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GUIDELINES

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of paraphilias

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Abstract

Objectives. The primary aim of these guidelines was to evaluate the role of pharmacological agents in the treatment and management of paraphilia, with a focus on the treatment of adults males. Because such treatments are not delivered in isolation, the role of specific psychosocial and psychotherapeutic interventions was also briefly covered. These guidelines are intended for use in clinical practice by clinicians who diagnose and treat patients with paraphilia. The aim of these guidelines is to improve the quality of care and to aid physicians in clinical decisions. *Methods.* The aim of these guidelines was to bring together different views on the appropriate treatment of paraphilias from experts representing different continents. To achieve this aim, an extensive literature search was conducted using the English language literature indexed on MEDLINE/PubMed (1990–2009 for SSRIs) (1969–2009 for antiandrogen treatments), supplemented by other sources, including published reviews. *Results.* Each treatment recommendation was evaluated and discussed with respect to the strength of evidence for its efficacy, safety, tolerability and feasibility. *Conclusions.* An algorithm was proposed with six levels of treatment for different categories of paraphilias.

Key words: *Paraphilia, sex offenders, antiandrogens, antidepressants, treatment guidelines*

An historical perspective

Whilst it is almost certainly the case that all human societies through history have imposed boundaries or limits on the types of sexual behaviour regarded as acceptable, a degree of variation across cultures has occurred, whilst within cultural traditions, change in sexual mores may occur over time. Within this historical context, it is therefore evident that societies require a concept of sexual deviancy, but that it is subject to evolving changes of social perspective. Reference to biblical Israel as well as ancient Greece indicate historical influences of both a religious and a secular nature, of which the religious is more associated with moral condemnation of sexual deviance and the secular with greater liberalism (Group for the Advancement of Psychiatry 2000).

A range of factors are relevant to social perceptions as to whether certain sexual behaviour is to be regarded as sexually deviant. These include the degree of consent, the location of the sexual behaviour, the age of those involved, the nature of the sexual act, whether any distress or harm may occur, the frequency of the type of sexual practice in society and the degree of distaste felt by others about the particular sexual behaviour (Tewksbury 2003).

It was not, however, till the end of the nineteenth century that sexual deviance was to become regarded as a medical phenomenon, with the publication of *Psychopathia Sexualis* describing cases of sexual murder by the German psychiatrist, Krafft-Ebing (1886). Krafft-Ebing's emphasis on the connection between sexual fantasy and the compulsion to kill reflects the

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laying down of knowledge on paraphilias already over a century ago (Schlesinger 2004). The interest by German psychiatry in sexual deviance at the turn of the twentieth century is further illustrated by a case of a man with paedophilic tendencies described by another great German psychiatrist, Emil Kraepelin (Johnstone 1913).

Despite the initial origins of medicalisation of sexual deviance having been claimed by clinical psychiatry, during the twentieth century the main focus of study and indeed treatment was that of psychoanalysis. Freud's early theory of sexuality remains the basis of the psychoanalytic understanding of sexual deviance (Freud 1905/1953; Rosen 1997). Subsequently a century of psychoanalytic thought has contributed to the assessment and treatment of sexual deviance (see especially Fenichel 1954; Stoller 1975; Kernberg 1991; Rosen 1997).

Yet running alongside the psychoanalytic perspective of sexual deviance resulting from a psychological developmental abnormality of sexual maturation was also a trend towards the pathology being more one which was organically determined. Freud himself saw the roots of perversion in a combination of biological and developmental factors (Rosen 1997). The British author, Havelock Ellis (Ellis 1933) and the German physician, Magnus Hirschfield (1948), attempted to reform public attitudes towards a range of sexual behaviour especially homosexuality, by advocating that such behaviour constituted a medical condition rather than merely sinful decadence.

Having rescued the paraphilias from the purview of sin, their delineation as perversions, for which the psychoanalysts received most criticism, came under challenge after the Second World War (Group for the Advancement of Psychiatry, 2000). The particular preferred categories of mental disorder used in major textbooks were now to be seen in relation to the beginning of a unifying tradition of international classifications by the World Health Organisation and the American Psychiatric Association.

The evolution of the notion of deviant sexuality has led to a degree of confusion as to its legitimacy as genuine medical conditions rather than sexual lifestyle choices or in some cases sexual behaviour determined by criminal disposition. The case for paraphilias as real medical entities is based on their inclusion in the international classifications, that they can be diagnosed according to various defined symptoms and behaviour, that they might be regarded as a form of impulse control disorder (Pearson 1990) or on the obsessional compulsive spectrum (Stein et al. 1992), or as an intrinsic abnormality of sexual development as earlier noted, that they have a high level of comorbidity with a range of other mental disorders (Gordon and Grubin 2004), they may be associated with elevated risk of harm to self and others and that there is increasingly effective treatment available. The validity however of paraphilias as a medical diagnosis is ambiguous in that they are excluded in the mental health legislation of many nations as a basis for compulsory detention (Gordon 2008). Additionally further debate and greater clarity is required in resolution of some of the problems in diagnosis of paraphilias, including are deviant sexual fantasies a sufficient parameter or whether they require to be acted upon in overt behaviour, or conversely where sexual fantasies are denied but deviant sexual behaviour is present, the duration necessary of the fantasies or behaviour, whether the paraphilia is regarded as present when opportunity for exposure to potential victims is absent, for example when in prison, the evaluation of the intensity of the fantasies or urges and the degree of occupational or social deterioration (Laws and O'Donohue 1997; Marshall 2006).

The beginnings of treatment of the paraphilias can be traced back to the late nineteenth century at a similar time though not directly connected to the new concept of sexual deviance as a medical condition. This initial treatment approach was that of surgical castration, used first for therapeutic purposes in 1892 in Switzerland in regard to a patient with imbecility and neuralgic pain of the testis and hypersexuality (Sturup, 1972). In his paper, the Danish psychiatrist Sturup (1972) outlined that castration had been known throughout history, being reported in Greek mythology and a particular problem of auto-castration for religious reasons during early Christianity, but also used elsewhere for judicial reasons for sex crimes, and as a deliberate measure to produce euneuchs in eastern harems and to produce operatic sopranos in Italian boys up till the eighteenth century. During the twentieth century, surgical castration for some sex offenders was used not only in the United States, but in certain European countries including Denmark, Norway and The Netherlands as well as in Germany and Switzerland (Bremer 1959; Langeluddeke 1963; Sturup 1972; Cornu 1973; Heim and Hursch 1979; Ortmann 1980; Heim 1981; Wille and Beier 1989). Patients in these European studies were varied in diagnosis and the type of sex offender but the effects of surgical castration seems to have resulted in marked reduction in sex offence recidivism. Surgical castration for sex offenders in Europe has not been continued since the early 1970s, though it is still available with careful safeguards in Germany. As a therapeutic technique for sex offenders it was never embraced in Britain and its legality even on a voluntary basis questioned (Stone and Thurston 1959). Surgical castration was legally reintroduced for sex offenders in certain US states in 1996 and thereafter (Weinberger et al. 2005).

Whilst surgical castration for selected sex offenders has been the predominant surgical approach used, some limited use was also made in post-war West Germany of neurosurgery (Roeder 1966; Roeder et al. 1972). As with surgical castration the technique is irreversible. However, given the complexity of the treatment of paraphilias, the reality that treatments used in the past can be rejuvenated, and the biological aspects of paraphilias, the past use of psychosurgery should not be overlooked.

By the 1940s, some attempts had been made to treat sex offenders by medical methods using oestrogens (Foote 1944; Golla and Hodge 1949; Symmers 1968), but due to feminising side-effects, this was supplanted in the 1960s by antilibido medication reducing testosterone levels. Cyproterone acetate is available in most countries, administered orally; but a depot form is available which is also used in Europe (Gordon and Grubin, 2004; Sammet, 2005), whilst in the United States, medroxyprogesterone acetate is the drug of choice (Meyer et al. 1992a). Unlike surgical castration, the effects of antilibido medication are reversible on discontinuation. A more recent and promising development in the treatment of paraphilias is the use of luteinizing hormone releasing hormone agonists. These are given by depot injection, reduce testosterone to very low levels and result in very low levels of recidivism (Rousseau et al. 1990; Dickey 1992; Thibaut et al. 1993).

There is also emerging evidence for the use of selective serotonin reuptake inhibitors, SSRIs (Stein et al. 1992; Saleh 2004). This follows longstanding evidence for reduction in male libido using almost any psychotropic medication including benperidol (Sterkmans and Geerts 1966), thioridazine (Sanderson 1960), fluphenazine depot (Bartholomew 1968), clomipramine (Wawrose and Sisto 1992), lithium (Cesnik and Coleman 1989) and buspirone (Fedoroff 1992).

Whilst a biological approach is probably essential in the treatment of patients with severe paraphilias, a psychotherapeutic context to the treatment is equally necessary. Aversion therapy had tapered out by the 1980s and gradually gave way to cognitive behavioural therapy. An optimum formula for treatment of paraphilias may well be a combination of cognitive behavioural therapy and antilibido medication administered in a dynamic psychotherapeutic framework.

Ethical issues

The treatment of patients with paraphilias, irrespective of which method of treatment is employed, has always been undertaken through a minefield of clinical and ethical dilemmas. There have been ethical objections to the treatment of sex offenders using psychodynamic psychotherapy (Adshead and Mezey 1993), aversion therapy (King and Bartlett 1999), surgical castration (Alexander et al. 1993) and antilibido medication (Mellela et al. 1989). The major ethical issues regarding sex offenders including paraphilias may reflect the need for public safety balanced against the public and even professional orientation towards punishment rather than treatment even where treatment is appropriate and effective (Bowden 1991; Berlin 2003; Ward et al. 2007 on the human rights of the sex offender in the context of treatment and rehabilitation; Elger 2008 about prisoners included in research programs).

Paraphiliac sex offenders referred for hormonal treatment are often the object of some external coercion, be it from a court decision or under the pressure of their family, employers or other involved persons. From an ethical point of view, the patient may be subjected to hormonal treatment 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 paraphiliac disorder diagnosed by a psychiatrist after a careful psychiatric examination.
- The hormonal treatment address specific clinical signs, symptoms and behaviours and is adapted to the person's state of health.
- The person's condition represents a significant risk of serious harm to his health or to the physical or moral integrity of other persons.
- No less intrusive treatment means of providing care are available.
- The psychiatrist in charge of the patient agrees to inform the patient and receive his or her consent, to take the responsibility for the indication of the treatment and for the follow-up including somatic aspects with the help of a consultant endocrinologist, if necessary.
- The hormonal treatment is part of a written treatment plan to be reviewed at appropriate intervals and, if necessary, revised.

When a sex offender is subject to coerced treatment, the decision to subject that person to hormonal treatment may be taken by a psychiatrist having the requisite competence and experience, after examination of the person concerned and after his or her informed consent has been obtained. However, consent is sometimes given in circumstances (e.g., prison or detention in a secure hospital), where the person is subject to some constraint. Whilst treatment may facilitate improvement and

release or discharge, this is not necessarily the case. In cases of doubt of the validity of patient's consent, afterwards withdrawal of his consent or non-compliance with the treatment the decision to subject a sex offender to coerced treatment should be taken by a court or another competent body. The court or other competent body should:

- act in accordance with procedures provided by 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.

Clinical context

The terms sex offenders and paraphilias will be used in the following text. In order to clarify the respective use of these words, it is important to remember that, not all sex offenders suffer from a paraphilia, but only part of them, and that, not all patients with a paraphilia are sex offenders (in many cases, they only suffer from deviant sexual fantasies or urges, or their deviant sexual behaviour does not involve a non consent person or a child).

Definition and classification

According to the Diagnostic and Statistical Manual Disorder, Fourth Edition, Text Revision (DSM IV-TR) or to the International Classification of Mental Diseases (ICD-10th), paraphilias are defined as sexual disorders which are characterized by "recurrent, intense, sexually arousing fantasies, sexual urges or behaviours, generally involving (1) non human objects, (2) the suffering or humiliation of oneself or one's partner, or (3) children or other non-consenting persons that occur over a period of 6 months" (criterion A), which "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (criterion B). DSM IV-TR describes eight specific disorders of this type (exhibitionism, fetishism, frotteurism, paedophilia, sexual masochism, sexual sadism, voyeurism and transvestic fetishism) along with a residual category called "paraphilia not otherwise specified".

The term paraphilia comes from the Greek prefix "para" meaning around or beside and "philia" an ancient Greek word for love. The term paraphilia first appeared in the third version of the DSM classification. In the first version of the DSM published in 1952, sexual deviations were conceptualized as a subclass of sociopathic personality disturbances (Malin and Saleh 2007).

Patients with the exclusive form of a paraphilia may not be able to be sexually aroused by anything other than their paraphiliac imagery or behaviour. By contrast, patients with the non-exclusive form may be aroused by other sexual fantasies, stimuli and behaviours, although their paraphilias may interfere with their overall sexual preferences.

Most paraphilias are chronic, lasting for many years if not a lifetime.

Simply having paraphilia is obviously not illegal. Acting in response to paraphiliac urges, however, may be illegal and, in some cases, subjects the person with paraphilia to severe sanctions.

Paraphilias include:

Exhibitionism: The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving the exposure of one's genitals to an unsuspecting stranger. The onset usually occurs before the age of 18 and the condition seems to become less severe after the age of 40.

Frotteurism: The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving touching and rubbing against a non-consenting person. Usually, it begins by adolescence. Most acts of frottage occur when the person is aged 15–25 years, after which there is a gradual decline in frequency.

Voyeurism: The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving the act of observing an unsuspecting person who is naked, in the process of disrobing, or engaging in sexual activity. The onset in usually before the age of 15.

Fetishism: The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving the use of nonliving objects (e.g., female undergarnments or shoes, etc.). Usually, it begins by adolescence and it concerns mostly males.

Sadomasochism: Suffering or humiliation of oneself or one's partner (i.e. sexual masochism and sadism, respectively) may be considered as paraphilias.

Sexual masochism: The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving the act (real, not simulated) of being humiliated, beaten, bound, or otherwise made to suffer. It may eventually result in injury or even death.

Sexual sadism: The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving acts (real, not simulated) in which the psychological or physical suffering (including humiliation) of the victim is sexually exciting to the person. It begins commonly by early adulthood. Sexual sadism may be associated with rapes.

Rape is not included in this classification as it represents an expression of aggression rather than a specific paraphilia. However a small number of rapists may meet the criteria for having a paraphilia (often exhibitionism or paedophilia, sometimes sexual sadism).

Pedophilia: (for review see Hall and Hall 2007) The sexual activity involves prepubescent children, generally aged 13 years or younger. Paedophiles must be at least 16 years old and must be at least 5 years older than the victim. For juvenile paedophiles, no age is specified and clinical judgment must be used (the sexual maturity of the child and the age difference must be taken into account). In at least 90% of cases, paedophiles are males. Dickey et al. (2002), in their sample of 168 sex offenders, reported that paedophiles were older as compared with rapists and sexual sadists. However, there is a clearly scientifically established reduction in recidivism related to age. There are also age related changes in libido due to reduction in testosterone levels.

Paedophiles may be sexually attracted to males (9–40% of cases according to Hall and Hall (2007)), females (even more frequent) or both. Those attracted to females usually prefer 8- to 10-year-old children, whereas, those attracted to males usually prefer slightly older children. Paedophilia may be limited to incest (inside the family), this subgroup may represent 20% of paedophilic subjects (Cohen and Galinker 2002; Cohen et al. 2007). Paedophilia may be exclusive (attracted only to children) or not. Among about 2500 male paedophiles, Hall and Hall (2007) reported that only 7% were exclusively attracted to children. The term hebephilia is used to describe sexual interest for either male or female peripubescent children or adolescents. Infantophilia is used to describe individuals interested in children younger than 5 years. Paedophiles may also be classified as to whether child pornography and/or a computer was used to engage the child in sexual activity (Seto et al. 2006). These distinctions are important in the selection criteria for studies of sexual behaviour.

Paedophilic subjects who act on their urges with children may limit their activity to undressing the child and looking, exposing themselves, masturbating in the presence of the child, or gentle touching and fondling of the child. Others perform fellatio or cunnilingus on the child or penetrate the child's vagina, mouth or anus with their fingers, foreign objects, or penis and use varying degrees of force to do so. These activities are commonly explained with excuses or rationalizations that they have educational value for the child, that the child derives sexual pleasure from them, or that the child was sexually attractive, especially in those attracted to males. Violence is rarely used (Cohen and Galinker 2002; Hall and Hall 2007). Child molestation is not necessarily synonymous with paedophilia (Abel and Harlow, 2001).

Paraphilias not other specified: Paraphilias not other specified are also mentioned in the DSM-IV-TR classification. They include, but they are not limited to: telephone scatologia (obscene telephone calls), necrophilia (corpses), partialism (exclusive focus on part of a body), zoophilia (animals), coprophilia (feces), klismaphilia (enemas) and urophilia (urine).

In total, more than 50 types of paraphilias have been described, most of them being far more common in men (about 99% in Europe) than in women, but the percentage of women is increasing in the US (Abel and Harlow 2001; Hall and Hall 2007, for review). Except for sexual masochism, which is about 20 times less likely to affect men than women, paraphilias are quite unlikely to be diagnosed in women. Paraphiliacs often have more than one type of deviant sexual behaviour (e.g., one-third of paedophiles are also exhibitionists) (Bradford et al. 1992; Bradford 1999, 2001); according to Hall and Hall (2007), 50–70% of paedophiles have more than one paraphilia. The onset of paraphiliac sexual interest usually occurs before the age of 18.

Comorbidities associated with Paraphilias

Many paraphiliacs show evidence of major axis I mental illness including affective disorders, substance abuse disorders, schizophrenia, other psychotic disorders, dementia (especially temporal and/or frontotemporal dementias) and other cognitive disorders (Kafka and Hennen 2002). Paraphilias can occur within the context of axis II disorders, such as borderline or antisocial personality disorders and mental retardation, and axis III disorders, such as temporal lobe epilepsy or brain trauma (trauma to the limbic system may lead to changes in sexual preference; previous head trauma may be a predisposing risk factor for paedophilia, especially when head trauma occurred before the age of 6, Blanchard et al. 2002); Kleine Levin and Klüver Bucy

syndromes (50% of patients have inappropriate sexual behaviours); Huntington's disease (10% of patients complain of inappropriate sexual behaviours). Paraphilias can also occur in patients undergoing dopamine receptor agonist therapy (e.g., in Parkinson's disease). Few data are available regarding the treatment of dopamine-associated inappropriate sexual behaviours. Use of dopaminergic dose reduction and antidepressants or neuroleptics have been proposed (Guay 2008).

Paraphilia is not often associated with schizophrenia or bipolar disorder; in a review, Marshall (2006) have reported a low prevalence of psychotic disorders (1.7–16%). In some cases, the paraphilia is secondary to the psychotic illness and subsides when the psychosis is successfully treated, whilst in other cases, the paraphilia is independent of the psychosis and may need treatment in its own right (Smith and Taylor 1999; Baker and White 2002). In contrast, the prevalence of addictive disorders varied from 8 to 85%, the prevalence of personality disorders from 33 to 52% (among them antisocial personality disorder was the most frequently observed), the prevalence of depressive disorders varied from 3 to 95% and the prevalence of anxiety disorders may vary from 3 to 64%, attention deficit and hyperactivity disorders (ADHD) may also represent 36% of cases and eating disorders 10% of cases (Kafka and Prentky (1998, 110 adult outpatients); Dunsieth et al. (2004, 113 male forensic patients); Raymond et al. (1999, 45 male paedophilic sex offenders)). A high comorbidity of impulse control disorders (e.g., explosive personality disorder, kleptomania, pyromania, pathological gambling) has been noted in paedophiles (30–55%) (in Hall and Hall 2007). Methodological biases, such as the heterogeneity of both the samples and the diagnosis criteria used, may have contributed to the discrepancies observed between the studies.

In juvenile sexual offenders, from 60 to 90% of psychiatric comorbidity has been reported (in most cases, personality disorders such as conduct or borderline personality disorders, substance use disorders, ADHD or impulse control disorders and mood or anxiety disorders were observed) (Abel et al. 1988; Kavousi et al. 1988; Shaw et al. 1996; Galli et al. 1999; Bladon et al. 2005 (141 cases)); high rates of learning difficulties were also reported. Juvenile offenders constitute a heterogeneous population. When treated they show lower recidivism rates than adults; but the recidivism risk is higher for those with antisocial/impulsive and unusual/isolated personality (Worling, 2001).

Paraphilias are commonly associated with sexual hyperactivity, often with compulsive and/or impulsive features (Kafka and Prentky 1992a). Paraphilias often result in a variety of psychological disturbances, such as guilt, depression, shame, isolation, and impaired capacity for normal social and sexual relationships.

