ONLINE EXCLUSIVE

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# Q/ Are SERMs safe and effective for the treatment of hypogonadism in men?

**EVIDENCE-BASED ANSWER**

A/ **YES.** For both normal-weight and obese men with low testosterone levels and hypogonadal symptoms, selective estrogen receptor modulators (SERMs), such as clomiphene citrate (CC) and enclomiphene citrate (EC), appear to be effective and safe for improving serum testosterone levels (strength of recommendation [SOR]: **C**, disease-oriented outcomes from randomized controlled trials [RCTs] and cohort studies). Studies also show that symptom improvement is comparable to that with exogenous testosterone replacement and similar to eugonadal men (SOR: **B**, patient-oriented outcomes from retrospective cohort studies).

## Evidence summary

### Alone or in combination with hCG, clomiphene citrate is effective

A 2018 multicenter prospective RCT (n = 283) compared the serum testosterone response in men (mean age, 41.8 ± 10.4 years) with hypogonadism before and after treatment with either CC, human chorionic gonadotropin (hCG), or a combination of both therapies.[1] All patients wanted to maintain fertility, had normal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, had no history of testosterone therapy, had low (< 300 ng/dL) serum testosterone levels on at least 2 samples, and had at least 3 positive symptoms from the quantitative Androgen Deficiency in the Aging Male questionnaire (qADAM; a 10-item, graded-response tool measuring symptom severity from 1 to 5).

Patients were randomized into either the CC group (50 mg oral; n = 95), the hCG group (5000 IU injections twice weekly; n = 94), or the CC + hCG group (n = 94). Testosterone levels were measured at baseline and at 1 and 3 months after therapy initiation; qADAM questionnaire scores were also recorded but ultimately not used due to concerns with baseline heterogeneity among groups.

Average baseline serum testosterone levels for the CC, hCG, and CC + hCG groups were 243 ng/dL, 222 ng/dL, and 226 ng/dL, respectively. By 3 months, these levels had increased to 548 ng/dL (95% CI, 505-591) in the CC group, 467 ng/dL (95% CI, 440-494) in the hCG group, and 531 ng/dL (95% CI, 492-570) in the CC + hCG group. While there was not a significant difference between the CC and CC + hCG groups at 3 months ($P$ = .579), both groups were superior to the hCG-only group ($P$ = .002 for each).

### CC and testosterone gel are comparable; testosterone injection is better

In a 2014 retrospective study, researchers reviewed the charts of 1150 men taking any form of testosterone supplementation therapy (TST). They compared treatment efficacy and qADAM satisfaction scores in 93 age-matched men with symptomatic hypogonadism who were treated with either CC (n = 31), testosterone injections (n = 31), or testosterone topical gel (n = 31).[2] Eugonadal men not taking TST (n = 31) served as controls.

Inclusion criteria were based on treatment regimens of CC and TST. Participants in the treatment groups had a baseline total

testosterone level < 300 ng/dL and had reported ≤ 3 positive symptoms on the qADAM questionnaire. Treatment regimens included CC (25 mg orally once daily), testosterone injections (testosterone cypionate 100 to 200 mg intramuscularly once weekly), and testosterone gel (Testim 1% or AndroGel 1.62%, 2 to 4 pumps/d).

The study results demonstrated an increase in median testosterone from baseline levels in all treatment groups when compared to placebo: CC (from 247 to 504 ng/dL), testosterone injections (from 224 to 1104 ng/dL), and testosterone gels (from 230 to 412 ng/dL) ($P < .05$). Men receiving testosterone injections had the highest increase in serum testosterone levels (956 ng/dL).

While the final mean serum total testosterone was highest in the testosterone injection group (1014 ng/dL; $P < .01$), the mean levels for those using CC and those using testosterone gels were comparable (525 ng/dL vs 412 ng/dL). Serum estradiol levels were also higher in men receiving testosterone injections, compared to men using CC, those using testosterone gels, and those not receiving TST (6.0 vs 2.0, 2.0, and 2.0 ng/dL, respectively; each $P < .01$).

The qADAM scores for hypogonadal symptoms showed no significant difference in men treated with CC, testosterone injections, and testosterone gels and those not receiving TST (35, 39, 36, and 34, respectively). Men receiving testosterone injections reported greater libido (range, 1-5) than men using CC, those using testosterone gels, and those not on TST (4 vs 3, 3, and 3; $P = .047$, .04, and < .01, respectively), but it is uncertain if this is clinically meaningful.

### Enclomiphene citrate demonstrates improvement in hormone levels

A 2014 Phase II RCT investigated the effects of oral EC—a trans-isomer of CC—compared to topical testosterone 1% gel (T gel) in 124 men with secondary hypogonadism.[3] Entry criteria included a baseline morning total testosterone level of < 250 ng/dL on 2 occasions. Participants were divided into 4 groups: 12.5-mg dose of EC, 25-mg dose of EC, T gel, and placebo.

The EC groups and the T gel group had comparable increases in testosterone levels after 3 months of treatment, without statistical significance. The 3-month change in serum testosterone level from baseline was 217 to 471 ng/dL (95% CI, 399-543) in the 12.5-mg dose group; 209 to 405 ng/dL (95% CI, 349-462) in the 25-mg dose group; and 210 to 462 ng/dL (95% CI, 359-565) in the T gel group. The placebo group had a decrease in serum testosterone levels, from 213 to 198 ng/dL (95% CI, 171-226).

