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Expert Review of Endocrinology & Metabolism

ISSN: 1744-6651 (Print) 1744-8417 (Online) Journal homepage: https://www.tandfonline.com/loi/iere20

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To cite this article: Joshua A Earl & Edward D Kim (2019) Enclomiphene citrate: A treatment that maintains fertility in men with secondary hypogonadism, Expert Review of Endocrinology & Metabolism, 14:3, 157-165, DOI: 10.1080/17446651.2019.1612239

To link to this article: https://doi.org/10.1080/17446651.2019.1612239

Published online: 07 May 2019.

EXPERT REVIEW OF ENDOCRINOLOGY & METABOLISM
2019, VOL. 14, NO. 3, 157–165
https://doi.org/10.1080/17446651.2019.1612239

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DRUG PROFILE

Enclomiphene citrate: A treatment that maintains fertility in men with secondary hypogonadism

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ABSTRACT

Introduction: Hypogonadism is an important issue among the male population. Treatments such as exogenous testosterone have become very popular. One of the adverse effects of testosterone is its suppression of fertility. This has lead to the use of alternative therapies such as selective estrogen receptor modulators (SERMs) that aim to correct hypogonadism without reducing fertility.

Areas covered: The SERM, clomiphene citrate, which is approved by the FDA for the treatment of ovarian dysfunction, has been shown to have beneficial effects on male hypogonadism. Clomiphene citrate exists as a mixture of both the cis-isomer (zuclomiphene) and the trans-isomer (enclomiphene). The literature has suggested that most of the beneficial effects of clomiphene are due to the trans-isomer enclomiphene. Zuclomiphene contributes little to the intended outcomes. The purpose of this drug profile is to examine the available literature on the trans-isomer enclomiphene.

Expert opinion: Enclomiphene has been shown to increase testosterone levels while stimulating FSH and LH production. Initial studies demonstrated that enclomiphene maintains the androgenic benefit of clomiphene citrate without the undesirable effects attributable to zuclomiphene. This article reviews the difficulties associated with the FDA approval of a new molecular entity related to the treatment of hypogonadism.

ARTICLE HISTORY
Received 17 January 2019
Accepted 24 April 2019

KEYWORDS
Serum testosterone; selective estrogen receptor modulator; spermatogenesis; secondary hypogonadism; topical testosterone; enclomiphene

1. Overview

Hypogonadism is defined as the inability of the testicles to produce adequate physiologic levels of testosterone or normal spermatozoa. The cause of hypogonadism can be due to defects in the testicles or the hypothalamic-pituitary-gonadal axis. If the defect occurs in the testicle it, is considered primary hypogonadism. If the defect occurs outside the testicle, it is considered secondary hypogonadism. Primary hypogonadism can be caused by congenital abnormalities such as Klinefelter syndrome, or etiologies that are related to testicular damage such as trauma, ischemia, chemotherapy or radiation. Secondary hypogonadism can be caused by hyperprolactinemia, severe obesity, iron overload syndromes, the use of opioids, glucocorticoids, androgenic–anabolic steroid (AAS) withdrawal syndrome, or processes that damage the hypothalamus or pituitary. When the cause of secondary hypogonadism is clearly demonstrated it is termed organic hypogonadism. When the cause is not clearly demonstrated it is termed functional hypogonadism. Patients with secondary hypogonadism will have low serum testosterone associated with low sperm counts and low or inappropriately normal gonadotropins [1].

The regulation of male testosterone production, as well as spermatogenesis, is a highly complex process. Pulsatile release of GnRH from the hypothalamus is necessary to stimulate the pituitary gland to produce both luteinizing hormone (LH) and follicle stimulating hormone (FSH) under normal physiologic conditions [2]. LH stimulates Leydig cells in the testes to produce testosterone. FSH acts on Sertoli cells to stimulate spermatogenesis. Testosterone and dihydrotestosterone, the products of Leydig cell function, act upon a negative feedback loop on both the hypothalamus and the pituitary. Inhibin B produced by Sertoli cells also serves in a similar negative feedback capacity. Testosterone is also metabolized to estradiol (E2) which then functions in a negative feedback loop to reduce FSH and LH release from the pituitary [3,4]. (Figure 1)

Hypogonadism is a major concern for the male community. The prevalence of hypogonadism, defined as morning testosterone less than 300 ng/dl, is estimated to be 38.7% in men over the age of 45 [5]. It has also been shown to be correlated with the many co-morbidities found in metabolic syndrome, including diabetes, obesity, and hypertension. Wu *et al.* demonstrated in the European male aging study that rising BMI was more strongly correlated with testosterone levels even more so than age [6]. (Figure 2) Even with the most conservative definition of hypogonadism statistical projections estimate that by 2025 6.5 million american men will suffer from symptomatic hypogonadism [7].

The current treatment paradigm has typically involved offering testosterone replacement therapy to those men who have symptomatic hypogonadism [1]. An increase in testosterone prescriptions was observed between 2010 and 2013 particularly in the population between 40 and 64 years of age and was of significant concern to the FDA (Figure 3). This growth was attributed in part to direct to consumer advertising [8]. An increase in obesity in this age group has also been cited as a possible cause [9]. In 2016 Snyder et al. published the T trials.

