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REVIEW ARTICLE

The World Federation of Societies of Biological Psychiatry (WFSBP) 2020 guidelines for the pharmacological treatment of paraphilic disorders

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ABSTRACT

Objectives: The primary aim of these guidelines is to evaluate the role of pharmacological agents in the treatment and management of patients with paraphilic disorders, with a focus on the treatment of adult males. Because such treatments are not delivered in isolation, the role of specific psychotherapeutic interventions is also briefly covered. These guidelines are intended for use in clinical practice by clinicians who diagnose and treat patients, including sexual offenders, with paraphilic disorders. The aim of these guidelines is to bring together different views on the appropriate treatment of paraphilic disorders from experts representing different countries in order to aid physicians in clinical decisions and to improve the quality of care.

Methods: An extensive literature search was conducted using the English-language-literature indexed on MEDLINE/PubMed (1990−2018 for SSRIs) (1969−2018 for hormonal 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. The type of medication used depends on the severity of the paraphilic disorder and the respective risk of behaviour endangering others. GnRH analogue treatment constitutes the most relevant treatment for patients with severe paraphilic disorders.

Conclusions: An algorithm is proposed with different levels of treatment for different categories of paraphilic disorders accompanied by different risk levels.

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Paraphilic disorder; sex offender; antiandrogen treatment; SSRI; GnRH agonist

1. A historical perspective

While it is almost certainly the case that all human societies have historically imposed boundaries or limits on the types of sexual behaviour regarded as acceptable, there has been variation across cultures. In addition, within cultural traditions, changes in sexual mores have also occurred. It is, therefore, evident that societies maintain concepts of sexual deviancy, but they are subject to evolving changes of social perspective. Reference to biblical Israel as well as ancient Greece indicates historical influences of both a religious and secular nature, of which the religious are 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 influencing social perceptions concerns whether specific sexual behaviours are regarded as sexually 'deviant.' These include degrees of consent, geographical location of the sexual behaviours, the ages of those involved, the nature of the sexual acts, whether any distress or harm may occur, the prevalence of the sexual practice in society and the degree of aversion felt by others about the specific sexual behaviour (Hensley and Tewksbury 2003).

It was not until the end of the nineteenth century that sexual deviance came to be regarded as a

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medical phenomenon, with the publication of 'Etude medico-légale sur les attentats aux moeurs 7th edition' by the French psychiatrist Ambroise Tardieu (1878) and then 'Psychopathia Sexualis' by the German psychiatrist, Krafft-Ebing (1886), describing a range of sex crimes, including sexual murders. Krafft-Ebing's emphasis on the connection between sexual fantasy and the compulsion to kill reflects views about paraphilic disorders beginning a century earlier (Krafft-Ebing 1886; reviewed in Schlesinger 2004). The interest by some German psychiatrists in sexual deviance at the turn of the twentieth century is further illustrated by the case history of a man with paedophilic tendencies described by Emil Kraepelin (Johnstone 1913).

Despite the initial medicalisation of sexual deviance by clinical psychiatrists, during the twentieth century, the main focus of study and treatment was psychoanalytic. Freud's early theory of sexuality remains the basis of psychoanalytic explanations of sexual deviance (Rosen 1997; Freud 1905/1953). Subsequently, a century of psychoanalytic thought has contributed to one perspective on the assessment and treatment of sexual deviance (see especially Fenichel 1954; Stoller 1975; Kernberg 1991; Rosen 1997).

Running alongside the psychoanalytic perspective of sexual deviance, one resulting from a psychological, developmental abnormality of sexual maturation, was a trend towards viewing the pathology as being organically determined. Freud himself saw the roots of perversion as a combination of biological and developmental factors (Rosen 1997). The British psychologist, Havelock Ellis (Ellis 1933) and the German physician, Magnus Hirschfield (1948), attempted to reform public attitudes towards a range of sexual behaviours primarily homosexual behaviours, by advocating that such behaviours constituted a medical condition rather than merely 'sinful decadence.'

