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Paraphilic Disorders: Diagnosis and Treatment

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Definition, diagnosis, and comorbidities

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR), paraphilias are defined as sexual disorders characterized by recurrent, intense, sexually arousing fantasies, urges, or behaviors, over a period ≥6 months, generally involving:

(1) non-human objects;
(2) suffering or humiliation of oneself or one's partner;
(3) children or other non-consenting persons (criterion A).

These fantasies, urges, and behaviors produce clinically significant distress or impairments in social, occupational, and other important areas of functioning (criterion B).

For pedophilia, voyeurism, exhibitionism, and frotteurism, the diagnosis can be made also in the absence of personal distress, if the individual acts on the sexual urges. With the other paraphilias (not involving other persons), the diagnosis can be made only if the sexual urges and/or fantasies produce the effects listed in criterion B (see below).

SCIENCE REVISITED

Paraphilia definitions (DSM-IV-TR; 302)

Criterion A

Recurrent, intense, sexually arousing fantasies, urges, or behaviors, which occur over a period of ≥6 months, generally involving:

- non-human objects;
- suffering or humiliation of oneself or one's partner; or
- children or other non-consenting persons.

Criterion B

- which cause clinically significant distress or impairments in social, occupational, and other important areas of functioning.

Hormonal Therapy for Male Sexual Dysfunction, First Edition. Edited by Mario Maggi.

Table 8.1. Different kinds of paraphilias, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edn, Text Revision (DSM-IV-TR) classification. Identification code numbers from DSM-IV-TR in parentheses

Exhibitionism (302.4)	Exposure of genitals to unsuspecting strangers (is NOT the same as public urination)
Fetishism (302.81)	Use of non-living objects as a repeatedly preferred or exclusive method of achieving sexual excitement (e.g. leather goods, clothing, undergarments, fabrics, shoes). (If female clothing is used in cross-dressing or devices are used to directly stimulate the genitals – e.g. vibrator – this is NOT a fetishism).
Frotteurism (302.89)	Touching and rubbing against a non-consenting person
Pedophilia (302.2)	Children are the sexual target (perpetrator is ≥16 years old and ≥5 years older than the victim).
Sexual masochism (302.83)	Perpetrator receives the humiliation/suffering (practice can even lead to death, especially during "hypoxyphilia" or sexual arousal during hypoxia).
Sexual sadism (302.84)	Perpetrator inflicts the humiliation/suffering on another (generally, severity increases over time).
Transvestic fetishism (302.3)	Wearing clothing of the other sex for sexual arousal.
Voyeurism (302.82)	Observing sexual activity or naked/disrobing individuals.
Paraphilias Not Otherwise Specified (302.9)	This category is included for coding Paraphilias that do not meet the criteria for any of the specific categories. Examples include, but are not limited to, telephone scatologia (obscene phone calls), necrophilia (corpses), partialism (exclusive focus on part of body), zoophilia (animals), coprophilia (feces), klismaphilia (enemas), and urophilia (urine).

DSM-IV-TR describes 8 specific disorders of this type, along with a residual category called "paraphilias not otherwise specified" (Table 8.1).

In total, more than 50 types of paraphilias have been described, most of them being more common in men (~90% in Europe) than in women, except for sexual masochism.

The average age expression of the disorder is paraphilia-specific. Paraphilias may begin in childhood or early adolescence, but paraphilic sexual interest frequently becomes more defined during adolescence. The mean ages of onset of paraphilias are: transvestic fetishism, 13.6 years; fetishism, 16.0 years; voyeurism, 17.4 years; non-incestuous homosexual pedophilia, 18.2 years; exhibitionism, before 18 years; sadism, 19.4 years; and non-incestuous heterosexual pedophilia, 21.1 years. Therefore, the onset of most paraphilic disorders is around the time of puberty, running a chronic course. The frequency of sexual acts may increase or decrease over time, but often diminishes with advanced age (≥60 years old).

Stimuli can be either obligatory for erotic arousal and always a component of the sexual activity ("exclusive paraphilia"), or can be episodic (e.g. only if the individual is stressed) and the individual may be aroused by other fantasies, stimuli, and behaviors, although their paraphilias may interfere with their overall sexual preference ("non-exclusive paraphilia").

Paraphiliacs often have more than one type of deviant sexual behavior and 50–70% of pedophiles seem to have more than 1 paraphilia.

Paraphilias can be graded from mild to catastrophic, depending on the history of victimization and, if present, the number of victims, their age, and the degree of victimization (level of intrusiveness: penetrative or not) are considered. Severe cases would involve more than 1 victim or a child, and there would be penetration to some degree. In general, individuals with exhibitionism or pedophilia make up the majority of apprehended sex offenders. The mean number of victims for one pedophile is around 20.

It is important to remember that not all sex offenders suffer from paraphilias, but only a part of them and, vice versa, that not all patients with paraphilias are sex offenders. In fact, paraphilic subjects, in many cases, only suffer from deviant sexual fantasies or urges, or their deviant sexual behavior does not involve a non-consenting person or a child. These subjects may present for treatment because of the associated distress of their personal lives. In contrast, other paraphilic behaviors may lead to sex offenses, a major public health problem defined as any violation of established legal or moral codes of sexual behavior. For example, clinically defined sexual behaviors such a pedophilia, voyeurism, frotteurism, and exhibitionism are also considered sexual offenses but, for instance, fetishism and transvestic fetishism are not. On the other hand, crimes such as rape are not classified as paraphilias. Simply having a paraphilia is obviously not illegal. However, acting in response to paraphilic urges may be illegal and, in some cases, subjects the person with paraphilia to severe sanctions.

CAUTION

While some paraphilias can be associated with strange sexual behaviors, they are not necessarily associated with offenses.

