Pharmacotherapy of Paraphilias With Long-Acting Agonists of Luteinizing Hormone–Releasing Hormone: A Systematic Review

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Background: In addition to psychotherapy, pharmacotherapy is an important treatment option for paraphilias, especially in sexual offenders. Cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) are commonly used but can have serious side effects. Selective serotonin reuptake inhibitors (SSRIs) may also be effective in less severe cases. Recent research shows that luteinizing hormone–releasing hormone (LHRH) agonists may offer a new treatment option for treatment of paraphilic patients.

Method: MEDLINE was searched for clinical trials, case-control studies, case reports, and other clinically and theoretically important literature published between 1980 and November 2002 on the treatment of paraphilia with LHRH agonists. Keywords included *LHRH agonists*, *GnRH-agonists, antiandrogens, paraphilia*, *pedophilia*, and *sex offenders*.

Results: We found 4 case reports, 1 case-control study, 7 open uncontrolled studies, and 1 study comparing patients receiving CPA with those receiving LHRH agonist treatment in forensic hospitals. In total, the studies reported on a sample of 118 treated patients with different forms of paraphilias (sadism, pedophilia, exhibitionism, voyeurism). Nearly all of the studies used self-reports to measure the effects of medication. Duration of follow-up was between 6 months and 7 years and revealed that there were no relapses if patients remained under treatment. Patients previously treated with other agents like CPA, MPA, or SSRIs reported better effects when taking LHRH agonists.

Conclusion: Although there is a need for further research, LHRH agonists offer a treatment option for patients with severe paraphilia. We propose a differentiated pharmacologic treatment regarding side effects, symptomatology, and severity.

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Testosterone plays a crucial role in male sexuality.[1] The behavioral effects of testosterone and dihydrotestosterone are mediated through androgen receptors that are widely but selectively distributed throughout the brain, i.e., in the septal region, the pituitary, and the hypothalamus.[1,2] Testosterone also influences erection and ejaculation,[2] and, vice versa, sexual activity seems to increase testosterone levels.[3] Androgens appear to regulate the action of a wide range of neurotransmitters. There is some evidence from animal studies that testosterone modulates 5-HT_{1A} and 5-HT_{1B} receptor effects on impulsive aggression.[4] The role of testosterone in human aggression is less clear. Male prisoners with a history of violent crime during adolescence[5] or chronic violent behavior[6] had higher testosterone levels than prisoners convicted for nonviolent crimes. High free testosterone levels in the cerebrospinal fluid (CSF) discriminated violent from nonviolent alcoholic offenders.[7] Research on aggression in rhesus monkeys has distinguished 2 types of offensive aggression: impulsive aggression, resulting from loss of impulse control and associated with low CSF 5-hydroxyindoleacetic acid concentrations, and assertive, competitive (and less violent) aggression, associated with high levels of CSF free testosterone.[8] However, most correlative studies of androgens and aggression are characterized by their inconsistency and by wide variations in subject characteristics, sample size, hormonal measures (e.g., total vs. free levels, plasma vs. CSF levels), and aggression measures used.[1,9]

Surgical castration had been widely used to treat paraphilias with aggressive behavior until the onset of pharmacologic treatment with cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) in the 1970s and

showed low recidivism rates in sex offenders.[10] CPA antagonizes the biological effects of testosterone mainly through a competitive inhibition at androgen receptors. A number of side effects such as gynecomastia, weakness, weight gain, thromboembolism, depression, and hepatocellular damage limit its use.[10] MPA is a potent progestational agent with a dose-dependent inhibition of gonadotropin secretion that reduces testosterone production in the testes. Possible side effects include weight gain, malaise, nightmares, headaches, muscular cramps, dyspepsia, gallstones, and diabetes mellitus.[10]

Many authors have suggested a close relationship between paraphilias and the obsessive-compulsive disorders, hypothesizing a dysregulated serotonin system, and formulated the concept of paraphilic and nonparaphilic compulsive sexual behavior.[2,11] Although there is growing evidence about the efficacy of selective serotonin reuptake inhibitors (SSRIs) in paraphilia, most studies were uncontrolled, retrospective, or case reports.[12]