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Article highlights

- Clomiphene Citrate is used off label to treat secondary hypogonadism in men desiring to preserve fertility.
- The active isomer of clomiphene is enclomiphene while the other isomer zuclomiphene may actually antagonize the desired effects.
- Enclomiphene has been shown to raise testosterone levels in similar fashion to transdermal testosterone.
- Enclomiphene has also been showed to preserve sperm concentration when compared with exogenous testosterone replacement.
- No rigorous studies have demonstrated symptomatic benefit with enclomiphene.
- The FDA denied approval of enclomiphene on the grounds that no symptomatic benefit was identified.
- Enclomiphene serves as an example of how difficult it is to gain approval for a new molecular entity for the treatment of secondary hypogonadism.

This study demonstrated that for men aged 65 years or older testosterone replacement therapy had beneficial effects in terms of sexual function, mood, and to a lesser extent physical vitality. In the sexual function portion of the trial men treated with testosterone showed greater sexual activity scores on the Psychosexual Daily Questionaire (PDQ-Q4), increased sexual desire by Derogatis Interview for Sexual Function (DISF-M-II) scores, and increased erectile function scores by the International Index of Erectile Function (IIEF). In the physical function portion of the trial, 6-minute walking distances did not increase significantly in the testosterone group but did increase significantly when patients from all the trials were included. Scores on the Physical function domain also increased significantly in the testosterone group. In the Vitality trial, there was noted to be no significant improvement with testosterone in the Functional Assessment of chronic illness therapy Fatigue scale although a significant difference was identified when all three studies were analyzed together. The T-trials confirmed that testosterone therapy has a variety of positive effects on men with secondary hypogonadism particularly concerning sexual function and to a lesser extent mood and physical function. Although there is some debate about whether or not testosterone therapy is associated with adverse cardiovascular events, no increase in cardiovascular events was observed in the T-trials. Conversely, low testosterone is considered an independent risk factor for cardiovascular disease. In the bone trial testosterone therapy significantly increased bone mineral density and in the Anemia trial testosterone treatment was shown to significantly increase hemoglobin. All of these studies illustrated that testosterone replacement can have a variety of positive effects on men with demonstrated functional secondary hypogonadism. As a result of this testosterone replacement therapy is widely used in this population [10,11].

A well-known physiologic consequence of testosterone replacement therapy is a decrease in intra-testicular testosterone production and spermatogenesis. This occurs due to the inhibition of both LH and FSH production in the pituitary by exogenous testosterone [12]. The World Health organization studied 271 men receiving exogenous testosterone therapy as a male contraceptive agent. They found that 157 of these men (65%) were azoospermic within 6 months, highlighting the negative impact of exogenous testosterone on spermatogenesis [13]. Exogenous testosterone has also been shown to have adverse effects on estradiol, hematocrit, and serum lipid profiles, although this is largely at supra-physiologic levels [10,14]. Men with concerns about fertility, at increased risk for prostate cancer, elevated hematocrit, untreated obstructive sleep apnea, heart failure, recent myocardial infarction, stroke, or thrombophilia are recommended not to begin testosterone replacement therapy per Society of Endocrinology guidelines [1]. While the aforementioned T trials have demonstrated the potential benefits of testosterone replacement, two important factors must be considered. First, the benefit of testosterone replacement must be balanced against the adverse effects on spermatogenesis and fertility. Secondly, testosterone replacement has typically been studied in the aging male population while the average

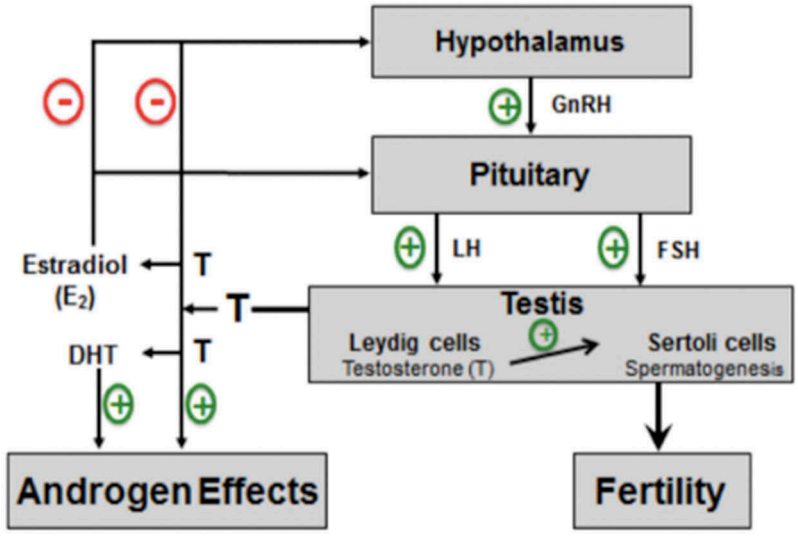

Figure 1. Hypothalamic-pituitary-gonadal axis.

