Transfeminine Science

Low Doses of Cyproterone Acetate Are Maximally Effective for Testosterone Suppression in Transfeminine People

By Aly W. | First published July 1, 2019 | Last modified February 20, 2021

Abstract / TL;DR

CPA is a progestogen and antiandrogen which is widely used in transfeminine hormone therapy. It is far more potent as a progestogen than as an androgen receptor antagonist. CPA has typically been used at doses of 1 to 2 mg/day as a progestogen in cisgender women and at doses of 50 to 300 mg/day as an antiandrogen. At typical antiandrogen doses of CPA, there is profound progestogenic overdosage as well as associated side effects and risks. CPA has antigonadotropic effects due to its progestogenic activity and thereby suppresses testosterone levels. By itself, CPA can maximally suppress testosterone levels by 50 to 70%, and in combination with even small amounts of estrogen, it can fully suppress gonadal testosterone production and thereby reduce testosterone levels by about 95%—or well into the female range. Although doses of CPA of 50 to 100 mg/day have been used in transfeminine people historically, it is now clear that 5 to 10 mg/day CPA has maximal or near-maximal effectiveness in terms of suppression of testosterone levels. CPA alone is most commonly available as 50-mg tablets. These tablets can be split with a pill cutter and taken once every day to once every other day to achieve an overall CPA dosage of 6.25 to 12.5 mg/day. These lower doses of CPA are not only much more cost-effective than traditional doses but are also likely to have better tolerability and safety. Due to the retained effectiveness of lower CPA doses and the known dose-dependent risks of CPA, CPA doses used clinically in transfeminine people have been in a rapid decline.

Introduction

This article is about the dosage of cyproterone acetate (CPA), a progestin and antiandrogen, for use in hormone therapy for transfeminine people. It argues for the use of lower doses of CPA and goes fairly in-depth to justify these doses. If you're only interested in recommended doses of CPA for transfeminine people, they can be found in the Recommended Dosages section below.

Potency, Conventional Dosages, and Health Risks

CPA is a potent progestogen, with an ovulation-inhibiting dosage of about 1 mg/day and endometrial transformation dosage of about 1 to 3 mg/day in cisgender women (Wiki; Wiki-Table; Endrikat et al., 2011). These dosages of CPA are similar in strength of progestogenic effect to those of normal progesterone production and levels during the luteal phase of the menstrual cycle in premenopausal women (which are about 25 mg/day and 15 ng/mL, respectively). When used as a progestogen in cisgender women, for instance in birth control pills and menopausal hormone therapy preparations, CPA is formulated at a dose of 1 or 2 mg per tablet (Wiki).

In contrast to its progestogenic activity, CPA is far less potent as an androgen receptor (AR) antagonist (Wiki). When used as an antiandrogen, it is generally given at a dosage of 50 to 300 mg/day, both in cisgender women and men. A dosage of 50 to 100 mg/day is typical for androgen-dependent skin and hair conditions like acne and hirsutism in women and a dosage of 100 to 300 mg/day is typically used for prostate cancer in men (specifically 100 to 200 mg/day for the combination of CPA with surgical/medical castration and 200 to 300 mg/day for CPA monotherapy) (Wiki). As such, CPA is generally formulated at a dose of 50 or 100 mg per tablet for use in androgen-dependent conditions (Wiki). As an antiandrogen, CPA has a dual mechanism of action of both suppressing testosterone levels via its progestogenic activity at low doses and additionally blocking the actions of testosterone directly at the AR at higher doses.

Because CPA is so much more potent as a progestogen than as an AR antagonist, there is *profound* overdosage of progestogenic effect when CPA is used as an antiandrogen at typical clinical dosages. This is described in the following three literature excerpts:

> Like chlormadinone acetate, its parent compound, CPA is also a strong progestogen with the endometrial transformation dose of both drugs being between 20 and 30 mg. […] To take full therapeutic advantage of its antiandrogenicity, CPA must be administered in doses per month that are 30 times the physiological equivalent of progesterone production in the cycle. CPA, although the most useful compound available in this field at the moment, cannot be considered therefore an ideal antiandrogen, all the more as some of the side effects may be related to the progestational overdosage rather than to the administered antiandrogenic activity. […] Adverse reactions like tiredness, lassitude, and increase in body weight are possibly due to the enormous overdose of progestational activity in the formula which is necessary to take full advantage of the antiandrogenicity of CPA. (Hammerstein et al., 1975)