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

The evolution of the concept of 'deviant' sexuality has led to confusion about its legitimacy as a genuine medical condition 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 behaviours, 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 co-morbidity 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. Further debate and better data are required to resolve some of the problems in diagnosis of paraphilias, including whether 'deviant' sexual fantasies are sufficient to make the diagnosis or if they must also be acted upon. Other diagnostic considerations include whether sexual fantasies and or 'deviant' behaviours are sufficient, the necessary duration and persistence of the fantasies or behaviours, how significant the degree of opportunity to act on the paraphilic interest is, the intensity of the fantasies or urges and the degree of occupational or social deterioration resulting (Laws and O'Donohue 1997; Marshall 2006; for a more detailed review of varied perspectives of the paraphilias beginning last century, see Gordon 2008 and Fedoroff 2009).

The beginning of treatment of the paraphilias can be traced back to the late nineteenth century, 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 to treat a patient with 'imbecility' who reported neuralgic pain of the testes and 'hypersexuality' (Sturup 1972). Sturup (1972) reported that castration had been described in Greek mythology, in the practice of auto-castration for religious reasons by the scoptics during early Christianity, its judicial use for sex crimes, and as a method to create eunuchs in eastern harems as well as to produce male 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 USA 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 varied in diagnosis and type of sex

offence but surgical castration resulted in a marked reduction in reported sex offence recidivism.

Surgical castration for sex offenders in Europe has been discontinued since the early 1970s, though it is still available in some situations in Germany and the Czech Republic. 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 individual US states in 1996 and thereafter (Weinberger et al. 2005). While surgical castration for selected sex offenders was the predominant surgical approach; some limited use of neurosurgery was also made in post-war West Germany (Roeder 1966; Roeder et al. 1972). As for surgical castration, neurosurgery is irreversible.

By the 1940s, some attempts were made to treat sex offenders with oral oestrogens (Foote 1944; Golla and Hodge 1949; Symmers 1968), but due to feminising side effects, this was supplanted in the 1960s by medications intended primarily to reduce testosterone levels. Cyproterone acetate (CPA) is available in most countries, administered orally or by depot injection, and is used in some European countries (e.g. Germany), and Canada (Gordon and Grubin 2004; Sammet 2005), while in the USA, medroxyprogesterone acetate (MPA) is available (Meyer et al. 1992). Unlike surgical castration, the effects of antiandrogen medications are reversible on discontinuation. A more recent and promising development in the treatment of paraphilias is the use of luteinising hormone-releasing hormone agonists. These are given by depot injection to reduce testosterone to very low levels, as is seen in surgical castration. Reports of low levels of recidivism have been documented (Rousseau et al. 1990; Dickey 1992; Thibaut et al. 1993).

There is also evidence for the use of selective serotonin reuptake inhibitors (SSRIs) (Stein et al. 1992; Bradford et al. 1995; Bradford and Gratzer 1995; Bradford 1996; Saleh 2004). This follows evidence for reduction in anxiety and, in some cases, sex drive using psychotropic medications 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).

While pharmacological interventions are often essential in the treatment of patients with severe paraphilias, psychotherapeutic interventions are also necessary. Aversion therapy had tapered out by the 1980s and gradually gave way to cognitive behavioural therapy (CBT). Optimal treatment of paraphilic disorders involves pharmacologic and psychologic therapy aimed at decreasing harmful paraphilic interests and replacement with non-paraphilic interests and behaviours with non-harmful ones (Murphy et al. 2014).

2. Ethical concerns

The treatment of patients with paraphilic disorders, especially those who have committed sexual offences, irrespective of which method of treatment is employed has always been undertaken within 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 antilibidinal medications (Mellela et al. 1989). The major ethical issues regarding sex offenders may reflect the need for public safety balanced against the public and even professional orientation towards punishment and retribution rather than treatment, even when 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 concerning prisoners included in research programmes).

Sex offenders with paraphilic disorders referred for hormonal treatment are often the subject of some external coercion, be it from a court decision or under pressure from their families, employers or other involved persons.

According to the Belgian Advisory Committee on Bioethics, hormonal treatment should be prescribed only if all of the following conditions are met (https://www.coe.int/t/dg3/healthbioethic/Activities/08_Psychiatry_and_human_rights_en/Rec(2004)10%20EM%20E.pdf):

- The person has a paraphilic disorder diagnosed by a psychiatrist after a careful psychiatric examination.
- The hormonal treatment addresses 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 (in other words, if less invasive measures are sufficient to reduce the risk to an acceptable level and decrease the level of suffering, they should be used as a priority). However, the

availability of 'less restrictive' (but possibly less beneficial) alternatives should not preclude the option of choosing to initiate treatment by means of a sex-drive-lowering hormonal intervention.
- The psychiatrist in charge of the patient agrees to inform the patient and receive his or her consent, to take responsibility for the indication of the treatment and for the follow-up, including physical 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.