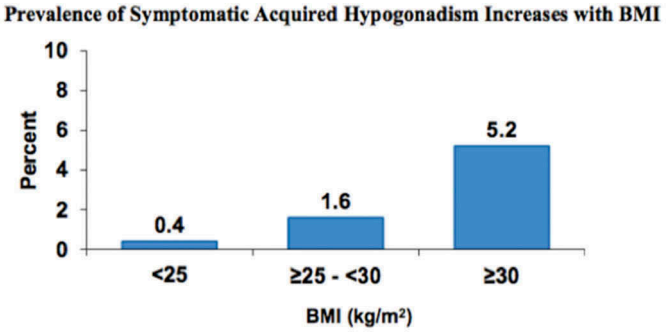

Figure 2. Prevalence of symptomatic acquired hypogonadism increases with BMI.

man with hypogonadism who is concerned with fertility is usually younger. For this reason, alternative treatments for hypogonadism have been explored. These agents include aromatase inhibitors like anastrozole, partial estrogen agonists such as tamoxifen, and selective estrogen receptor modulators such as clomiphene citrate [15]. Human chorionic gonadotropin has also been used for the treatment of hypogonadotropic hypogonadism as a replacement for LH with good results including beneficial effects on both 25-OH-vitamin D levels and sperm profiles [16].

It has been previously demonstrated that pulsatile GnRH is a prerequisite for normal physiological production of LH, FSH, and subsequently Testosterone. This pulsatile secretion of GnRH results in rising levels of LH. Testosterone levels, as a consequence of cyclical LH stimulation, peak in the morning, trough in the early evening, and then steadily rise overnight back towards a morning peak [17]. Testosterone mediates a negative feedback effect on LH production, at least in part, directly at the level of the hypothalamus, but requires aromatization to estradiol to exert any negative feedback effect at the level of the pituitary. Because testosterone appears to mediate this effect through estradiol, the modulation of estrogen receptor signaling appears to profoundly alter the negative feedback mechanism [18].

Clomiphene citrate is FDA-approved to induce ovulation in women. It has also been used for years off-label to restore testosterone levels and potentially restore sperm counts in men with hypogonadism. The drug is a combination of the en-(trans) and zu-(cis) isomers. Enclomiphene is an estrogen antagonist. Zuclomiphene does not produce estrogen antagonism, and its effects are not fully understood [19] Clomiphene citrate exists as a mixture of two isomers, enclomiphene the trans-isomer (62%), and zuclomiphene the cis-isomer (38%). Studies have indicated that enclomiphene acts as an estrogen antagonist while zuclomiphene acts as an estrogen agonist. Huang *et al.* illustrated this point by showing that zuclomiphene acts as an agonist on pituitary 17-beta estradiol receptors while enclomiphene acted as an estrogen receptor antagonist in pituitary cell cultures [20].

In 2015 Fontenot *et al.* conducted a study in mice illustrating that the differences between enclomiphene and zuclomiphene could be quite drastic. Seventy-five mice were divided into 5 treatment groups: placebo, 40mg/kg enclomiphene, 4mg/kg enclomiphene, 40mg/kg zuclomiphene, and 4mg/kg zuclomiphene. After completion of the 90-day dosing period the mice were sacrificed and the tissues were examined. Testicles, epididymis, seminal vesicles, and mice as a whole were all significantly decreased in weight in the zuclomiphene group when compared to the enclomiphene group. Histologically there was noted to be degeneration of the seminiferous tubules and Leydig cells on histological analysis in the zuclomiphene groups compared with the others. The zuclomiphene groups exhibited significantly lower testosterone, LH, and FSH (although this last effect was seen only in the high dose zuclomiphene group). Conversely, the enclomiphene groups showed testosterone and LH levels within the normal ranges. The highest FSH level was seen in high dose enclomiphene group [21]. This study underscored the concept that clomiphene citrate is composed of two very different isomers with potentially opposing effects.

Clomiphene citrate has demonstrated both agonistic and antagonistic effects on estrogen receptors. Kurosawa *et al.* showed that clomiphene citrate exhibited approximately 30% of the agonistic effect of estradiol when interacting with the estrogen

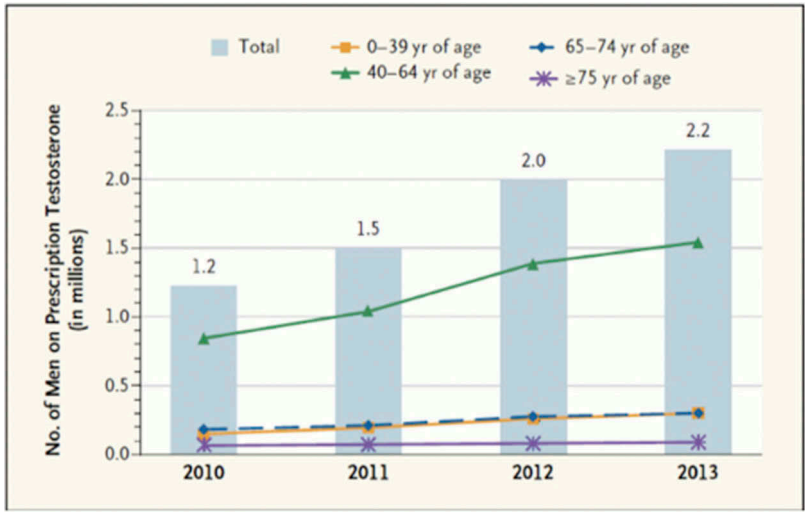

Figure 3. Testosterone prescriptions over time (Nguyen et al.).

receptor alpha, while exhibiting no agonistic effect on estrogen receptor beta. Meanwhile, in the same carefully controlled en vitro experiments, it was shown that the antagonistic effect of clomiphene was highly dose dependent when examining the ER-alpha, but completely antagonistic effect on the ER-beta [22].

