



## Effective Health Care

### Low Testosterone in Men

#### Results of Topic Selection Process & Next Steps

The nominator, American College of Physicians (ACP), is interested in a new systematic review on the treatment of low testosterone in adult men to inform the creation of a new guideline. Specifically, ACP is interested in the benefits and harms of testosterone replacement therapy (TRT) for men with low or low normal testosterone and whether these benefits and harms vary by individual characteristics.

We identified an in-process review that will cover the scope of this nomination. It will be used to inform a guideline by the American Urological Association. The review will be made available by the guideline developer upon request. Therefore, a new review would be duplicative of an in-process product. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

#### Topic Brief

**Topic Name:** Low Testosterone in Men

**Topic #:** 0688

**Nomination Date:** June 29, 2016

**Topic Brief Date:** November 23, 2016

#### Authors

Stephanie Veazie  
Kara Winchell  
Rose Relevo  
Ryan McKenna  
Mark Helfand

**Conflict of Interest:** None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

#### Summary of Key Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: We identified 6 completed and 5 in-process reviews examining testosterone-replacement therapy in adult men. One in-process review is currently being conducted to inform a guideline by the American Urological Association. It will fully cover the scope of the nomination.

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## Introduction

Low testosterone in men has been linked to erectile dysfunction, infertility, fatigue, osteoporosis, hot flashes and a decrease in muscle mass.<sup>1</sup> Between 2010 and 2013, the number of patients receiving testosterone replacement therapy (TRT) in the U.S. increased from about 1.3 million to 2.3 million, with 60% prescribed by primary care physicians.<sup>2</sup> In 2014, an FDA advisory committee examined evidence on the safety of TRT for men with age-related hypogonadism, as recent research suggested TRT may be associated with increased cardiovascular risk.<sup>3</sup> The committee voted to limit the current indication to only those with classic (ie, not age-related) hypogonadism and supported the need for additional studies on the benefits and harms of TRT.<sup>3</sup>

Topic nomination #0688 was received on June 29, 2016. It was nominated by the American College of Physicians (ACP). After discussion with the nominator, they requested that we focus on the third key question of the nomination, focused on treatment. The key question for this nomination is:

Key Question 1. What are the benefits and harms of testosterone replacement therapy for men with low or low normal testosterone or free testosterone, and are these benefits and harms affected by:

- a. Baseline testosterone or free testosterone level
- b. Baseline symptoms
- c. Age
- d. Obesity
- e. Opioid use

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes of interest. See Table 1.

**Table 1.** Key Question and PICOs

Key Question	1. What are the benefits and harms of testosterone replacement therapy (TRT) for men with low or low normal testosterone or free testosterone, and are these benefits and harms affected by: a. Baseline testosterone or free testosterone level b. Baseline symptoms c. Age d. Obesity e. Opioid use
Population	Adult men with low or low normal testosterone without a clear clinical cause for hypogonadism other than aging, obesity, or chronic opiate use.
Interventions	TRT
Comparators	No TRT, including placebo
Outcomes	Benefits (eg, reduction of symptoms of fatigue, weakness, sexual dysfunction, and hot flashes; improvement in mental health; improvement in physical health; improved quality of life)  Harms (including but not limited to increased mood/anger symptoms, polycythemia, clots, increased risk of prostate cancer, cardiac events)

Abbreviations: TRT= testosterone replacement therapy

## Methods

To assess topic nomination #0688 *Low Testosterone in Men* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of each step in our assessment determining the need for further evaluation of the next step. Details related to our assessment are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States. -
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
  
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

### Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

### Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions. Appendix B includes the list of the sources searched and potentially relevant titles identified by our research librarian.

### Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

## Results

### Appropriateness and Importance

This is an appropriate and important topic. Between 2010 and 2013, the number of patients receiving testosterone replacement therapy in the U.S. increased from 1.3 million to 2.3 million.<sup>2</sup> Testosterone deficiency in the United States may be directly responsible for \$190-525 billion in health care costs over a 20 year period.<sup>4</sup> See appendix A for details.

### Desirability of New Review/Duplication

A new evidence review examining treatment for low testosterone in men would be duplicative of an in-process product. See Table 2, Duplication column for the systematic review citations that were determined to address the key question.

**Table 2.** Key question with the identified corresponding evidence reviews

Key Question	Duplication (Completed or In-Process Evidence Reviews)
KQ 1. Benefits and harms of testosterone replacement therapy	Total number of completed or in-process systematic reviews: 11 • Other: 6 <sup>5-10</sup> • Other (in process): 5 <sup>11-15</sup>
KQ 1a. Effects by baseline testosterone level	Total number of completed or in-process systematic reviews: 2 • Other: 1 <sup>5</sup> • Other (in process): 1 <sup>15</sup>

KQ 1b. Effects by baseline symptoms	Total number of completed or in-process systematic reviews: 2 • Other (in process): 2 <sup>14,15</sup>
KQ 1c. Effects by Age	Total number of completed or in-process systematic reviews: 6 • Other: 1 <sup>6</sup> • Other (in process): 5 <sup>11-15</sup>
KQ 1d. Effects by Obesity	Total number of completed or in-process systematic reviews: 2 • Other (in-process): 2 <sup>14,15</sup>
KQ 1e. Effects by Opioid Use	Total number of completed or in-process systematic reviews: 1 • Other (in-process): 1 <sup>15</sup>

Abbreviations: TRT= Testosterone replacement therapy

## Summary of Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: We identified 6 completed<sup>5-10</sup> and 5 in-process<sup>11-15</sup> reviews examining testosterone-replacement therapy in adult men. One in-process review<sup>15</sup> to inform an American Urological Association guideline will fully cover the scope of the nomination. It will be made available upon request by the guideline developer.