Men with paraphilic disorders 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 licenced clinical professionals, after examination of the person concerned. In the case of hormonal treatment, it must include freely given revocable informed consent. Indeed, these treatments must remain a choice to be made by the patient on the basis of medical advice. However, consent is sometimes given in circumstances (e.g. prison or detention in a secure hospital), where the person is subject to some restriction of liberty, which raises the issue of whether consent is freely given and fully informed. While treatment may facilitate improvement and release or discharge; this is not necessarily the case. In cases where there is doubt of the validity of the patient's consent, 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 another competent body should:

- act in accordance with procedures provided by law based on the principle that the person concerned should be seen and evaluated;
- not specify the content of the treatment but order the sex offender to comply with the treatment plan proposed by the psychiatrist and approved by the competent patient, or in cases of incompetence, by a confident substitute decision-maker.

3. Clinical context

The terms 'sex offenders' and 'paraphilic disorders' are used in the following text. In order to clarify the particular use of these terms, it is crucial to be aware that most sex offenders do not suffer from a paraphilic disorder. Also, not all patients with paraphilic disorders are sex offenders (in many cases, they only suffer from paraphilic sexual fantasies or urges, and their paraphilic sexual behaviour does not involve non-consensual or otherwise illegal acts). This report focuses only on men with paraphilic disorders.

Adolescents and women are not included in these guidelines. Adolescents have been reviewed in previously published guidelines on this topic (review: Gerardin and Thibaut 2004; WFSBP guidelines: Thibaut et al. 2016). Women with paedophilic disorders have been reviewed in a previous paper (Lamy et al. 2016).

3.1. Definitions and classifications

3.1.1. Definitions

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 DSM III. In the first version of the DSM published in 1952, sexual deviations were conceptualised as a subclass of sociopathic personality disturbances (Malin and Saleh 2007).

The research on the natural history of the paraphilic disorders show that they usually manifest around puberty with deviant sexual fantasies, deviant urges and deviant sexual behaviour starting in late adolescence or early adulthood (Abel et al. 1988; Bradford et al. 1992; Bradford and Ahmed 2014; for paedophilia (at around 15 years-old in half of cases) see Tozdan and Briken 2015, 2019). The presence of a paraphilia is not illegal. However, acting in response to paraphilic urges involving non-consenting partners is illegal and may subject a person with a paraphilic disorder to legal sanctions. Paraphilic behaviour may involve 'hands-on' contact with victims for example paedophilic disorder or 'hands-off' behaviour such as exhibitionistic disorder. Most paraphilias have been described as chronic, lasting for many years if not a lifetime. This may especially be the case for the very fixated and exclusive forms (e.g. exclusive paedophilia). However, there is no evidence that paraphilic interests cannot change and/or respond to therapy (Briken et al. 2014; Fedoroff 2018). In total, more than one hundred 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: Fedoroff 2010); except for sexual masochism, which is less likely to affect men than women (Castellini et al. 2018). Research has shown that most men suffering from paraphilic

disorders actually have more than one paraphilia (Abel et al. 1988; Bradford et al. 1992). There is usually a primary paraphilic disorder and the predominant deviant sexual behaviour would be in the direction of the primary paraphilia (Abel et al. 1988; Bradford et al. 1992; Bradford 1999, 2001); according to Hall and Hall (2007), 50–70% of people with paedophilia have more than one paraphilia, while Taktak et al. (2016) reported more than one paraphilia in only 13% of 307 sex offenders.

The paraphilic disorders can be graded from mild to catastrophic, depending on victimisation, the number of victims, their age and the degree of victimisation. There are few studies about sexual murderers. Briken et al. (2006) have reported a higher level of sexual sadism in sexual murderers with paraphilic disorders. Sexual arousal has been shown to differentiate homicidal child molesters from non-homicidal child molesters (Firestone et al. 1998; Gratzer and Bradford 1995). Roberts and Grossman (1993) and Barbaree and Marshall (1989) have reported 305 cases of sexual homicides in Canada (1974–1986, 4% of the total number of homicides): the victims were mainly women (80%) under the age of 30; perpetrators were males under the age of 25 years in 50% of cases. Only 2–3% of them were serial murderers.