Later, animal studies were conducted on baboons, in which the animals were given 1.5mg/kg/day of zuclomiphene, enclomiphene, or clomiphene citrate and serum hormone levels were subsequently analyzed. They found that clomiphene citrate significantly raised serum testosterone from 170 ng/dl to 559 ng/dl. However, Enclomiphene raised serum testosterone by a much greater extent increasing it from 170 ng/dl to 1144 ng/dl. Zuclomiphene did not significantly impact testosterone levels and had the additional effect of increasing total cholesterol levels [23]. The anti-estrogenic effects of clomiphene may be due almost entirely to the action of enclomiphene while zuclomiphene may actually counteract the desired effects. This initial animal study supported the rationale for pursuing enclomiphene as a treatment for hypogonadism.

Nonclinical studies on both rodents and dogs were also conducted. Nine-month dog studies showed that enclomiphene was well tolerated up to doses 20mg/kg with a metabolism that is very similar to humans. Folding of the lens was observed at doses in excess of 10mg/kg. It is worth noting that this dose is 40 times greater than that used in human studies [9].

Clomiphene citrate appears to function both as an antagonist and an agonist in its role as an estrogen receptor modulator. While clomiphene citrate is efficacious in the treatment of hypogonadism its contradictory actions suggest there could be better options. The trans-isomer enclomiphene appears to be responsible for the desired anti-estrogen effect. Wiehle *et al.*, in study involving 48 men with hypogonadism, demonstrated that enclomiphene successfully inhibits the negative feedback on the hypothalamic-pituitary-gonadal axis via estrogen receptor signaling. They compared the men treated with enclomiphene to those taking topical testosterone. They found no significant difference in testosterone levels between the two populations. There was a significant difference between groups for LH and FSH levels. LH levels for men receiving enclomiphene citrate 25 mg were higher (approximately 12 IU/L) than those for men receiving transdermal testosterone (approximately 4IU/L, $P < 0.001$). The decrease in FSH associated with transdermal testosterone was also significant ($P = 0.0002$) [24].

When used in the correct patient population enclomiphene may offer significant elevations in testosterone levels without suppressing LH or FSH. It accomplishes this by preventing estrogen receptor mediated negative feedback at the level of the pituitary and hypothalamus. This could result in the correction of testosterone levels and hypogonadal symptoms without suppressing spermatogenesis. In addition to the aforementioned benefits, enclomiphene lacks the estrogen receptor agonist activity seen with clomiphene citrate that is caused by the cis-isomer zuclomiphene. This may mitigate some of the estrogenic side effects which can be seen in some men, and increase the clinical efficacy of the primary mechanism of action.

The structure of enclomiphene citrate,

(2-{4-[(E)-2-chloro-1,2-diphenylethenyl]phenoxy}ethyl)diethylamine) is that of the trans-isomer of the triphenyl ethylene stilbene derivative clomiphene that exists as a citrate salt. The stilbene structure with its 1,2 diphenylthylene moiety allows it to associate with estrogen receptors and function as an agntogonist by competing with estradiol for binding sites. After taking enclomiphene citrate there is a rapid rise in serum levels. Absorption is increased by the presence of food. The drug has a very large volume of distribution >20,000 L. Peak levels are obtained between 2 and 3 hours after administration followed by first-order degradation of serum levels. Although the serum half-life is thought to be 7 h one study has suggested that it might be closer to 10 h in some people [9,21]. Excretion is 61.5% in the feces 8.2% in the urine. It has also been observed that drug levels did not completely return to baseline as anticipated. The pharmacologic effects on testosterone, LH, and FSH seem to persist much longer after the drug has been removed. These observations were likely secondary to accumulation of the drug in the tissues as well as downstream alterations in the signaling process caused by estrogen receptor antagonism [9,25,26].

2. Clinical efficacy

The first phase I study of enclomiphene was ZA-001. This was a placebo-controlled study that lasted 2 weeks comparing 5 mg and 10 mg Androgel 1% to 12.5 mg, 25 mg, and 50 mg enclomiphene in men with secondary hypogonadism. Both Androgel 1% and enclomiphene increased testosterone levels in a dose-dependent manner. Androgel 1% resulted in significant suppression of LH and FSH while enclomiphene did not. It was also determined that the effects of enclomiphene on LH and FSH did not change significantly between 25 mg and 50 mg. Future studies would thus focus on the 12.5 mg and 25 mg doses. ZA-003 was a placebo-controlled double-blind study that followed subjects for 6 months on enclomiphene 12.5 mg, 25 mg, Androgel, and placebo. After 6 months both Androgel and enclomiphene significantly elevated testosterone levels. Androgel significantly suppressed LH and FSH levels while enclomiphene normalized LH and FSH. Sperm concentrations were also measured and showed that they were suppressed with Androgel but preserved within the normal range for both doses of enclomiphene. While symptoms like libido and sexual function were recorded the study did not identify a significant difference between enclomiphene and placebo [9].