For some individuals, paraphiliac fantasies or stimuli are obligatory for erotic arousal and are always included in sexual activity. In other cases, the paraphiliac preferences occur only episodically (during periods of stress), whereas, at other times the person is able to function sexually without deviant stimuli or fantasies.

Sex offending and Paraphilias

While some paraphilias can be associated with strange sexual behaviour, they are not necessarily associated with offences. These patients may present for treatment because of associated distress to their personal lives. In contrast, other paraphiliac behaviours may lead to sex offences, a major public health problem defined as any violation of established legal or moral codes of sexual behaviour. The paraphilias can be graded from mild to catastrophic, depending on history of victimization and if positive, the number of victims, their age and the degree of victimization (level of intrusiveness: penetration or not) are considered. Severe cases would involve more than one victim or a child and there would be penetration to some degree. There are few studies about sexual murderers, Briken et al. (2006) have reported a higher level of sexual sadism in sexual murderers with paraphilias or paraphilia-related disorders.

In general, individuals with exhibitionism or paedophilia make up the majority of apprehended sex offenders. Paedophilia can devastate the lives of the victims. The mean number of victims for one paedophile is around 20. Cohen et al. (2002) reported a median number of 11 unknown victims for those who are attracted to males and of 1.5 for those attracted to females. In case of intrafamilial paedophilia, the median number was 4.5 for those attracted to females and 5 for those attracted to males. Moreover, in an anonymous survey conducted among 377 extra-familial paedophilic subjects, the mean number of victims reported by paedophiles attracted to females was 20 as compared with 150 among those attracted to males; in the case of intrafamilial paedophilia the rates dropped, respectively, to 1.8 and 1.7 (Hall and Hall 2007).

Incarceration may stop a paedophile from committing illegal sexuality against children, but it does not change a paedophile's internal sexual orientation. Treating paedophilia provides a more human

and lasting solution than incarceration and may at least be used concomitantly.

Aetiology

Sexual arousal is dependent on neural, hormonal, genetic factors and on the complex influence of culture and context. The aetiology of paraphilias is still unclear despite years of research. Various psychological, developmental, environmental, genetic, and organic factors have been discussed, but none of the theories fully explains paraphiliac behaviours. The causes are probably multifactorial, rendering treatment difficult.

The frequency reported for paedophiles who were abused as children range from 28 to 93% vs. 15% for controls (for review about social factors, see Hall and Hall 2007).

We will focus on the major biological determinants of paraphiliac behaviours:

Testosterone, the main androgen produced by the testes, plays clearly a major role, not only in the development and maintenance of the male sexual characteristics, but also in the regulation of sexuality, aggression, cognition, emotion, and personality (Rubinow and Schmidt 1996). In particular, it is a major determinant of sexual desire, fantasies and behaviour, and basically it controls the frequency, duration and magnitude of spontaneous erections. The effects of testosterone (and of its reduced metabolite 5α-dihydrotestosterone (DHT)) are mediated through their actions on the intracellular androgen receptor. Testosterone secretion is regulated by a feedback mechanism in the hypothalamo-pituitary-testis axis. The hypothalamus produces the gonadotrophin hormone-releasing hormone (GnRH), which is released in a pulsatile manner and stimulates the anterior pituitary gland to produce the luteinizing hormone (LH). LH stimulates the release of testosterone from the testes, which in turn inhibits the hypothalamus and the pituitary. Testosterone has been shown to restore nocturnal penile tumescence responses in hypogonadal adult man with impaired nocturnal penile tumescence. A minimal level of testosterone is necessary for sexual drive in males; however, the threshold remains questionable. Testosterone levels do not correlate with the intensity of sexual drive. Although rigidity and tumescence seem androgen-dependent, erections in response to visual erotic stimuli are not dependent on androgens, but erections in response to auditory stimuli possibly are (Carani et al. 1992). Whether, or to what extent, erections as a result of fantasies and tactile stimulation are androgen-dependent remains controversial (Meston and Frohlich, 2000).

There is no clear evidence that subjects with paraphilias have higher basic testosterone levels, nor data indicating an increased androgen receptor activity. In paraphiliacs, no difference in self-reported measures of sexual behaviour was reported with regards to baseline serum testosterone levels (below or above 300 ng/dl) (Kravitz et al. 1996). A marked hypersecretion of LH was reported in response to GnRH in paedophiles, as compared to controls and other paraphiliacs, whereas baseline LH and testosterone values were within the normal range. These data may indicate a hypothalamo-pituitary-gonadal dysfunction in paedophiles (Gaffney and Berlin, 1984). The expected benefit of suppressing testosterone to castration level probably derived from decreasing sexual arousal in general.

Serotonin and dopamine affect to a lesser extent sexual behaviour, as shown in animal and human studies (Bradford 1999, 2001; Kafka 2003). Enhancing central serotonin activity in the hypothalamus may inhibit sexual behaviour in some mammalian species (Lorrain et al. 1999). Low 5-hydroxyindole acetic acid concentrations in the cerebrospinal fluid are associated with severe aggression, which results from impaired impulse control in juvenile male primates while testosterone is more associated with competitive aggression (Dee Higley et al. 1996). Selective serotonin reuptake inhibitors (SSRIs) are associated in humans with sexual side effects (e.g., decreased libido, impaired orgasm and ejaculation). Activation of the $5HT_2$ receptors may impair sexual functioning and stimulation of the $5HT_{1A}$ receptors may facilitate sexual functioning (Meston and Frohlich 2000).

Paedophilia was accompagnied by increased plasma concentrations of catecholamines in one study (Maes et al. 2001). Nine paedophiles had a greater magnitude of cortisone and prolactin level responses to metachlorophenylpiperazine (a serotonine agonist) vs. controls. It may indicate a serotoninergic disturbance in paedophilia.

Oestrogens have little direct influence on sexual desire in either males or females (Meston and Frohlich 2000).

Specific brain regions are involved in sexual behaviour. In animals, lesions to the medial preoptic area, which is connected to the limbic system and brainstem, significantly impair the male copulatory behaviour (Meisell and Sachs 1994) by impairing the ability to recognize a sexual partner (McKenna 1999). Electrical stimulation of the paraventricular nucleus elicits penile erections (Chen et al. 1997).

Paraphilias or at least conditions that look very much like paraphilias, have also been reported as the result of brain trauma especially during childhood (Lehne 1984; Simpson et al. 1999; Langevin 2006), temporal or frontal lobe damage (Hucker et al. 1986; Langevin et al. 1989; Mendez et al. 2000) Kluver-Bucy syndrome or epilepsy (Hill et al. 1957; Mitchell et al. 1954), especially in men.

Recently, the brain areas activated in eight adult healthy males during visually evoked sexual arousal were evidenced using positron emission tomography (Stoléru et al. 1999). There were visual association areas (inferior temporal cortex, bilateral) and paralimbic areas related to highly processed sensory information with motivational states and to the control of autonomic and endocrine functions (right insula, right inferior frontal cortex, left anterior cingulated cortex). Activation of some of these areas was positively correlated with plasma testosterone levels. However, the link between neuronal activity and deviant sexual behaviour remains unclear.

The temporal lobe is involved in erotic discrimination and arousal threshold and deserves special attention in paedophilia. Cohen et al. (2002) reported decreased glucose metabolism in the right inferior temporal cortex and the superior ventral frontal gyrus of seven heterosexual non-exclusive, non-incest paedophiles vs. seven controls. Cantor et al. (2008) have reported in the left and right temporal and parietal brain regions a decreased white matter volume in 44 male pedophiles as compared with 53 subjects convicted for non-sexual crimes. Schiltz et al. (2007) have observed a decreased right amygdala volume in 13 male paedophiles (heterosexual in six cases, homosexual in three cases and bisexual in four cases) as compared with 15 controls (without any paedophilia). This abnormality could appear early in life in relation with environmental or hormonal factors and could later be associated with changes in sexual interest. The amygdala could be involved in sexual behaviour in relationship with past sexual experiences. Some of the changes may have resulted from life experiences such as being physically or sexually abused as children.

Schiffer et al. (2007) using MRI in 18 paedophiles (nine homosexual and nine heterosexual) vs. 24 controls (12 homosexual and 12 heterosexual) found decreased gray matter volume bilaterally in the ventral striatum, insula, orbitofrontalcortex and cerebellum of the paedophiles.

Prevalence of paraphiliac behaviour

Actual prevalence/incidence figures are not available for paraphilias.

Criminal reports. Few paedophiles ask for treatment before sex offending. The prevalence is usually estimated through criminal reports. In France, 22% of the prisoners are sex offenders. In the UK prisons, about 11% of the population had committed sexual offences in 1998; in the United States, juveniles account for 17% of individuals arrested for sex offences (Home Office Recording crime statistics 1998–2001, Report UK Government, London, 1997). Rape and indecent sexual assault on a female constitute by far the majority of sex offences notified to the UK recording crime statistics in 1998. However, the prevalence of sexual offences reported against children is increasing. Of men born in England and Wales in 1953, seven in 1000 had a conviction for a sexual offence against a child by the age of 40 years (Marshall 1997).

Prevalence of paraphiliac fantasies in the general population. In a population of 193 students, Briere and Runtz (1989) have reported 21% of subjects having paedophilic fantasies. According to Pithers (1995), 15–20% of their population of male students and 2% of females would like to have a sexual relationship with a child if that would be allowed, 40% of males reported sexual fantasies of women' rapes.

Prevalence of sex offences reported by the general population. Many sexual assaults are unreported. The major methodological biases are the definition of sex offending, the victims' ages, the choice of the sample and the type of interview (self questionaire, face to face interview, phone interview, number and type of questions), the response rate (Goldman et al. 2000). In a survey of students, when using the definition of sexual abuse as "any event that the young person reported as unwanted or abusive before they were 18 years old", 59% of women and 27% of men answered positively. When the definition was narrowed to "those cases involving some form of penetration or coerced masturbation where the abuser was at least 5 years older", the percentage felt to 4% of women and 2% of men (Creighton 2002). In France, 11% of women aged 18–39 reported unwanted sexual relationship (Bajos 2008). In a review, Hall and Hall (2007) found that 17–31% of women and 7–16% of males declared unwanted sexual relationship before the age of 18.

The National Society for the Prevention of Cruelty to Children reported, in the year 2000, that 16% of girls and 7% of boys had been sexually assaulted before the age of 13. The incidence of children aged below 18 placed on child protection registers for sexual abuse was six in 10,000 in the year 2000. The mean number of victims for one paedophilic was estimated around 20 children.

Sexual offence is noteworthy underestimated, either because offenders have never been apprehended or the offence did not result in conviction (Elliot et al. 1995; Harris and Grace 1999). For example, men convicted of sexual offences against children claim five or more undetected sexual assaults for which they have never been apprehended (Elliot et al. 1995). In a study of 360 reported rape cases, only about 10% resulted in conviction (Harris and Grace 1999).

The consequences of sexual offences clearly depend on the type of sexual offence. In the case of raped paedophilia, the consequences to the victim are serious and the effects apparent many years after the initial event (Banyard et al. 2001; Leonard and Follette 2002).

Recidivism rate. Recidivism is a major concern, in the treatment of paraphilia, especially in paedophilia. Most people recognize that incarceration alone will not solve sexual violence. Treating the offenders is critical in an approach to preventing sexual violence and reducing victimization.

The definition of the term recidivism needs to be clarified. According to Greenberg (1998) and Prentky et al. (1997) different definitions may include sexual offences, non-sexual offences or both, convictions or self-reported offenses. Comparison between studies is difficult due to methodological differences: duration of follow-up, type of paraphilias, definition of recidivism, type of victims, previous offences and or previous convictions, retrospective or prospective design, outpatients or prisoners, type of treatment and compliance, drop-out rate, period of active treatment only or short periods after treatment is terminated in addition in some studies, statistical analyses, etc. It remains difficult to identify those individuals at risk of relapse.

The mean estimate re-conviction rate for sexual offences is 13% (lower with incest offenders 4%, as compared with boy victim paedophiles 21%) (Hanson and Bussiere 1998) and it has been found to double (from 11 to 22%) after 5 years in untreated offenders (Morrison et al. 1994). Soothill and Gibbens (1978) found that in sex offenders, the recidivism rate rose by about 3% per year, and at the end of the follow-up period (22 years), 48% had recidivated. Current estimates from the prison service suggest that 15% of child abusers leaving prison are reconvicted for a further sexual offence within 2 years (Beech et al. 2002). Treated offenders had less reconviction than non treated offenders, both at 2-year (5.5 and 12.5%, respectively) and at 4-year follow-up (25 and 64%, respectively) (Marshall and Barbaree 1990).

Three recent meataanalyses have reported rates of recidivism and risk factors (Hanson et al. 2003; Hanson and Morton-Bourgon 2005; Craig et al. 2008). The recidivism rate increased from 15% at 5 years to 27% at 20 years of follow-up. Paedophiles attracted to boys are more likely to reoffend (35% at 15 years) as compared to those attracted to girls (16% at 15 years) and to those who offended within their family (13% at 5 years) (Harris and Hanson 2004, 4700 sex offenders).

Some dynamic risk factors were identified such as psychopathy and antisocial behaviour. Denial, low self estim, addictive disorders (mostly alcoholism or drug abuse) and psychiatric comorbid disorders may also increase the risk of recidivism. Dynamic risks may be addressed and psychotherapeutic treatments may help to improve these factors.

The following risk factors need precise evaluation of sexual offenders in order to identify them but unfortunately they cannot be improved: previous sexual offences (especially rapes) or non-sexual offences (especially those with violence) increase the risk of recidivism (Hall and Hall 2007). Sex offenders with intellectual disabilities or sequels of head injury are particularly susceptible to re-offend after stopping therapy. The strongest predictor of sexual re-offence was sexual interest in children as measured by phlethysmography (especially when victims are unknown). An early age of onset is also associated with an increased risk (Barbaree et al. 2003). A past history of sexual abuse or physical violence during childhood may increase the risk (Hanson and Bussiere 1998). Finally, a great number of paraphilic interests reported by the offender increase the likelihood of reoffense (Hall and Hall 2007).

Some scales have been proposed in order to improve the evaluation of the risk of recidivism in sex offenders but until now, none is really predictive of any risk (for review Seifert et al. 2005; Hall and Hall 2007).

Evaluation of a paraphiliac

Demographic and clinical characteristics.

demographic characteristics of the subject: age, gender, current and past marital status, number of children (age and gender if any), current and past employment status (with or without children), education level;

conventional and paraphiliac sexual fantasies and activity (frequency and type), exclusive or non exclusive paraphiliac behaviour, age at onset of paraphiliac behaviour, type and number of paraphilia, gender and age of victims, intra familial or not (known or unknown victim), internet use or video use, violence, previous convictions for sexual or non-sexual offences, family and personal history of sexual disorders, previous treatments

for sexual offending and compliance, alcohol or illicit drug consumption before paraphiliac sexual behaviour, age of puberty, …;

family and personal history of psychiatric disorders, suicide attempts, history of brain trauma, current dementia, previous or current psychiatric or non psychiatric diseases and treatment, previous history of sexual abuse or use of violence, …;

empathy, coping with stress, impulsivity, interpersonal relationships, insight, motivation for treatment, cognitive distorsions, denial, degree of mental retardation if any….

Diagnosis of paraphilia. Number and type of paraphilias; comorbidity with axis 1 or axis 2 of the DSM classification (especially addictive disorders or personality disorders); comorbidity with somatic diseases if any; cognitive evaluation if mental retardation or dementia; careful medical examination, blood measurements and/or plasma hormone levels if hormonal treatment is needed. Baseline osteodensitometry could be necessary in case of hormonal treatment.

Therapeutic approaches

Treatment modalities currently used in paraphiliacs behaviours fall into three categories: bilateral orchidectomy (surgical castration, for review see Heim and Hursch 1979), psychotherapy, and pharmacotherapy. Stereotaxic neurosurgery and oestrogen administration have been attempted but are not any more in use, due to the high risks displayed (respectively, those inherent to the invasive technique, and serious side effects or complications such as breast carcinoma). Pharmacotherapy and hormonal treatment should be part of a comprehensive treatment including psychotherapy and, in most cases, behavioural therapy.

Methods and limitations

Methods. These guidelines are intended for use in clinical practice by clinicians who diagnose and treat patients with paraphilia. The aim of these guidelines is to improve the quality of care and to aid physicians in clinical decisions. Although these guidelines are based on the available published evidence, the treating clinician is ultimately responsible for the assessment and the choice of treatment options, based on knowledge of the individual patient. These guidelines do not establish a standard of care nor do they ensure a favourable clinical outcome if followed. The primary aim of the guidelines is to evaluate the role of pharmacological agents in the treatment and management of paraphilia, with a focus on the treatment of adults males. Because such treatments are not delivered in isolation, the role of specific psychosocial and psychotherapeutic interventions is also briefly covered.

The aim of these guidelines is to bring together different views on the appropriate treatment of paraphilias from experts representing all continents. To achieve this aim, an extensive literature search was conducted using the English-language literature indexed on MEDLINE/PubMed (1990–2009 for SSRIs) (1969–2009 for antiandrogen treatments), supplemented by other sources, including published reviews. The guidelines presented here are based on data from publications in peer-reviewed journals (according to previous WFSBP guidelines, Soyka et al. 2008). The evidence from the literature research was summarized and categorized to reflect its susceptibility to bias (Shekelle 1999). Each treatment recommendation was evaluated and discussed with respect to the strength of evidence for its efficacy, safety, tolerability and feasibility. It must be kept in mind that the strength of recommendation is due to the level of efficacy and not necessarily of its importance. Four categories were used to determine the hierarchy of recommendations (related to the described level of evidence):

Level A: there is good research-based evidence to support this recommendation. The evidence was obtained from at least three moderately large, positive, randomised, controlled, double-blind trials (RCTs). In addition, at least one of the three studies must be a well-conducted, placebo-controlled study.

Level B: there is fair research-based evidence to support this recommendation. The evidence was obtained from at least two moderately large, positive, randomised, double-blind trials (this can be either two or more comparator studies or one comparator-controlled and one placebo-controlled study) or from one moderately large, positive, randomised, double-blind study (comparator-controlled or placebo-controlled) and at least one prospective, moderately large (sample size equal to or greater than 50 participants), open-label, naturalistic study.

Level C: there is minimal research-based evidence to support this recommendation. The evidence was obtained from at least one randomised, double-blind study with a comparator treatment and one prospective, open-label study/case series (with a sample of at least 10 participants), or at least two prospective, open-label studies/case series (with a sample of at least 10 participants) showing efficacy.

Level D: evidence was obtained from expert opinions (from authors and members of the WFSBP Task Force) supported by at least one prospective, open-label study/case series (with a sample of at least 10 participants).

No level of evidence or Good Clinical Practice (GCP): This category includes expert opinion-based statements for general treatment procedures and principles. The guidelines were developed by the authors and arrived at by consensus with the WFSBP Task Force, consisting of international experts in the field.

Limitations. Most reports on the treatments of paraphilias are case reports or series. In general, treatment efficacy studies are marked by some methodological biases and are being extremely difficult to conduct for several reasons: small sample sizes leading to false negative results; difficulties to conduct studies with forensic patients; sex offending is not socially acceptable and those who suffer from them rarely seek treatment voluntarily (many studies obtained their paedophilic or sexual offender populations from prisons or legally mandated sexual treatment groups; paedophiles able to control their impulses are usually not included in studies. This sampling introduces the possibility that the findings of lower IQ and personality disorders are more characteristic of paedophiles who were arrested); ethical considerations would not allow performing double-blind placebo-controlled studies in potential offenders (for review Marshall and Marshall 2007); the outcome measurements such as self reports of conventional and paraphiliac sexual activity, plasma testosterone levels which may not be reliable indicators of treatment response, etc.

Comparisons between studies is often difficult due to methodological differences: duration of follow-up, type of paraphilias, definition of recidivism, type of victims, previous offences and or previous convictions, retrospective or prospective design, outpatients or prisoners, type of treatment and compliance, statistical analyses, etc.

In addition, specific problems occur when randomisation is adapted to psychological treatments (Guay 2009). The therapist can have a significant impact on therapeutic outcomes if, he or she, can adapt treatment to the learning style and interpersonal approach of each subject and ajust therapy to the fluctuations in the subject's motivation and mood. Controlled study design do not allow many of the features of an effective therapist–subject relationship.

Bilateral orchidectomy

In Europe, surgical castration was done on modern psychiatric indication for the first time in Switzerland in 1892, as an "imbecile" was cured from his neuralgic pain from the testes and his hypersexuality.