Rape is usually a legal term as opposed to a clinical one and is often not associated with a paraphilic disorder. However, some serial rapists may meet the criteria of a paraphilia (e.g. exhibitionism, frotteurism, voyeurism or sexual sadism). Money (1986) previously identified raptophilia as a separate paraphilia. He further noted that criteria for sexual sadism include sexual interest towards coercive sex with adult females (rape) (Money 1990). Barbaree and Marshall (1989) have suggested a continuum between normal sexual behaviour and occasional rape under the influence of illicit drugs or violent pornography.

The consequences of sexual offences are influenced by the type of sexual offence. In the case of rape and paedophilia, the consequences to the victim can be severe, and the effects may not be fully apparent until many years after the initial event (Banyard et al. 2001; Leonard and Follette 2002; Thibaut 2015).

3.1.2. Classifications

According to the Diagnostic and statistical manual of mental disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013), paraphilias are defined as sexual disorders, which are characterised by 'recurrent, intense sexually arousing fantasies, sexual urges, or behaviours involving sexual activity with (1) non human objects, (2) the suffering or humiliation of oneself or one's partner, or (3) a prepubescent child or children (generally aged 13 years or younger, the perpetrator is at least aged 16 years and at least 5 years older than the child or children) or other nonconsenting persons that occur over a period of at least 6 months' (criterion A), which 'cause clinically significant distress or impairment in social, occupational, or other important areas of functioning' (criterion B). New criteria for the diagnosis of paraphilia were included in the DSM-5, making a distinction between having a paraphilia (atypical sexual interest) and having a paraphilic disorder: the individual has acted on these sexual urges, or the sexual urges or fantasies cause marked distress or interpersonal difficulty (criterion B of paraphilic disorder). DSM-5 describes eight specific disorders of this type (exhibitionistic disorder, fetishistic disorder, frotteuristic disorder, paedophilic disorder, sexual masochism disorder, sexual sadism disorder, voyeuristic disorder and transvestic disorder) along with a residual category called 'paraphilia not otherwise specified.'

In the International Classification of Mental Diseases, Eleventh Edition (ICD-11; World Health Organization 2019) 'F65: Disorders of sexual preference' was renamed as Paraphilic Disorders which consists primarily of patterns of atypical sexual arousal that involves others whose age or status renders them unwilling or unable to consent (e.g. prepubertal children, an animal, a non-consenting individual exposed to an exhibitionist, etc.). The preference has been present for several months, which is more flexible than the six-month requirement in DSM-5. Finally, both ICD-11 and DSM-5 require that the affected person's sexual urges/fantasies have been acted upon or cause marked distress or interpersonal difficulty (Reed et al. 2016; Krueger et al. 2017).

3.2. Type and severity of paraphilic disorders (DSM-5/ICD 11)

The following disorders have traditionally been selected for specific listing and assignment of specific diagnostic criteria in DSM because they are relatively common, in relation to other paraphilic disorders and some of them entail actions for their satisfaction that, because of their noxiousness or potential harm to others, are classed as criminal offences. These disorders do not exhaust the list of possible paraphilic disorders. Many other distinct paraphilias have been identified and named, and almost any of them could, by virtue of its negative consequences for the individual or for others, rise to the level of a paraphilic

disorder. The diagnoses of the other specified and unspecified paraphilic disorders are therefore indispensable.

3.2.1. Exhibitionistic disorder

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 concerns, mostly males. The condition seems to become less severe after the age of 40.

3.2.2. Frotteuristic disorder

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 and concerns mostly males. Most acts of frottage occur when the person is aged 15–25 years, after which there is a gradual decline in frequency. The prevalence of frotteurism is estimated between 7.9 and 9.7% in the general population (Johnson et al. 2014).

3.2.3. Voyeuristic disorder (spying on others in private activities)

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 is usually before the age of 15.