Luteinizing hormone–releasing hormone (LHRH) agonists are widely used in the treatment of prostatic cancer.[13] In recent years, there have also been several reports of the efficacy of LHRH agonists in paraphilic patients. LHRH is a decapeptide that is synthesized by a loose network of cells in the basal forebrain (within the hypothalamus) and is secreted directly into the hypophysioportal circulation. The secretion is pulsatile and stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, which drives the production of testosterone in the testes.[13] The neurons responsible for LHRH secretion do not originate in the central nervous system, but migrate into it during fetal life from the olfactory placode.[14] LHRH neurons also project to extrapituitary sites, such as the olfactory bulb and amygdala, where the hormone may act as a neuromodulator.[15]

In a study with a small sample size, Gaffney and Berlin[16] evaluated the hypothalamic-pituitary-gonadal axis in men with pedophilia (N = 7), men with nonpedophilic paraphilias (N = 5), and a control group (N = 5) by infusion of 100 μg of a short-acting synthetic LHRH agonist. There were no significant differences among the 3 groups in age, height, weight, testosterone level, or baseline LH or FSH level. Only pedophiles responded with a marked elevation of LH (but not of FSH). This elevation was interpreted as a possible hypothalamic-pituitary-gonadal dysfunction in pedophiles. These findings were confirmed by Bain et al.,[17] who compared 26 pedophiles and 16 nonviolent non–sex offenders. Pedophiles had higher baseline levels of LH and FSH but lower levels of testosterone. However, when age and substance abuse were controlled for, the differences were not statistically significant. After the LHRH injection, pedophiles showed a greater increase in LH (but not in FSH) than the control group, even when age, substance abuse, and baseline levels of testosterone were taken into account. These findings support the hypothesis of disorders in hormone regulation in pedophilia, such as endocrine changes in prenatal or neonatal life imprinted into the hypothalamus or other hormone-sensitive areas, decreased hormone catabolism, or increased end-organ sensitivity.[17]

The continuous (in contrast to the physiologically pulsatile) application of long-acting LHRH agonists suppresses reversibly the pituitary-gonadal axis by a downregulation of the gonadotroph cells. In this application, secretion of LH and FSH is inhibited, and testosterone and dihydrotestosterone drop to castration levels. Synthetic LHRH agonists (leuprolide, nafarelin, goserelin, and triptorelin) have an enhanced potency relative to the native LHRH.[15] In this critical review, we analyze the current literature on the treatment of paraphilias and sex offenders with LHRH agonists.

METHOD

The literature was reviewed using MEDLINE, which was searched for articles published between 1980 and November 2002. Keywords included *LHRH agonists*, *GnRH-agonists*, *antiandrogens*, *paraphilia*, *pedophilia*, and *sex offenders*. Other clinically and theoretically important information was also used. Articles were selected if they contained data from clinical trials, case-control studies, or case reports or other relevant findings.

RESULTS

We found 13 articles with empirical findings: 4 case reports,[18–21] 1 case-control study,[22] 7 open uncontrolled studies,[23–31] and 1 study comparing patients receiving CPA with those receiving LHRH agonist treatment in forensic hospitals[32] (Table 1). In total, these studies reported on a sample of 118 patients treated with LHRH agonists (leuprolide and triptorelin).

Most of the findings have been presented in single case reports. In 1985, a German group[18] reported on the successful treatment of a homosexual pedophile. Oral and intramuscular CPA application had no sufficient effect. The patient's basal testosterone level with CPA remained in the normal range (351 ng/dL). The patient was frightened of committing new offenses and became depressive and suicidal. After the medication was changed to leuprolide, serum testosterone level dropped to 27 ng/dL and pedophilic symptoms decreased more than with CPA treatment. Rousseau et al.[19] treated a male exhibitionist with triptorelin and the antiandrogen flutamide. Although serum testosterone levels fell to castration levels and the patient stopped his exhibitionistic behavior after 4 weeks (self-report), he maintained his erectile capacity as well as masturbatory and coital activities. Hot flashes were the only side effect. Dickey[21] described a patient with multiple paraphilias (pedophilic fantasies, fetishism,

Table 1. Results From Outcome Studies of Paraphilic Patients and Sex Offenders Treated With LHRH Agonists