In Europe, estimated recidivism rates based on re-arrest or conviction were 2.5–7.5% in surgically castrated sex offenders versus 60–84% before castration (n=1200) with a maximal follow-up of 20 years (Heim and Hursch 1979). There was no change in the object of the sexual desire or sexual orientation. The effect on non-sexual crimes was less obvious. Forty to 50% of subjects were satisfied with the outcome of castration, whereas 20–30% felt often depressed following castration. Thirty-five percent of young surgical castrates retained sexual functioning (sex drive and potency) (Heim and Hursch 1979) and 19 out of 38 castrated sex offenders, whose penile erections were measured while viewing a sex movie, exhibited full erections (Eibl 1978). In a prospective study (follow-up 15 years), Zverina et al. (1991) reported that 18% of 84 castrated sex offenders retained sexual functioning and that 21% were able to maintain sexual relationships with their sexual partner. A recent review of studies of castrated sex offenders reported a very low level of recidivism (a Danish study including 900 sex offenders reported a risk of 1%) (Weinberger et al. 2005). Stepan et al. (1989) reported an increased risk of bone demineralization in these castrated subjects.

In several states in the USA, and in some European countries, surgical castration is still allowed. In some countries (e.g., Germany) the "Law on Voluntary Castration" provided that voluntary castration could be available to men aged at least 25, when they are seriously disturbed and potentially dangerous. A board of experts reviews the request in order to establish if castration is necessary for the prevention of further sexual offences. California passed a law in 1996 that mandated chemical castration for repeat child molesters. Several other states have considered passing such laws (e.g., California, Florida, Louisiana, Iowa, Colorado, Massachusetts, Michigan, Texas, Washington, etc.).

Although it has been shown that surgical castration reduces paraphiliac fantasies and behaviours (*Level D of evidence*), there are alternative and less invasive treatments available. Surgical castration has now been abandoned in most European countries. It is worthwhile to mention, however, that post-castration recidivism rates are among the lowest rates among all forms of treatments. However, some physically castrated paedophiles have restored their potency by

taking exogenous testosterone and then abused again (Stone et al. 2000).

The main effect of surgical castration is a reduction of the circulating androgen level by removing the testes where approximately 95% of the testosterone is produced. Current knowledge about hormonal treatment arises from surgical castration of sex offenders.

Psychotherapy and behaviour therapy

This treatment approach is beyond the scope of this study.

Psychotherapy is an important aspect of treatment, although debate exists concerning its overall effectiveness for long term prevention of new offenses. Several studies have reported that the best outcomes in preventing repeat offenses against children occur when pharmacological agents and psychotherapy are used together (Mc Conaghy 1998; Hanson and Morton Bourgon 2005).

Psychotherapy can be divided into individual and group/family therapies. Most commonly it is a combination of individual and group therapies.

Individual therapy is represented by insight-oriented, cognitive behavioural and supportive psychotherapies. There could be as many definitions of psychodynamic or psychoanalytic therapy as they are studies.

In a recent review about psychological interventions in sex offenders, Brooks-Gordon et al. (2006) evaluated adults who have been convicted or cautioned for sexual offences or who sought treatment or were considered to be at risk of sexual offending. They gave interesting definitions of psychotherapies used in sex offender populations. They suggested that "well-defined" cognitive behavioural therapy occured when the report made explicit that the intervention involved: (1) recipients establishing links between their thoughts, feelings and actions with respect to target symptoms; (2) correction of person's misperceptions, irrational beliefs and reasoning biases related to target symptoms and (3) either or both of the following: recipients monitoring their own thoughts, feelings and behaviours with respect to target symptoms and/or promotion of alternative ways of coping with target symptoms. Psychoanalysis was defined as regular individual sessions with a trained psychoanalyst. Analysts were required to adhere to a strict definition of psychoanalytic technique. Psychodynamic psychotherapy was defined as regular individual therapy sessions with a trained psychotherapist or a therapist under supervision. Therapy sessions were based on a psychodynamic or psychoanalytic model. Sessions could rely on a variety of strategies, including explorative insight-oriented, supportive or directive activity applied flexibly. Therapists should have used a less strict technique than in psychoanalysis.

The general strategy toward psychotherapy with paedophiles is a cognitive behavioural approach (addressing their cognitive distorsions) combined with empathy training, sexual impulse control training, relapse prevention and biofeedback (Hall and Hall 2007). In almost all published studies, cognitive behavioural therapy was used. Sex offenders employ distorted patterns of thinking which allow them to rationalize their behaviour, including beliefs such as children can consent to sex with an adult and/or victims are responsible for being sexually assaulted. Behavioural therapy programs for sex offenders seek to tackle and change these distorted attitudes as well as other major factors which can contribute to sexual offending, including inability to control anger, inability to express feelings and communicate effectively, problems in managing stress, alcohol and drug abuse, or deviant sexual arousal. In North America, cognitive-behavioural therapy is the standard treatment for paraphiliacs who are not at high risk of victimization (Marshall et al. 2005).

Research studies in the USA into different treatment programs in prisons and in the community have identified reductions in re-offence rates (Grossmann et al. 1999) or no statistically significant difference (Marques et al. 2005). Hall (1995) in an overview reported a small but significant overall reduction of recidivism rate in treated subjects vs. comparison groups (12 controlled studies), comprehensive cognitive-behavioural and hormonal treatments were superior to purely behavioural treatment. The average rate of sexual recidivism was 19% in treated groups vs. 27% in controls (mean effect size: d=–0.24). The strongest effect came from comparisons between treatment completers and dropouts. When the dropout studies were removed, the treatment effect was no longer significant. Alexander (1999) reviewed 79 studies on psychosocial sex offender treatment. The mean difference in recidivism was 5% in favour of treatment (d=0.12). However, the majority of studies contained no control group. In the same way, Gallagher et al. (1999), considered 23 comparison-group studies examining psychological treatments. Treated groups showed 10% less sexual recidivism than controls and the overall effect size was large (d=0.47) with a significant treatment effect for cognitive-behavioural treatments.

In a comprehensive metaanalysis of different treatment programs (Hanson et al. 2002) (cognitive-behavioural n=29, behavioural n=2, systemic n=3, other psychotherapeutic n=7, unknown category

$n=2$ vs. no treatment) (43 studies, 23 in institutions, 17 in the community and three in both, 5000 treated sex offenders vs. 4300 not treated), the sexual offence recidivism rate was 12.3% in treated sex offenders as compared with 16.8% in the no-treatment group during an average 46-month follow-up period using a variety of recidivism criteria (OR: 0.81; 95% CI: 0.71–0.94 with considerable variability across studies; mean effect size $d=0.13$). These treatments were equally effective for adults and adolescents (three studies, 237 subjects) and for institutional and community treatments. Cognitive behavioural and systemic treatments were associated with reductions in sexual recidivism (from 17.4 to 9.9%). Older forms of treatment (prior to 1980) appeared to have little effect.

Kenworthy et al. (2004) published a recent Cochrane metaanalysis of nine randomised controlled trials (RCT) (500 adult sex offenders of whom 52% were paedophiles, maximal duration of follow-up of 10 years). Psychodynamic, psychoanalytic, behavioural or cognitive–behavioural therapies were compared with each other, drug treatment or standard care in institutional or community settings. Among all studies, the most interesting were the two following studies: (1) cognitive-behavioural group therapy (Marques et al. 1994) may reduce re-offence at 1 year for child molesters when compared with no treatment ($n=155$, 1 RCT, relative risk (RR) any crime: 0.41, 95% CI: 0.2–0.82, number needed to treat (NNT): 6, 95% CI: 3–20); (2) the largest trial (Romero 1978, in Romero and Williams 1983) compared broadly psychodynamic group therapy with no group therapy in 231 paedophiles, exhibitionists or guilty for sexual assaults. Re-arrest over 10 years was greater, but not significantly, for those allocated to group therapy ($n=231$, 1 RCT, RR 1.87 95% CI: 0.78–4.47). In summary, this Cochrane analysis concluded that the effects in clinical trials have been extremely variable (from helpful to harmful even in the same study): one study suggested that a cognitive approach resulted in a decline in re-offending after 1 year; another large study showed no benefit for group psychotherapy and suggested the potential for harm at 10 years.

Losel and Schmucker (2005), in a recent metaanalysis of 69 studies containing 80 independent comparison studies (more than 22,000 individuals in total), reported the efficacy of psychotherapy or pharmacological treatment on the recidivism risk in sex offenders (primary outcome) as compared with no treatment. Nearly one-half of the comparisons addressed cognitive-behavioural programs and one-third of the studies have been published since 2000. The 74 studies reporting data on sexual recidivism revealed an average recidivism rate of 11.1% for treated groups and 17.5% for comparison groups. However, when they calculated the recidivism rates for treated and comparison subjects, taking into account the respective sizes of treatment and comparison groups, the difference in recidivism rates disappeared completely (11% in each group). The effects measured using odds ratios (OR) ranged from 0.17 to 33.33. The mean OR for sexual recidivism was highly significant (all kinds of treatment) (OR: 1.70, 95% CI: 1.35–2.13; equivalent $d=0.29$) with a absolute difference between treatment and comparison groups of 6.4% (37% reduction from the baseline rate of comparison groups). There was considerable heterogeneity. For violent recidivism, the mean OR was 1.90 with a absolute difference between treatment and comparison groups of 5.2% (44% reduction from the baseline rate of comparison groups). Physical treatment (surgical castration) had higher effects than non-physical treatment (psychosocial) (OR: 7.37, 95% CI: 4.14–13.11 vs.OR: 1.32, 95% CI: 1.07–1.62). Of non-physical treatment, only cognitive-behavioural treatments and classic behaviour therapy had a significant impact on sexual recidivism. When only behavioural therapies were considered (35 studies) the OR was 1.45, 95% CI: 1.12–1.86).Whether the treatment was delivered in an individual or group format did not result in significant outcome differences. The effect size for cognitive-behavioural treatment is slightly smaller than that reported by Hanson et al. (2002) (OR=1.45 vs. 1.67, respectively). The other approaches (insight-oriented treatment, therapeutic communities, other psychosocial programs) did not significantly influence recidivism.

In summary, the efficacy of cognitive behavioural therapy for sex offenders is such as to indicate a modest reduction in recidivism (Losel and Schmucker 2005), but this is doubted by studies with longer follow-up periods (Maletzki and Steinhauser 2002; Kentworthy et al. 2004) *(Level C of evidence)*. The other approaches (insight-oriented treatment, therapeutic communities, other psychosocial programs) do not seem to reduce recidivism *(No level of evidence)*. Moreover, the longer the observation periods, the higher the recidivism rates, leaving the impression that the durability of psychological therapies is limited. Furthermore, most of these studies were not conducted with the most dangerous sex offenders which means that they cannot be generalized to all sex offenders. Well conducted studies, randomised controlled trials with longer follow-up durations are needed.

Pharmacotherapy with psychotropic drugs

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

Psychotropic drugs. The use of psychotropic medications in paraphiliac behaviours is not new. No randomized controlled trials have documented their efficacy. Unfortunately, the level of evidence is very poor (case reports, small sample size, lack of power, lack of controlled studies) *(No level of evidence)*.

Lithium carbonate (Ward 1975; Cesnik and Coleman 1989; Balon 2000; Zourkova 2000) (no controlled studies were conducted); tricyclic antidepressants (clomipramine, desimipramine) (for review, Krueger and Kaplan 2000), mirtazapine (Coskun and Mukaddes 2008); antipsychotics (benperidol, thioridazine, haloperidol, risperidone (Tennent et al. 1974; Zbytovsky 1993; Bourgeois and Klein 1996 (fluoxetine plus risperidone 6 mg/day); Zourkova 2000, 2002; for review, Hall and Hall 2007; Hughes 2007)); and anticonvulsivants (carbamazepine, topiramate, divalproate) (Nelson et al. 2001; Varela and Black 2002) have been sporadically used over the years.

No clear efficacy was observed using lithium or anticonvulsivants when no bipolar disorder was associated with paraphilia. However, Bartova et al. (1978) evaluated lithium therapy in 11 patients treated with 900 mg/day for 5 months. Deviant sexual tendencies disappeared in six patients. Nausea occured in two cases. No prospective trials have documented topiramate effectiveness in paedophilia but several case reports have described topiramate's effectiveness in reducing unwanted sexual behaviours (prostitutes, compulsive viewers of pornography, compulsive masturbation (dose range 50–200 mg, 2–6 weeks are required before efficacy) (Fong et al. 2005; Khazaal and Zullino 2006; Shiah et al. 2006).

Concerning the use of antipsychotics, in a placebo-controlled cross-over study (18 weeks), chlorpromazine 125 mg/day, benperidol 1.25 mg/day and placebo were compared in 12 paedophiles in a security hospital (Murray et al. 1975). There were no statistically significant differences in most comparisons. Extrapyramidal side effects were frequently observed with benperidol. In spite of rare cases of sex offences related to delusions in schizophrenic patients, no clear efficacy was reported with the use of antipsychotics in paraphilia. Ten patients (Bartova et al. 1978) were receiving fluphenazine decanoate (12.5–25 mg every 2–3 weeks i.m. for 3–4 months). Deviant sexual tendencies disappeared in five cases and were reduced in four cases. Extrapyramidal symptoms and orthostasis occurred in eight patients.

Concerning tricyclic antidepressants, methodological biases are observed, most of the studies are case reports and few research-based evidence was reported. Interestingly, a double-blind crossover study showed that clomipramine and desipramine as compared with placebo reduced equally paraphiliac behaviour in eight subjects (from 50 to 70% as compared to baseline scores) (seven out of 15 dropped out of the study) (Kruesi et al. 1992: 15 subjects with paraphilias (paedophilia, two; phone sex, seven; exhibitionism, four; sexual sadism, one) and/or compulsive masturbation (four), mean age 31 years, treatment periods of 5 weeks, mean dose clomipramine: 163 mg/day (75–250), mean dose desipramine: 213 mg/day (100–250)). There was no preferential response to the more specific serotoninergic antidepressant. In two cases, treatment was restarted after paraphilic relapse. However, the side effects observed with clomipramine have limited its use in paraphilias (Leo and Kim 1995).

An open study reported the efficacy of naltrexone (100–200 mg/day for at least 2 months) in 15 out of 21 juvenile males with sexual hyperactivity and compulsive masturbation (Ryback 2004) (reduction in time spent in sexual fantasies and masturbation). Increasing dosage to $\geq$200 mg/day did not increase efficacy in poor or non-responders. Five out of six non-responders benefited from leuprolide therapy. Relapse occured in the 13 patients in whom naltrexone was decreased below 50 mg/day.

Serotoninergic selective reuptake inhibitors (SSRIs). The rationale for the use of serotoninergic antidepressants in sexual offenders is based on several lines of evidence:

- The first piece of evidence comes from advances in research on the role of serotonin and specific subtypes of 5HT brain receptors on sexual behaviours. Animal models showed that decreased 5HT levels increased sexual appetitive behaviours while enhanced central 5HT activity reduced them. Increased levels of serotonin in the hypothalamus inhibited sexual motivation and the testosterone signal while increased levels of serotonin in the prefrontal cortex enhanced emotional resilience and impulse control. In paedophilia, decreased activity of the 5HT presynaptic neurons and up regulation of postsynaptic $5HT_{2A}$ receptors had been reported.
- Another line of support comes from the clinical observation of the similarities of paraphiliac fantasies, urges and behaviours with obsessive/compulsive and Tourette symptoms. Similar brain abnormalities in corticostriatal circuits have been documented. As SSRIs have been proved to be efficacious in the treatment of OCD, it seems logical to use them in paraphiliacs and hypersexual subjects.
- Relationships have been found between 5HT dysregulation and specific dimensions of

psychopathology: antisocial impulsivity, anxiety, depression and hypersexuality (Kafka and Coleman 1991; Beech and Mitchell 2005). SSRIs use has shown to decrease impulsivity.

- Important Axis I and Axis 2 comorbidities have been reported in juvenile and adult paraphiliacs and hypersexual subjects: mood and/or anxiety disorders; conduct and impulse control disorders; ADHD; substance and alcohol abuse; borderline, avoidant, schizoid and antisocial personality disorders. It is recommended that this comorbid disorders should be treated as well.
- Increased knowledge about secondary effects of SSRIs on sexual behaviour suggested the opportunity of using these side effects for treatment of sexual deviance. Indeed, a medication that enhances central serotoninergic transmission has been found to reduce fantasies and paraphiliac behaviour (Jacobsen 1992). Abusive subjects also report high feelings of loneliness, fear of intimacy and isolation. SSRIs can increase affiliative behaviours secondary to increase of vasopressin and oxytocin, and thus produce additional beneficial effect.
- Lastly, chronic administration of SSRIs increases the level of BDNF, which has neuroprotective effects on hippocampal, striatal and mesencephalic dopaminergic neurons. This results in increased neuronal plasticity and consequently in an increased capacity for changing behaviour. In conjunction with cognitive-behaviour therapy, or schema based interventions that address enduring personality characteristics and deficits arising from childhood problems such as abuse, SSRIs may increase the impact of such therapies.

Thus, raising synaptic 5HT levels by SSRIs would have a range of beneficial effects on the brain of sexual offenders (Bradford 1996; Saleh 2004).

Research evidence on the efficacy of antidepressants for treatment of sexual offenders has been reported.

In the past decade, numerous case reports have described the efficacy of SSRIs or clomipramine in the treatment of paraphilias, as well as non-paraphiliac hypersexuality (Gijs and Gooren 1996; Bradford and Greenberg 1996; Balon 1998). Interestingly, a double-blind crossover study showed that clomipramine and desipramine reduced equally paraphiliac behaviour in eight subjects (seven of 15 dropped out) (Kruesi et al. 1992). There was no preferential response to the more specific serotoninergic antidepressant. The efficacy of paroxetine in one case and clomipramine side effects limited clomipramine use (Leo and Kim 1995; Stewart and Shin 1997).

A bibliographic search of the English-language-literature indexed on MEDLINE/PubMed was conducted (from year 1990-to year 2009). The following search terms were used: antidepressants, sex offenders. Additional publications were identified through internet. Papers were analyzed critically, to assess current state of research on this topic.

Two meta-analysis on the effectiveness of all kinds of treatments for sexual abusers including only controlled randomized studies stated that no controlled randomized studies have been published on antidepressants (White et al. 2000, Cochrane Library; Losel and Schmuker 2005, Campbell Collaboration Group).

Comissioned by the Health Technology Assessment Program at Birmingham University, UK, Adi et al. (2002) conducted a systematic review of the currently available evidence on effectiveness of the use of SSRIs for the treatment of sex offenders. The search was conducted up to 2001, and included qualitative analysis of cohort and case studies, using Cochrane's criteria for assessment of bias risk. One hundred and thirty studies were found, but only nine studies were finally considered acceptable for the metaanalysis: Perilstein et al. 1991; Stein et al. 1992; Kafka and Prentky 1992b; Kafka, 1994; Coleman et al. 1992; Bradford et al. 1995; Fedoroff 1995; Greenberg et al. 1996; Kafka and Hennen 2000). Altogether, these studies included a total number of 225 patients (3–58). All of them were case series, reporting pre-post psychometric comparisons within subjects in a short time. Only one study had more than 1 year follow-up, only one was prospective and none of them included measures of recidivism reduction. The research group considered that all of the studies were vulnerable to bias, which may have affected their validity. The main one was the lack of control groups. The scales used in assessing the outcomes were subjective. The length of follow-up was insufficient to assess major long-term consequences on re-offence. In many studies, heterogeneous groups of paraphiliacs were included. Exhibitionism, compulsive masturbation and paedophilia were the most frequent paraphilias in which SSRIs showed improvement. In most cases, other psychiatric diagnoses were associated to paraphilias (mostly affective disorders or OCDs).

In spite of these methodological limitations, the results are promising. Eight studies showed some significant reduction from baseline in the frequency of masturbation and in the intensity of deviant fantasies; depression, anxiety, sexual activity, penile tumescence and general adaptation in paraphiliac and sexually compulsive patients were also decreased. One study conducted by Stein et al. in 1992 showed only efficacy in compulsive patients. The researchers concluded that there is preliminary evidence of

potential value of SSRIs in treatment for sexual abusers. Their recommendation for future studies was to include control groups receiving only psychotherapy, only medication, combined treatments and placebo. Their economic analysis showed potential for cost-effectiveness, as they stated that additional cost would only include drugs cost.

A review of the studies showed effectiveness of different antidepressants in sexual abusers: fluoxetine (Bianchi 1990; Kafka 1991, Kafka and Prentky 1992b; Lorefice 1991; Perilstein et al. 1991; Bradford and Gratzer 1995; Emmanuel et al. 1991); sertraline (Kafka 1994; Bradford et al. 1995); clomipramine (Kruesi et al. 1992; Ruby et al. 1993); fluvoxamine (Zohar et al. 1994; Greenberg et al. 1996); paroxetine (Abouesh and Clayton 1999) and nefazodone (Coleman et al. 2000, retrospective study, 14 males with non paraphilic sexual compulsions). Kafka and Prentky (1992b) reported that fluoxetine (20–60 mg/day) for 12 weeks reduced preferentially the frequency of paraphiliac behaviours in 20 male paraphilic subjects (exhibitionism, phone sex, sadism, fetishism, frotteurism) at week 4, and hypothesized that SSRIs may even facilitate normal sexual arousal. In the same way, physiological measures of sexual arousal (penile plethysmography) showed a decrease in paedophilic arousal (by 53%), and improved or maintained normal arousal after 12 weeks of sertraline treatment (Bradford 1999, 2001).