3.2.4. Fetishistic disorder (using non-living objects or having a highly specific focus on non-genital body parts)

The individual has recurrent, intense, sexually arousing fantasies, sexual urges or behaviours involving the use of non-living objects (e.g. female undergarments, shoes, etc.). Usually, it begins by adolescence and concerns, mostly males. This disorder was removed from the ICD 11 classification. Yet, in some cases, fetishism may be associated to sex offences when physical aggression may be associated to fetishism (e.g. to steal women's shoes).

3.2.5. Sexual masochism disorder (undergoing humiliation, bondage or suffering)

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. This disorder was removed from the ICD 11 classification.

3.2.6. Sadism disorder (inflicting humiliation, bondage or suffering)/coercive sexual sadism disorder

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. Discussions about sexual sadism and sexual masochism are often confused by the fact that paraphilic disorders involve non-consent while consensual variations are not disorders (Fedoroff 2008). This disorder was renamed coercive sexual sadism disorder in the ICD-11 classification and is clearly distinguished from consensual sadomasochistic behaviours that do not involve substantial harm or risk.

3.2.7. Paedophilic disorder (sexual focus on children)

There is a persistent or predominant preference for sexual activity with a prepubescent child (Tanner stages 1 and 2), generally aged 13 years or younger as well as with early pubertal children (Tanner stages 3–5) (ICD-11 criteria; Marshall and Tanner 1970). Both ICD and DSM classifications specify that the affected person must be 16 years and at least five years older than the sexually desired children. For juvenile paedophiles, in clinical practice, no age is specified and clinical judgement must be used (the sexual maturity of the child and the age difference must be taken into account). The DSM-5 further specifies that individuals in late adolescence who are in ongoing sexual relationships with 12–13-year-old do not fit the criteria for paedophilia (Seto et al. 2016). Similarly, in ICD-11, the diagnosis of paedophilia does not apply to sexual behaviours among pre- or post-pubertal children with peers who are close in terms of age. The sexual preference for pubertal children has been named hebephilia and finally was not included in the DSM-5 (Blanchard 2013). Infantophilia is used to describe individuals interested in children younger than 5 years. The DSM-5 distinguishes between an exclusive and a non-exclusive type of paedophilia (whether the person can be sexually aroused only by children or also by older persons), a gender preference (sexually attracted to males and/or to females) and a limitation to incest (for a recent review, see Tenbergen et al. 2015).

Most people diagnosed with paedophilia are male. However, victim surveys have found that a female perpetrator was reported by between 14 and 24% of sexually abused males and by between 6 and 14% of sexually abused females (Green 1999).

Dickey et al. (2002) in their sample of 168 sex offenders reported that men with paedophilia referred for assessment were older than rapists and sexual sadists. However, there was a reduction in recidivism related to age. There are also age-related changes in libido due to a 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 8–10-year-old children, while those attracted to males usually prefer older children. Incest (inside the family) may represent 20% of paedophilic subjects (Cohen and Galynker 2002; Cohen et al. 2007). Those exclusively attracted to males have a higher risk of recidivism (Hall and Hall 2007).

Among 2500 men with paedophilic disorders, Hall and Hall (2007) reported that only 7% were exclusively attracted to children. Among 345 paedophiles admitting one or more sexual offences against children, 37% have solely used child pornography, 21% committed exclusively hands-on sexual contacts with a minor and 42% have committed both (Neutze et al. 2012). People with paedophilia may also be classified on the basis of interest in child pornography. Babchishin et al. (2015) compared the characteristics of online child pornography-only offenders, typical (offline) sex offenders against children and offenders with both child pornography and contact sex offences against children (mixed). Based on 30 studies, offenders who committed contact sex offences were more likely to have access to children than those with only child pornography offences. In contrast, offenders who used the Internet to commit sexual offences had greater access to the Internet than those with contact sex offenders. Differences between the groups were not limited to different opportunities to offend. Sex offenders against children and mixed offenders were found to score higher on indicators of antisociality than online child pornography offenders (CPO). CPO were also more likely to have psychological barriers to sexual offending than sex offenders against children and mixed offenders (e.g. greater victim empathy). Mixed offenders were found to be the most paedophilic, even more than CPO offenders. These distinctions are important in the selection criteria for studies of sexual behaviour.