Kaminetsky *et al.* in 2013 published a randomized, open label, fixed dose, active control, two center phase IIB study on 12 men with secondary hypogonadism. The men had previously been treated with topical testosterone. After 3 months of treatment with enclomiphene citrate, there was a significant increase in testosterone levels. At 6 months both the patients treated with enclomiphene and those on transdermal testosterone had significantly elevated serum testosterone levels of 545 ± 268 and 525 ± 256, respectively. LH and FSH increases were seen in the enclomiphene group but not in the transdermal gel group. All seven men treated with enclomiphene had improved sperm counts at the end of the 6-month period, but this was not observed in the transdermal gel group. Despite the small size of the study, it opened the door for more robust studies to demonstrate enclomiphene's efficacy [27].

A 2013 study by Wiehle *et al*. gave 52 hypogondal men doses of up to 50 mg of enclomiphene daily for 14 days and then followed them for 7–10 days following cessation of treatment. Once again testosterone levels increased significantly across all enclomiphene and transdermal testosterone groups. However, it was noted that the transdermal testosterone was much more likely than enclomiphene to induce supra-physiologic testosterone levels, possibly related to application practices. Enclomiphene maintained physiologic testosterone levels throughout the study. Transdermal testosterone was also noted to cause significant increases in dihydrotestosterone when compared to the placebo or enclomiphene group. A steady-state level of enclomiphene was obtained at a 25 mg dose with once-daily dosing. This suggested that enclomiphene exerts it effects largely by restoring normal physiologic governance of testosterone production [25].

Wiehle *et al*. followed up the 2013 studies with a larger phase II clinical trial in 2014 (ZA-203). The double blind, placebo-controlled, multi-center study enrolled 124 participants. The subjects were males with a previous diagnosis of secondary hypogonadism and testosterone levels <250 ng/dl. The patients were then randomized into 4 groups. There was a 12 mg enclomiphene group, a 25 mg enlcomiphene group, a transdermal testosterone gel group, and a placebo group. Patients then went through a 3-month dosing period during which hormone levels were checked periodically. Patients in both the enclomiphene and transdermal testosterone arms experienced significant increases in testosterone from 217.2 to 471.9 ng/dl for the 12.5 mg enclomiphene group, 209.8–405.8 ng/dl for the 25 mg enclomiphene group, and 210.0–462.6 ng/dl for the transdermal testosterone group. LH and FSH levels were decreased from 3.9 to 1.4 mIU/ml and 6.0 to 2.4 mIU/ml, respectively, for the testoserone group. Both of the enclomiphene groups experienced an increase in both FSH and LH. These findings were also reflected in the semen analyses conducted as part of the study. At the beginning of the study, 3 of 19 men in the transdermal testosterone group had sperm concentrations <15 million per ml. By the end of the study period, 10/19 men had sperm concentrations of <15 million per ml, significantly different than all of the other groups ($p = 0.008$, $p = 0.0007$, and $p = 0.007$). Neither enclomiphene groups showed significant degradation of sperm concentrations. This study further supported the ability of enclomiphene to raise serum testosterone to levels comparable with transdermal testosterone gels. It further illustrated that enclomiphene has a positive effect on LH and FSH levels thus potentially preserving spermatogenesis [28].

Before proceeding with phase III studies, the FDA requested another study to help identify the lowest efficacious dose. This study was conducted in 2013 by Wiehle *et al.* (ZA-204). They set out to establish the pharmacodynamic properties of enclomiphene on serum testosterone and LH. The study was conducted as a randomized, single-blind, two-center, phase II study. Forty-eight men were enrolled in the study and randomized to one of 4 groups. The four groups received either 6.25 mg of enclomiphene citrate daily, 12.5 mg of enclomiphene citrate daily, 25 mg of enclomiphene citrate daily, or transdermal testosterone. The patients then had blood levels drawn throughout the first 24 h to determine pharmacokinetic and pharmacodynamic properties. The patients were then followed for 6 weeks. Both transdermal testosterone ($p = 0.025$) and enclomiphene citrate 25 mg ($p = 0.016$) had significantly increased testosterone levels although there was much more variability in the levels for transdermal testosterone. LH levels were also found to be significantly higher for 25 mg enclomiphene when compared with 12.5 mg enclomiphene ($p = 0.025$), 6.25 mg enclomiphene ($p = 0.006$), and with transdermal testosterone ($p = 0.001$). These effects were also found to persist for at least a week following the cessation of therapy in the 25 mg group. This study illustrated that enclomiphene is effective in raising testosterone levels in the target population. Furthermore, 12.5 mg is more effective than 6.25 mg enclomiphene in regards to raising testosterone and 25 mg enclomiphene was superior to both. The effects on testosterone levels persisted for some time after the discontinuation of enclomiphene, which was in stark contrast to what was observed from the transdermal testosterone group [9].