Study	N	Diagnosis (N)	Treatment	Previous Treatment (N)	Length of Follow-Up	Comment
Allolio et al, 1985[18]	1	Pedophilia	Leuprolide	CPA	No follow-up	Better effect than CPA
Rousseau et al, 1990[19]	1	Exhibitionism, alcoholism	Triptorelin, flutamide	…	6 mo	Although testosterone fell to castration levels, the erectile capacity was maintained
Dickey, 1992[21]	1	Exhibitionism, voyeurism, pedophilic fantasies, fetishism	Leuprolide	CPA, MPA	6 mo	Better effect than CPA and MPA, but paraphilic fantasies remained the same
Marcus et al, 1993[20]	1	Exhibitionism	Leuprolide	MPA	No follow-up	
Cooper and Cernowsky, 1994[22]	1	Pedophilia	Leuprolide	CPA, placebo	4 y	Better effect than CPA measured by phallometry and self-report
Thibaut et al, 1993,[23] 1996[24]	6	Pedophilia (4), exhibitionism (1), exhibitionism/sadism (1)	Triptorelin	CPA (5)	1–7 y	Two patients withdrew from treatment and relapsed within 8–10 wk
Gottesmann et al, 1997[25]	4	Rape (1), pedophilia (1), exhibitionism (1), fetishism (1)	Leuprolide	MPA (3)	10 mo	Better effect than MPA
Hansen and Lykke-Olesen, 1997[26]	30	Recidivistic, dangerous sex offenders	Triptorelin, CPA	None	…	Five persons still in prison with freedom-related privileges, 12 released on probation but still under treatment, 5 stopped treatment, 1 of those relapsed
Rösler and Witztum, 1998[27]	30	Pedophilia (25), mixed (5)	Triptorelin	CPA (9), antidepressive agents (7), neuroleptics (9), lithium (2)	Up to 42 mo	Better effect than CPA and SSRIs, 2 relapses after switching to CPA because of side effects with triptorelin; in 11 of 18 patients, significant bone mineral loss
Briken et al, 2001[29]	11	Sadism (4), pedophilia (4), impulse-control disorder (3)	Leuprolide	CPA (6)	1 y	Better effect than CPA, no relapses
Krueger and Kaplan, 2001[28]	12	Pedophilia (6), mixed (6)	Leuprolide	MPA (2), antidepressive agents (9), other (7)	Up to 57 mo	No relapses
Czerny et al, 2002[32]	19	Mixed group of sex offenders; inpatients of German forensic hospitals	Different LHRH agonists (19), CPA (29)	…	Median of 10.3 mo (LHRH agonists)	Only small differences in LHRH agonists compared with CPA
Grasswick and Bradford, 2002[31]	1	Sadism and pedophilia	Leuprolide	CPA	4 y	Mild and reversible osteoporosis with leuprolide

Abbreviations: CPA = cyproterone acetate, LHRH = luteinizing hormone–releasing hormone, MPA = medroxyprogesterone acetate, SSRI = selective serotonin reuptake inhibitor.
Symbol: … = no information given.

voyeurism, exhibitionism) who was treated over the course of 32 months with MPA (550 mg per week). Masturbation rates and paraphilic fantasies decreased only marginally, despite a drop in testosterone level from 28.9 to 0.9 nmol/L. Medication was switched to CPA (500 mg per week) with similar results. After a switch to leuprolide (7.5 mg depot), self-reported masturbation and deviant sexual behavior began to decline after 2 weeks, while the content of masturbatory fantasies remained the same. The patient experienced no unwanted side effects. Cooper and Cernowsky[22] reported on the treatment of a heterosexual pedophile with placebo, CPA (100 or 200 mg/day), no treatment, and leuprolide (7.5 mg per month for 24 weeks). Leuprolide suppressed (better than CPA or placebo) self-reported and phallometric measures of sexual arousal and reduced testosterone level to near zero.

Thibaut et al.[23,24] treated 6 patients with severe paraphilias (pedophilia, sadism, exhibitionism) with triptorelin. The longest follow-up was 7 years. Two patients abruptly withdrew from treatment and relapsed within 8 to 10 weeks. Gottesmann et al.[25] treated 4 males (1 rapist and 1 patient each with pedophilic, exhibitionistic, and fetishistic behavior) with monthly injections of 3.75 mg of leuprolide for a mean treatment time of 10 months. Prior MPA therapy had failed in 3 of the patients. Decrease in testosterone levels was lower than with MPA and was correlated with decreased erections, ejaculations, and paraphilic fantasies and behavior. Weight gain was the only side effect noted in 1 patient.