People with paedophilic disorder who act on their interests with children may limit their activity to undressing the child and looking, exposing themselves, masturbating in the presence of the child or 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 sometimes explained with excuses or rationalisations 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 (Thibaut 2013, 2015).

Not all child sexual offenders (CSO) have paedophilic disorders; similarly not all paedophilic men necessarily commit child sexual abuse. The proportion of paedophilic disorders among CSO is about 40–50% (Maletzky and Steinhauser 2002; Seto 2008). Conversely, the proportion of men with paedophilia who sexually abused children is about 43% (Seto et al. 2006). One theory is that the other 50% of individuals who abused children are those who did so without a sexual attraction to children; i.e. they lacked the necessary social skills to develop and maintain emotional and sexual relationships with appropriately aged peers and therefore turned to 'replacement partners' in children as a kind of 'surrogate' (Seto 2008; Mokros et al. 2012). They may also be looking for novelty. Sexual violence against children can be included in antisocial behaviour with sexual and nonsexual violence; or may include people with a personal history of sexual violence who may replicate the sexual violence suffered in childhood with their younger siblings or later with their children.

The DSM-5 describes paedophilic interest as 'fluctuating.' Some have sometimes described paedophilia as a lifelong individual trait (Seto 2008). However, other studies raise questions about the stability of paedophilic sexual interest by considering whether the interest is exclusive or not (Tozdan and Briken 2017; Tozdan, Kalt, Dekker, et al. 2018; Tozdan, Kalt, et al. 2018). Others have argued that successful therapeutic alteration of sexual preference and reduced reoffending in paedophilic CSO may be due to control of symptoms rather than the actual disappearance of paedophilia (Thibaut et al. 1996; Marshall et al. 2005). Paedophilic behaviours occurring after brain lesions have been discussed as behavioural manifestations of pre-existent latent paedophilic urges due to general impulse disinhibition.

3.2.8. Transvestic disorder (engaging in sexually arousing cross-dressing)

This disorder was removed from the ICD-11 classification.

3.2.9. Paraphilias not other specified are also listed in the DSM-5 classification

They include, but they are not limited to, telephone scatologia (obscene telephone calls), necrophilia (corpses), partialism (exclusive focus on a part of a body), zoophilia (animals), coprophilia (feces), klismaphilia (enemas), europhilia (urine), etc.

In the ICD-11, 'Other paraphilic disorders' involve non-consenting individuals. An additional category named 'Other paraphilic disorder involving solitary behaviour or consenting individuals' was created for use when 'Other paraphilic disorders' are associated to marked distress or significant risk of injury or death (e.g. asphyxiophilia).

3.3. Comorbidities associated with paraphilias

Many people with paedophilic disorders who are arrested show evidence of comorbid personality disorders or psychiatric disorders including affective disorders, substance use disorders, schizophrenia, other psychotic disorders, dementia (primarily temporal and/or frontotemporal dementia) and other cognitive disorders (30% according to Kafka and Hennen 1999; 51% according to Taktak et al. 2016). Paraphilia is not often associated with schizophrenia or bipolar disorder; in a review, Marshall (2006) reported a low prevalence of psychotic disorders (1.7–16%). In some cases, the paraphilia is secondary to psychotic illness and subsides when the psychosis is successfully treated, while 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 lifetime addictive disorders varied from 8 to 85% (mainly alcohol use disorders), 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 varied 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); Kafka and Hennen 2002 (120 cases of paraphilias including 60 sex offenders: 72% of mood disorders and 38% of anxiety disorders (social phobia 22%), alcohol use disorders 30% and ADHD 35%); Dunsieth et al. 2004 (113 male forensic patients); Raymond et al. 1999 (45 male paedophilic sex offenders); for review, Tenbergen et al. 2015)). High comorbidity of impulse control disorders (e.g. explosive personality disorder, kleptomania, pyromania and pathological gambling) has been noted in subjects with paedophilic disorders (30–55%) (Hall and Hall 2007). Methodological biases, such as the heterogeneity of both the samples and the diagnostic criteria used, may have contributed to the discrepancies observed between studies.

