

The Hormonal Treatment of Sexual Offenders

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The hormonal treatment of sexual offenders is part of a pharmacological approach to the reduction of the sexual drive. Sexual drive reduction can also be brought about by stereotaxic neurosurgery and castration. These other methods of sexual drive reduction are closely related to the pharmacological approach, and all are dependent on the complex interactions between higher central nervous system functions, located in the cortex and limbic systems, and neuroendocrine mechanisms mediated via the hypothalamic pituitary axis, the gonads, and their various feed-back mechanisms. The higher functions of the central nervous system are channeled through the hypothalamic-pituitary axis where complex neurological correlates of behavior are transformed into neuroendocrine responses.

Gonadotrophin releasing factor (GRF) is released from the hypothalamus irregularly in bursts. The antero-pituitary in response releases luteinizing hormone (LH) and follicular stimulating hormone (FSH), also in episodic bursts of secretion. In the normal male, FSH acts on the germinal epithelium of the seminiferous tubules to produce spermatazoa. LH stimulates the Leydig cells to secrete testosterone that is then released into the serum where it forms approximately 95 percent of the plasma testosterone. The other 5 percent is secreted from the adrenal cortex through $\Delta 4$ -androstenedione.¹

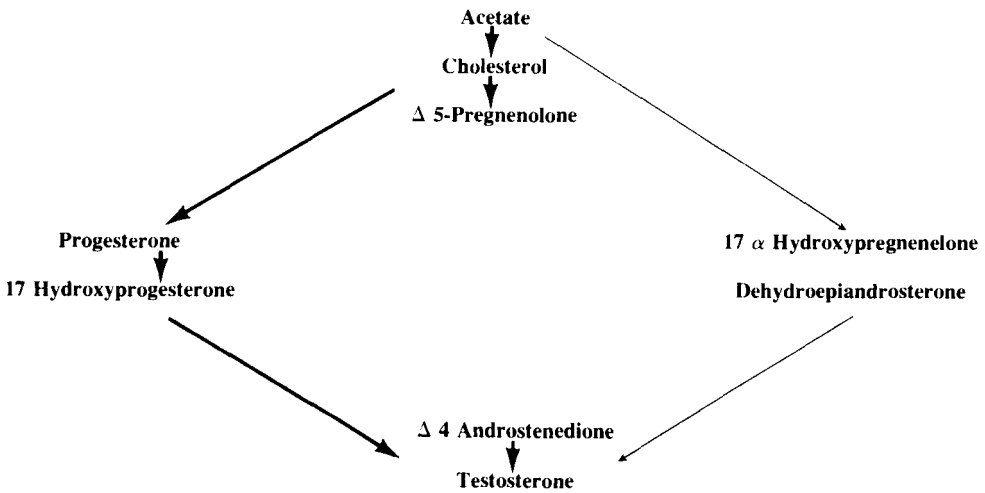
During puberty, both sexes show an increase in the volume of gonadotrophin secretion, and in the male this is associated with increased testosterone secretion during sleep. There is an associated circadian rhythm resulting in sleep related increases in gonadotrophic hormone production.¹ Testosterone in the male regulates spermatogenesis and is responsible for the development of secondary sex characteristics. Estrogens are also produced by the testes. The exact role of oestrogens in the male reproductive system is not fully understood.¹

Testosterone (T) is the principal androgen produced by the Leydig cells of the testes, and it is a 17 hydroxylated c-19 steroid. It is transported in the plasma by testosterone-binding globulin (TBG), which binds about 97 to 99 percent of circulating testosterone. The free testosterone is assumed to be the metabolically active portion.¹ Testosterone is carried to various target glands, such as the prostate where it is converted into dihydrotestosterone (DHT). DHT and T are the important androgens involved in sexual activity.¹

Testosterone (T) is secreted episodically, and multiple peaks can be observed if continuous blood sampling is performed. It is also subject to a diurnal variation with peak levels between 8 a.m. and 10 a.m.¹

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Diagram 1. Testosterone Metabolism



Testosterone (T) and dihydrotestosterone (DHT) are broken down mainly into 17 ketosteroids and excreted in the urine. The testes account for approximately 30 percent of urinary ketosteroid production.¹

Consideration of these factors accounts for a single random morning sample yielding a result within 20 percent of the true mean value 68 percent of the time.² Three consecutive samples taken approximately 10 minutes apart between 8 a.m. and 10 a.m. would increase the reliability.³ Serum testosterone concentration can be measured by a double isotope derivative, competitive protein binding, and radioimmunoassay. The free testosterone is not usually estimated and the normal range is 0.26-1.44 micrograms/100 mL. of blood.¹