Hansen and Lykke-Olesen[26] reported on their work in a closed institution for offenders in need of psychiatric treatment. From 1989 to 1997, they treated recidivistic dangerous sex offenders with a combination of triptorelin and CPA (both administered by depot; doses were not reported). CPA was added to triptorelin to block the androgen receptors, thus ensuring against illegal procurement of anabolic steroids. Of the 30 men who started treatment, 7 discontinued early: 1 man died after 2 months due to coronary occlusion (no relation to medication was found), 2 were diagnosed with hepatitis C, and 4 men did not accept hormonal castration as a long-term treatment. The other 23 persons were treated with pharmacotherapy and psychotherapy: 5 were still in prison, but with freedom-related privileges; 12 had been released on probation, but were still undergoing treatment; and 5 were released on probation with a limited period of supervision and stopped treatment thereafter. One of these 5 individuals relapsed 9 months after he had stopped treatment. Among the offenders treated with triptorelin plus CPA, there had been no relapse. All patients showed dissocial personality structures, and a number of them reported sadistic sexual fantasies. When the fantasies disappeared in the course of treatment, the patients were able to talk about the fantasies. The majority stated that the effects were positive and they felt more relaxed. Side effects were increased weight and perspiration, individual cases of gynecomastia, and a single case of temporary urine incontinence.

Rösler and Witztum[27] treated 30 "treatment-resistant" paraphilic outpatients in an uncontrolled, observational study with monthly intramuscular injections of 3.75 mg of triptorelin and supportive psychotherapy for 8 to 42 months. Sixteen had previously been convicted of sex crimes. Twenty-two had other psychiatric disorders in addition to paraphilia (including 9 cases of personality disorder and 5 cases of schizophrenia in remission) and were receiving other psychotropic medications if necessary. Nine had previously been treated with CPA without sufficient effect (CPA treatment was stopped 12 months before triptorelin administration). Seven had also received SSRIs (serotonergic drug treatment was stopped 2 months before triptorelin administration). The effects of triptorelin plus supportive psychotherapy were evaluated with the Three Main Complaints Questionnaire and the Intensity of Sexual Desire and Symptoms Scale. No sexual offenses were committed during triptorelin therapy. The severity of the paraphilia as measured by self-reports ($p < .001$) and testosterone levels decreased significantly. Six men stopped treatment after 8 to 10 months. Two of the men stopped treatment because of side effects and thereafter received CPA (200 mg/day). Both were subsequently prosecuted for sexual offenses and sentenced to prison. In 11 of 18 men, bone mineral density decreased significantly, and most men had transient pain at the sites of injection. Other side effects were hypogonadism, hot flashes, decreased growth of facial and body hair, asthenia, and muscle tenderness. Twenty-one men reported erectile failure. This effect was proportional to age and found in all men older than 35 years. In a recent article, Rösler and Witztum[15] reported on the concomitant administration of small doses of testosterone (25–50 mg of testosterone enanthate per month) to prevent bone mineral loss and to ameliorate the erectile dysfunction (whereas paraphilic fantasies should remain suppressed).

Krueger and Kaplan[28] reported on 12 patients who were treated without a legal mandate with leuprolide. To counteract an increase of testosterone at the beginning of treatment ("flare-up" effect), patients received flutamide for the first 30 days. Leuprolide was administered intramuscularly at a dose of 3.75 or 7.5 mg monthly. Diagnoses of the heterogeneous group included pedophilia (in 1 case, with sadistic fantasies), exhibitionism, and voyeurism. Secondary diagnoses were affective and personality disorders, addictions, and, in 1 case, XYY karyotype. The duration of treatment was between 6 and 57 months. The patients reported reduced sexually deviant arousal and, in 1 case, reduced sadistic fantasies. Testosterone fell to castration levels. The 2 patients who were treated for a longer period (35 and 57 months) suffered from bone demineralization. Other side effects were ejaculatory and erectile dysfunctions, gynecomastia,

nausea, and depression. However, 1 patient who had previously undergone a left frontal lobectomy was not affected in sexual performance by leuprolide.

In our study group,[29,30] we treated 11 patients with long-lasting deviant sexual behavior (pedophilia, sadism, sexual impulsiveness) that had already caused legal consequences. The most common comorbid diagnoses were personality disorders and learning disabilities. Six patients had already received CPA without sufficient improvement of deviant fantasies or were suffering from intolerable side effects. All subjects received a subcutaneous depot of 11.25 mg of leuprolide once every 3 months. For the first 2 weeks, we additionally administered CPA (300 mg) to reduce the "flare-up" effect. The length of the follow-up was 1 year. All patients reported a reduction in paraphilic activities, and no sexual offenses were committed during therapy. Side effects were depression, weight gain, and pain at the site of the injection. There was also a reduced frequency of erection, ejaculation, and masturbation.