Some authors have compared effectiveness of SSRIs to other treatments: a retrospective study, conducted by Greenberg et al. (1996), in 58 paraphiliacs, 17–72 years of age (mean age: 36), compared the effectiveness of fluvoxamine ($N=16$), fluoxetine ($N=17$) and sertraline ($N=25$). Seventy-nine percent of subjects received concurrent psychotherapy. The major paraphilias were paedophilia (74%), exhibitionism (14%), sexual sadism (12%). Comorbid disorders were borderline personality disorder (31%), depression (28%), alcohol dependence (17%). Results showed a significant decrease in deviant fantasy intensity and frequency from weeks 4 to 8, and no further improvement at week 12. Fluvoxamine, fluoxetine and sertraline were found equally effective. Adverse effects were similar for the three drugs (insomnia, delayed ejaculation, headache, drowsiness, reduced sexual drive, diarrhea, nausea).

Paraphiliacs and hypersexual males not responding to sertraline for at least 4 weeks were offered fluoxetine and six of the nine subjects showed clinical improvement (Kafka 1994). No paedophiles were included in this study, and most subjects had co-morbid mood disorders.

Kruesi et al. (1992) studied 15 paraphiliacs in a double-blind comparison of clomipramine and desipramine versus placebo. Both were found to be effective.

By contrast, fluvoxamine (200–300 mg/day, one case), clomipramine (400 mg/day) or fluoxetine (60–80 mg/day, three cases) did not improve paraphiliac behaviours in five subjects after 2–10 months of treatment (Stein et al. 1992, retrospective open study). However, co-morbid non-sexual obsessive-compulsive disorder (OCD) symptoms improved in these patients.

There are several other interesting reports on SSRIs treatment combined with other interventions: Bradford and Greenberg (1996) reported that psychotherapy plus SSRIs was more effective than psychotherapy alone.

Kafka and Hennen (2000) added amphetamine, methylphenidate, pemoline or bupropion to SSRIs to counteract tolerance effects and to treat residual depressive or ADHD symptoms (open study, 26 male patients with paraphilias). The adjunction led to a significant additional decrease in paraphilia or paraphilia-related disorders. The same authors gave anecdotal unpublished information in 2006 about 50–100 non-bipolar, non-psychotic paedophiles treated with SSRIs, mood stabilizers or psychostimulants.

Greenberg and Bradford (1997) compared 95 patients receiving SSRIs plus psychosocial intervention versus 104 subjects having only psychosocial treatment. Both strategies reduced paraphiliac behaviours, but only the SSRIs reduced fantasies and desires within 12 weeks.

Krauss et al. (2006) reported marked reduction of paraphiliac symptoms in an open, uncontrolled retrospective study of 16 male paraphiliacs receiving SSRIs in combination with psychotherapy. The only double-blind study by Wainberg et al. (2006), compared 20–60 mg citalopram versus placebo in 28 homosexual men with compulsive sexual behaviour in a 12-week trial. Efficacy was measured using the Yale-Brown OCD scale. Treatment effects were seen on sexual desire/drive ($P=0.05$), frequency of masturbation ($P=0.01$) and pornography use ($P=0.05$).

A 23-year-old female paedophile was treated with sertraline (50 mg/day) (Chow and Choy 2002). The frequency and intensity of sexual interest in female children decreased and the effect was maintained at 1 year. Concurrent impulsive behaviours were also decreased.

A critical analysis of all studies that involved the use of SSRIs in the treatment of paraphilias concluded that the results of psychotropic drug interventions are not favourable *(Level C of evidence)*. The only double-blind study by Wainberg et al. (2006), was conducted in males with compulsive behaviour and cannot be generalized to sex offenders.

Rösler and Witzum (2000) suggested that they might be effective only in men with a definite OCD component to their sexual behaviour. Indeed, one proposed mechanism of action relates the anti-obsessional effects of SSRIs to the hypothesis that hypersexuality and some paraphilias may be related to OCDs, or even impulsive control disorders (Stein et al. 1992).

However, the above-mentioned studies draw attention to an alternative for treating paraphilias that are accompanied by OCD, impulse control disorders, or depressive disorders. But, despite the increasing clinical use of SSRIs for paraphilias and hypersexuality, double-blind controlled trials with these agents are still lacking. SSRIs have already been included in clinical practice for the treatment of sexual offenders, with specific indications, although more research demonstrating efficacy is very much needed. Several authors conclude that many reasons exist for the lack of research on antidepressant treatment of sexual offenders:

- lack of interest of governments to promote their use in these patients and to fund research;
- ethical barriers prevent double-blind studies in paraphiliac men being carried out;
- sexual offenders constitute a highly stigmatized population of patients.

Clinical recommendations for the use of SSRIs in the treatment of sexual abusers are the following:

- there is some evidence that sertraline reduces deviant sexual behaviours without affecting or even with improving normal sexuality (Bradford et al. 1995; Bradford, 2000);
- 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 behaviours (Bradford and Fedoroff 2006);
- taking into account clinical data, Bradford (2000), Bradford and Fedoroff (2006) and Kafka (personal communication), recommended SSRIs prescription in mild paraphilias, in paraphiliac juveniles, in cases that have comorbidity with OCD and depression and in maintenance treatment.

Several guidelines have been developed for the treatment of sexual offenders, which are summarized regarding to the indication of SSRIs:

- The Association for the Treatment of Sexual Abusers (ATSA Practice Standards and Guidelines for the Evaluation, Treatment and Management of Adult Male Sexual Abusers 2004, Oregon) included SSRIs as one of the interventions for the control of sexual arousal, within a comprehensive treatment program. They stated that this medication was supported by multiple clinical trials and specified that SSRIs could have a specific effect of reducing arousal, independently of their antidepressant quality. Though not formally approved, their off label use had become a standard of care. These guidelines recommends SSRIs for patients with high level of arousal that cannot be controlled with cognitive behavioural therapies, adding that informed and motivated patients are good candidates.
- In his algorithm, Hill et al. (2003) integrates levels of severity and comorbid conditions, within a comprehensive treatment plan, where all patients receive psychotherapy and pharmacotherapy for comorbid disorders. Pharmacotherapy is recommended for all patients with strong paraphiliac fantasies/compulsions and risk of sexual offenses. In mild and moderate cases, SSRIs are signaled as first choice of treatment, especially for those with depressive, anxious or obsessive/compulsive features.
- The American Academy of Child and Adolescent Psychiatry (AACAP 1999; Shaw 1999) practice parameters for the assessment and treatment of children and juveniles who are sexual abusers recommend the following aims for treatment: confronting denial; decreasing deviant sexual arousal; facilitating non deviant sexual interests; promoting victim empathy; enhancing interpersonal and social skills; assisting with value clarifications; clarifying cognitive distortions; teaching to recognize internal and external antecedents of sexual offending. The treatments recommended for these age groups are cognitive behavioural interventions, psychosocial interventions and SSRIs. The use of antiandrogens is discouraged under 17 years of age. Research showed that they may delay onset of puberty and bone growth.

Oestrogens

The first study was published in 1949 (Golla and Hodge). Despite its efficacy (Whittaker 1959; Bancroft et al. 1974), numerous side effects have been reported (nausea, weight gain, feminization, breast cancer, cardiovascular and cerebrovascular ischemic disease, thromboembolism) (Field 1973). Breast carcinoma was also reported in transsexual individuals during the use of Oestrogen treatment (Symmers 1968). They must not be used in sex offenders or subjects with paraphilia *(No level of evidence and major side effects)*.

Pharmacotherapy with antiandrogens or GnRH analogues

Methods. A review of the existing literature was conducted using MEDLINE/PubMed (1969–2009). The following key words were used: androgen antagonists, gonadotrophin-releasing hormone, cyproterone acetate, medroxyprogesterone 17-acetate, paraphilias, sex offences, sexual behaviour, incest. All available papers reporting hormonal treatment of paraphilias in English or French were considered. Sixty-five studies concerning hormonal treatment were used in this review. Within these 65 papers, about 30 studies were included, among them few were controlled studies.

Limitations. The criteria used for the measurement of treatment efficacy differed between the studies (frequency of conventional and paraphiliac sexual activity or fantasies reported by the patient, plasma testosterone levels, sexual or non-sexual reoffence; penile plethysmography (using audio or visual erotic stimuli, video including chidren, rapes or adults may be used but, according to Marshall and Fernandez (2000), many methodological flawns may limit the use of this technique), different types of paraphilias were included, the duration of follow-up may vary from months to years, side effects were not reported in many studies, in most of controlled studies a cross-over methodology was used). In most countries, clinical trials are not allowed while sex offenders are in jail, moreover conducting controlled studies comparing antiandrogen treatment with placebo in outpatients is not ethical.

Antiandrogens. Steroidal antiandrogens 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 testosterone and dihydrotestosterone (DHT). These compounds interfere with the binding of DHT (the androgen which plays the dominant role in androgenic response) to androgen receptors and they have been shown to block the cellular uptake of androgens.

Medroxyprogesterone acetate (MPA) is a progesterone derivative that acts as a progestogen and, like testosterone itself, exerts negative feedback on the hypothalamo-pituitary axis, resulting in decreases in both GnRH and LH release. MPA also induces the testosterone-α-reductase, which accelerates testosterone metabolism, and reduces plasma testosterone by enhancing its clearance. In addition, MPA increases testosterone binding to the testosterone hormone-binding globulin (TeBG), which reduces the availability of free testosterone, and finally it may also bind to androgen receptors (Southren et al. 1977).

MPA is currently used as a contraceptive, as a treatment for endometriosis or breast cancer. MPA was the first drug studied in the treatment of paraphilias. MPA is available in some countries and may be prescribed as an intra muscular (i.m.) depot preparation (150 or 400 mg/ml) (300–500 mg/week) or per os (2.5, 5 or 10 mg) (50–100 mg/day); oral administration may be used even if its absorption is more erratic (Gottesman and Schubert 1993). The first report of its efficacy in reducing sexual drive was published in 1958 in healthy males (Heller et al. 1958). The drug was first noted for its efficacy in the treatment of one case of paraphilia by Money in 1968 and has since been used in the USA.

More than 600 cases have been reported among different studies including 12 case reports (23 subjects), 13 open or controlled studies (including three double-blind cross-over studies).

Case reports. Twelve case reports including 23 subjects were found (Berlin and Coyle 1981; Berlin and Meinecke 1981; Cordoba and Chapel 1983; Bourget and Bradford 1987; Cooper et al. 1987, 1990; Ross et al. 1987; Cooper 1988; Weiner et al. 1992; Stewart 2005; Light and Holroyd 2006; Krueger et al. 2006). All subjects were males, aged from 17 to 85 years (in 13 cases, subjects were aged above 65 years old and exhibitionism or hypersexuality was associated with dementia). Paedophilia was observed in five cases (in association with exhibitionism, mental retardation or schizophrenia in four of five cases). In one case, testosterone level before treatment was 880 ng/100 ml (Berlin and Meinecke 1981). MPA (100 mg/4 weeks to 750 mg/week i.m. or 100–300 mg/day per os) was used for 2 months to 4 years. Testosterone, FSH and LH levels, clinical interviews, self reports of sexual activity and fantasies, penile plethysmography (in two cases using audio stimuli and in one case using nocturnal plethysmography) were used as outcome measurements. In all cases, except for one, deviant sexual behaviour and fantasies disappeared within 3 weeks; in the remaining case, erectile reponses to audio sexual stimuli were increased with MPA (Cooper et al. 1987). Testosterone levels decreased to 10–20% of baseline levels. Four weeks after treatment interruption, the clinical effects returned to baseline and, in two cases, the subjects relapsed. Weight gain was reported in three cases, depressive disorder was observed in one case, adrenal suppression (MPA was replaced with GnRH agonists) was described in one case; in the remaining cases, side effects were not reported. In eight cases, previous

antipsychotic treatment was used without any efficacy. Some case reports support the use of MPA for the treatment of hypersexuality or paraphiliac behaviours in older patients with dementia. Beneficial effect of MPA (300 mg/week for 1 year) on acting out (compulsive masturbation, exhibitionism and rape attempts) was reported in four patients (75–84 years old) with dementia (Cooper 1987). Exhibitionism and rape attempts in two men with dementia (71 and 84 years old) were successfully treated with MPA (150–200 mg/2 weeks) (Weiner et al. 1992).

Open and controlled studies (13 studies, see Table I). Among the 13 studies, three were double-blind cross-over studies (comparing MPA and placebo) including 51 paedophiles and eight sex offenders (Wincze et al. 1986; Hucker et al. 1988; Kiersch 1990), nine were open studies and one was a retrospective study (275 sex offenders, Maletzky et al. 2006).

Efficacy, dosage, duration of treatment:

Treatment outcome measures were the following: self reports of deviant and/or non-deviant sexual fantasies and activity, testosterone levels; plethysmography was used in four studies. Paedophilia or exhibitionism were reported in 27 and 15% of about 600 cases, respectively. Paraphiliacs were only males aged from 14 to 85 years old. Psychiatric comorbidities were the following: dementia, alcoholism, mental retardation and psychopathy in most cases. Only three schizophrenic patients were included in these studies. MPA was prescribed as an i.m. depot preparation (100–900 mg/week) or per os (60–300 mg/day). Reduction of sexual behaviour and complete disappearence of deviant sexual behaviour and fantasies were observed after 1–2 months in the majority of cases in spite of maintained erectile function during plethysmography in some studies. In contrast, Langevin et al. (1979) reported no reduction of sexual behaviour in healthy controls with MPA treatment (100 mg/day).

The re-offence rate for 334 individuals taking depot MPA was greater than with CPA, with a mean rate of 27% at the end of the follow-up (range 6 months to 13 years) as compared with 50% before treatment (Meyer and Cole 1997). Money et al. (1975), using MPA in a few cases, reported no reduction in nonsexual crimes in sex offenders with antisocial behaviour.

In 12 cases, recidivism of deviant sexual behaviour during MPA treatment was reported using different criteria (Langevin et al. 1979; Money et al. 1981; McConaghy et al. 1989; Cooper et al. 1987; Kiersch 1990; Kravitz et al. 1995, 1996). Some studies reported increased recidivism after MPA was stopped (Money et al. 1981; Meyer et al. 1992a,b; Gottesman and Schubert 1993). Drug abuse, previous head trauma, learning disabilities, single status, personality disorders increased the recidivism risk, higher initial testosterone levels (Meyer et al. 1992a). Early treatment interruption was also a risk factor. McConaghy et al. (1989) reported a lower efficacy of MPA in juveniles.

Gottesman and Schubert (1993) reported no deviant sexual behaviour with 60 mg/day of MPA. These authors recommanded a low dose when side effects were observed and when there was a low risk of sex offence.

Cooper (1986) recommended a minimal duration of MPA treatment of 2 years.

Side effects

The adverse effects of MPA included weight gain (18%, max 9 kg), headache (9%), nausea, asthenia, gynecomastia, lethargy, insomnia, leg cramps (<1%), spermogram abnormalities, erectile dysfunction, increased blood pressure, hot flushes, diabetes mellitus (<1%), gallstones (1%) (Meyer et al. 1992b), transient increased levels of hepatic enzymes, depressive syndrome, adrenal suppression, decrease in testicular volume, Cushing syndrome (in a 30-year-old male with paedophilia treated with MPA, 300 mg/day for 4 years) (Krueger et al. 2006) and thromboembolic phenomena (1%). Pulmonary embolism is the most severe side effect reported. No bone mineral loss was described but osteodensitometry was not used. Mean plasma concentrations of LH and total testosterone were significantly reduced, FSH levels did not change (for review see Guay 2009).

Guidelines

In conclusion many subjects received MPA treatment but most studies were not controlled, and some biases were observed (small size of samples, short duration of follow-up, cross-over study design, retrospective study design). In addition, severe side effects were observed with MPA. The benefit/risk ratio did not favor the use of MPA which was abandonned in Europe (*Level C of evidence*).

Testosterone, FSH, LH and prolactine plasma levels, hepatocellular blood tests, blood cell count, electrocardiogram, fasting glucose blood level, blood pressure, weight, calcium and phosphate blood levels, kidney function, bone mineral density must be checked before treatment. Informed consent must be obtained.

The use of MPA has to be carefully managed medically, via physical examination, especially for the effects of feminisation. Depression, emotional

Table I. Changes in sexually deviant behaviours in chronic paraphiliac male patients treated with medroxyprogesterone acetate (MPA)(open and controlled studies).

Reference	Characteristics of the patients paraphilias or sex offending behaviour Other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
Double-blind studies					
Wincze et al. 1986 USA ***Double-blind cross-over controlled study*** *N*=3 males	*N*=3 males (36–60 years old) Paedophiles (3)	MPA 160 mg/day per os and/or **placebo** (No treatment 7 days, placebo 14 days, MPA 160 mg/day for 42–56 days, placebo for 21–42 days) Duration of follow-up: 1–3 months	Self reports of spontaneous sexual activity Testosterone levels Penile plethysmography (visual erotic deviant stimuli) Nocturnal penile plethysmography	Reduction of sexual activity (self report) Less obvious with plethysmography Reduction of testosterone levels with MPA No increase of sexual behaviour at the end of the placebo period	None
Hucker et al. 1988 Canada ***Double blind cross-over study*** *N*=48 males	*N*=48 males Paedophilia *Comorbidity:* Mental retardation	18 subjects gave their consent for treatment and 11 remained in the study until the end of follow-up: MPA (5) 300 mg/day per os **Placebo** (6)	Self reports	Deviant sexual fantasies disappeared MPA>Placebo	Not reported
Kiersch 1990 USA ***Double blind cross-over study*** *N*=8 males	*N*=8 (<40 years old) Sex offenders with previous convictions *No comorbidity* *Exclusion criteria* Mental retardation Psychosis Brain lesion Depressive disorder	MPA 100–400 mg/week i.m. (16 weeks) versus **Placebo** (saline i.m.) (16 weeks) Duration of follow-up: 22–64 weeks (4 cases)	Testosterone levels Plethysmography (audio deviant and non-deviant sexual stimuli) Self reports	Reduction of testosterone levels with MPA Reduction of response to deviant and non-deviant sexual stimuli (6) Effect maintained while placebo on treatment Reduction of masturbation frequency (6) In 1 case increase of deviant sexual fantasies with MPA In 1 case sex offending while on placebo No change in sexual orientation	Erectile dysfunction(1) Glaucoma (1) Headache (1)

(Continued)

Table I. *(Continued)*

Reference	Characteristics of the patients paraphilias or sex offending behaviour Other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
Open studies	*N*=37 males exhibitionists	MPA 100–150 mg/day per	Testosterone levels	After 2 years: *n*=3 no	Nausea (1)
Langevin et al. 1979		os+Psychotherapy (*n*=15)	Clinical interviews	deviant sexual behaviour	Weight gain (1)
Canada		Versus	Recidivism rate	20/37 early ttt interruption	
Open study		Psychotherapy alone (*n*=17)		Psychotherapy alone:	
N=37+8 males		Versus MPA alone (*n*=5)		6/17 relapse	
Control group		Duration of follow-up: 15 weeks		MPA+ Psychotherapy	
N=10				1/5 relapse	
	N=8 males exhibitionists	MPA (100 mg/day per os)	Testosterone levels, Self	MPA: significant decrease	None
		or placebo	reports	of testosterone levels	
			Plethysmography with	Reduction of deviant sexual	
			deviant sexual stimuli	fantasies	
				Plethysmography:	
				Placebo=MPA	
	N=10 heterosexual male subjects	MPA (100 mg/day per os)	Plethysmography	No difference between	
	without paraphilia	or placebo		MPA and placebo	
				in controls	
Money et al. 1981	*N*=20 males			*N*=17 No deviant	None
USA	Aged 26–56 years			sexual behaviour	
Open study	Paedophilia (11)	MPA 150–600 mg i.m. per week		*N*=3 relapse (1 with alcohol)	
N=20 males	Exhibitionism (5)		Clinical interviews	At the end of the	Not reported
	Sexual sadism (1)			study *n*=11 stopped	
	Voyeurism (1)	Duration of follow-up:		MPA and relapsed	
	Sexual masochism (1)	3 months to 5 years			
	Transvestism (1)				
	Incest (1)				
Gagne 1981	*N*=48	MPA	Testosterone	*N*=40 Improvement	
Canada	Previous convictions for sex	200 mg i.m. 2–3 times per	levels (1/month)	within 10 days to 3 weeks	
Open study	offences (39)	week for 2 weeks then 1–2 times	Clinical interviews	Reduction of	
N=48 males	Paedophiles (27)	per week for 4 weeks then 100 or	(2/month)	deviant sexual activity	Asthenia for
	Exhibitionism (6)	200 mg every 2 weeks for 12 weeks		and fantasies and arousal	3 days after
	Voyeurism (1)	then 100 mg every 1–4 weeks for		Reduction of testosterone	injection (40)
	Incest (3)	8 months		levels (25% of baseline levels)	Weight gain
	Rape (4)	+ Psychotherapy		Improvement of social	(max 9 kg) (28/48)
	Others (2)			functioning within 2–3 months	Headache (10)
	Transvestism (2)	Duration of follow-up:		Similar efficacy	Insomnia (7)
		12 months		between those with	Hot flushes (14)
				or without previous	Nausea (1)
				convictions	Thrombophlebitis (1)
	Comorbidity			Treatment interruption:	Impotence (when
	Alcoholism (7)	Hospitalization		1 case (thrombophlebitis)	testosterone levels
	Psychopathy (7)	for the first 4 weeks		5 cases against medical	approached 25% of
				advice: no relapse	baseline levels)