Many studies have consistently found high prevalence rates of comorbid psychiatric disorders in patients with paraphilia. Associated psychiatric disorders include major Axis I mental illness, as affective disorders, substance abuse disorders, schizophrenia, other psychotic disorders, and dementia (especially temporal and/or fronto-temporal dementias). Moreover, paraphilias can occur within the context of personality disorders, such as borderline or antisocial personality disorders, within mental retardation, and other medical conditions, such as temporal lobe epilepsy or brain trauma, Huntington disease, and Kluver Bucy and Kleine Levin syndromes. Finally, paraphilias may also occur in patients undergoing dopamine receptor agonist therapy, for example for Parkinson's disease. Paraphilias often result in a variety of psychological disturbances, such as guilt, depression, shame, isolation, and impaired capacity for normal social and sexual relationships.

The differential diagnosis includes developmental disability, dementia, personality changes due to general medical conditions, substance intoxication, manic episodes, and schizophrenia.

Prevalence of paraphilias

Actual prevalence/incidence figures are unavailable for all of the paraphilias. According to a few studies, paraphilic sexual fantasy seems to be common in the general population.

The prevalence of paraphilias is mainly derived from the prevalence of sex offenses. However, the latter number is often underestimated, either because offenders have never been apprehended or the offense did not result in conviction. Moreover, many sexual assaults are unreported or undisclosed by the victim, due to feelings of shame or guilt.

Surveys have provided some useful data regarding the epidemiology of pedophilia. In one US survey of 4,000 females, 24% stated

that they had experienced sexual interaction with a male ≥5 years older than themselves when they were ≤14 years old. Intercourse occurred in only 3% of cases, with minor petting or fondling without genital involvement in 31% of cases. In a Canadian National Population Survey of 2008 subjects (1,005 females, 1,003 males) 18.1% (23.5 and 12.8% of females and males, respectively) reported that they had been victims of sexual violence when they were children or adolescents.

Recidivism is a major concern in the treatment of paraphilia, especially in pedophilia. Published recidivism rates among pedophiles range from 10–50%, depending on how subjects are grouped. Non-related pedophiles exhibit higher rates, while incestuous pedophiles have the lowest rates. Homosexual and bisexual pedophiles have higher rates than heterosexual pedophiles (50 and 25%, respectively). Moreover, higher rates of recidivism seem to be also associated with more deviant sexual practices, addictive disorders (mostly alcoholism or drug abuse), psychiatric comorbid disorders, attraction to younger children, display of more sociopathic or antisocial personality traits, higher rates of treatment non-adherence, and a greater number of paraphilic interests reported by the offender. It is important to remark that no test or instrument capable of predicting the future activity of a pedophilic individual exists.

Etiology

Although the etiology of the paraphilias is unknown, the neurophysiology of sexual arousal has been the subject of much research and has led to the pharmacologic approaches used today. Sexual arousal is dependent on neural (sensory and cognitive), hormonal, and genetic factors, and in humans, the complex influences of culture and context.

Many physiological substances produce stimulating or inhibiting effects on different sexual processes in the central nervous system, the peripheral nerves, and the genital organs. α1-Adrenergic and dopaminergic neurotransmission enhances sexual arousal, as does parasympathetic muscarinic neurotransmission. Serotonergic neurotransmission reduces sexual arousal. Norepinephrine (via alfal-adrenoceptor activation) and acetylcholine (via muscarinic receptor activation) stimulate sexual arousal. Numerous neuropeptides enhance sexual arousal (enkephalins, oxytocin, gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)), either by themselves or by enhancing production of other compounds. Hormones that affect sexual arousal include prolactin (reduces it), testosterone (T)/dihydrotestosterone (DHT, increases it), and estrogen/progesterone (increases it).

In particular, T plays a well-known crucial role in male sexuality. Some evidence in animal models shows that T modulates serotonin receptor effects on impulsive aggression. The role of this hormone in human aggression is less clear. Male prisoners with a history of violent crime during adolescence or chronic violent behavior seem to have higher T levels than prisoners convicted for non-violent crimes. Moreover, a study has reported that high free T levels in the cerebrospinal fluid discerned violent from non-violent alcoholic offenders. However, most studies focused on this topic are characterized by inconsistency.

Furthermore, many authors have suggested a close relationship between paraphilias and the obsessive-compulsive disorders, hypothesizing a dysregulated serotonin system.

Ethical issues

The treatment of patients with paraphilias, irrespective of which method of treatment is employed, has always been surrounded by clinical and ethical dilemmas.

The major ethical issues regarding sexual offenders, including paraphilias, may reflect the dispute between the need for public safety and on the other hand, the consent of the

patient to be treated. Moreover, such kinds of crimes make the public and even professional opinion lean toward punishment rather than treatment, even when appropriate and effective. For example, imprisonment may stop pedophiles from committing illegal sex acts against children, but it does not change the pedophile's internal sexual orientation. Treating pedophilia is critical in an approach to preventing sexual violence and reducing victimization. In addition, it provides a more humane and lasting solution than imprisonment and may at least be used concomitantly.

Paraphilic sex offenders may be ordered by a judge to undergo treatment as part of a rehabilitative aspect of sentencing. Moreover, this decision should be made by a psychiatrist with the required qualifications, after examination of the person concerned and after an informed consent has been obtained. However, doubts about the validity of consent have risen, because consent is sometimes given in situations where the person is subject to some external pressure. In cases of doubt with regard to the validity of the patient's consent, after withdrawal of his consent or non-compliance with the treatment, the decision to subject a sex offender to coerced treatment should be made by a court or another competent body.

The court or other competent body should:

- act in accordance with procedures provided by the law, based on the principle that the person concerned should be seen and consulted;
- not specify the content of the treatment, but force the sex offender to comply with the treatment plan negotiated with the psychiatrist.