> Fixson (1963) tested CPA in ovariectomized women after pre-treatment with oestrogens; with a transformation dose of 20–30 mg this proved a powerful progestogen. The potency

> of CPA in the menses delay test is not exactly known, but has been estimated to be below 1 mg/day (Miller and Jacobs 1986). In relation to this progestational potency, its antiandrogenicity must be considered rather weak. Thus, in order to take full advantage of the latter, 100 mg CPA must be given daily, i.e. three times the cyclic transformation dose per day (Hammerstein and Cupceancu 1969); notably, this parameter is equivalent to the total progesterone production of a corpus luteum throughout its entire cyclic life span. (Hammerstein, 1990)

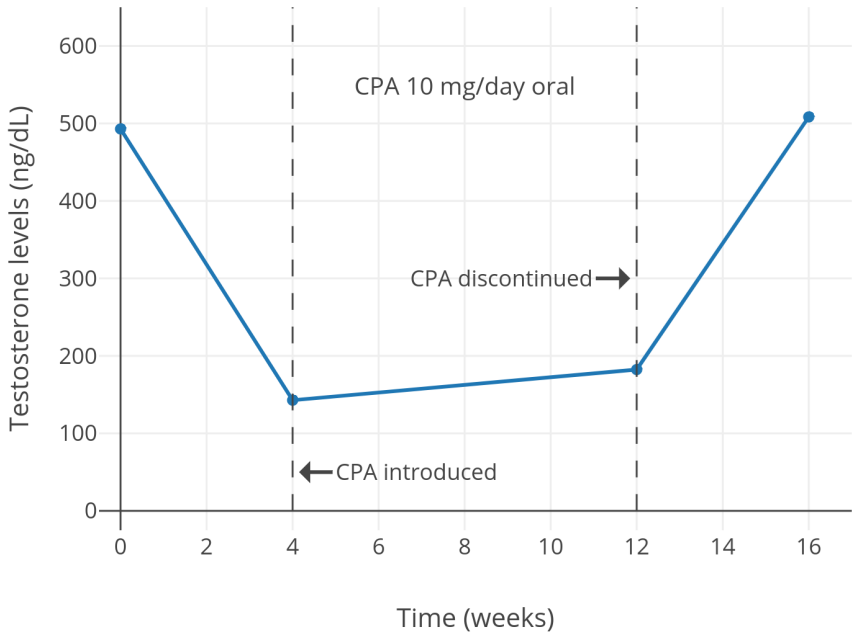
> CPA may be characterized endocrinologically as possessing strong progestational [and] moderate anti-androgenic […] potencies. […] Its progestational activity, in terms of the transformation dose in the oestrogen-primed human endometrium, is 20–30 mg [per month/cycle] which is comparable to that of chlormadinone acetate and other strong progestogens. To take full clinical advantage of its anti-androgenicity not less than 50–100 mg CPA must be taken orally per day, which totals 2 to 3 times the progestational activity the female organism is exposed to throughout a complete ovulatory menstrual cycle. Thus unless much lower and less efficacious doses of CPA are used, a tremendous progestational overdosage must be accepted. […] As already pointed out CPA is endocrinologically not a well-balanced compound because of the strong preponderance of the progestational over the anti-androgenic potency. A way to avoid the heavy progestogen overdosage inherent with the high-dose reverse sequential therapy would be to combine the low-dose contraceptive formulation just mentioned with a pure anti-androgen such as free cyproterone. […] It must be emphasized that CPA is far from being an ideal drug for the anti-androgenic treatment of hirsutism because its progestational potency is much too strong and it is not effective when administered topically. Therefore it is worthwhile looking for better-balanced anti-androgenic compounds for the future. (Hammerstein, 1979)