(Continued)

Table I. *(Continued)*

Reference	Characteristics of the patients paraphilias or sex offending behaviour Other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
Meyer et al. 1985 USA Open study *N*=23 males	*N*=23 males Aged 22–45 years (mean 29) Paedophilia (12) Rapists (6) Exhibitionism (2) Genital self mutilation (3) *Comorbidity:* Alcoholism (2)	 MPA 300–400 mg/week i.m. Duration of follow-up: 1–83 months (mean 18 months)	Testosterone, LH, FSH levels MPA levels Spermograms Testis volume (every 6 months) No evaluation of treatment efficacy	 Reduction of testosterone levels MPA plasma levels >50 ng/ml No report of treatment efficacy	Weight gain (2/3 cases> 5 pounds) Increased blood pressure Spermogram changes Gallstones (3) Gut diverticulosis (1) Diabetes mellitus (1) Increased insuline levels (3) Headache (1) (decrease of MPA dosage) Sedation Decreased testis volume Transient increased levels of hepatic enzymes (3) 3 Pregnancies while MPA treatment of male partners
Mc Conaghy et al. 1989 Australia Open study *N*=45 males	*N*=45 Aged 14–72 years (mean 32; 6 cases <19) Sex offenders Paedophilia Exhibitionism Fetishism Voyeurism *Comorbidity* Mental retardation (1)	**1st Study** Psychotherapy alone (20) (Covert sensitization, Imaginal desensitization) **2nd Study** MPA (4 juveniles, 12 adults, 7 required MPA later) or Psychotherapy (10) (imaginal desensitization) or both MPA+ ID (10) MPA 150 mg i.m. per month for 4 months Duration of follow-up: 1 year	 Testosterone levels Self reports	**1st study** covert sensitization < imaginal desensitization **2nd study** Same efficacy between the 3 groups, reduction of deviant sexual behaviour Less efficacy in juveniles: 3 juveniles while receiving MPA: sex offence 3 cases without MPA: sex offence	 None
Meyer et al. 1992a USA Open study *N*=61 males	*N*=40 (MPA treatment) Aged 16 to 78 years Sex offenders Paedophilia (23) Rapist (7) Exhibitionism (10)	MPA (400–800 mg/week i.m.) Versus Psychotherapy alone Duration of follow-up: 6–12 years	Testosterone, LH, FSH levels Recidivism rate of deviant sexual behaviour	Reduction of testosterone levels with MPA Recidivism decreased with MPA (7/40) versus 12/21 with psychotherapy alone At the end of MPA treatment 10 relapsed	Weight gain (13) Gastro intestinal symptoms (2) Dizziness (1) Headache (1) Increased blood pressure (3) Diabetes mellitus (3)

(Continued)

Table I. *(Continued)*

Reference	Characteristics of the patients paraphilias or sex offending behaviour Other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
	N=21 (Psychotherapy) Sex offenders who disagree with MPA treatment Paedophilia (14) Exhibitionism (6) Voyeurism (1) No denial No psychopathy *Comorbidity:* Head trauma (5) Drug or alcohol abuse (*n* ?) Personality disorders or depressive disorders (33%) Micro penis (2)			Risk factor of recidivism: single, drug abuse, previous head trauma, learning disabilities, personality disorders, higher initial testosterone level	Gallstones (4) Leg cramps (2)
Gottesman and Schubert 1993 USA Open study *N*=7 males	*N*=7 males Aged 25–47 years With>2 paraphilias Paedophilia (3) Sexual sadism (1) Zoophilia (1) Voyeurism (3) Exhibitionism (3) Sexual masochism (1) Fetishism (1) Transvestism (1) Phone scatologia (1) *Comorbidity:* Hodgin's disease Schizophrenia No previous pharmacological treatment, in 4 cases previous psychotherapy failed	MPA **60 mg/day** (10–18 months)+ Psychotherapy	Testosterone, LH, FSH levels (1/month) Self reports of deviant sexual behaviour Number of morning erections/week and number of ejaculations/ week	Reduction of testosterone levels (50–75%) Reduction of deviant sexual fantasies and morning erections No deviant sexual behaviour in 6 cases Increase of sexual desire in 2 cases at treatment onset 1 case of treatment resistance at 3 weeks In 2 cases early treatment interruption (10 and 12 weeks) 1 lost to follow-up, 1 recidivism (rape)	Headache 1st week (1) Weight gain (2)

(Continued)

Table I. *(Continued)*

Reference	Characteristics of the patients paraphilias or sex offending behaviour Other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
Kravitz et al. 1995 USA Open study *N*=29 males	*N*=29 males Aged 18–77 years (mean 38) Paedophilia (22) Exhibitionism (6) Frotteurism (1) *Comorbidity:* Mild mental retardation (5)	MPA 300–500 mg i.m./week + Psychotherapy (group)(26/29) Duration of follow-up: 6 months	Self report (deviant and non-deviant sexual fantasies, sexual activity, masturbation) Plethysmography (before MPA and every 6 months Testosterone levels (every 3 months) Blood pressure and weight Recidivism	No deviant sexual behaviour Reduction of non-deviant sexual behaviour Reduction of testosterone levels 1 case: recidivism with MPA (exhibitionism, self report, no conviction) 7 cases: early MPA interruption	Pulmonary embolism (1) Leg cramps (12) Weight gain (10) Headache (10) Asthenia (7) Sedation (5) Depressive disorder (4) Testis pain, Erectile dysfunction (4) Virus hepatitis (1) 1 case: pregnancy of the male's partner
Kravitz et al. 1996 USA Open study *N*=13 males	*N*=13 males Aged 24–77 years (mean 43) Paedophilia (10) Exhibitionism (3) >2 paraphilias (6) Mean IQ 102	MPA i.m. 300 mg/week (*n*=5) 400 mg/week (*n*=1) 600 mg/week (*n*=5) 900 mg/week (*n*=1)+ Psychotherapy (10/13 cases) Duration of follow-up: 6–12 months (*n*=5)	Id above Subjects divided into two groups: Normal pretreatment testosterone levels (9) Low pretreatment testosterone levels (4) (and longer duration of treatment)	Reduction of testosterone levels in most cases No deviant sexual behaviour or fantasies in 6 cases (group 1) and 2 cases (group 2) No significant difference for MPA dosage between group 1 and 2 1 case of recidivism with MPA Testosterone levels returned to normal levels after treatment interruption (longer duration in older subjects)	Not reported
Retrospective study					
Maletzky et al. 2006 USA Retrospective studies (hospital records) *N*=275 males	*N*=275 (clinical files) Sex offenders, prisoners Paedophilia Exhibitionism Rapist *Comorbidity*?	**Group 1:** MPA (200–400 mg/week i.m.) (*N*=79) (mostly paedophiles) **Group 2:** MPA recommanded but not used (*N*=55) DepoProvera Scale score >7 or Static 99 score >4) **Group 3:** MPA not recommanded (*N*=141)+ Behavioural therapy	Recidivism of sexual deviant behaviour	MPA>no treatment: no deviant sexual behaviour with MPA versus deviant sexual behaviour observed in respectively 30% and 26% of subjects in groups 2 and 3	Not reported

disturbances must be evaluated every 1–3 months. Every 6 months, glucose blood levels, calcium and phosphate blood levels, blood pressure, weight must be controlled. Bone mineral density must be checked every year in case of increased osteoporosis risk.

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 or uterine diseases, diabetis mellitus, severe depressive disorder, allergy to MPA, active pituitary disease.

Cyproterone acetate (CPA) is a synthetic steroid, similar to progesterone, which acts both as a progestogen and an antiandrogen. Direct CPA binding to all androgen receptors (including brain receptors) blocks intracellular testosterone uptake and metabolism. Indeed, CPA is a competitive inhibitor of testosterone and DHT at androgen receptor sites. In addition, it has a strong progestational action, which causes an inhibition of GnRH secretion and a decrease in both GnRH and LH release (Jeffcoate et al. 1980; Neuman 1977).

CPA is used predominantly in Canada, the Middle East and Europe and is registered in more than 20 countries for the moderation of sexual drive in adult men with sexual deviations as well as for non-operable prostate cancer (Androcur). It is also used as a treatment for precocious puberty or hirsutism. CPA may be given either by injection (depot form: 100 mg/ml (200–400 mg once weekly or every 2 weeks) or as tablets (50 and 100 mg, 50–200 mg/day). In the United States, it is only available in a low dosage form in a combination product with ethinyl-estradiol.

The first clinical use of CPA in sex offenders (predominantly exhibitionists) occurred in Germany (Laschet and Laschet 1967, 1971), in a open study, which showed an efficacy of CPA in 80% of abnormal sexual behaviour.

Case reports. Melior et al. (1988) reported the case of a female aged 40 with compulsive masturbation and sexual aggression. CPA (50 mg/day from J1 to J15) and ethinyl-estradiol (50 µg/day from J5 to J25 every month) decreased significantly deviant fantasies, erotic dreams. Compulsive masturbation disappeared. CPA was stopped at 6 months after lactose intolerance and reintroduced at a dosage of 25 mg/day with the same efficacy. Previous treatments (psychotherapy, antidepressants, antipsychotics) had failed.

Fourteen patients were reported in nine case reports (Cooper et al. 1972; Lederer 1974; Bradford and Pawlack 1987; Grinshpoon et al. 1991; Thibaut et al. 1991; Byrne et al. 1992; Cooper et al. 1992; Eriksson and Eriksson 1998; Gooren et al. 2001). Two paedophiles with mild to moderate mental retardation, one exhibitionist, other non-specified sex offenders (aged from 23 to 70 years, in two cases dementia was associated with sexual desinhibition) were receiving CPA (50–200 mg/day or 275–300 mg i.m. every 2 weeks), from 4 weeks to 10 years. Hormonal levels, self report rating scales and, in some cases, plethysmography were used. In most cases, deviant sexual behaviour disappeared within 2 weeks except for one case; in this latter case, CPA was withdrawn after 2 weeks due to side effects (Byrne et al. 1992). Cooper et al. (1992) reported a better efficacy with 200 mg/day of CPA as compared with 100 mg/day. Some side effects were reported: asthenia, erectile dysfunction, gynecomastia (one case was treated using radiotherapy), osteoporosis and hip fracture (one case, 52 years old, 300 mg/2 weeks, after 10 years of CPA) (Gooren et al. 2001), depressive disorder (one case). In one case, treatment was stopped after 2 weeks due to asthenia and muscular loss (Byrne et al. 1992). Thibaut et al (1991) reported a concurrent decrease in non-sexual aggressiveness while CPA was used. In most cases, testosterone levels decreased.

Open and controlled studies (10 studies, see Table II). Among the 10 studies, two were double-blind cross-over comparative studies (CPA vs. ethinyl-estradiol, 12 sex offenders, Bancroft et al. 1974) (CPA vs. MPA, seven paedophiles, Cooper et al. 1992b), two were double-blind cross-over studies including, respectively, nine sex offenders and 19 subjects with paraphilias and comparing CPA with placebo (Cooper 1981; Bradford and Pawlack 1993a), one was a single-blind study (five paedophiles, CPA vs. placebo, Cooper et al. 1992a) and the five remaining studies were open studies.

Efficacy, dosage, duration of treatment

About 900 male subjects were included in 10 open and double- or single-blind cross-over studies. About 20% of the cases were paedophilic patients. The most frequent comorbidities observed were mental retardation and psychopathy. CPA (50–300 mg/day per os or i.m. 300–600 mg every 1 or 2 weeks) was associated with a significant decrease of self-reported sexual fantasies or activity and frequency of masturbation and a disappearance of deviant sexual behaviour in about 80–90% of cases within 4–12 weeks. Morning erections, ejaculations and spermatogenesis were decreased. In most cases, 100–200 mg/day was sufficient. Moreover, in 80% of the cases, 100 mg/day oral CPA was sufficient. Depending on dosage, the authors suggested that CPA could be used as a chemical castration agent or as a reducer of sexual drive, allowing erecting ability in non-deviant sexual behaviour.

Table II. Changes in sexually deviant behaviours in chronic paraphiliac male patients treated with cyproterone acetate (CPA) (open and controlled studies).

Reference	Characteristics of the patients Paraphilias and sex offending behaviour other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
Double-blind studies					
Bancroft et al. 1974 USA ***Double blind cross-over study*** *N*=12 males	*N*=12 Males Aged 22–34 years Sex offenders	**CPA** 100 mg/day **versus** 0.01 mg/day **ethinyl-estradiol** 3 periods of 6 weeks (no treatment, CPA or estradiol)	Sexual interest, sexual activity Plethysmography Testosterone levels	CPA or ethinyloestradiol: Both drugs significantly decreased sexual interest and activity Only CPA decreased responses to erotic stimuli (plethysmography)	Depressive disorder 1 case on day 3 of CPA (treatment interruption)
Cooper 1981 Canada ***Double blind cross-over study*** *N*=9 males	*N*=9 Males Sex offenders (hypersexuality 4 and exhibitionism 4, voyeurism 2, fetishism 1, and incestuous behaviour 1 case)	**CPA** 100 mg/day **versus placebo** 5 periods of 4 weeks (No treatment, CPA 100 mg/day/Placebo, No treatment, Placebo/CPA, No treatment)	Testosterone levels Sexual fantasies and activity for the last 7 days Number of erections/day Sexual interest and masturbation (visual rating scale 0–100)	With CPA, reduction of testosterone levels (485 to 365), decrease of sexual activity (0.7 to 0.25), number of erections (1 to 0.35), orgasm and sexual interest (70.7 to 28) in general and while masturbation (94 to 40) ($P<0.05$) Reversible within 30 days of CPA interruption	Not reported
Cooper et al. 1992a Canada ***Single blind cross-over study*** *N*=5 males	*N*=5 Males Aged 21–31 years Paedophiles *Comorbidity* Psychopathy (2) Alcoholism (1) IQ 75–89 (3 cases)	CPA 100 mg/day **or placebo** Duration of follow-up: 16 weeks (Placebo 4 weeks/CPA 100 mg/day 8 weeks/placebo 4 weeks)	Testosterone, LH, FSH, prolactine levels 1/month Nocturnal erections, Plethysmography (1 per sequence) with audio and visual deviant and non-deviant sexual stimuli Nocturnal penile plethysmography	Decrease of nocturnal erections (by 62%) and of erections after sexual stimuli (video (67% reduction)>audio stimuli (23% reduction)) Decrease of testosterone (78%) LH (42%) FSH levels (14%) during CPA treatment No statistical analyses Returned to baseline 4 weeks after CPA interruption	Not reported
Cooper et al. 1992b Canada ***Double blind cross-over study*** *N*=7 males	*N*=10 paedophiles (3 dropped out during the initial placebo period) Mean age: 30 years (23–37) >/ 2 paraphilias Exhibitionism 1 Sexual sadism 4 Rapist 1 Fetishism 2 Zoophilia 1 Transvestism 2	**CPA versus MPA** 100–200 mg/day 7 periods of 4 weeks (Placebo/MPA or CPA 100 mg/day/MPA or CPA 200 mg/day/Placebo/MPA or CPA 100 mg/day/MPA or CPA 200 mg/day/Placebo	Testosterone FSH LH levels Sexual fantasies, masturbations, morning erections, deviant sexual behaviour, Plethysmography, (audio and visual deviant and non-deviant sexual stimuli)	CPA and MPA: same efficacy dose dependent Decrease of sexual fantasies, masturbations, morning erections, penile response to erotic stimuli, CPA and MPA same efficacy within 4–8 weeks, (maximal effect at 8 weeks) Decrease of testosterone, LH, FSH levels with both treatments, levels returned to normal levels after 3 weeks of placebo 5 patients preferred MPA and 3 CPA No statistical analyses	Reduced ejaculate volume

(Continued)

Table II. *(Continued)*

Reference	Characteristics of the patients Paraphilias and sex offending behaviour other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
	Comorbidity: Psychopathy 3 Alcoholism 2 Drug abuse 1 Mental retardation 1 In 3 cases denial and patients were excluded	No statistical analyses			
Bradford and Pawlack 1993a Canada ***Double blind cross-over study*** *N*=19 males	*N*=19 Males Mean age: 30 years Range: 19–45 years Paedophiles 12 Frotteurism 1 Rapists 2 Fetishism 1 Incest 2 Exhibitionism 1 *Exclusion criteria* Thromboembolism, cardio vascular disease, carcinoma, hepato cellular disease, psychosis, diabetis, depressive disorders, organic brain disease	**CPA** 50–200 mg/day **versus placebo** Duration of follow-up: 13 months (four 3-month treatment periods) (No treatment 1 month/ CPA 200 mg/day or placebo double-blind 3 months/CPA 50–200 mg/day or placebo for 3 months double-blind successively) (CPA dosage could be changed every month during the last period) **Statistical analyses performed**	Testosterone, LH, FSH, prolactine levels Plethysmography (visual stimuli) BPRS, Buss Durkee Inventory, Rating scales for sexual interest and activity	Significant reduction of testosterone (50%) and FSH (30%) levels Significant increase of prolactine levels (X2) No change for LH Significant decrease of sexual arousal, fantasies and activity (5.65±4.7 to 3.59±4.2) and decrease of BPRS scores CPA> Placebo and CPA>No treatment on sexual fantasies and desire No statistical difference observed using phallometry	No significant difference for side effects Mean weight gain with CPA: 1.3 kg
Open studies					
Laschet et Laschet 1971 Germany Open study *N*=110 males	*N*=110 Males 29 paedophiles Exhibitionism Sexual sadism 80% sex offenders	Cyproterone acetate 50–200 mg/day Duration of follow-up: 4 months-4 years	Not reported		
Mothes et al. 1971 Germany Open study *N*=352 males	*N*=352 30% paedophiles	CPA 100–300 mg/day Duration of follow-up: max 3 years	Each year self report of sexual activity		

(Continued)

Table II. *(Continued)*

Reference	Characteristics of the patients Paraphilias and sex offending behaviour Other conditions	Treatment conditions	Outcome measures	Efficacy	Side effects
Davies 1974 USA Open study (case reports) N=50 males	N=50 Males 16 Sex offenders (women or children) 4 violent sexual fantasies 13: oligophrenia with compulsive masturbation 10 hypersexuality 4 chromosomal aberrations 3 elderly with sexual disorders Exhibitionism/hypersexuality *Comorbidity:* Mental retardation	CPA 50–100 mg/day In some cases (n?) 200 mg/day Duration of follow-up: max 3 years	Clinical observation No rating scales	Reduction of deviant sexual behaviour (16 sex offenders) No relapse 3 years after ttt interruption in sex offenders	Blood tests: no change Gynecomastia (2) Increased severity of diabetis mellitus (1)
Laschet et Laschet 1975 Germany Open study *N*=300 males	*N*=300 Males	CPA Duration of follow-up: 8 years Dosage: cyproterone acetate 50–200 mg/day oral or i.m. 300–600 mg every 1 or 2 weeks	Testosterone levels	Improvement in 90% of cases	*At onset:* Decrease of number of erections and ejaculations Spermatogenesis decreased Asthenia Depressive symptoms Weight gain *At 6–8 months* Gynecomastia (20%) Decreased pilosity Decreased sebum
Bradford and Pawlack 1993b Canada Open study *N*=20 males	*N*=20 Males Aged 18–60 years 15 Paedophiles 3 Incest 2 Paedophilia and exhibitionism *Exclusion criteria*: Carcinoma, thromboembolism, hepato cellular disease, depressive disorder, diabetis mellitus, alcoholism, psychosis,	CPA 50–200 mg/day (mean 85) Duration of follow-up: 9–12 weeks	Testosterone levels Plethysmography (audio deviant and non-deviant sexual stimuli) before CPA and after 2 to 3 months	Decrease of testosterone levels mostly in patients with higher (7 cases/17) (but normal>28 nMol/l) baseline levels Maximal efficacy within 8–12 weeks Decrease of penile tumescence depends on type of visual stimuli (deviant>non-deviant) Decrease of spontaneous erections and of non-deviant sexual fantasies	No side effects reported

The efficacy was maintained while on treatment for up to 8 years in a sample of 300 males with paraphilia (cyproterone acetate 50–200 mg/day oral or i.m. 300–600 mg every 1 or 2 weeks) (Lashet and Lashet 1975).