From an ethical point of view, if the paraphilic sex offenders need hormonal therapy, this should be allowed only if all of the following conditions are met (Belgian Advisory Committee on Bioethics 2006 www.health.fgov.be/bioeth; Council of Europe 2004):

- the person has a paraphilic disorder diagnosed by a psychiatrist after a careful psychiatric examination;
- the hormonal treatment addresses specific clinical signs, symptoms, and behaviors and is adapted to the person's state of health. It must be part of a more detailed treatment program which, in addition to the psychiatric part, also considers the psychological and social aspects. The hormonal treatment cannot be the only measure imposed on sex offenders on the basis of the nature of the crimes committed;
- the person's condition represents a significant risk of serious harm to his health or to the physical or moral integrity of other persons;
- when hormonal castration is considered, the advice of an endocrinologist is required first;
- hormonal treatment is a medical treatment for which the psychiatrist in charge of the patient takes responsibility:
  - for the indication;
  - to inform the person involved and to receive his consent
  - for the follow-up, including somatic aspects with the help of a consultant endocrinologist, if necessary;
- the therapist will always give preference to the least intrusive intervention to obtain a particular result. If a less intrusive alternative treatment exists instead of hormonal treatment, this alternative must be preferred;
- the hormonal treatment is part of a written treatment plan to be reviewed at appropriate intervals and, if necessary, revised.

☆ TIPS & TRICKS

How to evaluate a sex offender/paraphilic subject:

- demographic characteristics of the subject;
- age, gender, marital status, children (number, gender, and age), educational level, employment status (with or without children);

- family and personal history of psychiatric disorders and sexual disorders or related treatment, suicide attempts, history of sexual abuse or use of violence.

Characteristics of paraphilia:

- conventional and paraphilic sex fantasies and activities, exclusive or not exclusive paraphilic behavior, age at onset of paraphilic behavior, type and number of paraphilia, gender and age of victims, intra-familial or not, internet or video use, violence, alcohol or illicit drug consumption before paraphilic behavior;
- interpersonal relationships, insight, empathy, coping with stress, impulsivity, motivation for treatment;
- comorbidity with Axis 1 or Axis 2 of the DSM classification, comorbidity with somatic diseases, cognitive evaluation (dementia, mental retardation).

Therapeutic approaches

The heterogeneous characteristics of paraphilias demand that treatment options are integrative and include a number of different approaches. Treatment modalities currently used for paraphilic behaviors fall basically into 3 categories:

1) Psychotherapy
2) Pharmacotherapy
3) Androgen deprivation (surgical/chemical castration)

The aim of psychotherapeutic interventions is, in general, to change the sexual behavior of the offender leaving libido intact; pharmacological interventions seek to greatly diminish or altogether eradicate sexual desire and capacity.

The treatment choice will essentially depend on:

- the patient's previous medical history;
- the patient's compliance;
- the intensity of the paraphilic sexual fantasies;
- the risk of sexual offense.

The aims of the treatment for paraphilias are:

- to control paraphilic fantasies and behavior in order to decrease the risk of recidivism;
- to control sexual urges;
- to decrease the level of distress of the paraphilic subject.

Therefore, the effectiveness of any therapy is usually determined by the degree of reduction in intensity of the abnormal sexual fantasies, desire, and behavior. However, the decrease or abolishment of the recidivism of the abnormal sexual behavior is considered to be the single most important index of therapeutic success.

Limitations in assessing treatment efficacy

In general, treatment efficacy studies are marked by some methodological bias and are extremely difficult for several reasons: small sample sizes leading to false negative results and difficulties in conducting studies with forensic patients; sex offending is not socially acceptable and those who suffer from it rarely seek treatment voluntarily. Most reports on the treatments of paraphilias are case reports or series. Moreover, due to ethical reasons (high risk of recidivism, low level of motivation of the patient, denial, prisoners in most cases, etc.), the great majority of pharmacological studies are uncontrolled studies without placebo comparison. In addition, inasmuch as sexual offenses are typically under-reported, recidivism rates identified from official criminological records also represent an under-representation of the "true" recidivism rate. Very large samples,

including a matched control group, and long follow-up periods, would be necessary to identify a truly statistically significant effect of treatment on outcome.

Psychotherapy

Psychotherapy can be divided into individual and group or family therapy. Most commonly, it is a combination of both approaches. The psychoanalytic treatment for paraphilic patients is more valued for its meaningful approach in understanding than for its outcome evidence. Cognitive behavioral therapy is today the most frequently used therapy and cognitive behavioral principles are the basis of the prison-based sex offender treatment programs. This approach is aimed at changing internal processes, along with changing overt behavior, such as social skills or coping behaviors. This type of therapy has been considered the "gold standard" non-pharmacologic approach offered to pedophiles. Treatment could be focused on altering deviant sexual arousal patterns, addressing social skill deficits that may contribute to sexually delinquent behavior, challenging beliefs that can facilitate sex offending behavior, and developing strategies to prevent a re-occurrence of sexual offenses. Behavioral techniques, which decrease sexual deviancy, involve olfactory aversion conditioning (using an unpleasant smell, such as ammonia), covert sensitization (imagine deviant sexual experience until arousal and then imagine a powerful negative experience), aversion therapy (exposure to deviant material followed by aversive stimulus), and masturbatory satiation to decrease deviant sexual arousal and cultivate appropriate sexual response patterns. Moreover, treatments are designed to improve a sex offender's social competence, interpersonal and functional social skills, and self-esteem. The psychosocial treatment dimension has broadened to include training in anger management, relaxation, and interventions to promote empathy with the victim and awareness.

Irrational beliefs, such as beliefs that sex with children is a way to teach them about sexuality or that most women enjoy being raped, can contribute to an individual's justifying and engaging in deviant and criminal sexual behavior. Treatment to alter distorted beliefs entails the identification of and challenges to these kinds of cognitive distortions through cognitive restructuring techniques. However, these kinds of approaches are costly, and the effects in clinical trials have been extremely variable (including helpful, not helpful, and/or harmful, even in the same trial). This extreme variability may be related, in part, to the need for the offender to admit guilt and accept personal responsibility before success is possible, and to the media who bias the public to believe in the universal failure of these treatments. The cognitive behavioral therapy for sex offenders brings a modest reduction in recidivism, but this is not supported by studies with longer follow-up periods. The other approaches (psychosocial programs, therapeutic communities, insight-oriented treatment) do not seem to reduce recidivism.

