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Testosterone replacement therapy is currently the standard of treatment for hypogonadism, however, testosterone replacement alone is not always sufficient due to the multiple metabolic pathways involved in the transformation or breakdown of testosterone.¹

Testosterone is converted to estradiol via aromatase. Estrogens such as estradiol generate negative feedback to the hypothalamus and pituitary gland reducing the amount of follicle stimulating hormone (FSH) and luteinizing hormone (LH) secreted. This negative feedback loop resulting in reduction of FSH and LH (gonadotropins) decreases testosterone production which can compromise the utility of testosterone therapy alone for hypogonadism.¹

Adjunct therapies such as aromatase inhibitors (anastrozole, letrozole etc.) or estrogen receptor antagonists ([clomiphene](#), [enclomiphene](#), [tamoxifen](#), etc.), or GnRH antagonists such as sermorelin are sometimes used instead of or in combination with testosterone supplementation to prevent the negative feedback loop associated with estradiol.^{1,2}

One study evaluating combination treatments with anastrozole and testosterone, concluded that anastrozole given in conjunction with testosterone replacement therapy kept estrogen levels low and attenuated adverse effects typically associated with elevated estrogen levels that can occur with testosterone replacement therapy alone.³

Other studies evaluating clomiphene citrate versus testosterone replacement therapy have noted the benefit of clomiphene for raising testosterone levels and combating hypogonadism.⁴ Though testosterone is necessary for spermatogenesis, exogenously administered testosterone, in the form of testosterone replacement therapy, can inhibit FSH and LH secretion by the pituitary gland, resulting in decreased spermatogenesis.²

Studies evaluating ingredients that work to prevent this adverse effect on spermatogenesis, including anastrozole and clomiphene among others, have demonstrated efficacy for increasing FSH or LH and improvements in spermatogenesis.^{4,5,6} To learn more about these active pharmaceutical ingredients (APIs) as well as others used for this purpose, check out a summary table of the listed APIs and the studied dosages and routes for each of these ingredients on our Fagron Academy [site](#)!

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Citations:

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4. Dadhich P, Ramasamy R, Scovell J, Wilken N, Lipshultz L. Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men. *Indian J Urol.* 2017;33(3):236-240. doi:10.4103/iju.IJU_372_16
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