Animal research has resulted in the isolation of areas of the brain that accumulate sex hormones and where the sexual behavior can be affected by a variety of induced lesions. Further, various studies of the metabolism of testosterone also have contributed to the understanding of the central mediation of male sexual behavior. Enzyme systems for the metabolic breakdown of the testosterone have been found in the hypothalamus and other parts of the limbic system.⁴⁻⁷ Testosterone is broken down in two directions, either via aromatization to estrogens or to nonaromatizable androgens such as androstenedione. Despite some conflicting findings in most of the animal species tested, androgens, which are capable of being broken down into estrogens (via aromatization), appear to have a stronger behavioral effect than the nonaromatizable androgens.⁷ One would therefore expect anti-estrogens and also enzyme inhibitors blocking aromatization of testosterone to estrogen to abolish androgen-induced sexual be-

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haviors, however research in this area⁷⁻¹¹ has produced both negative and equivocal results.⁷ The main nonaromatizable testosterone derivative dihydrotestosterone (DHT), when combined with estradiol in some studies, has led to a potentiating effect, possibly pointing toward a combined effect. This most likely occurs through the central mediation areas but is not fully understood and is controversial.⁷ It is also complicated by different animal species being used in experimentation, with a possibility of different metabolic pathways.^{5,7,12-15}

The present state of knowledge supports a correlation between plasma testosterone and sexual drive. This has been studied through castration in animals and humans, and more recently, through the effects of cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA). The pharmacological suppression of sexual drive has developed from the observed effects of various drugs on male sexual activity over the last 40 years and essentially supports this correlation.

Originally estrogens were used to reduce the sexual drive in males,¹⁶⁻²⁰ but the use of these drugs has been limited because of side effects such as nausea, vomiting, and feminization. A serious complication of this type of treatment was noted by Symmers (1968) who observed carcinoma of the breast in a transsexual after surgical and hormonal treatment with estrogen.^{20,21} Estradiol implants have also been used.^{20,22}

Sexual drive reduction by the phenothiazines also has been described. Thioridazine,^{20,23-25} fluphenazine ethanate,^{20,26} and more specifically a butyrophenone benperidol,^{20,27,28} are described as being the most effective agents. Beaumont *et al.* (1974)²⁹ found normal LH levels in men and testosterone either below normal or at the lower limits of normal and found the levels rose on withdrawal of the medication. The actual mechanism responsible for these effects remains controversial, but the lowering of plasma testosterone would support the ability of these drugs to reduce the sexual drive.

The most recent pharmacological agents used for sex drive reduction are cyproterone acetate (CPA), an antiandrogen, and medroxyprogesterone acetate (MPA). Both CPA and MPA effectively reduce the circulating serum testosterone and most likely reduce the sex drive as result of this disruption in testosterone metabolism.

Medroxyprogesterone Acetate (MPA)

The initial observation that progesterone derivatives may have a sex drive reducing effect was described by Heller *et al.* (1958).³⁰ They investigated the effects of these steroids on the male reproductive system and used 17 alpha-ethyl 19-nortestosterone, 17-alpha ethynyl 19 nortestosterone and 17 alpha-ethynyl-17 hydroxyestrin-3-one nortestosterone, which are mostly female oral contraceptives. The subjects selected were healthy males, and comprehensive hormonal determinations were conducted. The significant observations were a reduction in testicular size and a reduction in spermatazoa production. Most significantly after three or four weeks of treat-

ment, all subjects noted a complete loss of libido and had difficulty in producing seminal fluid specimens by masturbation. It also was noted that libido returned within one to two weeks following the withdrawal of therapy, and by six weeks was at a pre-treatment level in all cases.

Subsequently medroxyprogesterone acetate (MPA) was used as a substitute in North America. This was due in part to cyproterone and cyproterone acetate (CPA) being unavailable. Methyl-testosterone (19-nor-17-alpha-methyltestosterone) had been used by Servais in Belgium for pharmacological reduction of sexual drive.