In summary, to date there is much debate concerning the overall effectiveness of psychotherapy approaches for the long-term prevention or Androgen deprivation therapy of new offenses and several studies have reported that the best outcomes in preventing repeat offenses against children occur when pharmacological agents and psychotherapy are used together.

Pharmacologic Therapies

Pharmacological treatments are used in order to decrease the general level of sexual arousal.

The use of psychotropic medications in paraphilic behavior is not new, but there are no randomized controlled trials that have documented their efficacy. Unfortunately, the level of evidence is very poor.

Lithium carbonate, tricyclic antidepressants (clomipramine, desimipramine), mirtazapine, antipsychotics (benperidol,

thioridazine, haloperidol, risperidone), and anticonvulsants (carbamasepine, topiramate, divalproate) have been sporadically used over the years.

Selective serotonin reuptake inhibitors (SSRIs)

Research evidence on the efficacy of antidepressants for treatment of paraphilic sexual offenders has been reported. The World Federation of the Society of Biological Psychiatry recommends the use of SSRIs in the treatment of sexual abusers in the case of:

- *juvenile paraphilias*: paraphilias usually start at adolescence and are limited to deviant fantasies related to masturbation between 12 and 18 years. SSRIs given at this stage could prevent acting out of deviant behaviors;
- *mild paraphilias*;
- *comorbidity with obsessive-compulsive disorder, impulse control disorder or depression*: some paraphiliacs clearly suffer from an inability to resist their sexual urges, which have a strong compulsive element and often cause a considerable subjective distress in maintenance treatment.

The rationale for the use of SSRIs in sexual offenders is based on the following evidence:

- it is well known that increased levels of serotonin (5HT) in the hypothalamus inhibit sexual motivation and the T signaling, while increased levels of serotonin in the prefrontal cortex enhance emotional resilience and impulse control. In pedophilia, decreased activity of the 5HT presynaptic neurons and up-regulation of postsynaptic 5HT-2A receptors has been reported.
- SSRIs have been shown to decrease impulsion in antisocial impulsion, anxiety, depression, and hypersexuality.
- Important Axis 1 and Axis 2 comorbidities have been reported in juvenile and adult paraphilics and hypersexual subjects. It is recommended that this disorder be treated as well.

On these bases, several guidelines have been developed for the treatment of sexual offenders, which are summarized regarding the indication of SSRIs:

- The Association for the Treatment of Sexual Abusers included SSRIs as one of the interventions for the control of sexual arousal, within a comprehensive treatment program. These guidelines recommend SSRIs for patients with high levels of arousal that cannot be controlled with cognitive behavioral therapies, adding that informed and motivated patients are good candidates.
- The American Academy of Child and Adolescent Psychiatry recommends cognitive behavioral interventions, psychosocial interventions, and SSRIs for children and juveniles who are sexual abusers. The use of antiandrogens is discouraged under 17 years of age, as they could delay the onset of puberty and bone growth.

Androgen deprivation (surgical or hormonal castration)

Androgens play a crucial role in sexual interest and associated sexual arousal, which is defined as a state that motivates the individual toward the experience of sexual pleasure and possibly orgasm. Consequently, a reduction in circulating T may be helpful in decreasing sexual interest, arousal, fantasies, and behaviors, resulting in either a marked reduction or abolishment of the paraphilic manifestations. This principle has been put into practice in the androgen deprivation therapy for sex offenders. Moreover, it has been reported that serum T levels predicts sexual recidivism and higher T levels have been found to be associated with more invasive sexual crimes in sexual offenders. In fact, the benefit of androgen deprivation therapy is in diminishing the intensity of the eroticized urges that energize

unacceptable paraphilic behaviors and it can, in turn, facilitate the resisting of those urges.

On the other hand, normal levels of androgens play a crucial role in male bone health and are required for a large number of metabolic aspects, mood, erythropoiesis, sebaceous gland activities, and several other functions. Therefore, severe androgen deprivation is associated with several pathological effects on these biological systems. In particular, androgen deprivation therapy with surgical castration, antiandrogens, or analogs of gonadotropin-releasing hormone (GnRH analogs) induces in men a rapid bone loss, typically in the spine, hip, and forearm, but also at appendicular skeletal sites such as the femoral neck. Bone mineral density decreases within 1 year after the start of these therapies, with a continuing decrease causing bone loss thereafter (~3–7% per year in lumbar spine). The consequent increased risk of osteoporotic fracture is increased even further by changes in body composition induced by hormonal castration, such as increases in weight and body mass index and decreases in lean body mass and muscle mass/strength. It is therefore recommended that bone mineral density be measured by dual energy X-ray absorptiometry (DEXA) before the therapies start, in particular in subjects at high risk, to detect pre-existing osteoporosis and to monitor significant bone loss over time. Effective prophylactic and therapeutic strategies for this musculoskeletal effect are being investigated; they include calcium (1,200–1,500 mg/day) and vitamin D supplementation (400–800 IU daily). Patients should be advised to abstain from smoking and excessive alcohol use. Moreover, bisphosphonates (e.g. oral alendronate or risedronate, and parenteral pamidronate or zoledronic) have been successfully used in reducing bone loss in patients receiving antiandrogens. The use of this class of drug is recommended in men with ostedensitometry-proven osteoporosis or in men with osteopenia and pre-existing bone insufficiency fractures (due to minimal trauma). Furthermore, parathyroid hormone (or a congener such as teriparatide) therapy, and selective estrogen receptor modulators, such as raloxifene, are also being investigated. Finally, a low-dose androgen supplementation (e.g. testosterone enanthate 25–50 mg/month) has been considered. This latter, moreover, may also ameliorate the erectile failure and thus improve appropriate sexual relationships with partners, whereas all paraphilic manifestations remain totally suppressed.