ZA-301 and ZA-302 were paired, double-blind, placebo-controlled, multi-center, phase III trials that compared both sperm concentrations and testosterone levels between enclomiphene and placebo. The target populations included men with BMI > 25, secondary hypogonadism, and normal baseline sperm concentration. Patients were randomized to either the enclomiphene group or the placebo group. The enclomiphene groups were started at 12.5mg/day but were titrated up to 25mg/day after 6 weeks if morning testosterone concentration was below 300 ng/dL. In both studies enclomiphene significantly increased the percentage of patients with testosterone in the normal range by 64.4% and 64.3% over placebo in ZA-301 and ZA-302, respectively. While more patients on enclomiphene had a greater than 50% reduction in sperm concentration when compared to placebo the absolute difference was small and the findings were not statistically significant [22].

In 2015 Kim *et al*. performed two parallel, randomized, double-blind, double-dummy, placebo-controlled phase III studies (ZA-304 and ZA-305). The primary goal of these studies was to compare two different doses of enclomiphene citrate to 1.26% testosterone gel. Inclusion criteria selected overweight men, aged 18–60 years of age with an established diagnosis of secondary hypogonadism. The cutoff for serum testosterone was <300 ng/dl and <9.4 IU/L for LH. The men were then randomized to one of four arms including enclomiphene 12.5 mg, enclomiphene 25 mg, 1.26% transdermal testosterone gel, and placebo. The patients were then followed for 5 months, during which they had 10 clinic visits and 1 overnight stay. Baseline labs and a semen sample were obtained at the beginning of the study. Testosterone levels at 2 weeks were higher for both enclomiphene doses (12.5 mg and 25 mg) as well as transdermal testosterone ($p < 0.001$). These differences were also seen carried out to week 4 ($p < 0.001$). The enclomiphene group reached its steady state at about week 4. The transdermal testosterone group never achieved this. No changes in testosterone were seen between weeks 4 and the end of the study. After cessation of treatment, the testosterone levels in the enclomiphene groups did not return to baseline ($p < 0.001$) while the transdermal testosterone group's levels fell below baseline ($p = 0.07$). This validated observations seen in previous

studies. As predicted the LH levels rose by a significant amount for the enclomiphene groups ($p < 0.001$) throughout weeks 0–2 and weeks 2–4, with levels stabilizing from week 4 through the end of the study. LH levels decreased from baseline in the transdermal testosterone group by a significant margin ($p < 0.001$). There was no change in LH levels in the placebo group ($p = 0.98$). Changes in FSH mirrored that of LH with the enclomiphene group increased, the testosterone group decreased, and the placebo group remaining unchanged ($p = 0.001$, p,0.001, and $p = 0.10$, respectively). FSH levels averaged greater than 9 IU/L after 4 weeks of treatment in the enclomiphene groups. In the testosterone group, FSH levels steadily decreased to a nadir at the end of the study but did recover some to 5.2 IU/L compared with the baseline of 6.1 IU/L. Sperm counts exhibited a slight but non statistically significant increase in the enclomiphene groups. However, the testosterone groups exhibited a significant decrease in sperm counts from both baseline and from the enclomiphene group ($p < 0.001$). 63.5% of the men in the enclomiphene group met the goal of sperm concentrations of 10 million sperm per ml and testosterone concentrations in the normal range of 300–1040 ng/dl, significantly greater ($p < 0.001$) than the testosterone group (24.7%) and the placebo group (5.8%). (Figure 4) Additionally, the diurnal testosterone profile seen with enclomiphene much more closely mirrored physiologic conditions than did the profile exhibited by transdermal testosterone [19].

Previous studies have suggested that there is a benefit to using enclomiphene in the male with secondary hypogonadism. Despite these promising results the studies did not address actual pregnancy achieved on therapy or any symptomatic outcomes in relation to hypogonadism. Furthermore, the authors acknowledged that the degree of testosterone elevation achieved by the transdermal testosterone gel was not as robust has been demonstrated in previous studies. While it is acknowledged that the aim of these studies was primarily to show biological efficacy, perhaps the greatest weaknesses of ZA-304 and ZA-305 is that they did not attempt to address the impact of enclomiphene therapy on sexual function, insulin resistance, diabetes, and obesity. This is important when considering that these factors are thought to be some of the driving forces leading to hypogonadism in this population. Nevertheless, These two studies demonstrated that exogenous testosterone has deleterious effects on sperm counts and that enlcomiphene can achieve comparable increases in serum testosterone while successfully preserving and even restoring the normal hypothalamic-pituitary-gondadal axis. The effects achieved a steady state that did not fluctuate easily and persisted well after discontinuation of the medication. This theoretically improves its efficacy with patients in which medication compliance is an issues. In summary, enclomiphene increased serum testosterone without adversely impacting spermatogenesis.

3. Adverse effects

The adverse effects of enclomiphene have been extensively studied during the phase II and phase III trials. The drug seems generally well tolerated. Typically, one of the most talked about adverse effects associated with SERMs is the increased risk of venous thromboembolism. However, the incidence of this has been found to be very low [9] Wiehle *et al.* in their 2013 study mentioned several secondary measures including adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and Insulin like growth factor I (IGF-I). They noted no significant change in ACTH or TSH from baseline to the end of the study. They did note a decrease IGF-I levels from an average of 94–101 ug/L at baseline to 54–62 ug/L at the end of the study. The authors proposed that the anti-estrogenic effects of enclomiphene on the liver may have altered the production of hGH and in turn IGF-I, which are known to be induced by estrogen. This theory remains purely speculation at this juncture. The clinical significance of this finding is currently unknown as all of the levels remained within normal physiologic ranges. Regardless, this does shed some light on possible unintended effects of enclomiphene [24].