Also, the EC groups demonstrated increases in LH and FSH levels from baseline to 3 months, while the T gel group showed a suppression (to low-normal range) in both levels: LH, 1.4 mIU/mL (decrease of 4.4 mIU/mL) and FSH, 2.4 mIU/mL (decrease of 2.4 mIU/mL). Among a subset of men (n = 67) who had at least 2 assessments at the end of 3 months, the researchers also analyzed changes in sperm concentration, using the lower limit of normal (15 million/mL). The number of men with a low sperm concentration increased significantly in the topical T gel group (16% to 53%) compared to the 12.5-mg EC group (decrease from 16% to 12%; $P = .0008$) and the 25-mg EC group (decrease from 5% to 0%; $P = .0007$), as well as compared to the placebo group (increase from 8% to 15%; $P = .007$).

### With EC, testosterone remains elevated after treatment cessation

A 2016 2-center parallel, double-blind, placebo-controlled RCT evaluated the effect of 2 doses of EC (12.5 mg and 25 mg; n = 85) vs testosterone gel (1.62%; n = 85) vs placebo (n = 86) on serum testosterone, LH, FSH, and sperm counts in 256 overweight and obese men ages 18 to 60 years who had 2 morning testosterone measurements < 300 ng/dL and a low or inappropriately normal LH level for 16 weeks.[4] All baseline characteristics, including age, BMI, sperm concentration, and serum total testosterone were statistically consistent within groups at both centers. For men receiving EC who did not achieve a testosterone level > 450 ng/dL, there was an uptitration from 12.5 mg to 25 mg at Week 4.

All active treatment groups showed increases in testosterone level during treatment ($P < .001$); however, FSH and LH levels

**Men with low or low-normal serum luteinizing hormone levels may be good candidates for the use of SERMs for management of testosterone deficiency.**

**Both the American Urological Association and the Canadian Urological Association support the use of SERMs, especially in hypogonadal men who are interested in fertility preservation.**

increased in the EC group and decreased in the testosterone gel group ($P < .001$). Serum testosterone levels improved to 428.8 ng/dL (95% CI, 395-462) and 368.8 ng/dL (95% CI, 307-431), respectively, in the combined EC and testosterone gel groups at 16 weeks. Of note, total testosterone levels after cessation of treatment (off-drug point) rapidly decreased below baseline in the testosterone gel group compared to the pooled EC group, which remained elevated above baseline for at least 7 days.

Composite end-point analysis was performed, with success considered if men achieved both testosterone in normal range (300-1040 ng/dL) and sperm concentrations $\geq 10 \times 10^6$. The pooled data studies showed EC was more successful than testosterone gel in achieving both endpoints (63.5% vs 24.7%; $P < .001$). No difference in the incidence of treatment-related adverse effects between groups was noted.

### There were no major adverse effects, even after 3+ years of treatment

A 2019 retrospective cohort study of 400 men treated for symptomatic hypogonadism with CC sought to determine if improvements in testosterone, hypogonadal symptoms, and adverse effects were similar for those treated for ≤ 3 years (n = 280) and those treated for > 3 years (n = 120).[5] Outcomes included serum testosterone and estradiol levels, symptom improvement (by qADAM questionnaire), and adverse effects.

All participants had a baseline testosterone level < 300 ng/dL, and all participants received CC therapy. Men received 25 mg/d with titration to 50 mg/d when testosterone did not improve to ≥ 300 ng/dL after 4 weeks.

When comparing outcomes across the 2 groups, there were no significant differences. Serum testosterone levels improved to 579 ng/dL (95% CI, 554-605) and 542 ng/dL (95% CI, 504-580) in the ≤ 3 years and > 3 years groups, respectively. Meanwhile, 79% of men in the ≤ 3 years group reported symptom improvement (improvement in libido, erection, or 3 other of the 10 domains of the qADAM questionnaire), while 77% of those in the > 3 years group reported improvement ($P = .60$).

Finally, the percentage of men reporting adverse effects did not significantly differ between groups: 9% in the ≤ 3 years group and 8% in the > 3 years group ($P = .85$). The most common adverse effects reported in order of frequency were mood changes, blurred vision, breast tenderness, hypertension, hematocrit changes, and flushing. No major adverse events (eg, myocardial infarction, cerebrovascular accident, venous thromboembolism, suicidal behavior) were reported in any patients.

Of note, although measured estrogen levels at the end of treatment were similar for both groups (54.8 pg/mL in the ≤ 3 years group vs 54.6 pg/mL in the > 3 years group), 37% of patients treated for > 3 years did receive anastrozole treatment for hyperestrogenism compared to 15% in the ≤ 3 years group ($P = .05$). The authors caution, though, that due to only 20% of the cohort patients having data on pre- and post-treatment estradiol levels, the study was likely underpowered to detect true differences among subgroups.

## Recommendations from others

Current American Urological Association and Canadian Urological Association Guidelines note that while greater study on nontraditional testosterone therapies is needed, both organizations support use of SERMs, especially in hypogonadal men who are interested in fertility preservation, as increases in endogenous serum testosterone production do not impact fertility potential, unlike exogenous hormonal replacement.[6,7] Additionally, men with low or low-normal serum LH levels may also be good candidates for the use of SERMs for management of testosterone deficiency.

## Editor's takeaway

Laboratory data (disease oriented) consistently shows that SERMs effectively increase testosterone levels to those comparable with testosterone gels. SERMs resulted in higher semen counts and maintained LH and FSH levels, but there were instances of hyperestrogenism. Data on longer-term benefits and

adverse effects of both SERMs and testosterone supplementation are still needed. JFP

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