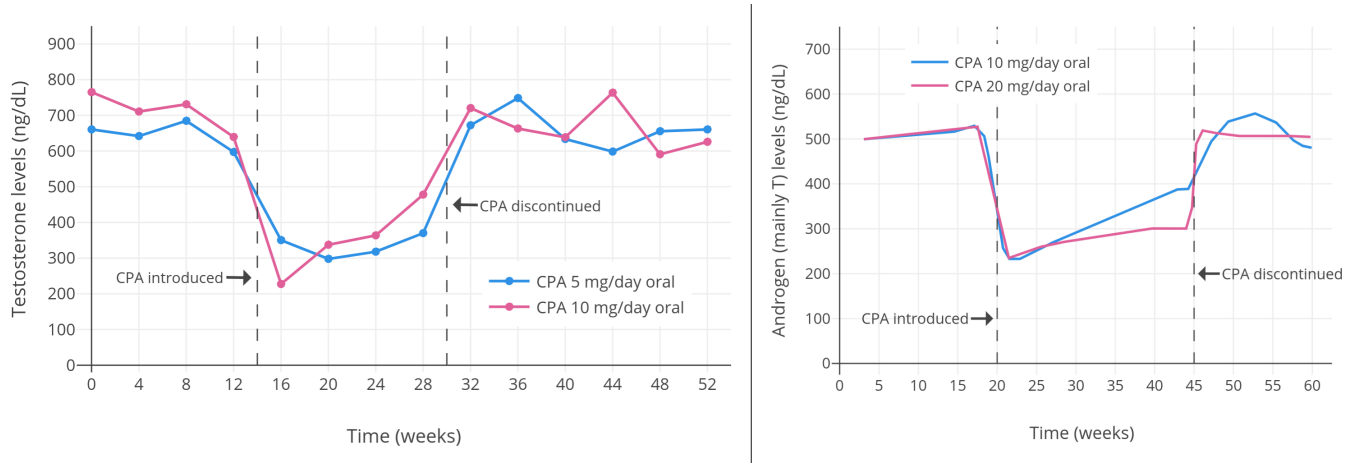
The massive overdosage of progestogenic effect that occurs at such dosages of CPA is likely responsible for the known adverse effects and risks of higher doses of CPA (Wiki; Aly W., 2018) such as fatigue, depression, weight gain, high prolactin levels (Wiki), benign brain tumors (Aly W., 2020; Wiki; Wiki-Table; Wiki-Table), blood clots (Wiki), and cardiovascular complications (Wiki). Such risks are dose-dependent and have not been associated with 1 or 2 mg/day CPA (except for an increased risk of blood clots in combination with oral ethinylestradiol—which is to be expected). The risk of liver toxicity with CPA is also dose-dependent, with elevated liver enzymes occurring mostly only at a dosage of 20 mg/day and above and rare cases of liver failure occurring almost exclusively at dosages of 100 mg/day and above (Wiki; Wiki-Table). As such, there is good rationale for using the lowest possible effective dosage of CPA, an approach that is likely to minimize risks.

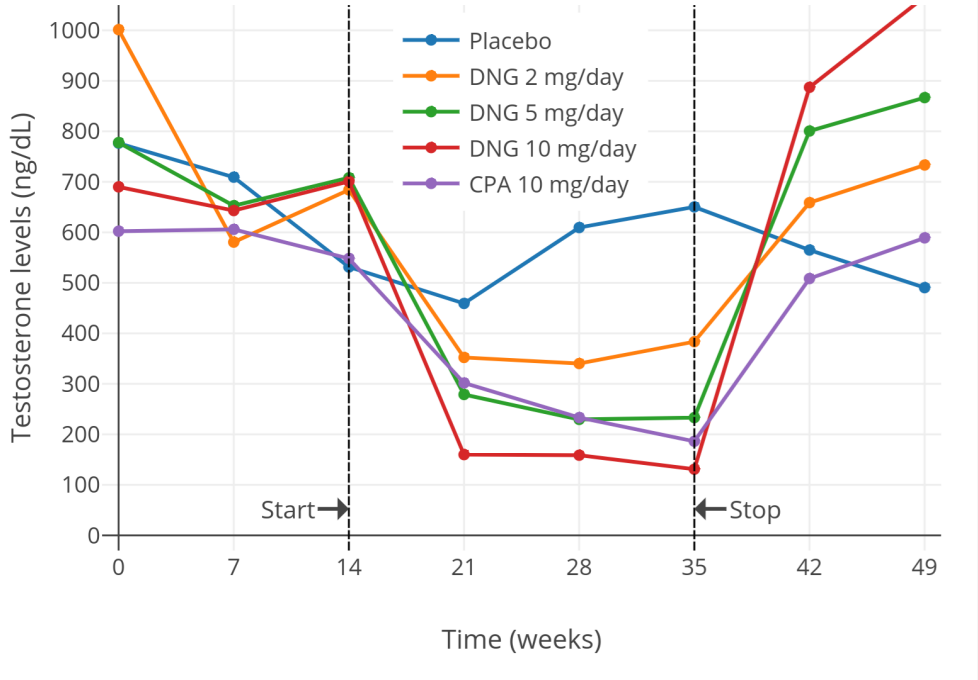
In transfeminine people, CPA has historically been used at a dosage of 50 to 100 mg/day. Notably however, the Endocrine Society published the latest edition of their clinical practice guidelines for the hormonal therapy of transgender people in 2017 and reduced their recommended dosage of CPA from 50 to 100 mg/day to 25 to 50 mg/day (Hembree et al., 2017; Hembree et al., 2009). This was probably motivated in part by increasing knowledge and awareness of the risks of higher doses of CPA. However, it is likely that even these new lower dosages are still far in excess of what is really needed.