In another study,[32] we investigated which antihormonal treatment strategies are currently used in the 67 German forensic psychiatric hospitals. Thirty-two hospitals (48%) responsible for 2070 patients answered. Twenty-three percent of the patients were admitted to the institution for sex offenses (47% child abuse, 31% rape, 7% homicide or attempted homicide). Twelve percent of these patients received either CPA (N = 29) or LHRH agonists (N = 29), although LHRH agonists are not officially approved for the treatment of paraphilic patients. The paraphilic diagnoses included pedophilia, sadomasochism, exhibitionism, fetishism, and voyeurism. The mean duration of treatment with CPA was 22.6 months, and with LHRH agonists, 10.3 months. Information about treatment response was available in only 19 of 29 patients treated with LHRH agonists (the other patients took part in another study). According to the psychiatrists' judgment, there were only small differences in efficacy between CPA (greater reduction of sexual activity) and LHRH (greater reduction of fantasies). No effect was reported in 3 cases in each group (CPA: 10%; LHRH: 17%). An increase in sexual fantasies was reported in 1 patient treated with CPA. Two patients had previously been treated with CPA without success. After the switch to the LHRH agonists, the intensity of sexual desire and symptoms was noticeably reduced. The most severe side effect with CPA was probably a case of thromboembolism. Allergic reactions, osteoporosis, and cardiovascular side effects or hepatocellular damage were not reported.

The purpose of 7 case reports recently presented by Grasswick and Bradford[31] was to investigate the relationship between osteoporosis, surgical castration (N = 2), and the use of CPA (N = 4) and leuprolide (N = 1). Data collected included length of androgen suppression, highest dose of medication, risk factors for osteoporosis, and bone mineral density results. The free testosterone levels of the surgically castrated patients and the patient receiving leuprolide were significantly suppressed, and bone mineral densities indicated only mild osteopenia or mild osteoporosis. Osteoporosis in the leuprolide case was reversible with etidronate and vitamin D therapy. Two of the patients taking CPA showed significant osteoporosis, although the free testosterone levels were in the low-normal range. Results of this limited case study indicate that osteoporosis is a concern with both LHRH agonists and CPA.

DISCUSSION

The fact that patients with paraphilias are often mandated for treatment under court order complicates the administration of informed consent and the participation in clinical trials, especially for new treatment strategies. An ideal design should compare treated and untreated samples of sex offenders who are randomly assigned to groups. Because of legal and ethical reasons, such a design is rarely achieved, and until now there has been no such study of treatment of paraphilia with LHRH agonists. Other important variables concern sampling factors (sample size, type of patients and offenses, first and second diagnoses, type of treatment program and setting), duration of follow-up, definition of recidivism, and assessment of improvement. Another problem is the lack of standardized and reliable measurements of paraphilic fantasies, arousal, and behavior. In some studies of CPA, sexual response was measured by penile plethysmography (penile erectile response to stimuli). Bradford and Pawlak[33] treated 19 patients with 3-month periods of CPA treatment alternating with placebo. While medicated, patients reported significantly less sexual arousal and activity (self-report). However, plethysmography found no differences between baseline, placebo, and active medication periods. Some patients showed increased deviant arousal while they were on treatment with medication and decreased arousal in the placebo period. None of the studies mentioned above except 1 case report[22] on LHRH agonists was conducted with penile plethysmography.

The study with the largest sample size[27] used self-reports to measure the effect of the medication. The other studies used self-reports, retrospective analyses, the case report form, or made no specifications of their measurement.