The advisory committee industry briefing document released by Repros Therapeutics Inc® (Woodland compiled all adverse events that were observed during any of the phase III

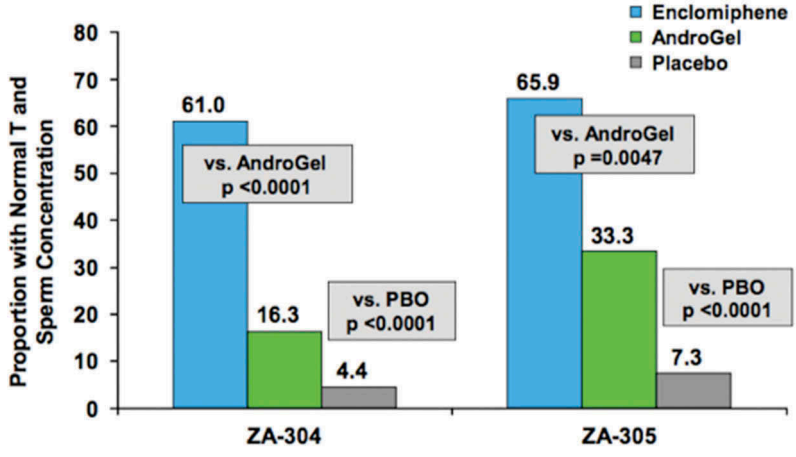

Figure 4. Results of ZA-304 and ZA-305.

trials. Headache was observed in 3.3%, nausea in 2.1%, diarrhea in 1.9%, nasopharyngitis in 1.7%, hot flush in 1.7%, arthralgia in 1.2%, and dizziness in 1%. Overall there was no evidence of drug toxicity and rates of adverse events were not significantly different from placebo. Furthermore, there was no difference in the rate of adverse events between the 12.5 mg dose and the 25 mg dose. Out of a cumulative total of 481 phase III subjects, only 11 had to discontinue the treatment due to adverse effects. Two patients had to discontinue due to increased hemoglobin, and 1 patient each discontinued for ocular discomfort, colitis, nausea, headache, decreased libido, orgasm dysfunction, urticaria, and hypertension. Only two deaths were recorded while patients were on enclomiphene. One was due to an ischemic stroke and the other was due to a motor vehicle collision. When adjusted for subject exposure years the rate of serious treatment adverse effects was lower in the enclomiphene group compared to placebo. The only cardiac events that were encountered in any of the placebo-controlled trials were: 1 AV Block, 1 congestive heart failure, 2 palpitations, and 1 ventricular asystole [9].

Much is known about the potential adverse effects of enclomiphenes parent drug clomiphene citrate. The adverse effects of clomiphene have been studied, however, this has typically been in a nonrigorous fashion. The FDA lists visual symptoms including blurred vision, scintillating scotomata, diplopia, and photophobia that have been reported in up to 1.5% of patients. Other symptoms include vasomotor flushing in 10.4%, abdominal discomfort/distension in 5.5%. nausea/vomiting in 2.2%, breast tenderness in 2.1%, and headache in 1.3%. The two major problems with this data involve the study population and the use of clomiphene. The data was largely collected from women on clomiphene at doses up to 200 mg, meaning that the results are not easily generalizable to men with hypogonadism. Additionally, it has previously been demonstrated that zuclomiphene has a very different activity profile when compared with enclomiphene. Therefore, the effects cannot be specifically attributed to one isomer or the other. Despite the difficulty in generalizing the data from clomiphene to enclomiphene, it does offer some clues as to the kind of adverse effects that should be more closely studied [9, 29,30].

In the 2016 phase, III clinical trial by Kim *et al.* the researchers noted that there was a 21% overall rate of adverse effects for which enclomiphene as a cause could not be completely excluded. These included one fatal automobile accident, hypertriglyceridemia, cerbrovascular accident, and anxiety in the 12.5 mg enclomiphene group. As well as psoriatic arthropathy and depression in the 25 mg enclomiphene group. One patient in the enclomiphene 25 mg arm had to withdraw from the study due to elevation in hemoglobin and hematocrit and another in the same group discontinued due to elevated PSA. The patient in the 12.5 mg group that suffered a cerebrovascular accident was also noted to have numerous other risk factors prior to initiating therapy with enclomiphene. There were no significant differences in adverse events between any of the treatment groups or placebo [19]. While these adverse outcomes cannot be completely ignored the likelihood that they were the result of therapy seems low. More dedicated research on the adverse effects of long-term enclomiphene will be necessary if the drug ever comes into more widespread use. Although the evidence is weak at best, early studies suggest that the side effect profile is not significantly worse than testosterone replacement therapy or clomiphene citrate. Ideally, future research will more clearly delineate and confirm this hypothesis.