Testosterone Suppression with Low and High Doses

Progestogens by themselves, including CPA, are able to considerably suppress testosterone levels in gonadally intact people assigned male at birth. Around a dozen small low-quality studies of low-dose CPA from the 1970s and early 1980s found that 5 to 10 mg/day CPA suppressed testosterone levels by about 40 to 70% in healthy young men (Table). A couple of individual studies notably reported virtually identical suppression of testosterone levels with 5 mg/day versus 10 mg/day CPA (both ~50% suppression; Wiki-Graph) and with 10 mg/day versus 20 mg/day CPA (both ~60–70% suppression; Wiki-Graph). This lack of additional testosterone suppression with a doubling of dosage *within studies* suggests that testosterone suppression with CPA might have actually been maximal at a dosage of only 5 or 10 mg/day. A more modern 2002 study, which used a newer and more reliable analytic method for quantification of blood testosterone, found that 10 mg/day CPA suppressed testosterone levels by 66%, from about 600 ± 150 ng/dL to about 185 ng/dL (SD not given) (Meriggiola et al., 2002a).







Figures: Testosterone levels during treatment with low doses of CPA alone in men. The bottom graph is the 2002 study using DELFIA to quantify testosterone levels. This study also assessed different doses of dienogest (DNG), which has an ovulation-inhibiting dose of 1 mg/day similarly to CPA.

Studies with other progestogens, such as desogestrel, dienogest, and medroxyprogesterone acetate, have consistently found that maximal suppression of testosterone levels in men occurs at a dosage that is between 5 and 10 times that of the ovulation-inhibiting dosage in cisgender women (Wiki; Wiki; Wiki). Based on an ovulation-inhibiting dosage of CPA of 1 mg/day, this would imply that suppression of testosterone levels with CPA would likely be maximal at a dose of between 5 and 10 mg/day. In accordance, this range matches up with the findings of the studies above.

Studies of much higher doses of CPA have shown little better suppression of testosterone levels than lower doses. Modern studies in healthy young adult and adolescent transfeminine people have found that 50 to 100 mg/day CPA alone suppresses testosterone levels by 46 to 61% (from 456–602 ng/dL to 226–294 ng/dL at 4–12 months) (Toorians et al., 2003; Giltay et al., 2004; T'Sjoen et al., 2005; Tack et al., 2017). Older studies in elderly men with prostate cancer have found greater suppression of testosterone levels with high-dose CPA monotherapy (by up to 70–80%, typically to between 50–200 ng/dL) (Gräf, Brotherton, & Neumann, 1974; Jacobi et al., 1980; Wiki-Graph; Knuth, Hano, & Nieschlag, 1984; Wiki-Graph; Schröder & Radlmaier, 2002; Nelson, 2011). The greater testosterone suppression in men with prostate cancer may be related to different blood-testing methodology between studies and/or to the fact that older men have weaker hypothalamic–pituitary–gonadal (HPG) axes and lower testosterone levels (Liu, Takahashi, & Veldhuis, 2017; Winters, Wang, & Fortigel Study Group, 2010).

Although progestogens can considerably suppress testosterone levels at maximally effective dosages, it has been found that a "recovery" or "escape phenomenon", in which testosterone levels eventually increase back to higher levels, occurs when progestogen monotherapy is used on a long-term basis. This has most notably been observed with the related progestogen megestrol acetate (Wiki), but has also been seen with CPA (Goldenberg & Bruchovsky, 1991; Saborowski, 1988; Jacobi, Tunn, & Senge, 1982). In one of these studies, testosterone levels were initially suppressed by CPA by about 70%, but increased back to about 50% of baseline between 6 and 12 months of therapy, remaining stable thereafter up to 24 months. The testosterone escape phenomenon should be kept in mind in the context of progestogen monotherapy for testosterone suppression. In contrast to progestogen monotherapy, this phenomenon has not been associated with combined estrogen and progestogen therapy.