Moreover, men treated with androgen deprivation therapy develop an increase in body and fat mass, hyperinsulinemia, hyperglycemia, insulin resistance, and impaired lipid profile, with an increased risk of developing metabolic syndrome, diabetes mellitus (by 40–50%), and cardiovascular diseases (by 10–20%). To reduce these side effects, it is important that patients adopt a healthy lifestyle and dietary behaviors, including smoking cessation and regular exercise. Such non-pharmacological interventions can be followed by statin therapy, in order to lower the blood low-density lipoprotein levels and reduce the risk of cardiovascular events. Proposed target levels, derived from research in type 2 diabetes, are as follows: low-density lipoprotein cholesterol levels, <2.6 mmol/l (100 mg/dl); fasting triglycerides levels, <1.7 mmol/l (150 mg/dl); and high-density lipoprotein cholesterol levels, >1.1 mmol/l (40 mg/dl).

Concerning mood disturbances, low T levels have been associated with an increased risk of depression, emotional disturbances, anxiety, fatigue, malaise, memory difficulties, asthenia, lack of drive, and listlessness. It should further be taken into account that paraphilic individuals suffer frequently from comorbid affective disorders or other mental illnesses, with an increased risk of bipolar depression after the start of hormonal therapy. Moreover, conviction, imprisonment, and the stigma and shame of being a sexual offender may

also increase the risk of depression. Sex offenders should therefore be carefully evaluated before the start of and during androgen deprivation therapy, for the presence of mental illnesses, to provide appropriate psychiatric treatment.

Other side effects of androgen deprivation include hot flushes and night sweats, which may reduce quality of life. Hot flushes can be effectively treated with megestrol acetate and SSRIs and selective serotonin-norepinephrine re-uptake inhibitors (SRNIs), which also may be beneficial in treating comorbid depressive symptoms. Moreover, other side effects that have been described are breast tenderness and gynecomastia, especially using cyproterone acetate. Radiation, at a single dose of 1,500 cGy per breast, has been used to prevent or treat painful/tender gynecomastia caused by this drug. After 3 and 6 years of follow-up, the further development of gynecomastia was halted, and pain and tenderness were reduced to minimal. Furthermore, besides impotence and its libido-reducing effects, androgen deprivation therapy also directly induces partial azospermia and infertility, although it provides no birth control assurance.

For all these reasons, effective and wise management of sex offenders treated with T deprivation therapy should include careful monitoring of side effects and their prevention. Sex offenders who start a treatment should furthermore be aware that this intervention is not without risk.

Androgen deprivation treatment should be used after other alternatives have been ruled out or when there is a high risk of sexual violence. Not every sex offender is a candidate for hormonal treatment, even if it has the advantage of being reversible once discontinued. Moreover, it cannot be frequently used in the treatment of juvenile sex offenders, because of the possible interference with the development or course of puberty (bone growth must be achieved and should be checked using X-rays).

Surgical castration

Orchidectomy reportedly produces definitive results, even in recidivist pedophilic offenders, by reducing thus from 5 to 2%. However, up to one-third of castrated males can still engage in intercourse. Therefore, it is not uniformly effective in producing impotence. Results can also be reversed by the administration of exogenous T, allowing re-offense. From the introduction of surgical castration in Switzerland in 1892 (as a treatment for hypersexuality) until the 1970s, this procedure has been used in many European countries and in the United States. Today, it is available only in Germany and in certain US states. One significant factor, considering limited prison health care budgets, is the substantial difference in cost between one-time surgical castration and ongoing chemical castration with anti-androgen drug therapy.

On the other hand, since medication is available that produces similar results, the Belgian Advisory Committee on Bioethics have recently advised that surgical castration can no longer be an option for the treatment of sex offenders.

Hormonal castration

Estrogens

Estrogen therapy has a long history of use in sex offenders. The first use of oral diethylstilbestrol (DES) was reported in 1940, followed in that decade and subsequent ones by the use of oral estronen. Estrogen therapy in males is associated with risk. Although breast cancer in males is extremely rare (lifetime risk of 1 in 1,000), there are case reports of breast cancer in men receiving estrogens. The major concerns with oral estrogen therapy in men are cardiovascular toxicity, including ischemic heart disease (myocardial infarction, angina, and heart failure), cerebrovascular disease (stroke and transient ischemic attacks), edema, and thromboembolism (deep venous thrombosis and pulmonary embolism). Although the initial negative data were associated with

high-dose DES therapy (5 mg/day), numerous trials using DES doses of 1–3 mg/day had cardiovascular adverse-event rates ranging from 10–35%. Concurrent administration of warfarin (1 mg/day) does not appear to lower these rates. Similar adverse-event potential exists with conjugated estrogen and estradiol.

In conclusion, estrogens must not be used in sex offenders or subjects with paraphilia.

Antiandrogens

Steroidal antiandrogens, such as Cyproterone Acetate and Medroxyprogesterone Acetate, have progestogenic activities in addition to their antiandrogenic effects which, through feedback effects on the hypothalamo-pituitary axis, inhibit the secretion of LH, resulting in a decrease in circulating levels of both T and DHT. These compounds interfere with the binding of DHT (the androgen that plays the dominant role in androgenic response) to androgen receptors and they have been shown to block the cellular uptake of androgens.