Brain disorders may also be associated with paraphilias, 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, mainly when head trauma with temporary unconsciousness occurred before the age of 13, Blanchard et al. 2002); Kleine Levin and Klüver Bucy syndromes (50% of patients with these disorders are reported to have inappropriate sexual behaviours); Huntington's disease (10% of patients complain of inappropriate sexual behaviours with onset after the development of inhibited orgasm (Fedoroff et al. 1994)). Paraphilias, and also hypersexuality, can occur in patients undergoing dopamine receptor agonist therapy, particularly with D2/D3 dopamine receptor agonists, such as pramipexole (32% of cases), ropinirole and pergolide (especially in Parkinson's disease, 3% of cases but also in patients with restless legs syndrome or prolactinomas).

Paraphilias are also sometimes associated with 'sexual hyperactivity' often with compulsive and/or impulsive features (Kafka and Hennen 2003; Chagraoui and Thibaut 2016). The relationships and boundaries between hypersexual behaviour and paraphilic disorders are poorly known. Engel et al. (2019) have compared 47 hypersexuals with 38 healthy controls. Paraphilias like exhibitionism, voyeurism, masochism, sadism, fetishism, frotteurism or transvestism were more prevalent in men with hypersexual disorders (47 *vs.* 3%). Men with hypersexual disorders were also more likely to report sexually coercive behaviour (70 *vs.* 20%) and a higher rate of having consumed images of child abuse at least once in their lives (81% *vs.* none).

Finally, paraphilic disorders often result in a variety of psychological disturbances, such as guilt, depression, shame, isolation and impaired capacity for healthy social and sexual relationships. Shame and stigma associated with paedophilia are essential barriers to seeking professional counselling (Jahnke et al. 2015; Levenson et al. 2017).

3.4. Intellectual disability and paraphilic disorders

Assessment and treatment of people with intellectual disability (ID) require attention to three issues: (a)

sensitivity to the past mistreatment of people with ID due to now-dismissed ideas of eugenics (Pfeiffer 1994) (b) an understanding that people with ID are more complicated rather than less complicated compared to people without ID (Griffiths and Fedoroff 2014) and (c) the importance of continually re-evaluating the efficacy of any pharmacologic treatment interventions.

3.4.1. Sensitivity to past mistreatment of people with intellectual disabilities

There is a history of the now wholly discredited eugenics movement that involved involuntary castration and sterilisation of males and females with an ID (Radford and Park 1996). Patients and their care providers are, therefore, understandably concerned when presented with treatment that includes 'chemical castration.' It is essential to explain that treatment with anti-androgens and/or GnRH analogues would be part of a larger individualised treatment plan and is not the same as castration because it is both voluntary and reversible. It is essential to inform the patient and his/her care providers that medications prescribed for the purpose of decreasing sex drive are prescribed only with full, informed, reversible consent; and that the medication's sex drive reducing effects are reversible on discontinuation of the medication. The working group is clearly against all forms of compulsory treatment of patients with antiandrogens and GnRH analogues. Importantly, while decreased fertility is a side effect of treatments that reduce testosterone, treatment with anti-androgens and GnRH analogues should not be relied upon as the sole means of contraception and, the intent of treatment with these medications is to temporarily reduce sex drive to enhance treatment and not to reduce fertility.

3.4.2. Complexity of diagnosis

People with ID often have comorbid and/or concurrent medical and psychiatric disorders. Studies involving the pharmacologic treatment of sex offenders with ID inevitably include participants with multiple medical and psychiatric issues (Barron et al. 2004; Lindsay et al. 2004). These issues have been explicitly identified as problematic for the design of accurate diagnosis, tailored treatment and definitive outcome studies (Griffiths et al. 2013). People with ID are at risk of being falsely diagnosed with paraphilic disorders due to impairment in social skills that are not sexually motivated (referred to as 'counterfeit deviance.') For example, a man who has lived in an all-male group home in which nudity was tolerated may be falsely labelled as an exhibitionist if he is transferred to a co-ed facility. Standard treatment for sexually motivated exhibitionism would be inappropriate in this case (Fedoroff 2016). It is also essential to identify the focus of treatment. For example, people labelled as paraphilic may engage in 'excessive masturbation' due to a lack of privacy, inhibited orgasm and/or impulsivity secondary to attention deficit disorder (Coskun et al. 2009).