Testosterone Suppression in Combination with Estrogen

CPA is generally used in combination with an estrogen in transfeminine people. Estrogens suppress testosterone levels similarly to progestogens. The combination of an estrogen and a progestogen is synergistic in terms of testosterone suppression and results in suppression of testosterone levels with lower doses than with either an estrogen or progestogen alone (Fink, 1979; Geller & Albert, 1983 [PDF]; Bastianelli et al., 2018). Although estrogens can suppress testosterone levels to an equivalent extent as surgical or medical castration (i.e., orchiectomy or GnRH agonists/antagonists), this normally requires relatively high estrogen levels. Estradiol levels of 200 to 300 pg/mL can suppress testosterone levels by about 90%, to around 50 ng/dL on average, while estradiol levels of about 500 pg/mL can suppress testosterone levels by about 95%, to around 15 ng/dL on average (Wiki; Wiki-Gallery). Because of the high and supraphysiological estradiol levels required for

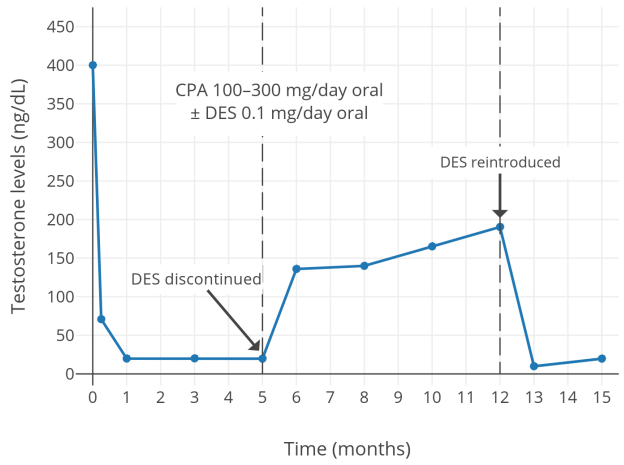
maximal or near-maximal suppression of testosterone levels, lower doses of estradiol are frequently combined with antiandrogens and/or progestogens to block or suppress remaining testosterone levels instead.

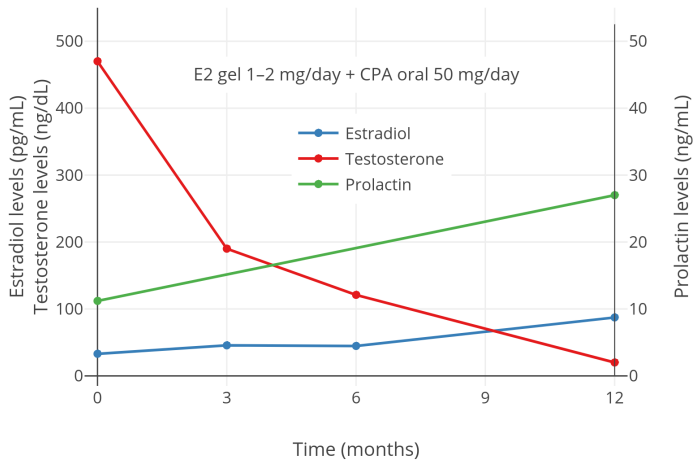
In the 1980s and 1990s, clinical studies in men with prostate cancer showed that the combination of a high dosage of a progestogen, such as 100 to 300 mg/day CPA or 40 to 160 mg/day megestrol acetate, with a low dosage of an estrogen, such as 0.1 to 0.2 mg/day diethylstilbestrol or 0.5 to 1.5 mg/day oral estradiol, was able to completely suppress gonadal testosterone production and reduce testosterone levels well into the male castrate range (<50 ng/dL) (Geller et al., 1981a; Geller et al., 1981b; Geller & Albert, 1983; Goldenberg et al., 1988; Johnson et al., 1988; Geller, 1988; Venner et al., 1988; Geller, 1991; Bruchovsky, 1991; Bruchovsky et al., 1993; Goldenberg et al., 1996). Here is a noteworthy and informative literature excerpt on this topic (Schröder & Radlmaier, 2002):