4. Conclusion

The use of selective estrogen receptor modulators has been shown to be beneficial for the treatment of men with secondary hypogonadism. Previous studies with clomiphene citrate have shown it to be safe and effective for long-term use [29]. Further analysis of the two isomers of clomiphene citrate has suggested that most if not all of the advantageous effects of the drug are due to the enclomiphene isomer, while zuclomiphene may, in fact, counter-act the intended effects of clomiphene citrate. This supports the rationale for using enclomiphene specifically as a treatment for secondary hypogonadism. Results from several phase II and phase III trials have shown that enclomiphene achieves comparable testosterone levels to transdermal testosterone replacement therapy while increasing physiologic production of LH and FSH. Furthermore, these effects persist for some time even after the cessation of therapy. This illustrates that enclomiphene acts through the restoration of the physiologic hypothalamic-pituitary-gonadal axis. Further studies are necessary to fully characterize the impact on the subjective symptoms of hypogonadism as well as to fully characterize the potential adverse effect profile. Subsequent studies should also investigate the role of enclomiphene when used in conjunction with testosterone replacement. This combination has not yet been robustly studied and may provide a way to reap the established benefits of testosterone replacement while limiting dose and potentially preserving fertility. Regardless, enclomiphene remains a very promising drug for men with secondary hypogonadism particularly those that want to preserve fertility. Unfortunately, due to the difficulty inherent in getting a new molecular entity approved by the FDA the future of enclomiphene looks bleak at best.

5. Expert opinion

Clomiphene citrate is widely used as an off-label treatment for men with secondary hypogonadism. Its appeal has been its oral formulation and absence of suppressive effects on the hypothalamic-pituitary-gonadal axis. However, rigorous studies of its safety and efficacy, especially regarding long-term use, for this population is lacking because this generic product has been available for decades.

Enclomiphene represents the purified trans-isomer of clomiphene citrate. Its primary advantage over clomiphene citrate is the absence of the estrogen agonist effects of the cis-isomer, zuclomiphene. Developed by Repros Therapeutics Inc. (Woodlands, TX) as Androxal, this new molecular entity was submitted for a New Drug Application (NDA) in 2015. Although the phase III randomized, blinded, comparator trial ZA-305 demonstrated significant improvements with enclomiphene on serum testosterone levels and preservation of sperm concentrations compared to Androgel 1.62%, this primary endpoint was determined to be an insufficient basis for FDA-approval. At question was the issue of demonstration of clinical benefit. The FDA placed a particular emphasis on the lack of measurable symptomatic improvement. At a December 2016 FDA Bone, Reproductive, Urologic Drugs Advisory Committee Meeting, lack of data indicating improvement of clinical symptoms

was cited as the reason for denying FDA approval for the new molecular entity.

Ideally, this therapy could become the primary medication for men with secondary hypogonadism who wish to preserve spermatogenesis. Men who do not desire children of their own do comparably well with testosterone replacement therapy if they are willing to accept the suppression of natural sperm production. However, many men with secondary hypogonadism would be good candidates for enclomiphene. With obesity being closely related to secondary hypogonadism and with obesity rates rising, the number of younger men with secondary hypogonadism who would desire to preserve fertility is increasing.

In summary, enclomiphene is a very promising drug for patients with secondary hypogonadism and who are concerned about the negative effects of exogenous testosterone. Despite the fact that there was clearly demonstrated efficacy without any substantial safety issues. The lack of clearly demonstrated symptomatic improvement in phase III studies prevented enclomiphene from obtaining FDA approval. The difficulty of demonstrating a symptomatic benefit for secondary hypogonadism may prove a substantial barrier for years to come.

5.1. Five-year view

The high prevalence and increasing incidence of obesity in western countries have lead to an increase in secondary hypogonadism, especially in the younger male population. The demand for treatment options for secondary hypogonadism is only going to increase. During the next 5 years, secondary hypogonadism will become less and less of a fringe medical issue and become one that takes a more prominent role both in terms of medical morbidity and economic impact. Unfortunately, there are no medications other than testosterone replacement therapy which have been rigorously studied in this specific population. Enclomiphene represents an important attempt to develop better therapy in this specific market. Despite enclomiphene's great potential, the outlook for the next 5 years looks very bleak. The original sponsor company Repros Therapeutic Inc.® (Woodlands, TX) was acquired in December 2017 by Allergan. After failing in 2015–2016 to get FDA approval for enclomiphene, further studies were put on hold. The drug has been rebranded as EnCyzix™. As of this writing, we are not aware of any immediate plans by Allergan (Dublin, Ireland) or Repros Therapeutics Inc.® (Woodlands, TX) to push for immediate FDA approval. The primary barrier to approval is the request by the FDA for a clear demonstration of symptomatic benefit. One of the obstacles to studying secondary hypogonadism is that most of the symptoms associated with it are non-specific. At this time there is no high quality validated questionnaires that could deliver the evidence that the FDA desires in a clear and unequivocal fashion. Despite this, due to the growing interest in this market, it is very likely that enclomiphene will resurface in the future in one form or another. Although the timetable for this is currently unclear.

Funding

This paper was not funded.

Declaration of interest

R Salvatori is on the advisory board for Pfizer and NovoNordisk. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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