Davies (1974) reported CPA efficacy in five juvenile males with deviant sexual behaviour or hypersexuality (mental retardation was observed in three cases); however, CPA must not be used before puberty and bone growth are completed.

Five comparative double- (or single-) blind crossover studies (Table II) have compared CPA with placebo, MPA or ethinyl-estradiol in 52 sex offenders. Brancroft et al. (1974) compared the effects of CPA with those of 0.01 mg ethinyl-estradiol twice a day. Both treatments equally decreased sexual interest, sexual activity with no major side effects (except for one case of early depressive disorder). Only CPA decreased responses to erotic stimuli (plethysmography). The first double-blind comparison between CPA and MPA concluded that MPA and CPA performed equally in seven sex offenders with no side effects except for those related to hypoandrogenism (no statistical analyses were performed) (Cooper et al. 1992b). In all studies, CPA, MPA and ethinyloestradiol showed the same efficacy which was higher as compared with placebo. The results of the evaluation of penile responses to a variety of erotic stimuli, using plethysmography, for CPA and MPA, have been less impressive than when subjective measures of improvement have been used. Using visual erotic stimuli, CPA or MPA had no significant or more variable effects on the erectile responses of sex offenders (Bancroft et al. 1974; Cooper et al. 1992a,b; Bradford and Pawlak 1993). These results are in accordance with the view that erections in response to visual stimuli are less androgen-dependent. By contrast, a consistent trend toward preferential suppression of deviant arousal using phallometric measures was observed during CPA treatment in a group of paedophiles with high but normal levels of testosterone (Bradford and Pawlak, 1993b). Among double-blind studies, only Bradford and Pawlak (1993a) performed statistical analyses and reported a statistically significant decrease in deviant sexual activity (CPA> placebo and CPA>no treatment).

The treatment effects of CPA or MPA were completely reversible, 1 or 2 months after medication interruption.

Seven studies examined the re-offence rates of 127 individuals taking CPA (Meyer and Cole 1997). A mean rate of 6% was found at the end of the follow-up period (less than the rate observed with MPA), as compared with 85% before treatment, with a duration of follow-up ranging from 2 months to 4.5 years. Many re-offences were committed by individuals who did not comply with therapy. In addition, a significant number of patients re-offended after stopping therapy. Some studies have reported reduced anxiety and irritability with CPA in their patients (Cooper et al. 1992a,b; Bradford and Pawlak 1993b).

In most studies, the duration of antiandrogen treatment was less than one year, Davies (1974) reported no recidivism during 3 years of follow-up after cessation of 5 years of CPA treatment in different types of paraphilias. According to Cooper (1986) a minimal duration of treatment of 2 years would be necessary. Although there is no consensus on the optimal duration of CPA or MPA treatment, many authors have written that 3–5 years of treatment are necessary (Gijs and Gooren, 1996).

Serum FSH and LH concentrations were either decreased or not affected by cyproterone acetate administration. Plasma testosterone levels were moderately decreased (for review, Guay 2009).

Side effects

Side effects were related to hypoandrogenism: asthenia, sleep disorders, depressive symptoms or disorders (Cooper et al. 1992a,b), hot flushes, pilosity changes, decreased sebum excretion rate, leg cramps, hair loss, spermatogenesis reduction (reversible), impotence, decrease of sexual activity and fantasies, reduced ejaculate volume and osteoporosis (Gis and Gooren 1996; Grasswick and Bradford 2003) were reported.

One hip fracture due to bone mineral loss was observed in a 52 year-old man after 10 years of CPA treatment (Gooren et al. 2001).

Or side effects were related to CPA itself: headache, dyspnea, weight gain, gynecomastia (20% of cases, reversible), thrombo-embolic phenomena (Czerny et al. 2002), increased level of prolactine, adrenal insufficiency or hyperplasia (0.5% of cases) (primarily described in juveniles with CPA (Laron and Kauli 2000)), hypertension, cardiac insufficiency (Reilly et al. 2000), decreased glucose tolerance, kidney dysfunction, pituitary dysfunction, anaemia (Hill et al. 2003), local pain at the injection site (depot formulation), nausea were reported, hepatocellular damage (especially when CPA dosage is >200–300 mg/day, after several months of treatment) it may be fatal, but serious hepatotoxicity is uncommon <1% (Heinemann et al. 1997). According to animal research data, CPA is suspected to induce liver cell carcinoma (Neuman et al. 1992; Kasper 2001). In patients with prostate cancer, cyproterone acetate increased the risk of venous thromboembolism more often as compared to flutamide or GnRH agonists monotherapy (3.5-fold). A history of venous thromboembolism or recent surgery or trauma increased the risk by 4- and

13-fold, respectively (for review of CPA side effects, Guay, 2009).

Guidelines

In conclusion, many subjects received CPA treatment but most studies were not controlled, and some biases were observed (small size of samples, short duration of follow-up in most cases, cross-over studies, retrospective studies) (*Level C of evidence*).

In addition, some severe side effects were observed with CPA.

In some countries the oral form is the only form available and treatment observance may be erratic. Testosterone level is 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.

Testosterone, FSH, LH and prolactine plasma levels, hepatocellular blood tests, blood cell count, electrocardiogram, fasting glucose blood level, blood pressure, weight, calcium and phosphate blood levels, kidney function, bone mineral density must be checked before treatment.

Side effects are dose related and careful monitoring of CPA dosage should decrease side effects and, in some cases, would allow non-deviant sexual behaviour (Hill et al. 2003). The use of CPA has to be carefully managed medically, via physical examination, especially for the effects of feminisation. Depression, emotional disturbances must be evaluated every 1–3 months. Every month for 3 months and then every 3–6 months biochemical monitoring of liver function is required (Reilly 2000; Hill et al. 2003). Every 6 months, prolactine, glucose blood levels, blood cell count, calcium and phosphate blood levels, blood pressure, weight must be controlled. Bone mineral density must be checked every year in case of increased osteoporosis risk (Reilly et al. 2000; Hill et al. 2003). Informed consent must be obtained.

CPA must not be used in case of: non-consent, puberty not completed especially when bone growth is not achieved, hepatocellular disease, liver carcinoma, diabetis mellitus, severe hypertension, carcinoma except prostate carcinoma, pregnancy or breast feeding, previous thromboembolic disease, cardiac or adrenal disease, severe depressive disorder, tuberculosis, cachexia, epilepsy, psychosis, allergy to CPA, drepanocytosis, pituitary disease (Reilly et al. 2000; Hill et al. 2003).

Pharmacotherapy with gonadotrophin releasing hormone (GnRH) analogues. In fact, MPA and CPA have shown inconsistent results in the treatment of sex offenders. In addition, poor treatment compliance is a major concern with oral CPA. Because of a substantial number of side effects, including gynecomastia, weight gain, thromboembolic phenomena and hepatocellular damage, there is a need for other effective treatments with fewer side effects.

The results obtained using surgical castration have motivated further research in GnRH analogues treatments.

GnRH analogues act initially at the level of the pituitary to stimulate LH release, resulting in a transient increase in serum testosterone levels (flare-up). After an initial stimulation, continuous administration of GnRH analogues causes rapid desensitization of GnRH receptors, resulting in reduction of LH (and to a lesser extent of FSH) and testosterone to castrate levels within 2–4 weeks (Belchetz et al. 1978; McEvoy 1999). They do not interfere with the action of androgens of adrenal origin. Forty percent of normal controls reported reduction in normal sexual desire with GnRH treatment (Loosen et al. 1994). In addition, GnRH containing neurons project into pituitary and extra-pituitary sites, such as the olfactory bulb or the amygdale. At these latter sites, GnRH is believed to act as a neuromodulator and, through this action, may be also involved in sexual behaviour (Kendrick and Dixson 1985; Moss and Dudley 1989). Moreover, the intracerebroventricular administration of GnRH suppresses aggression in male rats (Kadar et al. 1992).

Three analogues of the gonadotrophin-releasing hormone are available. GnRH analogues were approved in many countries for the treatment of advanced prostate cancer (Vance and Smith 1984; Smith 1986), endometriosis, precocious puberty, uterine fibromyomas, and female infertility (in vitro fertilization).

Triptorelin is a synthetic decapeptide agonist, analogue of the gonadotropin-releasing hormone (GnRH). Triptorelin was developed as a pamoate salt (3 mg, 1 month formulation or 11.25 mg, 3 month formulation). It was recently approved in Europe for the reversible decrease in plasma testosterone to castration levels in order to reduce drive in sexual deviations of adult men (triptorelin LA 11.25 mg).

Leuprorelin is a synthetic analogue of GnRH. It was developed as daily i.m. or monthly depot injections (3.75 or 7.5 mg, 1 month formulation or 11.25 mg, 3 month formulation).

Goserelin is also a synthetic analogue of GnRH. It was developed as daily i.m. or monthly depot injections (3.6 or 10.8 mg subcutaneously).

Case reports

Triptorelin: Hoogeveen and Van der Veer (2008) reported one case of male paedophilia with mental retardation and alcoholism treated with triptorelin (3.75 mg/month) for 37 months with good efficacy. Previous treatment with SSRIs, antipsychotic or psychotherapy failed. Biphosphonates and calcium were added preventively to GnRH for 35 months but bone mineral demineralization occured after 37 months, triptorelin had to be withdrawn and deviant sexual fantasies returned. Hot flushes and erectile dysfunction were also observed during treatment. Testosterone levels decreased from 22.8 before treatment to 1.3 nmol/l during treatment.

Leuprorelin: In 1985, Allolio et al. successfully treated a homosexual paedophiliac with leuprorelin.

Rousseau et al. (1990) reported the case of a male exhibitionist (35 years old) who received a combination of short-acting leuprorelin and the antiandrogen flutamide with no side effects reported during 26 weeks. The assessment of the sexual fantasies and activities was achieved through self-reports. Concurrently with the decrease of testosterone, a sharp decline in the deviant sexual activities and fantasies was observed. The deviant activities completely ended after 2–4 weeks. At 26 weeks, triptorelin was withdrawn and the deviant sexual behaviour returned 2 months after treatment discontinuation.

Dickey (1992, 2002) reported the case of a male patient (28 years old) with multiple paraphilia and hypersexuality successfully treated for 6 months (1992) and 10 years (2002) with long-acting leuprorelin (7.5 then 3.75 mg/month) as compared with previous MPA (max 550 mg/week for 32 months) or CPA treatment (200–500 mg/week for 14 months). He observed that suppression of androgen of testis origin alone was sufficient for treatment. Testosterone levels decreased from 28.9 to 0.8 nmol/l. Bone demineralization was observed after 3 years and treated with calcium and Vitamin D. Gynecomastia was also reported.

In one case of male paedophilia, a significantly greater decrease in self-report and phallometric measures of sexual arousal and activity was obtained with leuprorelin (7.5 mg/month), as compared with previous CPA treatment (100 or 200 mg/day with a dose effect) or placebo. The study design was a complex cross-over trial of successive 16-week periods and then, 36 and 42 weeks with CPA 100 and 200 mg/day, respectively, leuprolide acetate for 24 weeks after a 10-week washout period. Testostererone level was reduced to castration level with leuprolide acetate (Cooper and Cernovski 1994).

Single case reports of successful leuprorelin treatment (7.5 mg/month) of a patient with exhibitionism and Huntington's disease (Rich and Osview 1994), or of a 43-year-old male patient with exhibitionism, hypersexuality, frontotemporal dementia and Klüver-Bucy syndrome (Ott, 1995) were also published. Efficacy was reported at 3 months. Weight gain, aesthenia and muscular pain were reported.

Grasswick and Bradford (2003) reported bone mineral demineralization in 1/1 case of leuprorelide treatment (plus CPA 300 mg/day) as compared with 2/4 of CPA treatment and 2/2 cases of surgical castration (plus CPA) during a follow-up of 4 years in seven paraphiliac males aged from 36 to 61 years old (paedophilia in five cases, sexual sadism in one case). Vitamin D and calcium were used.

In the remaining case reports (Briken et al. 2004; Saleh et al. 2004; Saleh 2005), eight male paraphiliacs (exhibitionism, paedophilia, sexual sadism or paraphilia not specified) were receiving leuprorelin acetate (7.5 mg/month or 11.25 mg every 3 months in one case) for several months to one and a half years. Psychotherapy was associated with hormonal treatment. In seven cases, psychiatric comorbidities were associated. In seven cases, flutamide was used for 15 days to 6 weeks in association with leuprorelin acetate. In addition to self reports of sexual activity and fantasies, hormonal levels were measured and, in one case, plethysmography was also used. Using self report or plethysmography, deviant sexual behaviour and fantasies disappeared within 1–3 months after treatment introduction in seven of eight cases, concurrently to the decrease of testosterone levels (one relapse occured while the patient was receiving leuprorelin acetate). In most cases, side effects were not reported. Erectile dysfunction was reported in one case.

Goserelin: Brahams (1988) reported the efficacy of goserelin acetate in one case of homosexual paedophilia in a male patient with previous sex offences. Previous MPA (800 mg i.m. per week) or CPA (600 mg/day) treatments were unsuccessful.

Czerny et al. (2002) reported the efficacy of goserelin acetate in five cases.

Open and controlled studies (see Tables III and IV)

No randomised controlled studies were published

Triptorelin: Among the three studies, there were two open prospective studies (41 subjects with paraphilias including 32 paedophiles, 22/41 subjects were sex offenders, 1-month formulation) and one retrospective study (30 sex offenders).

Table III. Changes in sexually deviant behaviours in chronic paraphiliac male patients treated with triptorelin (open and controlled studies).

Reference	Characteristics of the patients Paraphilias and sex offending behaviour Other conditions	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption Evolution
Open studies							
Thibaut et al. 1993, 1996, 1998 France Open study $N=11$ males	$N=11$ males (aged 15–57) (mean age 25) Paedophilia (7) Exhibitionism (1) Sexual sadism and exhibitionism (1) Rapists (2) Previous sex offences (6) *Comorbidities:* Mild mental retardation (3) Bipolar disorder (1) Borderline personality disorder (1) AIDS (1)	CPA (4 patients) 150–300 mg/d for 6 months–3 years: Lack of efficacy (3 cases) Gynecomastia (1 case)	Triptorelin 3.75 mg/month+ CPA 200 mg/day (10 days to 1 year, one week before GnRHa to prevent a flare-up effect) + Psychotherapy Duration of follow-up: 7 months–7 years	Intensity of fantasies Frequency of masturbation and sexual activity Frequency of deviant fantasies and behaviour (Self-report scale: intensity of sexual desire and symptoms scale) Hormonal levels (Testosterone, FSH, LH, TeBG, Estradiol) Testis volume Osteodensitometry	Decreased levels of testosterone (22.9 ± 2.8 to 1.2 ± 0.3 nMol/l $P<0.1$) and of LH and estradiol but not TeBG No change in testis volume Deviant sexual fantasies and behaviour disappeared in 10/11 cases In 1 case, (testosterone level<1 nMol/l for 9 months) frequent paedophilic fantasies were maintained and he tried to have sexual contacts with a child Sexual activity decreased from 40 ± 10 to 0.6 ± 0.2 per week after 1st month ($P<0.01$) Sexual fantasies decreased from 57 ± 13 to 0.2 ± 0.1 after 1st month ($P<0.01$) In 4 cases non-deviant sexual activity and erectile capacities were maintained	Erectile failure (2) Hot flushes (1) Decreased libido (11/11) Vertebral bone loss after 3 years (1) Asthenia (1) Pain at the injection site (1) Depressive syndrome with suicidal attempt (1)	Treatment interruption (3 cases) at 12, 34 and at 58 months In the first 2 cases, relapse of deviant behaviour within 8–10 weeks In the 2nd case, the patient ask for treatment reintroduction (recurrence of deviant sexual fantasies) In the 3rd case no relapse but gradual increase of testosterone levels with testosterone +GnRH analogues (GnRH was stopped due to bone mineral loss) Hormonal levels returned to normal levels within 2 months 1 patient died (AIDS) 1 lost to follow-up
Rösler and Witzum 1998 Israel Open study $N=30$ males	$N=30$ (mean age 32 ± 8 years) Paedophilia (25) Exhibitionism (7) Voyeurism (2) Frotteurism (2) Sexual hyperactivity (30) More than 1 paraphilia:	CPA (9 patients) 150–300 mg/day for 4–10 years Stopped at least 1 year before the study SSRIs (7 cases) withdrawn at least 2 months	Triptorelin 3.75 mg/month +Psychotherapy +Psychotropic drugs (7 cases and in 2 cases 2 drugs) No CPA	Self-report scale (intensity of sexual desire and symptoms scale) (8-point scale) monthly, sexual activity, Three main complaints	Statistical analysis conducted on 24 cases (>/1 year treatment) No deviant sexual behaviour (5 ± 2 (range 2–8) of self report incidents of abnormal sexual behaviour at baseline decreased to 0 during treatment)	Hot flushes (6) Decreased facial and body hair growth (3)	5/8 relapses after interruption (in 3 cases due to side effects)

(Continued)

Table III. *(Continued)*

Reference	Characteristics of the patients Paraphilias and sex offending behaviour Other conditions	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption Evolution
	5 cases Previous sex offences (16) *Comorbidities: (22 cases)* Schizophrenia (5) Personality disorders (9) *Exclusion criteria:* Mental retardation Denial No sex offence No concurrent psychotherapy Prisoners	before the study Lithium (2) Antipsychotics (9)	Duration of follow-up: 8–42 months	questionnaire scale) (13-point scale) before treatment and at 12 months (severity of the 3 problems ascertained to most affect the subject) Testis volume (every 3 months) FSL LH testosterone levels (1/month) Osteodensitometry (2/year)	Decrease in sexual behaviour (intensity of sexual desire and symptoms scale: 8±0.2 to 2.7±2.3 at 6 months ($P<0.05$) and to 1.7±0.9 at 12 months and to 1.4±0.15 at 42 months) Maximal effect after 3 to 10 months (but significant vs. baseline after 1st month) Three main complaints Questionaire: First problem cited: paraphilia severity (score from 10±3 to 4±3 after 1-year treatment $P<0.001$) Decrease in LH levels (10.6±5.3 to 0.8±0.4) and testosterone levels (545±196 to 26±14 ng/dl at 6 months $P<0.05$)	Asthenia and myalgia (2) Muscular pain and at injection site Erectile failure (21) Decreased lumbar bone mineral density (11/18): Vitamin D+Calcium if necessary after 2 years (2 cases) Decreased testicular volume up to 50% after 36 months ($P<0.05$)	Testosterone levels returned to baseline levels within 2 months Replacement with CPA in 3/8 cases (200 mg/day): relapse in 2 cases, reintroduction of triptorelin in 2/8 cases
Retrospective study							
Hansen and Lykke-Olesen 1997 Retrospective study *N*=30 males	*N*=30 Males Previous sex offences Psychopathy (? cases)	No information	Triptorelin (dosage ?) + CPA (dosage ?) + Psychotherapy	Self report of sexual behaviour Recidivism	No follow-up clearly reported No relapse and decrease of deviant sexual fantasies while treated Only 5 cases maintained long term treatment	Weight gain Hot flushes Urinary incontinence (1) Gynecomastia Increased sweating	Interruption (7 cases): 1 death: cardiac disease, hepatitis C (2 cases), in 4 cases patients withdrew treatment In 5 cases, treatment interruption after released from prison: 1 relapse

Leuprorelin: Among the three studies, there were three open studies (28 subjects with paraphilias including 13 paedophiles, 16/28 subjects were sex offenders, 1- or 3-month formulation)

One retrospective study with different GnRHa treatments compared with CPA (58 subjects with paraphilias including 16 paedophiles, 19 cases with data available, 11 with leuprorelin acetate, three with triptorelin and five with goserelin acetate as compared with CPA alone in 29 cases).

In all studies, except for Rösler et Witzum (1998), CPA or flutamide was used in combination with GnRHa during the first weeks of GnRHa treatment.