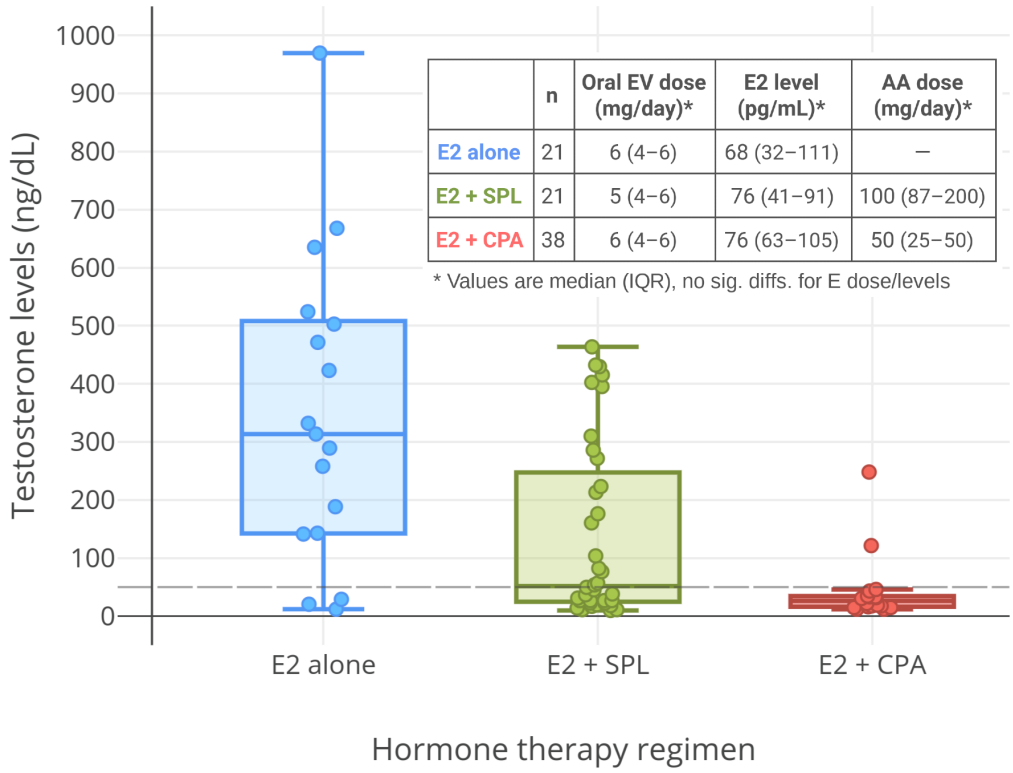
> CPA, as mentioned earlier, leads to an incomplete suppression of plasma testosterone levels, which decrease by about 70% and remain at about three times castration values. In a very systematic approach to the problem, Rennie et al. (59) investigated and compared 12 different procedures of androgen deprivation. These authors found that the combination of CPA with an extremely low dose (0.1 mg/d) of [diethylstilbestrol (DES)] led to a very effective withdrawal of androgens in terms of plasma testosterone and tissue dihydrotestosterone. The same group later showed that 200 mg of CPA, and even 100 mg/day, was sufficient to achieve a similar endocrine response, which was correlated to very favorable clinical responses in a Phase II situation (60,61). The approach has many potential advantages, and, from an endocrinological point of view, is very logical: this regimen combines the testosterone-reducing effects of two compounds, therefore, only small amounts of estrogen are required to bring down plasma testosterone to approximately castrate levels. Once castrate levels have been achieved, only low doses of CPA are necessary to counteract remaining androgens, mainly of adrenal origin. The regimen was shown to be associated with few side effects and a very low cost. The combination of low-dose CPA with low-dose DES was never studied in a Phase III situation in comparison to standard management. Considering the endocrine results and the observations in patients treated with this regimen (60), this combination treatment is very likely to be competitive with other standard forms of therapy.

A 2016 study of 50 mg/day CPA and 1 to 2 mg/day transdermal estradiol gel in transfeminine people showed that estradiol levels of about 45 pg/mL with CPA were insufficient to achieve female/castrate levels of testosterone, instead resulting in testosterone levels of about 120 to 190 ng/dL (Gava et al., 2016; Wiki-Graph). Conversely, estradiol levels of about 85 pg/mL with CPA achieved complete suppression of gonadal testosterone production, with resulting testosterone levels of about 20 ng/dL. As such, a certain minimum level of estradiol with CPA appears to be

required for complete testosterone suppression. A 2019 study of CPA and oral estradiol valerate indicated that testosterone levels were still fully suppressed with median estradiol levels of 76 pg/mL and 25th percentile estradiol levels of 63 pg/mL (Angus et al., 2019; Wiki-Graph).







	n	Oral EV dose (mg/day)*	E2 level (pg/mL)*	AA dose (mg/day)*
E2 alone	21	6 (4–6)	68 (32–111)	—
E2 + SPL	21	5 (4–6)	76 (41–91)	100 (87–200)
E2 + CPA	38	6 (4–6)	76 (63–105)	50 (25–50)

* Values are median (IQR), no sig. diffs. for E dose/levels

Figures: Testosterone levels with CPA plus low doses/levels of estrogens in men and transfeminine people. Note for the graph on the top right that the mean transdermal estradiol dosage increased between 6 and 12 months.

