- Careful planning to address prostate risk issues. In long-term clinical trials, the primary safety endpoint will be increased incidence of prostate cancer. Ascertaining such an increase could be complicated by prevalent occult prostate cancer and detection bias associated with testosterone-induced PSA elevation leading to an increased number of biopsies. There should be careful consideration of these issues in the planning of long-term trials of testosterone therapy.
- Attention to communicating risks and benefits to study participants, particularly in light of multiple outcomes and the potential for long-term risks. This will be especially important for long-term clinical trials.

Recommendation 5. Conduct Further Research. In addition to the research strategy for clinical trials recommended above, the committee recommends further investigator-initiated research on such issues as physiologic regulation of endogenous testosterone levels, mechanism of action of testosterone, and age-related changes in testosterone levels.