Despite the methodological limitations, LHRH agonists seem to offer an alternative to other currently used pharmacologic treatment strategies (SSRIs, CPA, MPA). According to Rösler and Witztum,[15] "long-acting GnRH [gonadotropin-releasing hormone] analogues are currently the most effective and promising medications…with the fewest side effects compared to other antiandrogens,"[p49] but their statement is controversial as,

Table 2. Protocol for the Treatment of Paraphilia With LHRH Agonists[a]

Baseline Screening Tests	Contraindications	Monitoring During Treatment	Possible Side Effects
Informed consent	Active pituitary pathology	Testosterone and complete blood count monthly for 4 mo, then every 6 mo	Osteoporosis, bone pain
Serum testosterone, LH, and FSH	Thromboembolic disorders	LH, FSH, urea nitrogen, and blood creatinine every 6 mo	Hypogonadism
Urea nitrogen and blood creatinine	Osteoporosis	Bone density scan yearly	"Flare-up" effect
Complete blood count			Allergic reactions
Liver function			Nausea, vomiting, constipation
Bone density scan			Weight gain
Cardiovascular status			Hot flashes, cold sweats
Test dose of 1 mg SC			Mood swings (depression)
			Sleep disturbances
			Hair loss
			Gynecomastia
			Headaches
			Dizziness

[a]Based on Kafka[12] and Reilly et al.[36]
Abbreviations: FSH = follicle-stimulating hormone, LH = luteinizing hormone, LHRH = luteinizing hormone–releasing hormone, SC = subcutaneous.

until now, there have been no comparative studies to corroborate it. Side effects such as osteoporosis are related to hormonal levels. Osteoporosis may occur more often under LHRH agonists as they cause low hormonal levels in the castration range.[34] However, osteoporosis has also been reported with CPA therapy.[31,35] Other risk factors such as smoking, alcohol use, low body mass index, and endocrine problems should be considered.[31] Reilly et al.[36] and Kafka[12] proposed protocols for the use of CPA, MPA, and LHRH agonists in the treatment of paraphilias to avoid serious side effects (Table 2).

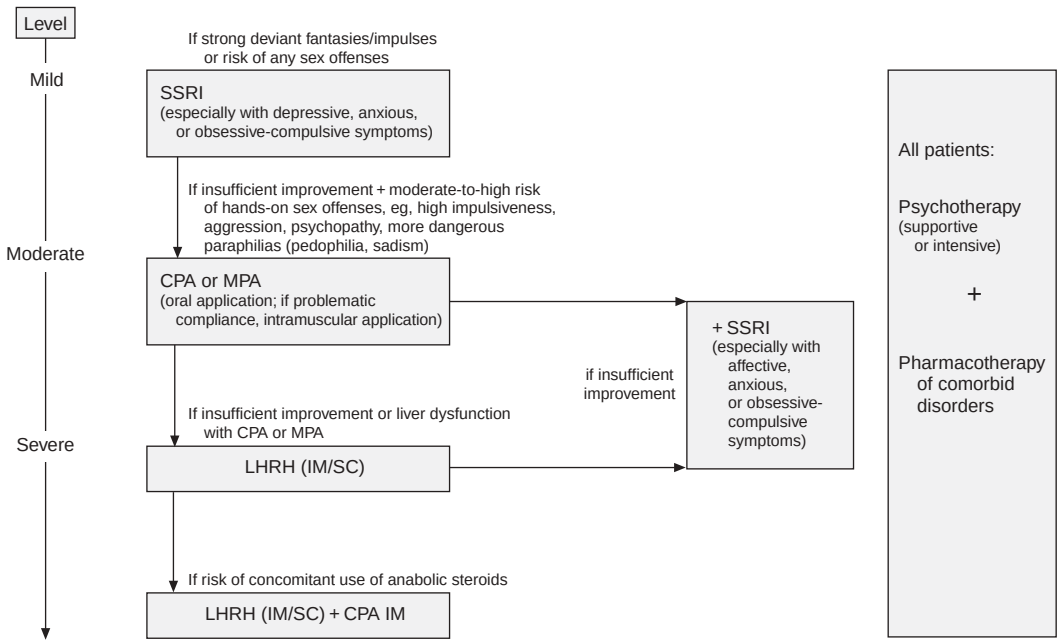
Although the prescription of LHRH agonists for paraphilic sex offenders is not an indicated use (not approved by the U.S. Food and Drug Administration), it could be justifiable if the individual poses a danger to other persons.[12] In such a context, it is prudent to document informed consent in a patient's record prior to drug administration. LHRH agonists produce hypogonadism and may decrease the number of Leydig cells or produce an atrophy of the seminiferous tubules.[36] Patients should be informed about the risk of a loss of fertility and libido in addition to the other side effects. LHRH agonists should not be given to patients with an active pituitary pathology. To screen for pituitary pathology, FSH, LH, and testosterone levels should be assessed prior to medication and every 6 months. Assessment of kidney function and a complete blood count should be obtained. Assessment of cardiovascular status, including an electrocardiogram, is necessary to prevent possible side effects such as changes in blood pressure, thromboembolic disorders, or worsening heart failures or ischemia. Osteoporosis is a long-term risk, and a baseline bone density scan should be performed prior to treatment and every year thereafter. Osteoporosis may possibly be prevented by administration of calcium and vitamin D or bisphosphonates. To reduce the risk of allergic reactions, a probatory subcutaneous injection of 1 mg of leuprolide should be administered. Because of the transitory increase in testosterone during the first 2 weeks, patients should be observed closely and concomitant CPA or flutamide treatment should be administered.