Cyproterone Acetate (CPA)

CPA is a synthetic steroid, similar to progesterone, which acts as a potent, dose-dependent antiandrogenic and progestational agent. Three potential mechanisms underlay its antiandrogenic effects. It inhibits the intracellular uptake of androgens, blocking their binding to the receptor through competitive inhibitions. It also blocks T (and estrogen) synthesis in the gonads. Finally, due to its powerful progestational activity, it causes inhibition of gonadotropin secretion, and blocks their compensatory rise expected to follow a decrease in serum T concentrations. This latter effect is in contrast with that of the pure antiandrogens (e.g. flutamide). When the latter agents compete with T for binding to androgen receptors, a compensatory rise in gonadotropin secretion occurs; this increase, in turn, stimulates T production and eventually overcomes the receptor blockade. The antiandrogenic effect of cyproterone acetate is believed to outweigh the progestational effect in terms of clinical efficacy in the treatment of paraphilias; however, it is the progestational effect that allows safe and effective long-term therapy. Equilibrium between these 2 influences requires many months of treatment (8–15 months on 100 mg/day and 15–20 months on 200 mg/day).

CPA has been approved for the treatment of prostate cancer, central precocious puberty, androgen-induced skin disorders (e.g. acne, seborrhea, idiopathic hirsutism, and alopecia), and reduction of the sex drive in sexual deviants. It is available as oral tablets (50 and 100 mg) and a depot formulation for intra-muscular (IM) injection (100 mg/mL) in many countries. It is available in the United States only in a low-dosage form, in a combination product with ethinyl estradiol.

Most of the clinical data regarding its use in abnormal sexual behaviors have been generated using the oral formulation (usual regimen, 50–200 mg/day; maximum, 600 mg/day). The IM formulation is usually administered as 300–600 mg every 1 or 2 weeks for this indication. During use for its approved indications, general malaise is a common occurrence early in therapy; flushes, dizziness, depression, venous thromboembolism (VTE), decreased pubic/facial hair growth, psychotic reactions, and increased (more common) or decreased body weight have also been reported. Gynecomastia, which occurs in about 20% of patients, can be temporary or permanent, unilateral or bilateral. Serious hepatotoxicity is not a common finding with CPA. Although large doses of this agent can produce hepatomas in rats, no evidence exists that the same happens in humans. Flutamide and CPA may be cross-reactive in terms of hepatotoxicity risk. The most serious potential adverse events of CPA are suppression of the hypothalamic-pituitary-adrenal axis and a reduction in the adrenal response to stress. Early data were conflicting, but more recent information is reassuring concerning the adrenal safety of this agent.

In some countries, the oral form is the only form available and treatment observance

may be erratic. In fact, using this formulation, T levels are not systematically decreased and measurements of plasma levels of CPA are not available in many countries. Poor treatment compliance is a major concern with oral CPA. On the other hand, compared with the oral formulation, injectable CPA (via IM depot injection) shows a lower tolerability, in terms of local pain (at the injection site), joint/muscle pain, headache, sleep disturbances, and nausea.

Side effects are dose related and careful monitoring of CPA dosage should decrease side effects and, in some cases, would allow non-deviant sexual behavior. The use of CPA has to be managed carefully medically, via physical examination, especially for the unwanted effects of feminization.

TIPS & TRICKS

Clinical assessment for subjects treated with CPA:

- Before treatment, check:
  - T, FSH, LH, and prolactin plasma levels, hepatocellular blood tests, blood cell count, electrocardiogram, fasting glucose blood level, calcium and phosphate blood levels, kidney function, blood pressure, weight, bone mineral density.
- Informed consent must be obtained.
- During CPA treatment, evaluate:
  - every 1–3 months: depression, emotional disturbances;
  - every month for 3 months and then every 3–6 months: biochemical monitoring of liver function;
  - every 6 months: prolactin, glucose blood levels, blood cell count, calcium and phosphate blood levels, blood pressure, weight;
  - every year, in case of increased osteoporosis risk: bone mineral density.

CAUTION

CPA treatment must not be used in cases of:

- non-consent
- puberty not completed, especially when bone growth is not achieved
- hepatocellular disease, liver carcinoma
- diabetes mellitus
- severe hypertension
- carcinoma, except prostate carcinoma
- pregnancy and breast feeding
- previous thromboembolic disease
- cardiac and adrenal disease
- severe depressive disorder, psychosis
- tuberculosis
- chachessia
- epilepsy
- drepanocytosis

Medroxyprogesterone Acetate (MPA)

Compared with CPA, MPA is less potent than an antiandrogen and progestogen, and relatively more progestogenic than antiandrogenic (as opposed to the "balanced" effects with CPA). MPA exerts negative feedback on the hypothalamo-pituitary axis, resulting in an inhibition of gonadotropin secretion and hence T production. A complete ablation of the latter is reached usually within 1–2 weeks after starting therapy. Moreover, MPA also induces the testosterone-α-reductase, which accelerates T metabolism, and reduces plasma T by enhancing its clearance.

MPA has been approved for the treatment of menorrhagia, secondary amenorrhea, and mild to moderate endometriosis, female contraception, catamenial epilepsy therapy; and the treatment of prostate, breast, and advanced endometrial/renal cancers.

MPA is available in some countries as oral tablets (2.5, 5, and 10 mg) and l50- and 400-mg/mL suspensions for IM injection. Although the oral route of MPA can be used (usual regimen, 100–500 mg/day), erratic oral bioavailability (within and between products and within and between subjects) has made

the IM formulation preferable. The majority of clinical trial data regarding MPA use in abnormal sexual behaviors has been generated using the IM formulation (usual regimen, 100–1,000 mg weekly).

MPA adverse events included reduced bone mineral density (virtually 100%), excessive weight gain (18%), headache (9%), malaise (5%), dyspepsia (5%), VTE (<1%), muscle cramps (<1%), gallstones (<1%), and diabetes mellitus (<1%). A recent study has reported the balanced effects on D-dimer levels and activated partial thromboplastin time values (which have opposing effects on VTE risk) in a sample of women using MPA. This latter result suggests that the potential risk of VTE with MPA may be lower than once thought.