Efficacy, dosage

Triptorelin: Two open prospective studies using triptorelin 1-month formulation were performed in sex offenders or paraphiliacs (Thibaut et al. 1993, 1996, 1998; Rösler and Witztum 1998). The data are summarized in Table III. Thibaut et al. (1993) reported the first open study of triptorelin in six patients with paraphiliac behaviours. Rösler and Witztum (1998) reported another open uncontrolled study of triptorelin in 30 patients with paraphiliac behaviours using a similar design. Czerny et al. (2002) in an open retrospective study compared different GnRHa treatments with CPA and three patients were receiving triptorelin in this study.

In total, 75 male subjects (aged from 15 to 57 years) with paraphilia were included in two prospective open studies ($n=41$), two retrospective studies ($n=30+3$) and one case report. The most frequent paraphilias observed, whenever reported, were paedophilia ($n=33$) and exhibitionism ($n=8$). In six cases, at least two paraphilias were observed in the same patients. In some cases, comorbidities were associated to paraphilias (mental retardation, schizophrenia or, in most cases, personality disorders). The outcome measures were self report of deviant and non-deviant sexual behaviour and fantasies (type, frequency, intensity), testosterone and LH levels. In Rösler'study, two scales were used: Intensity of sexual desire and symptoms scale, and the Three main complaints questionaire. Subjects were receiving depot triptorelin for some months to 7 years (3.75 mg/month). In the Thibaut et al. study, CPA was concurrently used for the first weeks of triptorelin in order to prevent the behavioural consequences of a flare up effect.

During triptorelin treatment, no deviant sexual behaviour was observed and no sexual offences were committed except for one case (Thibaut et al. 1993). Concomitantly to the rapid and sharp decrease of testosterone and LH levels, a reduction of non-deviant sexual behaviour was observed with a maximal effect after 1 or 3 months and deviant sexual fantasies disappeared. One-third of cases (13 cases) have previously received CPA without efficacy. In 10 cases (in three cases due to GnRH analogues side effects), treatment was abruptly interrupted and deviant sexual behaviour and fantasies reappeared in seven cases. In three cases, triptorelin was resumed with good efficacy and in three cases, CPA (200 mg/day) was introduced but without efficacy in two of three cases. In one additional case, triptorelin was gradually stopped using increasing testosterone supplementation in a patient with bone mineral loss and no relapse was observed.

In the retrospective study, in five cases, subjects interrupted GnRHa treatment when released from prison, one relapse was observed. These studies were only open studies without any comparison with placebo. No plethysmography was used. However in all cases, but one, triptorelin was successful and the deviant sexual behaviour completely disappeared during GnRH analogue treatment. Moreover, triporeline efficacy was superior to CPA efficacy in 13 out of 41 cases. In the Czerny et al. study, similar efficacies were observed with CPA and triptorelin.

Since the new sustained-release triptorelin palmoate 3-month formulation is as effective as the 1-month formulation in achieving and maintaining castrate testosterone levels, similar efficacy of both formulations on the reduction of drive in sex offenders can be inferred. Moreover, the 3-month formulation is expected to strongly improve the treatment compliance, on which long-term control of the paraphiliac behaviours largely depends. However, similarly, no controlled studies were conducted with this compound.

Leuprorelin: Four studies using leuprorelin (1- or 3-month formulations) were performed in patients with paraphiliac behaviours (Briken et al. 2001; Briken 2002; Krueger and Kaplan 2001; Czerny et al. 2002; Schober et al. 2005, 2006). The last of these studies was a double-blind study. The data are summarized in Table IV.

Forty-five male subjects were receiving leuprolide acetate (20–61 years old), they were included in three prospective studies including a cross-over study (Schober et al. 2005) (28 cases in total), one naturalistic study comparing CPA and GNRH analogues (Czerny et al. 2002; 58 cases, 11 with leuprorelin acetate) and 15 case reports (previously described). The Schober et al. study was a "masked" cross-over study (versus placebo) ($n=5$ sex offenders) but unfortunately was not intended

Table IV. Changes in sexually deviant behaviours in chronic paraphiliac male patients treated with leuprorelin (open and controlled studies).

Reference	Characteristics of the patients Paraphilias and sex offending behaviour other conditions	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects
Open studies						
Briken et al. 2001, 2002 Germany Open study *N*=11 males	*N*=11 males (19–57 years old) Paedophilia (7) Incest (1) Sadism with (3) or without paedophilia (1) Previous sexual offences (11) *Comorbidities:* Sexual impulsivity (3) Mental retardation (5) *Exclusion criteria:* Prisoners Neurological disorders	CPA (6 cases) 300 mg (form?) for 2 to 14 months SSRIs (4 cases) Antipsychotics (2 cases)	Leuprorelin acetate 11.25 mg/ 3 months+ CPA (300 mg depot for 2 weeks)+ Psychotherapy Duration of follow-up: 1 year	Intensity of fantasies Frequency of masturbation and sexual activity Frequency of deviant fantasies and behaviour (self-report Lickert scale) Testosterone levels	No deviant sexual behaviour 11/11 cases Decreased sexual activity and behaviour (>/1 masturbation/ day to 3–4/month at 3 months and one masturbation/month at 12 months) Fantasies decreased slightly less Testosterone levels decreased from 3.5–10.7 to 0.4	Depressive disorder Weight gain Pain at injection site Suicide attempt (1)
Krueger and Kaplan 2001 USA Open study *N*=12 males	*N*=12 Males (aged 20–48 years old) (mean age 35.5) Paedophilia (6) Exhibitionism (5) Voyeurism (3) Sexual sadism (1) Paraphilias NOS (2) *Comorbidities:* Mental retardation (1) Head trauma (2) Frontal lobectomy, Personality disorders Addictions, Depressive disorders, Chromosomal aberrations (1), Psychosis	MPA (2) 120 mg/day SSRIs (9) (high dosages) Other psychotropic drugs (7) No effect of previous MPA in 1 case or SSRIs (6 cases)	Leuprorelin acetate (3.75 or 7.5 mg/month)+ Flutamide 250 mg t.i.d. for 30 days + Psychotherapy (Cognitive or individual supportive) Duration of follow-up: 6–57 months	Self reports of deviant and non-deviant sexual activity and fantasies Testosterone FSH, LH levels Osteodensitometry	No relapse 12/12 cases Marked reduction of deviant and non-deviant sexual arousal and interest depending on pretreatment frequency and intensity Mean testosterone level (*n*=8) decreased from 493 ng/dl (baseline) to 22 while treatment In 2 cases, effect was maintained after treatment interruption for 2–4 years	Bone mineral loss (3)>35 months ttt Nausea (1) Depressive disorder (1) Mild gynecomastia (3) Decrease of erections except for one case (20 years old) One relapse after ttt interruption
Schober et al. 2005, 2006 USA **Prospective, repeated measures, non-randomized**	*N*=5 Males Mean age 50 years (38–58) Sex offenders convicted *Comorbidities:* Alcoholism (2) Depressive disorders (1) Personality disorders		Leuprorelin acetate (7.5/ month, then 11.25/3 months)+ Flutamide tid 250 Duration of follow-up: 12 months	Self reports Testosterone levels Plethysmography (erotic visual stimuli) (Abel assessment) Scales: Hare psychopathy	No change in sexual interest No statistical analysis of GnRH analogues efficacy vs. placebo Leuprolide acetate: Reduction of deviant and non-deviant sexual activity (masturbation rate decreased	Weight gain (mean 22 lbs) (5) Pain at injection site (4) Decrease in flaccid penile circumference Hot flushes (3) Gynecomastia (1) Erectile dysfunction (5) No hair loss, no asthenia,

(Continued)

Table IV. *(Continued)*

Reference	Characteristics of the patients Paraphilias and sex offending behaviour other conditions	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects
masked cross-over study	Psychopathy (5)	None	mg for 14 days	check list revised Minesota Sex	from 1.7/week at baseline to 0.1 at 12 months) with	no muscular pain
Not designed to evaluate GnRH efficacy	No denial No mental retardation		**Then** Placebo for 12 months	Offender Screening tool revised Y BOCS	leuprolide acetate > placebo (plethysmography, $P<0.05$) No deviant behaviour	In 1 case prostatic nodule at baseline decreased with GnRH
N=5 males	*At inclusion:* Minesota scale before inclusion: in 4 cases moderate risk of recidivism, in 1 case low risk Static 99 before inclusion: in 1 case high risk of recidivism, in 2 cases moderate risk, in 2 cases low risk Y BOCS: in 3 cases severe sexual compulsions, in 2 cases moderate sexual compulsions		+ Behavioural therapy for 2 years Total duration of follow-up: 2 years	Static 99 (sexual offender risk assessment) Frequency of masturbation or deviant sexual behaviour	Decreased testosterone levels Placebo: Increased sexual activity, fantasies and deviant fantasies with placebo after 2 months in 3 cases including a high risk of recidivism in 1 case Testosterone levels returned to baseline levels	
Retrospective study						
Czerny et al. (2002) Germany Open study, retrospective *N*=58 males	*N*=58 Males (mean age 38 years old) Paedophilia (16), Sadomasochism (3), Exhibitionism, Fetichism, Voyeurism *Comorbidities:* Mental retardation (24), alcoholism(8), personality disorders (26)	No data	Leuprorelin acetate (11) **Triptorelin (3)** **Goserelin acetate (5)** In 19 cases only data are available) + CPA for 2 weeks **OR** **CPA** (29) Dosage ? Mean duration of follow-up: 10.3 months (GnRH analogues) and 22.6 months (CPA)	Self reports Testosterone, LH, FSH levels	Efficacy of CPA= Efficacy of GnRH agonists Reduction in sexual activity and fantasies No efficacy in 3 cases in each group In 1 case with CPA treatment deviant sexual fantasies increased In 2 cases CPA was unsuccesful and replaced with GnRHa with good efficacy	Weight gain CPA (14) GnRHa (4) Gynecomastia CPA (10) GnRHa (4) Hot flushes CPA (2) GnRHa (4) Asthenia CPA (3) GnRHa (4) Hypogonadism CPA (1) GnRHa (1) Thromboembolism CPA (1) Depressive disorder CPA (2) Hair loss CPA (4) Blood pressure variations GnRHa (2) Bone demineralization GnRHa (1) Hypogonadism CPA (1) GnRHa (1)

(Continued)

Table IV. *(Continued)*

Reference	Characteristics of the patients Paraphilias and sex offending behaviour other conditions	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects
Case reports: Saleh et al. 2004 USA *N*=6 males	*N*=6 Males (aged 19–20 years old) Paedophilia (1) Frotteurism (1) Sexual sadism (1) Non specified paraphilia (3) *Comorbidities:* ADHD (2) Drug abuse (2) Bipolar disorders (5) Mental retardation (2) Psychopathy (2) Border line disorder (1) Conduct disorder (2) Klinefelter syndrome (1)	None	Leuprorelin acetate 7.5 mg/month + Flutamide for 14 days + Psychotherapy Duration of follow-up: 10–16 months	Intensity of fantasies Frequency of masturbation and sexual activity Frequency of deviant fantasies and behaviour (self-report scale Testosterone, FSH, LH, Estradiol levels	Sexual activity decreased Deviant sexual behaviour and fantasies disappeared	Retrograde ejaculation (1) Erectile failure (1)

for the study of leuprorelin efficacy. Schober et al. (2005) have compared behavioural therapy with leuprolide acetate or with placebo in a cross-over study including five paedophiles. In three cases, while subjects were receiving placebo treatment, deviant sexual fantasies returned and testosterone levels returned to baseline levels.

The most frequent paraphilias observed were paedophilia, sexual sadism and exhibitionism. Previous sexual offences were reported in 16 cases. In some cases, paraphilias were not specified. Mental retardation, alcohol abuse and personality disorders were the most frequently observed comorbidities. In addition to the outcome measures used, such as self report of deviant and non-deviant sexual behaviour and fantasies (type, frequency, intensity) or testosterone and LH levels, plethysmography was used in the Schober et al. study. In all cases, CPA or flutamide was concurrently used for the first weeks of triptorelin in order to prevent the behavioural consequences of a flare-up effect. Maximal duration of follow-up was 57 months (mean duration about 1 year). In most cases concurrent psychotherapy was used.

Concomitantly to the rapid decrease of testosterone levels, a reduction of non-deviant sexual behaviour was observed and deviant sexual fantasies disappeared. However, in one case report (Briken et al. 2004) the patient relapsed while treated with leuprorelin treatment and committed a sex offence.

Czerny et al. (2002), in an open retrospective study, compared the efficacy of GnRH analogues and CPA in 58 subjects. CPA and GnRH analogues showed the same efficacy with no effect on deviant sexual behaviour in three cases within each group. An increase in sexual fantasies was reported in one case with CPA treatment. In addition, in two cases previously treated with CPA, GnRH analogues were used instead of CPA because of insufficient reduction of sexual aggressive impulsiveness under CPA. In these latter cases, the intensity of sexual desire and symptoms was notabely reduced with GnRH analogues as compared with previous CPA treatment.

Cooper and Cernovsky (1994), using plethysmography in one male paedophile, have compared CPA and leuprolide acetate. The following treatment sequences were used: placebo (32 weeks in total), no treatment (52 weeks in total), CPA 100 mg/day (36 weeks), CPA 200 mg/day (42 weeks), leuprolide acetate 7.5 mg/month (24 weeks). Leuprolide almost totally suppressed both self report and phallometric measures of sexual arousal and reduced testosterone levels to castration levels. Leuprolide efficacy on phallometric data and self reports of sexual arousal

was superior to CPA efficacy (100–200 mg/day). No treatment and placebo shared the same lack of effect on all measurements.

Duration of GnRH agonist treatment

The duration of treatment necessary to achieve a complete disappearance of deviant sexual behaviour and the conditions of treatment interruption remains open. Efficacy was maintained for years and as long as the antiandrogen treatment was maintained (for example the maximal follow-up duration reported was 7 years for triptorelin and 10 years for leuprolide acetate). In Rousseau et al. study (1990), the authors reported recidivism when a successful treatment with leuprorelin and flutamide was abruptly stopped at 26 weeks. In the Thibaut et al. study (1996), the authors described recurrence of deviant sexual behaviour or fantasies within 8–10 weeks in two cases, when a successful GnRH agonist treatment was abruptly interrupted after, respectively, 12 and 34 months. Both subjects relapsed within 8–10 weeks. In the latter case, GnRH agonist treatment was reintroduced and the deviant fantasies disappeared again. By contrast, in a third case, after 4.5 years of effective GnRH agonist treatment, testosterone was gradually added to GnRH agonist (in order to avoid a possible rebound effect in sexual deviant behaviour after abrupt interruption of GnRH agonist treatment). When GnRH agonist and testosterone were stopped after 10 months of concurrent prescription (as soon as the testosterone level was back in the normal range), the deviant sexual behaviour did not return and this lack of deviant sexual fantasies or behaviour was maintained 1 year later. In Rösler's study (1998), in eight cases, triptorelin was interrupted after 8–10 months, paraphilia resumed in five cases in whom follow-up was possible. In Hanson's retrospective study (1997), five subjects stopped triptorelin when they left prison and in one case deviant sexual behaviour returned. In one additional case report, deviant sexual behaviour resumed when triptorelin was stopped because of bone mineral loss (Hoogeveen and Van der Veer 2008). In the Krueger and Kaplan study (2001), in one case, leuprolide acetate was stopped and deviant sexual behaviour reappeared. In Schober's study (2005), when leuprolide acetate was replaced with placebo, in three of five cases, deviant sexual behaviour returned within 2 months and, in one case, there was a high risk of sex offence.

In Thibaut et al.'s experience, a minimal duration of 3 years is necessary to establish a stable relationship with the patient and to allow him to accept his disease and the necessity of pharmacological treatment. For some patients, a life-long treatment may be needed.

Side effects

Bone mineral loss

In Thibaut et al. study, six young men (aged from 15 to 39) with paraphiliac behaviours were receiving triptorelin 3.75 mg/month. Duration of exposure to treatment ranged from 9 months to 7 years. Vertebral and/or femoral bone mineral density was measured before treatment and yearly in some patients. Decreased values of vertebral and femoral bone densities (0.95 and 0.8 g/cm^3, respectively), without clinical signs but requiring medical supervision, were recorded during the third year of triptorelin treatment in one patient aged 27. The corresponding normal ranges were 1.15 ± 0.15 and 0.9 ± 0.1 g/cm^3, respectively, for 17–30 years of age. It is to be noted that pubertal development was complete in the 15-year-old patient and bone age was 16 years 6 months when triptorelin treatment was started. Follow-up of bone mineral density revealed no abnormality during treatment in this young man.

In Rösler's study, 30 young men (mean age: 32 ± 8 years) with paraphiliac behaviours were receiving triptorelin 3.75 mg/month. Duration of exposure to treatment varied from 8 months to 3.5 years. Bone mineral density of the femoral neck and lumbar spine was measured before triptorelin treatment. The results were normal, except for 14 men who had low values for femoral neck ($78 \pm 8\%$ of the age-matched men values) or lumbar spine ($85 \pm 8\%$) bone mineral density. Seven had previously received CPA. The effect of triptorelin on bone mineral density was followed up in 18 men in whom all planned measurements were obtained. Among them, the bone mineral density of the femoral neck or lumbar spine was decreased in 11 men and did not change in seven men. In the group as a whole, the mean density decreased in the lumbar spine from $92.8 \pm 13.0\%$ of the aged-matched men value before triptorelin initiation to $86.5 \pm 10.7\%$ after 12 months of treatment; in the femoral neck it decreased from 84.5 ± 15.7 to $80.4 \pm 8.8\%$ at the same timepoints. The decrease was significant only in the lumbar spine ($P<0.05$ after 6 and 12 months of treatment versus the previous months). Two patients, who had progressive demineralization, were given oral calcium and vitamin D supplements after completing 24 months of triptorelin therapy.

Hoogeveen and Van der Veer (2008) reported bone demineralization in one patient aged 35 years after 37 months of triptorelin treatment in spite of biphosphonates and calcium treatment from 2 to 37 months. Triptorelin had to be stopped.

Krueger and Kaplan (2001) observed three cases of demineralization at 35 and 57 months, respectively, among 12 patients aged from 20 to 48 years old, receiving leuprolide acetate. Czerny et al. (2002) reported one case of bone mineral loss among 29 patients receiving GnRH analogues for a mean duration of 10 months. Dickey et al. (2002) observed demineralization after 3 years of leuprolide acetate treatment in a 28-year-old patient. Calcium and vitamin D were used. Grasswick and Bradford (2003) focused their study on bone mineral survey and reported demineralization in two of four cases with CPA, one case with leuprorelin and two of two with surgical castration, the follow-up duration was 4 years.

A yearly osteodensitometry was recommended by all authors as well as calcium and vitamin D supplementation in case of bone loss. Although the efficacy of calcium and vitamin D supplementation in osteoporosis prevention has not been studied in men on antiandrogen treatment, they are likely to benefit from calcium (1200–1500 mg daily) and vitamin D supplementation (400–800 IU daily), and should be advised to abstain from smoking and excessive alcohol use. A class of drugs, the biphosphonates (e.g., oral alendronate or risedronate, and parental pamidronate or zoledronic acid given every 12 weeks), inhibit bone resorption by their inhibitory effects on osteoclast activity. These drugs have been successfully used in reducing bone loss in patients receiving antiandrogens. Alendronate was found to reduce the incidence of vertebral fractures in men in randomized double-blind trials, but as yet there have been no randomized trials of reduction in fracture rates in men treated with antiandrogens. Nevertheless, the use of biphosphonates is recommended in men with osteodensitometry-proven osteoporosis or in men with osteopenia and pre-existing bone insufficiency fractures (due to minimal trauma). It should further be considered when there is evidence of progressive bone loss during antiandrogen treatment. Considering the role of oestrogens also in male bone health, selective oestrogen receptor modulators are also being investigated (for review see Giltay and Gooren 2009).

Other side effects

The patients also complained of hot flushes, asthenia, nausea, weight gain (2–13%), transient pain or site reaction at the site of injection (granulomas were observed with leuprolide in 4% of patients among 118), decreased facial and body hair growth (2–23%), blood pressure variations, decreased testicular volume (4–20%), episodic painful ejaculation (one case), diffuse muscular tenderness, sweating, depressive symptoms (two suicide attempts were reported, in one case in relationship with relapse at the end of the study (Briken et al. 2001), in the other case, previous suicide attempts were reported (Thibaut et al. 1993)) and finally mild gynecomastia (2–7%) (Hanson and Lykke-Olesen 1997; Krueger and Kaplan 2001; Czerny et al. 2002; Dickey 2002; Schober et al. 2005; for review see Guay, 2009).

Czerny et al. (2002) compared CPA with GnRH analogues (GnRHa) in 58 subjects (29 in each treatment group) and reported more frequently with CPA as compared with GnRH analogues: weight gain (14/29 vs. 4/29), gynecomastia (10/29 vs. 4/29), depressive symptoms (2/29 vs. 0/29), thromboembolism (1/29 vs. 0/29), hair loss (4/29 vs. 0/29). In contrast, hot flushes (4/29 vs. 2/29), asthenia (4/29 vs. 3/29), bone mineral loss (1/29 vs. 0/29) (at 10 months), blood pressure variations (2/29 vs. 0/29) were more frequent with GnRHa as compared with CPA. Hypogonadism was observed in one case with CPA versus one case with GnRHa.