LHRH agonists are not involved in cytochrome P450 metabolism, have a low degree of protein binding, and have not yet been reported as interacting with other drugs. Reilly et al.[36] concluded that there is a lack of knowledge about the long-term consequences of LHRH agonists (but also of CPA and MPA). Thus, the protocol might be modified according to clinical experience.

We share the opinion of Rösler and Witztum[15] that LHRH agonists are currently among the most effective medications in the treatment of paraphilias. However, following Reilly et al.[36] and Bradford,[2] we propose a differentiated algorithm concerning symptomatology, severity of illness, and side effects (Figure 1).

A treatment program should start with supportive or intensive (cognitive-behavioral, psychodynamic) psychotherapy and pharmacologic treatment of comorbid disorders (e.g., neuroleptic treatment in schizophrenic patients). In mild cases with strong deviant fantasies or impulses and any risk for sexual offenses, psychotherapy in combination with SSRI treatment should be considered, especially if the paraphilic patient shows additional symptoms such as anxiety, social phobia, depression, severe feelings of guilt, obsessions, or DSM-IV cluster C personality disorders and if paraphilia is less severe (no "hands-on" offenses, fetishism, exhibitionism). The treatment plan should take into account the fact that an escalation from less severe to severe paraphilias with more dangerous offenses occurs in a substantial number of patients. Duration of SSRI treatment should be as long as if treating obsessive-compulsive disorders and should be attempted with at least 1, but usually 2, different agents.[12] If there is insufficient improvement and a moderate-to-high risk of "hands-on" offenses, CPA/MPA alone or in combination with an SSRI should be given, especially in more impulsive, aggressive, and psychopathic cases (according to the Hare Psychopathy Checklist-Revised).[37] Side

Figure 1. Algorithm for the Pharmacologic Treatment of Paraphilias



Abbreviations: CPA = cyproterone acetate, IM = intramuscular, LHRH = luteinizing hormone–releasing hormone, MPA = medroxyprogesterone acetate, SC = subcutaneous, SSRI = selective serotonin reuptake inhibitor.

effects are dose related, so a careful titration could minimize them and may allow patients to maintain appropriate sexual behavior while eliminating deviant behavior.[38]

Intramuscular application of CPA or medication with LHRH agonists (also in combination with an SSRI) should be used especially in cases of severe sadism or pedophilia with noncompliance to medication. Although the number of studies is still small, LHRH agonists seem to be effective in some cases in which CPA and SSRIs failed and can offer an alternative for patients who experienced liver dysfunction with CPA. A caveat must be expressed for cases with severe psychopathy and antisocial personality disorders and only unreliable compliance with treatment: in such cases, the patient may counteract the antihormonal treatment with secret self-application of testosterone to neutralize the effect of the medication. Even if controlled by administration of regular blood tests, this form of noncompliance may still remain an important contraindication for antihormonal treatment. A combination of LHRH agonists and CPA could be a possible option for these patients.[26]

There is a need for further research with prospective, controlled studies using large sample sizes and better methods (especially penile plethysmography) to investigate the use of SSRIs, CPA, MPA, and LHRH agonists for more differentiated pharmacologic treatment of paraphilias.

Drug names: etidronate (Didronel and others), flutamide (Eulexin and others), goserelin (Zoladex), leuprolide (Lupron, Viadur, and others), medroxyprogesterone acetate (Depo-Provera and others), nafarelin (Synarel), testosterone enanthate (Delatestryl and others), triptorelin (Trelstar).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, goserelin, leuprolide, nafarelin, and triptorelin are not approved by the U.S. Food and Drug Administration for the treatment of paraphilia.

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