MPA was the first drug studied in the treatment of paraphilias. Unfortunately, most studies were not controlled and some biases were observed. Moreover, considering the severe side effects observed with MPA, the benefit/ risk ratio seems to be unfavorable and, therefore, its use has been limited.

Nevertheless, if clinicians decide to initiate MPA therapy for a paraphilia, they must take into consideration its toxicity potential and, in an attempt to prevent or ameliorate adverse events, the dose may be lowered, at the cost of reduced therapeutic efficacy. The use of MPA has to be carefully managed medically, via physical examination, especially for the effects of feminization.

TIPS & TRICKS

Clinical assessment for subjects treated with MPA:

- Before treatment, check:
  T, FSH, LH and prolactin plasma levels, hepatocellular blood tests, blood cell count, electrocardiogram, fasting glucose blood level, calcium and phosphate blood levels, kidney function, blood pressure, weight, bone mineral density.
- Informed consent must be obtained.
- During MPA treatment, evaluate:
  – every 1–3 months: depression, emotional disturbances;
  – every 6 months: glucose blood levels, blood pressure, weight;
  – every year, in case of increased osteoporosis risk: bone mineral density.

CAUTION

MPA treatment must not be used in case of:

- non-consent
- puberty not completed, especially when bone growth is not achieved
- adrenal disease
- pregnancy and breast feeding
- severe hypertension
- previous thromboembolic disease
- breast and uterine diseases
- diabetes mellitus
- severe depressive disorder
- allergy to MPA
- active pituitary disease

GnRH analogs

GnRH analogs are relatively new drugs approved in many countries for a variety of pediatric, obstetric, gynecological, and oncological disorders, such as central precocious puberty, endometriosis, uterine fibromyomas, female infertility (*in vitro* fertilization), breast cancer (in pre-menopausal women), and advanced prostate cancer. Recently, they have also been used in Gender Identity Disorder subjects.

GnRH analogs produce a complete "chemical castration," with hypoandrogenism as the only clinical effect. Their biological effects depend on their duration of use. Initially, the release of LH and FSH is stimulated, leading to elevations in sex hormone blood concentrations ("flare-up"). Continued use results in a suppression on account of the depletion and desensitizing of

the gonadotrope hypophyse cells. The result is reduced LH and FSH secretion and thus reduced sex hormone production until castrated levels within 2–4 weeks. Because of these time-dependent effects of the LHRH agonists, concurrent use of a pure antiandrogen (flutamide or one of its congeners) is recommended during the initial 1 or 2 months of LHRH agonist use. Using an oral antiandrogen counteracts the "flare-up" of the androgen-dependent response that occurs with the initial surge in serum androgen concentrations early during LHRH agonist therapy. Oral antiandrogen therapy can be stopped once this phase is over.

Three analogs of the gonadotrophin-releasing hormone are available:

1) Triptorelin is a synthetic decapeptide agonist, analog of the gonadotropin-releasing hormone (GnRH). It was recently approved in Europe for the reversible decrease in plasma T to castration levels, in order to reduce the drive in sexual deviations of adult men. It was developed as monthly or depot formulation.
2) Leuprolide is a synthetic analog of GnRH; it was developed as daily IM or depot injections.
3) Gasorelin is also a synthetic analog of GnRH. It was developed as daily IM or depot injections.

Adverse events include decreased testicular volume (4–20%), decreased pubic/facial hair growth (2–23 %), and vasomotor instability (hot flashes; 56–100%). Other adverse events include fatigue and malaise (6–18% each), weight gain (2–13%), gynecomastia (2–7%), and injection-site reactions (induration, burning, redness, itching, bruising, and pain). Most concerning is the reduction in bone mineral density that occurs almost universally due to androgen ablation.

Forty percent of normal controls reported reduction in sexual desire with GnRH treatment. In addition, GnRH containing neurons project into pituitary and extrapituitary sites, such as the olfactory bulb or the amygdala. At these latter sites, GnRH is believed to act as a neuromodulator and, through this action, may also be involved in sexual behavior. Thus, GnRH analogs, by inducing castrate T levels, progressively led to and maintained the inhibition of the fundamental elements of male sexuality: sexual fantasies, desire, and interest in sexual activities, resulting in either a dramatic decrease or an abolishment of the sexually deviant behavior.

The duration of treatment necessary to achieve a complete disappearance of deviant sexual behavior and the conditions of treatment interruption remain open.

Efficacy was maintained for years as long as the antiandrogen treatment was maintained. Despite there being no controlled studies and some biases were observed, the efficacy reported in these open studies was very high and, in most cases, subjects were previously treated with psychotherapy or other antiandrogens without efficacy.

The World Federation of Society of Biological Psychiatry (WFSBP) guidelines suggest that GnRH agonist treatments should be used after other alternatives have been ruled out or when there is a high risk of sexual violence and underline that GnRH analog treatment probably constitutes the most promising treatment for sex offenders with a high risk of sexual violence, such as pedophiles or serial rapists.

☆ TIPS & TRICKS

Clinical assessment for subjects treated with Long Acting GnRH analogs:

- Before treatment, check:
  T, FSH, LH, electrocardiogram, fasting glucose blood level, blood pressure, weight, calcium and phosphate blood levels, kidney function, bone mineral density (in case of personal or familiar osteoporosis risk or in patient over 50 years old).

- Informed consent must be obtained.
- During Long Acting GnRH treatment, evaluate:
  - every 1–3 months: depression, emotional disturbances
  - every 6 months: glucose blood levels, lipid profile, blood cells count, calcium and phosphate blood levels, blood pressure, weight
  - every year, in case of increased osteoporosis risk: bone mineral density.