Most patients reported progressive erectile dysfunction and decreased libido after 6–12 months of treatment. The lack of sexual interest toward women, with an inability to achieve or maintain an erection or perform sexual intercourse was proportional to age, occurring in some younger men but in all men older than 35 years.

The fact that one patient had severe gynecomastia under previous CPA treatment, which did not reoccur under triptorelin, is also to be mentioned.

In all patients, the standard blood biochemistry results remained within the normal ranges as measured after 6 months of triptorelin treatment.

Guidelines

In conclusion, there were no controlled studies, and some biases were observed (small size of samples, short duration of follow-up in most cases, open or retrospective studies) (*Level C of evidence*). However, the efficacy observed in these open studies was very high and in most cases, subjects were previously treated with psychotherapy or other antiandrogens without efficacy.

Blood pressure measurement, physical examination including weight measurement are necessary before treatment. Testosterone, FSH, LH plasma levels, electrocardiogram, fasting glucose blood level, lipide profile, calcium and phosphate blood levels, kidney function must be evaluated before treatment. Bone mineral density must be checked before treatment in case of personal or familial osteoporosis risk, or in patients over 50 years old, and every 2 years during GnRH treatment (or every

year, if increased risk of osteoporosis or if the patient is over 50 years old). Active pituitary pathology, severe chronic depressive disorder or allergy to hormonal treatment, alcohol and tobacco consumption must be assessed through interview of each candidate before hormonal treatment. Informed consent must be obtained.

The use of GnRHa treatment has to be carefully managed medically, via physical examination, especially for the effects of feminisation. Depression, emotional disturbances must be evaluated every 1–3 months. Every 6 months, fasting blood glucose levels, lipid profile, blood cell count, calcium and phosphate blood levels, blood pressure, weight must be controlled. Bone mineral density must be checked every year in case of increased osteoporosis risk (Reilly et al. 2000; Hill et al. 2003; Briken et al. 2003) or at least every 2 years. Calcium, vitamine D or biphosphonates must be prescribed in case of osteoporosis. Testosterone blood levels could be checked in case of risk of breaks in the therapy, or in case of risk of masked testosterone supplementation. Indeed, there is a risk that patients could antagonize their GnRH agonist treatment with testosterone supplementation but we could not find any specific data in the existing literature on this topic.

GnRHa must not be used in case of: non-consent, puberty not completed especially when bone growth is not achieved, severe hypertension, pregnancy or breast feeding, severe cardiac or renal disease, severe osteoporosis especially in case of prior fractures, severe depressive disorder, allergy to GnRHa, active pituitary disease.

When properly administered, with an appropriate protocol in place to detect and treat side effects should they develop, GnRHa treatments constitute no more or less of a risk than most other forms of frequently prescribed psychopharmacological agents.

GnRH agonist treatments should be used after other alternatives have been ruled out or when there is a high risk of sexual violence. Antiandrogens or GnRH analogues significantly reduce the intensity and frequency of sexual arousal but do not change the content of paraphilias. In spite of their efficacy, MPA and CPA treatments are associated with a high percentage of side effects which have considerably limited their use, especially for MPA in Europe. In addition, uncontrolled breaks in the therapy are often observed with oral CPA or MPA treatments. In contrast, long-acting GnRH analogues are more potent than CPA or MPA. Moreover, they induce fewer side effects, except for those related to hypoandrogenism. Long-acting GnRH analogues may be administered parentally once every one to three months. GnRH analogue treatment probably constitutes the most promising treatment for sex offenders at high risk of sexual violence, such as paedophiles or serial rapists.

Conclusion

In general, the quality of the evidence base supporting the use of all these treatments is rather poor.

A meta-analysis of 12 studies in sex offenders suggested a small but robust treatment effect (additional offences in 19% of treated vs. 27% of non-treated offenders) (Hall 1995). The best treatment effects were found with the following conditions: the highest recidivism rates, a duration of follow-up greater than 4 years, outpatients vs. institutional samples, and cognitive-behavioural and hormonal treatments vs. behavioural ones. Self-referred or highly motivated subjects are best responders to chemical treatment (Soothill and Gibbens 1978). A meta-analysis of factors predicting recidivism, based on 61 follow-up studies and including 23,400 sex offenders, found that failure to complete treatment was associated with higher risk of recidivism of sex offences (Hanson and Bussiere 1998). These data strongly suggest that therapeutic management of paraphiliac behaviours significantly reduces recidivism rate.

Not every sex offender is a candidate for hormonal treatment, even if it has the benefit of being reversible once discontinued. Some authors have proposed algorithms for treatment of paraphilias (Gijs and Gooren 1996; Bradford 2000; Rösler and Witztum 2000; Thibaut 2003; Maletzky et al. 2006; Guay 2009).

For paraphilias characterized by intense and frequent deviant sexual desire and arousal, which highly predispose the patient to severe abnormal behaviours (such as paedophilia or rape), a hormonal intervention using GnRHa may be needed after other alternatives had been ruled out. GnRH agonists have to be prescribed by a physician after informed consent is given. GnRH analogues reduce more dramatically and more consistently testosterone levels, and produced less variable results in the treatment of paraphiliac behaviours than MPA or CPA (Rösler and Witzum 1998; Thibaut et al. 1998). GnRH analogues produced castrate testosterone levels in all patients within the first months of treatment and abolished deviant sexual behaviours in more than 95% of patients with severe paraphiliac behaviours. Efficacy was maintained throughout the treatment duration in all responders. The direction of the sexual drive was not affected. In men who interrupted treatment, testosterone levels progressively returned to baseline. The studies did not support the specificity of GnRH analogues in reducing

sex drive for deviant versus normal stimuli. However, while treated, some patients maintained lower erectile capacities and were able to maintain some masturbation and coital activities, this was proportional to age.

GnRH analogues are more potent than CPA in reducing the effects of testosterone in tissues, or also may have a direct effect on the central nervous system in suppressing deviant sexual behaviour (Kadar et al. 1992). Furthermore, GnRH neurons project to extrapituitary sites where the hormone may act as a neuromodulator (Moss and Dudley, 1989). Finally, the use of long-acting GnRH analogues excluded the uncontrolled breaks in the therapy often observed with oral CPA treatment.

Thus, GnRH analogues, by inducing castrate testosterone 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 behaviour.

However, hormonal agents cannot be easily used in the treatment of sexually deviant juveniles owing to possible interference with the development or course of puberty (bone growth must be achieved and should be checked using X-rays) (Kahn and Lafond 1988; Bremer 1992; Bradford 1993; Worling and Curwen 2000; Gérardin and Thibaut 2004; Reitzel and Carbonell 2006).

Maletzky et al. (2006) proposed a scale intended for the evaluation of sex offenders and to guide antiandrogen use in paraphiliac subjects. This scale is composed of 13 items, each item with a different score number (1 or 2), a score superior or equal to seven could be an indication for antiandrogen treatment.

Definition of the items	Score number
Several victims	1
Several paraphilias	1
Preferential deviant sexual behaviour	1
Deviant sexual interest (Plethysmography or Abel Screen)	2
Don't live with the victim	1
Use of strength during sex offending	1
Male victim	2
Age <30 at liberation	1
Brain dysfunction	2
Previous psychiatric history	1
Sex offending as outpatient	1
Sex offending within institution	1
Previous treatment failure	2

However, Maletzki concluded that clinical judgement must remain the first criteria for treatment choice in case of sex offending.

General guidelines

Most people recognize that incarceration alone will not solve sexual violence. Treating the offenders is critical in an approach to preventing sexual violence and reducing victimization.

Paraphiliac men may be ordered by the judge to undergo psychiatric treatment as part of the rehabilitative aspect of sentencing, but these situations should leave treatment options up to the professionals. In case of antiandrogen treatment, it must include freely given informed consent. Indeed, these treatments must remain a choice to be made by the patient on the basis of medical advice. Somehow, in some cases, failure of the offender to accept the treatment could lead to sanctions by the court.

Prior to treatment, each individual should be carefully examined by at least one mental health professional, in order to identify and evaluate sex offenders (especially number and type of paraphilias and previous response to treatment if any), and if necessary protect and adequately treat offenders who are suffering from a major mental illness or mental retardation.

However, little is known about which treatments are most effective, for which offenders, over what duration, or in what combination. According to numerous reviews or meta-analysis, the combination of pharmacological and behavioural treatment coupled with close legal supervision appears to reduce the risk of repeated offense. However, the treatments do not change the subject's basic sexual orientation.

Because of ethical issues (high risk of recidivism, low level of motivation of the patients, denial, prisoners in most cases, etc.), the great majority of pharmacological studies are uncontrolled studies without placebo comparison and some methodological problems are observed. Marshall and Marshall (2007) have proposed two alternative designs for future sex offender studies: incidental designs and actuarially based evaluations. With incidental designs, the incidental non-treatment group is selected from the same population as the treatment group, the source being those not treated because limited resources prevent the treatment of all sex offenders or historical "controls" from facility archives. In actuarially based evaluations, the actual recidivism rates of treated subjects are compared with the expected recidivism rates form actuarial risk assessment instruments. This could be used when all subjects enter treatment.

Another major difficulty is the identification of standardized and reliable measures of sexual behaviour. Sex offenders' self-reports of their sexual activity and arrest records reports are usually used, but they do not constitute reliable indices of conventional or

paraphiliac sexual behaviour. In addition, the definition of recidivism is often different from one study to another. In the same way, the validity and reliability of the evaluation of sexual response via penile plethysmography which measures penile erectile responses to various visual or auditory erotic stimuli in a laboratory, are still a subject of debate. In any case, plethysmography should be used to predict further sex offences or to make a diagnosis. Moreover, various types of sex offenders are included in the same studies and makes it difficult to draw definite conclusions owing to the great heterogeneity of the samples of patients. Duration of follow-up periods is another source of variability among studies, long durations of follow-up being necessary to estimate the rates of recidivism.

Until now, there are no pharmacological studies conducted in sexual murderers and, in women, only few case reports were described.

National or international collaborative studies including large cohorts of well-defined paraphiliacs with long durations of follow-up are clearly needed to confirm these preliminary data, reporting the efficacy of pharmacological treatments in paraphilias. It would be also informative for future research to include a focus on all sex offenders including women and juveniles.

Based on the state of the art, we may propose the following guidelines:

The aims of the treatment of paraphilias are:

(1) to control paraphiliac fantasies and behaviours in order to decrease the risk of recidivism;
(2) to control sexual urges;
(3) to decrease the level of distress of the paraphiliac subject.

In addition to psychological and behavioural therapies, several pharmacological treatment options are available. The treatment choice will essentially depend on:

- the patient's previous medical history,
- the patient's observance,
- the intensity of paraphiliac sexual fantasies,
- the risk of sexual violence.

In all cases, treatment of comorbidities is necessary if any. In case of psychiatric comorbidities, pharmacological treatment such as benzodiazepines, antipsychotics, SSRIs or specific types of psychotherapy or behavioural therapy must be used. Hormonal treatment may be co-prescribed in case of lack of efficacy of adequate treatment of the psychiatric disease in order to control paraphiliac behaviour. However antiandrogen treatment may increase psychotic symptoms if any.

Reduced libido seems to make some offenders more responsive to psychotherapy (Murray 2000). Pharmacological interventions should be part of a more comprehensive treatment plan including psychotherapy and, in most cases, behaviour therapy.

Pharmacological interventions include

SSRIs

SSRIs are useful in paraphilias associated with obsessive-compulsive disorders, impulse control disorders, or depressive disorders. Some paraphiliacs clearly suffer from an inability to resist their sexual urges, which has a strong compulsive element and often causes considerable subjective distress. SSRIs can be effective in these cases, which are usually not associated with dangerous sex offending, especially in pure exhibitionists. The dosage must be increased to the dosages used in obsessive compulsive disorders in case of insufficiency or lack of efficacy of usual dosage.

Hormonal treatments

Not every sex offender is a candidate for hormonal treatment, even if it has the benefit of being reversible once discontinued. For paraphilias characterized by intense and frequent deviant sexual desire and arousal, which highly predispose the patient to severe paraphiliac behaviour (such as paedophilia or serial rapes), a hormonal intervention may be needed. The diagnosis of paraphilia must be carefully established and clinical characteristics of the patients listed (see section 2.4). Antilibidinal drugs may also be used in the treatment of sex offenders with mental retardation or cognitive dysfunctions. This has to be discussed with the patient's family or caregivers (Cooper 1995; Sherak 2000).

Antiandrogens or GnRH analogues have to be prescribed by a physician, after appropriate medical assessment.

Recommended clinical assessment of men before the start of androgen deprivation therapy and during follow-up:

Risk assessment before the initiation of hormonal treatment:

- physical examination; weight and blood pressure measurements; electrocardiogram; testosterone, testosterone-binding protein, LH, FSH and prolactine blood levels; hepatocellular and

Table V. Algorithm of pharmacological treatment of paraphilias.

LEVEL 1	
• Aim: control of paraphiliac sexual fantasies, compulsions and behaviours without impact on conventional sexual activity and on sexual desire	• Psychotherapy (preferentially cognitive behavioural therapy if available (Level C), no level of evidence for other forms of psychotherapy)
LEVEL 2	
• Aim: control of paraphiliac sexual fantasies, compulsions and behaviours with minor impact on conventional sexual activity and on sexual desire • May be used in all mild cases ("hands off" paraphilias with low risk of sexual violence, i.e. exhibitionism without any risk of rape or paedophilia) • No satisfactory results at level 1	• SSRIs: increase the dosage at the same level as prescribed in OCD (e.g., fluoxetine 40–60 mg/day or paroxetine 40 mg/day (Level C)
LEVEL 3	
• Aim: control of paraphiliac sexual fantasies, compulsions and behaviours with a moderate reduction of conventional sexual activity and sexual desire • 'Hands on' paraphilias with fondling but without penetration • Paraphiliac sexual fantasies without sexual sadism • No satisfactory results at level 2 after 4–6 weeks of SSRIs at high dosages	• Add a low dose antiandrogen (e.g., cyproterone acetate 50–100 mg/day) to SSRIs (Level D)
LEVEL 4	
• Aim: control of paraphiliac sexual fantasies, compulsions and behaviours with a substantial reduction of sexual activity and desire • Moderate and high risk of sexual violence (severe paraphilias with more intrusive fondling with limited number of victims) • No sexual sadism fantasies and/or behaviour (if present: go to level 5) • Compliant patient, if not: use i.m. form or go to level 5 • No satisfactory results at level 3	• First choice: full dosage of cyproterone acetate (CPA): oral, 200–300 mg/day or i.m. 200–400 mg once weekly or every 2 weeks; or use medroxyprogesterone acetate: 50–300 mg/day if CPA is not available (Level C) • If co-morbidity with anxiety, depressive or obsessive compulsive symptoms, SSRI's might be associated with cyproterone acetate
LEVEL 5	
• Aim: control of paraphiliac sexual fantasies, compulsions and behaviours with an almost complete suppression of sexual desire and activity • High risk of sexual violence and severe paraphilias • Sexual sadism fantasies and/or behaviour or physical violence • No compliance or no satisfactory results at level 4	• Long acting GnRH agonists, i.e. triptorelin or leuprolide acetate 3 mg/month or 11,25 mg i.m. every 3 months (Level C) • Testosterone levels measurements may be easily used to control the GnRH agonist treatment observance if necessary • Cyproterone acetate may be associated with GnRH agonist treatment (one week before and during the first month of GNRHa) to prevent a flare up effect and to control the relapse risk of deviant sexual behaviour associated with the flare up effect
LEVEL 6	
• Aim: control of paraphiliac sexual fantasies, compulsions and behaviours with a complete suppression of sexual desire and activity • Most severe paraphilias (catastrophic cases) • No satisfactory results at level 5	• Use antiandrogen treatment, i.e. cyproterone acetate (50–200 mg/day per os or 200–400 mg once weekly or every 2 weeks i.m.) or, medroxyprogesterone acetate (300–500 mg/week i.m if CPA not available) in addition to GnRH agonists (Level D) • SSRIs may also be added (No level of evidence)

renal functions evaluation; fasting blood glucose levels; lipid profile; blood count; calcium and phosphate plasma levels;
- previous history of thromboembolism (CPA or MPA), hepatic disease (CPA), liver carcinoma (CPA), tuberculosis (CPA), diabetis (CPA or MPA), cachexia (CPA), epilepsy (CPA), psychosis (CPA), adrenal disease (CPA or MPA), severe renal disease, severe hypertension, severe osteoporosis, prior fractures or cardiovascular events, family history of osteoporosis and cardiovascular disease, active pituitary pathology, severe chronic depressive disorder or allergy to hormonal treatment, alcohol and tobacco consumption must be assessed through interview of each candidate for hormonal treatment;
- in case of personal or familial osteoporosis risk or in patients over 50 year-old, baseline bone mineral density must be checked by using osteodensitometry;
- antiandrogen treatment must not be used in case of: non-consent, puberty not completed especially when bone growth is not achieved.

Informed consent must be obtained.

Medical survey is necessary during hormonal treatment:

- paraphiliac and non-paraphiliac sexual activity and fantasies (nature, intensity and frequency) and the risk of sex offence must be evaluated during the interview at least every 1–3 months through self reports of the patient;
- every 3–6 months, blood pressure, weight, must be controlled (plus blood cell counts, hepatocellular functions if CPA is used); depression, emotional disturbances; risk of feminisation must be evaluated;
- every 6 months, fasting blood glucose levels, lipid profile; calcium and phosphate levels must be controlled;
- every 2 years (or every year, if increased risk of osteoporosis or if the patient is over 50 years old), bone mineral density must be checked using osteodensitometry. Calcium, vitamin D or biphosphonates must be prescribed in case of osteoporosis;
- testosterone blood levels could be checked in case of risk of breaks in the therapy or in case of risk of masked testosterone supplementation.

These hormonal treatments should be used after other alternatives have been ruled out or when there is a high risk of sexual violence. Antiandrogens or GnRH analogues significantly reduce the intensity and frequency of sexual arousal but do not change the content of paraphilias. In spite of their efficacy, MPA and CPA treatments are associated with a high percentage of side effects which have considerably limited their use, especially for MPA in Europe. In addition, uncontrolled breaks in the therapy are often observed with oral CPA or MPA treatments. In contrast, long-acting GnRH analogues are more potent than CPA or MPA. Moreover, they induce fewer side effects, except for those related to hypoandrogenism. Long-acting GnRH analogues may be administered parentally once every 1–3 months. GnRH analogue treatment probably constitutes the most promising treatment for sex offenders at high risk of sexual violence, such as paedophiles or serial rapists. In spite of these new treatments, which induce chemically reversible castration, in several states of the United States and in some countries in Europe surgical castration is still allowed in place of chemical castration for repeat child molesters.

When properly administered, with an appropriate protocol in place to detect and treat side effects should they develop, antiandrogen therapy in general constitutes no more or less of a risk than most other forms of frequently prescribed psychopharmacological agents (Berlin 2009).

There is a risk that patients could antagonize their GnRH agonist treatment with testosterone supplementation but we could not find data in the existing literature about this risk. If there is any doubt, testosterone levels should be checked.

However, hormonal agents cannot be easily used in the treatment of juvenile sex offenders owing to possible interference with the development or course of puberty (bone growth must be achieved and should be checked using X-rays). In juvenile sex offenders, behavioural therapy and SSRIs are the first choice treatment (see section 3.3 on SSRIs). Bradford and Fedoroff (2006) recommended SSRIs prescription in mild paraphilias, in paraphiliac juveniles, in cases that have comorbidity with OCD and depression and in maintenance treatment. Antiandrogens might be used in case of high risk of sexual violence but only if puberty is achieved, especially bone maturation.

This algorithm distinguishes six levels of treatment for different categories of paraphilias (see Table V)

Psychotherapy is used in all offenders (in most cases behavioural therapy is preferred). In paraphilic subjects at high risk of reoffending, pharmacological treatment should be used as first line treatment. The combination of psychotherapy and pharmacological therapy is associated with better efficacy compared with either treatment as monotherapy (Hall and Hall 2007).

Treatment duration

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

According to the great majority of authors, a minimal duration of treatment of 3–5 years for severe paraphilia with a high risk of sexual violence is necessary. Hormonal treatment must not be abruptly stopped. In case of serious side effects, (thromboembolism or severe liver dysfunction) CPA or MPA treatment must be replaced with GnRH analogues. In case of severe osteoporosis, calcium, vitamin D and/or biphosphonates must be prescribed and osteodensitometry must be checked yearly.

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

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