The introduction and subsequent study of MPA in the U.S. has primarily been the responsibility of three co-workers, Money, Migeon, and Rivarola.³¹ The original decision to use MPA to suppress sexual drive occurred when a bisexual transvestite patient became involved in incestuous activity with his six-year old son, and a decision to go ahead and treat him with MPA was taken.³¹ Subsequently further studies of the use of MPA have been documented.³¹⁻³⁶

Table 1. Studies with MPA

Year	Author	Drug	No. of Cases	Dose	Duration of Follow up	Results
1970	Money	MPA	8	300-400 mg/wk	3 yr	Decreased sexual drive; decrease in serum testosterone; no permanent side effect
1975	Blumer <i>et al.</i>	MPA	22	100-300 mg/wk	1 yr	Suppression of sexual drive; some improvement in aggressive behavior in temporal lobe epileptics
1976	Money <i>et al.</i>	MPA	23	200-400 mg/wk	8 yr	Serum testosterone reduced; reduction in erotic fantasy; reduction in erections; reduction in actual sexual activity; some improvement in aggressiveness
1981	Gagné	MPA	48	200 mg IMI, 2 to 3 times/wk for 2 wks, then 200 mg once or twice a wk for next 4 wks. Subsequently 100 mg/wk every 2 wks for 12 wks. Thereafter 100 mg 1/wk to 1/mo depending on clinical response	12 mos	Diminution in sexual fantasy; diminution in sexual arousal; subjective report of disappearance of deviant behavior; suppression of plasma testosterone; decrease in erections & ejaculation; Side effects noted in all cases in conjunction with each injection for approx 72 hrs. 58% of pts had wt gain; 29% reported hot & cold flushes; 20% complained of headaches; 14% suffered nausea, & 2% suffered phlebitis

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MPA has as a mode of action, by the induction of the enzyme testosterone A-ring-reductase, in the liver and thereby accelerating testosterone metabolism.^{37,38} The effect of MPA on plasma testosterone appears to be twofold in that it decreases the production rate of testosterone by inhibiting the pituitary secretion of luteinizing hormone (LH) as well as inducing hepatic A-Ring-Reductase.^{37,38} MPA is also noted to inhibit follicle stimulating hormone (FSH).^{7,33,39,40} There is a relative difference between the suppression of LH output and FSH output by MPA. It has been shown that MPA reduces the production of testosterone from its precursors, and this is most likely due to the diminished secretion of LH.^{7,38,40} It is noteworthy that estrogen and testosterone are powerful inhibitors of gonadotrophin output.

MPA is usually administered in the form of a depot-injection in dosage levels of 300-400 mg. intramuscularly every seven to ten days. In one study, it was noted that sexual offenders receiving MPA reported a decreased frequency of erotic fantasy, erections, and ejaculation, when compared to pretreatment behavior.³² Further, some stopped their paraphilic behavior completely; presumably they had less drive to indulge in deviant sexual activity. A follow-up study showed the recurrence of deviant sexual behavior increased dramatically once the medication was discontinued. This is typical of the effect of MPA on sexual activity. Long-term follow-up studies of MPA in the U.S. have been conducted by Money in 1970 and 1976 where he reported the use of MPA in eight patients over a three-year period and subsequently 23 patients over an eight-year period.^{31,32} Further, Blumer, and Migeon (1975) reported on 22 patients studied over a 12-month period.³⁶ This particular study by Blumer and Migeon showed temporal lobe epileptics on MPA had a decrease in aggressive behavior. Berlin *et al.* (1981) and P. Gagné (1981) also reported a series of patients treated with medroxyprogesterone acetate.^{34,35}

In all these studies a reduction in libido is noted, and the effects appear to be fully reversible once the medication has stopped. These studies report a reduction in circulating testosterone. Major side effects reported are weight gain, lethargy, sweats, nightmares, dyspnea, hyperglycemia, hypogonadism, and leg cramps. Feminization has not been reported thus far. It also has been noted that the MPA decreases erotic fantasies even when serum testosterone levels remain relatively unchanged. MPA is reported to be associated with thrombotic disorders (phlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis) in some studies. It is noted that the drug causes fluid retention, and so precaution is needed in the case of persons suffering from epilepsy, migraine, asthma, and cardiac or renal dysfunction. Depression has been described in relation to the use of MPA, and further research is essential in this regard. In persons receiving estrogen and progesterone combination drugs, a decrease in glucose tolerance has occurred, and some precautions should be taken in relation to MPA.

Table 2. Side Effects of MPA Treatment

0-2 months	Serum testosterone decreased; erections decreased; ejaculation decreased; spermatogenesis decreased; sexual fantasies decreased; fatigue (and after each depot, Gagné 1981); improved psychosocial functioning; depression, restless, hot and cold flushes; nausea.
2 months	Weight gain; thrombophlebitis.