Fung et al. (2017) showed that the combination of either 25 or 50 mg/day CPA with a moderate dosage of oral estradiol (~3.5 mg/day) or transdermal estradiol (~3.5 mg/day gel or ~100 µg/day patch) resulted in equivalent and complete suppression of gonadal testosterone production (~95%

suppression of testosterone levels) in transfeminine people (Fung, Hellstern-Layefsky, & Lega, 2017). Such dosages of estradiol would be expected to achieve estradiol levels of around 100 pg/mL (Wiki). The Fung et al. (2017) study was notably published 6 months before the new 2017 Endocrine Society guidelines and was probably responsible for the decrease in their recommended dosage of CPA from 50 to 100 mg/day to 25 to 50 mg/day.

Few studies to date have assessed testosterone suppression with low-dose CPA in combination with a low or moderate dosage of an estrogen. However, based on the fact that 5 to 10 mg/day CPA alone is probably maximal in terms of suppression of testosterone levels, it is likely that such dosages of CPA will be similarly effective as higher dosages. In accordance, studies of 5 to 12.5 mg/day CPA plus upper physiological replacement dosages of testosterone have demonstrated undetectable gonadotropin levels (<0.5 IU/L) and hence complete suppression of testicular function in healthy young men (Meriggiola et al., 1998; Meriggiola et al., 2002b). Estradiol is a more powerful antigonadotropin than testosterone (Wiki), so these findings probably apply to physiological replacement levels of estradiol as well (e.g., mean levels of 100 to 200 pg/mL).

Accordingly, Meyer et al. (2020) assessed a dosage of CPA in combination with estradiol in 155 transfeminine people and found no difference in testosterone levels with 10, 25, or 50 mg/day CPA; testosterone levels were strongly suppressed with all three doses (to about 15–20 ng/dL on average, or into the lower end of the normal female range). The estradiol forms and doses used in this study were oral estradiol valerate (median 6 mg/day, range 3–10 mg/day), transdermal estradiol gel (median 2.25 mg/day, range 1.5–6 mg/day), and transdermal estradiol patches (100 µg/day in all cases). Estradiol levels were about 100 pg/mL on average, with an interquartile range (i.e., difference between 75th and 25th percentiles) of about 100 pg/mL. This study demonstrates that, provided estradiol levels are adequate, no more than 10 mg/day CPA is needed to fully suppress testosterone levels in transfeminine people. Another study likewise found no difference between <20 mg/day and >50 mg/day CPA in terms of testosterone suppression in transfeminine people (Even-Zohar et al., 2020).

Even doses of CPA lower than 5 mg/day (e.g., 2 mg/day) may be usefully effective for testosterone suppression if combined with sufficient levels of estradiol, although this has not been studied and remains to be validated. But there is certainly precedent for the notion when looking at studies with other progestogens. As an example, one study using 10 mg/day oral medroxyprogesterone acetate (equivalent to 1 mg/day CPA in terms of ovulation inhibition; Wiki-Table) observed 63% lower testosterone levels (215 ng/dL vs. 79 ng/dL) when added to estradiol and spironolactone therapy in transfeminine people (Jain, Kwan, & Forcier, 2019). Analogous effects on testosterone levels would be anticipated for very-low-dose CPA. Moreover, such dosages of CPA would have the advantage of actually being physiological in terms of progestogenic exposure.

Clinical Adoption of Lower Doses

In light of the risks of higher doses of CPA and the high capacity for testosterone suppression of lower doses of CPA, lower doses of the medication are being increasingly adopted clinically. See the supplementary page here for a collection of literature excerpts and personal communications evidencing the clinical adoption of lower CPA doses.

Androgen Receptor Antagonism with Higher Doses

The AR antagonism of CPA is relatively weak in terms of potency; dosages of CPA of 50 to 300 mg/day seem to be necessary for meaningful or considerable AR antagonism. Unfortunately, such doses also result in extreme progestogenic overdosage and are associated with considerably greater risks and adverse effects. As a result, the use of such dosages of CPA should probably no longer be considered advisable. Instead, from a rational standpoint, CPA should probably be used at lower doses simply as a progestogen to suppress testosterone levels. As such, the highest effective dosage of CPA for testosterone suppression, which is probably about 10 mg/day or less, should be around the maximal dosage of CPA that is used in transfeminine people. (A dosage of 12.5 mg/day is also acceptable.)