CAUTION

GnRH treatment must not be used in case of:

- non-consent
- puberty not completed especially when bone growth is not achieved
- pregnancy and breast feeding
- severe hypertension
- severe cardiac or renal disease
- severe osteoporosis, especially in case of previous fractures
- severe depressive disorder
- allergy to GnRH
- active pituitary disease

EVIDENCE AT A GLANCE

MPA and CPA treatment vs.long-acting GnRH analogs

Efficacy:

- Antiandrogen or GnRH analogs significantly reduce the intensity and the frequency of sexual arousal, but do not change the content of paraphilias.
- Long-acting GnRH analogs are more potent than CPA or MPA in reducing T levels, more dramatically and more consistently.

Side effects:

- MPA and CPA are associated with a high percentage of side effects, which have limited their use considerably.
- Long-acting GnRH induce fewer side effects (except for those related to hypoandrogenism).

Patient's compliance:

- Uncontrolled breaks in the therapy are often observed with CPA or MPA treatments.
- Long-acting GnRH analogs may be administrated parenterally once every 1–3 months, producing less variable results in the treatment of paraphilic behavior than CPA and MPA.

Algorithm of treatment of paraphilias

A treatment program should start with supportive psychotherapy and, in most cases, cognitive-behavioral therapy. In all cases, treatment of comorbidities is necessary, if there are any (Level 1). In case of psychiatric comorbidities, adequate pharmacological treatment, such as benzodiazepines, anti-psychotics, SSRIs, or specific types of psycho-therapies, must be used.

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, obsession, or personality disorders, and if the paraphilia is at low risk of sexual offense (Level 2).

If there is insufficient improvement and a moderate-to-high risk of "hands-on" offenses, low doses of antiandrogens, preferentially in combination with SSRIs, should be given. Side effects are dose related, so a careful titration could minimize them and may allow patients to maintain appropriate sexual behavior while eliminating deviant behavior (Level 3).

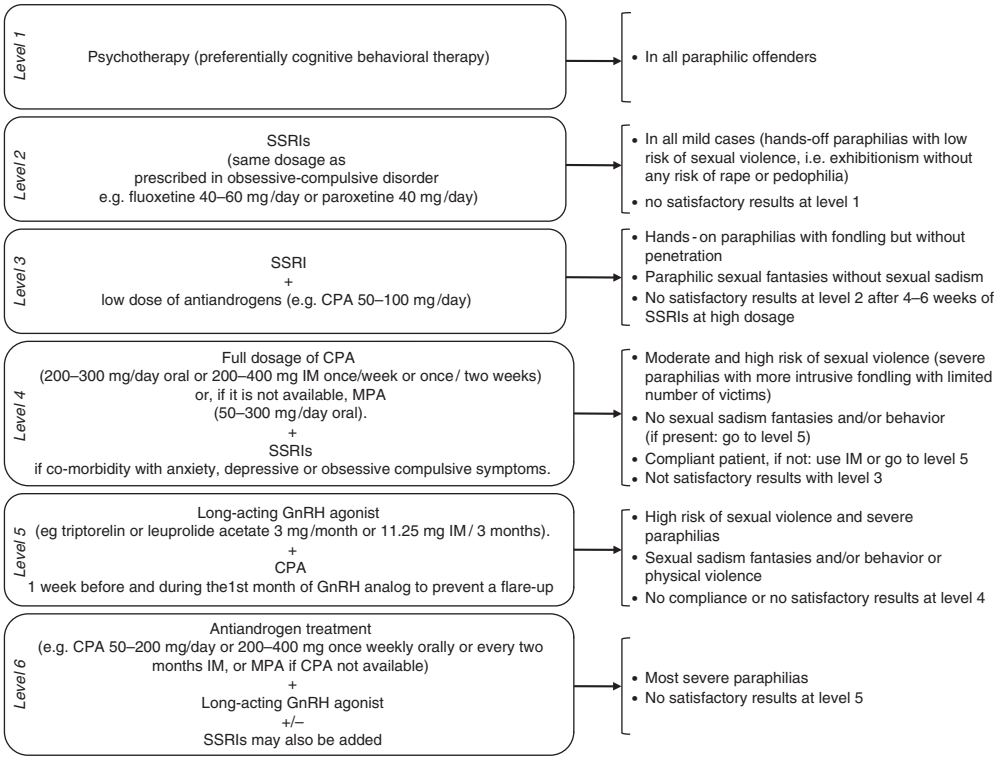

Figure 8.1. Treatment algorithm of paraphilias, modified from Thibaut F *et al.* The World Federation of Society of biological Psychiatry (WFSBP) Guidelines for the biological treatment of paraphilias. Altered from original source - *The Journal of Biological Psychiatry.* 11:604–55. 2011. SSRIs, Selective serotonin reuptake inhibitors, CPA, Cyproterone acetate; MPA, Medroxyprogesterone Acetate; GnRH, gonadotropin-releasing hormone; IM, intramuscolar.

Full dosage of CPA (or, if it is not available, MPA) should be added to SSRI treatment in subjects with a moderate to high risk of sexual offense (severe paraphilias with more intrusive fondling with limited number of victims), considering the intramuscular application in non-compliant patients (Level 4).

In case of high risk of sexual offense and severe paraphilias, sexual sadism fantasies and/or behavior or physical violence and no compliance or no satisfactory results at Level 4, use of GnRH agonist could be justifiable and useful (Level 5).

Finally, in most severe paraphilias, a combination of antiandrogens, GnRH agonist, and SSRI must be considered (Level 6).

In case of serious side effects (VTE or severe liver dysfunction), CPA or MPA treatment must be replaced with GnRH analogs.

For a summary of the treatment algorithm, see Figure 8.1.

Treatment duration

Paraphilia is a chronic disorder and sexual orientation will not change during the treatment.

In case of mild paraphilia, a treatment of at least 2 years might be used, after which, in case of treatment interruption, the patient must be carefully followed up. In case of recurrence of paraphilic sexual fantasies, treatment must be restarted.

For severe paraphilia with a high risk of sexual violence, a minimal duration of treatment of 3–5 years is necessary. In these patients in particular, hormonal treatment must not be stopped abruptly.

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