The various studies outlined above report positively that MPA given intramuscularly in a depot preparation every seven to ten days causes a decrease in erotic fantasy, the frequency of erection, and ejaculation and has been beneficial in treating the paraphilias by causing a reduction in sexually deviant behavior. Recently it has been reported that MPA can be reduced to 100 mg. on one occasion per week and up to one occasion per month with a continuation of the positive effects on sexual behavior.³⁵

MPA has been used predominantly for the treatment of menstrual disorders due to endogenous progesterone deficiency and for palliation of advanced endometrial carcinoma.

Cyproterone Acetate (CPA)

Cyproterone and its 17 alpha acetate derivative are synthetic steroids with a similar structure to progesterone. Lerner *et al.* (1960) and Dorfman and Dorfman (1960) first described two weak antiandrogen substances, alpha norprogesterone and delta-1-testolactone.⁴¹ Cyproterone was synthesized by Wiechart while searching for new progestogens.⁴¹ Cyproterone acetate (CPA) has subsequently become the most effective antiandrogen known.

In experimental animals, CPA has been shown to block the action of androgens at the target organ level.^{42,43} Experimental work has shown that it blocks the uptake of testosterone and dihydrotestosterone.^{7,44,45} When CPA is administered to pregnant animals it produces a marked feminization of the male fetuses as it prevents the intrauterine androgen secretion that normally occurs.⁴³ CPA also weakly suppresses the secretion of LH and to a greater degree FSH.^{7,46,47} Although not fully confirmed, it would appear the effect of CPA is limited to the genital and accessory genital organs and does not affect androgen uptake in the hypothalamic areas that mediate sexual behavior.^{7,8,15,48,49}

The mode of action of CPA at the molecular level involves a competitive inhibition of 5 alpha-dihydrotestosterone at specific receptor sites in the target organs.^{47,50,51} This appears to be the principal mode of action of CPA as it only has a weak inhibitory effect on the pituitary gonadotrophins LH and FSH. This mode of action differs significantly from that of MPA described above.

The first clinical studies involving the treatment of male patients with CPA were reported in 1967 and a favorable outcome was noted.^{41,52-54} Ott and Hoffet (1968) in a similar study reported a favorable treatment outcome.⁵³ Both Ott and Hoffet (1968) and Laschet (1967) noted that the

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urinary excretion of gonadotrophins was reduced but not completely suppressed by CPA.^{41,53} Sommerville (1970) in a sample of treatment cases, measured the serum testosterone and found the mean values were lower during active treatment when compared to the pretreatment phase.⁵⁵ Other clinical trials of CPA have been conducted by Craft (1970), Davies (1970), Cooper (1972), Mothes (1972), and Bancroft (1974).^{20,53,55-59} Laschet and Laschet (1975) reported extensively on an eight-year follow up of CPA in 300 subjects.^{52-54,57} The usual daily oral dose of CPA in these studies was 100 mg. in divided doses, but certain individuals were treated with up to 300 mg. per day. In most of these studies the patient acted as his own control, comparing active treatment to placebo effects.

Table 3. Studies with CPA

Year	Author	Drug	No. of Cases	Dose/Day	Duration of Follow up	Results
1969	Laschet <i>et al.</i>	CPA	84	100-200 mg	3 yr	Sex drive decrease 1-2 wks; noted that mentally subnormals and sexual offenders all improved. Schizophrenic and persons with brain damage, no improvement
1972	Cooper <i>et al.</i>	CPA	1	100 mg	12 wks	Plasma testosterone decreased 50%; morning erections disappeared; one week — not able to masturbate to orgasm; 3 wks. after stopping CPA sexual responsiveness returned to normal plasma testosterone to pre-treatment levels
1972	Mothes <i>et al.</i>	CPA	352	100 mg	7 yr	Sex drive decreased one to two weeks; weight gain; gynaecomastia 20% cases; inhibition of spermatogenesis reversible
1974	Bancroft <i>et al.</i>	CPA vs ethinyl oestradiol	12	50 mg BID .01 mg BID	3 mos	Both drugs significant sexual interest reduction compared to no treatment. Sexual attitude not affected. Patient became depressed on cyproterone
1975	Laschet <i>et al.</i>	CPA	300	50-200 mg 300-600 mg x1 wk. IMI	2 mos to 8 yr	Sexual drive reduction in 1 wk. Reversibility of effects in same order as onset of action, i.e., libido erection, orgasm, spermatogenesis

All studies report that CPA suppressed the sexual drive, usually within a short period after the onset of treatment ranging between one to three weeks. There was accompanying retarded ejaculation and on occasions, complete ejaculatory failure as reported by Ott and Hoffet (1968).⁵³ It was noted that in patients where sexual drive disturbance is associated with organic brain damage, the usual reduction in sexual drive did not occur and a subsequent decrease in deviant sexual behavior was not therefore expected. In most of the studies, psychotic patients were excluded although Ott and Hoffet (1968) did treat some schizophrenics.⁵³ They found the sexual drive was inhibited, although on some occasions the psychotic conditions worsened.