It must be emphasized that since the combination of an estrogen and CPA can easily suppress testosterone levels well into the female/castrate range (typically to *below* average female levels), there isn't necessarily a requirement for concomitant AR blockade. In any case, if AR antagonism to neutralize the remaining female/castrate levels of testosterone is still necessary or desired (e.g., to treat persisting acne, to maximize breast development potential, or for some other purpose), a low dosage of a non-progestogenic AR antagonist like bicalutamide or spironolactone can be added to CPA to more safely achieve this than use of higher CPA doses.

Recommended Dosages

Dosage for Testosterone Suppression

Estrogen Plus Cyproterone Acetate

The following recommended dosages of CPA in transfeminine people are for the combination of CPA with an estrogen and are specifically for achieving *maximal* suppression of testosterone levels:

Form	Min. dosage	Max. dosage	Amount
10 mg tablets	5 mg/day	10 mg/day	1/2 of a tablet to 1 whole tablet per day

Form	Min. dosage	Max. dosage	Amount
50 mg tablets	6.25 mg/day	12.5 mg/day	1/8th of a tablet to 1/4th of a tablet per day

Start with the minimum dosage of CPA for one month. After one month, have testosterone levels tested and confirm that they're in the normal female/castrate range (<50 ng/dL). Regardless of dosage, a concomitant minimum estradiol level of around 65 pg/mL needs to be attained in order to allow for complete suppression of testosterone levels with CPA. If testosterone levels aren't sufficiently suppressed after a month and estradiol levels are adequate, increase to the maximum CPA dosage and re-check testosterone levels after another month. Alternatively, the dosage of estradiol can be increased instead; higher estradiol levels result in greater testosterone suppression as well.

Cyproterone Acetate Alone

The use of CPA alone (i.e., as a monotherapy for testosterone suppression) is not recommended due to the risk of decreased bone mineral density and other symptoms of sex-hormone deficiency (Wiki; Aly W., 2019). In any case, the recommended dosages for CPA without an estrogen are essentially the same as those listed above of the combination of an estrogen with CPA for testosterone suppression. However, the higher CPA dose (10–12.5 mg/day) may be preferable for good measure in this scenario.

Dosage for Progestogenic Effects

The following recommended dosages of CPA in transfeminine people are for progestogenic effects similar to normal physiological exposure (equivalent of luteal-phase progesterone levels):

Form	Dosage	Amount
10 mg tablets	2.5 mg/day	1/4th of a tablet per day
50 mg tablets	3.125 mg/day	1/16th of a tablet per day

Additional Topics

Testosterone levels should ideally be assessed with blood work to ensure that they are indeed adequately suppressed during estrogen and CPA therapy.

For splitting CPA tablets into small fractions, a pill cutter can be used. Additionally, CPA can be taken once every 2 or 3 days instead of once every day to help further divide doses. It's notable that CPA has a relatively long half-life in the body of about 1.5 to 2 days (but possibly up to 4 days)

(Wiki; Wiki-Graph). Hence, taking it once every other day instead of once per day, or even less frequently like once every 3 days, has sound basis and is likely to be entirely viable.

If additional AR antagonism to block the remaining female/castrate-range levels of testosterone with estrogen plus low-dose CPA is desired, a low dose of an AR antagonist like bicalutamide (e.g., 6.25–25 mg/day) or spironolactone (e.g., 100–200 mg/day) can be added for this purpose.

Update

The GoLoCypro study (2019–2022) is being conducted by Dr. Judith Dean at the University of Queensland in Australia. It's assessing the influence of estradiol plus CPA on testosterone levels at five different CPA dose levels (12.5 mg 2x/week, 12.5 mg/2 days, 12.5 mg/day, 25 mg/day, and 50 mg/day) in a total of 120 to 350 transfeminine people. CPA doses are being titrated to the minimum that maintain testosterone levels within the therapeutic goal range of 0.5 to 1.5 nmol/L (14–43 ng/dL). The study is the first dose-ranging study of CPA in transfeminine people to be conducted and is eagerly anticipated due to the valuable information that it should provide in terms of the minimum effective dosage of CPA for adequate testosterone suppression in transfeminine hormone therapy.