## References

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14. Van den Broeck T, Dimitropoulos, K, Verze, P, Yuan, Y, Lam, T, Arver, S, Salonia, A. What are the benefits and harms of testosterone treatment for male sexual dysfunction? 2015; [http://www.crd.york.ac.uk/prospero/display\\_record.asp?ID=CRD42015028029](http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015028029). Accessed August 22, 2016.
15. American Urological Association. Protocol for a Systematic Review on Testosterone Replacement Therapy. 2016.

## Appendix A. Selection Criteria Summary-

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus of this review is on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. Between 2010 and 2013, the number of patients receiving testosterone replacement therapy in the U.S. increased from about 1.3 million to 2.3 million. <sup>2</sup>
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic is of high public interest. In 2014, a FDA advisory committee examined the safety of TRT for age-related hypogonadism, as recent studies indicated TRT was associated with increased cardiovascular risk. <sup>3</sup>
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of treatment of low testosterone.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, testosterone deficiency in the United States may be directly responsible for \$190-525 billion in health care costs over a 20 year period. <sup>4</sup>
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	We identified 6 completed <sup>5-10</sup> and 5 in-process <sup>11-15</sup> reviews examining testosterone-replacement therapy in adult men. One in-process review <sup>15</sup> will fully cover the scope of the nomination.

## Appendix B. Search for Systematic Reviews (Duplication)

Listed below are the sources searched and results of our search for existing and in-process systematic reviews. A research librarian conducted the search and selected potentially relevant evidence based on the key question in the nomination and the associated PICO. An investigator reviewed each of the links to evidence below for inclusion. The links below do not represent the evidence selected for inclusion (see main topic brief).

Treatment of Low Testosterone in Adult Men	
Source	Evidence
<b>Search for Duplication: August 16, 2016</b>	
<b>AHRQ and Other Federal Products</b>	
AHRQ: Evidence reports and technology assessments, USPSTF recommendations, and related DEcIDE projects, and Horizon Scan	None.
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program	None.
Cochrane Systematic Reviews and Protocols <a href="http://www.cochranelibrary.com/">http://www.cochranelibrary.com/</a>	None.
PubMed Health <a href="http://www.ncbi.nlm.nih.gov/pubmedhealth/">http://www.ncbi.nlm.nih.gov/pubmedhealth/</a>	<p><b><i>Synergetic effect of testosterone and phosphodiesterase-5 inhibitors in hypogonadal men with erectile dysfunction: A systematic review. 2012</i></b>  <a href="http://www.ncbi.nlm.nih.gov/pubmed/23093538">http://www.ncbi.nlm.nih.gov/pubmed/23093538</a></p> <p><b><i>Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. 2014</i></b>  <a href="http://www.ncbi.nlm.nih.gov/pubmed/24501728">http://www.ncbi.nlm.nih.gov/pubmed/24501728</a></p> <p><b><i>Testosterone supplementation and sexual function: a meta-analysis study. 2014</i></b>  <a href="http://www.ncbi.nlm.nih.gov/pubmed/24697970">http://www.ncbi.nlm.nih.gov/pubmed/24697970</a></p>
HTA (CRD database): Health Technology Assessments <a href="http://www.crd.york.ac.uk/crdweb/">http://www.crd.york.ac.uk/crdweb/</a>	None.
PROSPERO Database (international prospective register of systematic reviews and protocols) <a href="http://www.crd.york.ac.uk/prospero/">http://www.crd.york.ac.uk/prospero/</a>	<p><b><i>Beneficial and harmful effects of testosterone use in men: a systematic review and meta-analysis</i></b>  <a href="http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015019259">http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015019259</a></p>



	<p><i>Efficacy and safety of testosterone replacement therapy in adult men: a systematic review and network meta-analysis</i>  <a href="http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014009963">http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014009963</a></p> <p><b><i>Testosterone and its derivatives for the treatment of sarcopenia in elderly males: a systematic review and meta-analysis</i></b>  <a href="http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014009226">http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014009226</a></p> <p><b><i>The effect of testosterone replacement therapy on erythropoiesis in middle aged and aged men: a systematic review protocol</i></b>  <a href="http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015015839">http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015015839</a></p> <p><b><i>What are the benefits and harms of testosterone treatment for male sexual dysfunction?</i></b>  <a href="http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015028029">http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015028029</a></p>
<p>CADTH (Canadian Agency for Drugs and Technologies in Health)  <a href="https://www.cadth.ca/">https://www.cadth.ca/</a></p>	<p>None.</p>
<p>DoPHER (Database of promoting health effectiveness reviews)  <a href="http://eppi.ioe.ac.uk/webdatabases4/intro.aspx?ID=9">http://eppi.ioe.ac.uk/webdatabases4/intro.aspx?ID=9</a></p>	<p>None</p>
<p>ECRI institute  <a href="https://www.ecri.org/Pages/default.aspx">https://www.ecri.org/Pages/default.aspx</a></p>	<p>None.</p>