The known side effects of CPA are reversible. It has been noticed in the first weeks of treatment there may be an increase in fatigue, an increased desire for sleep, and occasionally transient depressive mood states. An increase in body weight also has been reported and gynaecomastia has been noted. An increase in the growth of head hair, a decrease in body hair, and a decrease in sebaceous gland secretion have also been noted, and more recently CPA has been considered for treatment of acne and prostatic carcinoma. The inhibition of spermatogenesis is dose dependent and is reversible. The desired effect of CPA treatment is a decreased level of sexual drive, with (in some cases) a decreased ability to ejaculate, and to achieve an erection. It has been reported that there is a decrease of sexual fantasies and dreams, but it is noted that no effects on the direction of sexual drive, or of erotic fantasy, seem to occur.

Table 4. Side Effects of CPA Treatment

(Laschet and Laschet 1975)

0 - 1½ mos	Serum testosterone decreased; erections decreased; ejaculate decreased; spermatogenesis decreased; sexual fantasies decreased; fatigue; hypersomnia; activity decreased; neurasthenia; depression; sexual drive decreased and psychopathology accompanying sexual drive disturbance; normalizes (i.e., labile affect, inner restlessness); negative nitrogen balance; weight gain
3 mos	Nitrogen balance to normal. CA ⁺ PO ₄ ⁻ normalize
6 - 8 mos	20% protracted and temporary gynaecomastia. Decrease in body hair; increase in scalp hair; decrease in sebum secretion

The consistent biochemical effect with CPA, as with MPA, is a reduction in the serum testosterone. The level of sexual drive reduction with both MPA and CPA appears to parallel serum testosterone levels although the exact relationship is much more complex than it first appears. The usual method of administration of CPA is via the oral route. The usual oral daily dose is 100 mg. in divided doses, 50 mg. on two occasions per day. In some instances up to 300 mg./day has been given in divided doses. More recently a depot, injectible form of CPA has been manufactured and is a reliable way of administration, particularly as it improves patient compliance. The usual depot intramuscular dose is 300-600 mg. every one or two weeks.

Conclusion

It is clear that a pharmacological suppression of the sexual drive can effectively be brought about by MPA or CPA. Although the exact site of action and mode of action of these drugs is not fully understood, few serious side effects have been documented, and all studies note the side effects are essentially reversible. Overall, MPA has potentially the most serious side effects such as thrombophlebitis and pulmonary embolism. Suppression of spermatogenesis may result in a relative increase in abnormal spermatozoa and contraception in married or cohabiting couples may be indicated as an extra precaution. Psychotic patients either in remission or actively psychot-

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ic can be treated with CPA or MPA with caution. The phenothiazines however are noted as suppressing the sexual drive, and the choice of a suitable phenothiazine is most likely to be more appropriate than the use of CPA or MPA. The therapeutic spectrum of CPA and MPA does not include suppression of sexual drive where an increase in sexual drive is associated with organic brain damage. This does not, however, necessarily exclude the use of CPA and MPA in the mentally retarded.

Biological research supporting a correlation between serum testosterone and aggression is only weakly supported by the studies of MPA and CPA. There has been some improvement in aggressive behavior in temporal lobe epileptics reported by Blumer *et al.* (1975) and some studies on CPA report improvements in aggressive behavior.³⁶ In general terms, there is a highly complex relationship between aggression and various biological factors in man, and MPA and CPA are not pharmacological agents suitable for the treatment of aggressive behavior per se but possibly reduce aggression that is sex drive related. The most likely mechanism is the onset of a "sexual calm" (that is well documented in various studies) when an individual with a high sexual drive has it suppressed. This is accompanied by an associated reduction in psychopathological features such as restlessness, lability of mood, and irritability that could have resulted in aggressive behavior. A transient depressed mood could be another factor worthy of consideration and is a noted effect of CPA and MPA treatment.

Further studies of CPA and MPA are needed, and a double-blind placebo crossover format should be attempted, despite the difficulties in organizing and implementing such a study.

Informed consent is an important associated issue in the treatment of sexual offenders. It is a controversial issue, and although it is fundamental prior to the instigation of a treatment regime using these pharmacological agents, a detailed discussion is beyond the scope of this article.

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