3.4.3. Re-evaluation of the efficacy of treatment interventions

All treatments should be continually evaluated for efficacy. Informed consent with the help of his/her legal guardian or substitute decision maker is mandatory for antiandrogen and GnRH analogue treatments. This is especially important in the case of a patient with ID. Patients with ID who agree to treatment with an antiandrogen or a GnRH analogue should receive a baseline bone density assessment and baseline sex hormone profile. This is because many patients with ID have baseline osteopenia or osteoporosis due to lifestyle and/or other medications. A baseline sex hormone profile is also essential to determine if the patient has a medical condition associated with a change in sex hormones (which may support an alternative treatment regime) and to establish 'return to normal' when the medication is discontinued. Since free testosterone levels undergo diurnal fluctuation, initial and follow-up hormone levels should be done at the same time of day.

3.4.4. Summary

People with ID may have paraphilic disorders but are also at increased risk of being falsely labelled as having paraphilias due to 'counterfeit deviance.' Respect for consent to treatment is of utmost importance since if it is not demonstrated by care-providers, it is far less likely the patient will accept that consensual treatment is essential. It is also essential to recognise that psychiatric disorders may present differently in patients who have ID and who may have difficulty in recognising or describing psychiatric symptoms (Fedoroff 1991; Barnhill et al. 2017).

In the interest of emphasising the importance of consent, it is advisable to review all the treatment options thoroughly and to include the patient in the process of deciding which treatments should be tried, and in which order. Specific measures of treatment efficacy should be agreed upon before beginning treatment and regularly reviewed to ensure treatment is working, and unnecessary medications are discontinued.

With these considerations, the treatment protocol described for people without ID in this monograph is applicable to people with paraphilic disorder(s).

3.5. Epidemiology of paraphilic behaviour and sexual offending

3.5.1. Prevalence of paraphilic fantasies and/or behaviours in the general population

In general, there has been little research conducted on the prevalence of paraphilia or paraphilic disorders in the general population or in nonclinical samples.

Långström and Seto (2006) found an incidence of being sexually aroused by exhibitionism (3%) or voyeurism (8%) in the general population with more men reporting they had engaged in exhibitionism and voyeurism compared to women (2450 subjects randomly selected, 18–60-years-old, from the general population of Sweden). In a population of 193 healthy male college students, Brière and Runtz (1989) using an anonymous self-report survey, reported that 21% admitted some degree of sexual interest in children, 9% had sexual fantasies involving children, 5% admitted masturbating to orgasm through this fantasy and 9% admitted that they would have sex with a child, if it were guaranteed they would never be caught. According to Pithers et al. (1995), 15–20% of their population of male university students and 2% of females would like to have a sexual relationship with a child if it was legal and 40% of male students reported sexual fantasies of women raped. Seto et al. (2015) using an anonymous school-based survey in 1978 young Swedish men (mean age: 18 years) reported that 4.2% of the young men reported they had viewed child pornography. Ahlers et al. (2011) observed that 57% of a German community sample of 373 males aged 40–79 years reported sexual interest in at least one paraphilic activity (46.9% of this group used them for arousal enhancement during masturbation and 43.7% acted out these patterns in a relationship). Fantasies of voyeurism (35%) and fetishism (30%) were the most frequently reported followed by sadism (22%), masochism (16%) and frotteurism (13%); paedophilia (10%) and exhibitionism (4%) were the lowest. Of these men, 6% masturbated to these paedophilic fantasies, and 3.8% admitted sexual contact with children below 13 years of age; only two participants reported to be distressed by their excitability to children. Dawson et al. (2016) conducted an online survey of approximately 1000 men and women to assess sexual experiences, sexual interests, sex drive and sexual behaviours. They found that men reported more significant interest in paraphilic activities than women as measured by fantasies, as well as reporting engaging in paraphilic behaviours more frequently. In the same way, Castellini et al. (2018), in a sample of 775 Italian university students (243 men and 532 women), reported that half of the men and 41.5% of women reported at least one paraphilic behaviour, with men reporting a higher prevalence of voyeurism, exhibitionism, sadism and frotteurism, and women reporting a higher prevalence of fetishism and masochism. Both general psychopathology and sexual dysfunctions were associated with hypersexuality, rather than with the content of sexual fantasies; an association between childhood adversities and hypersexuality was found only in women. Finally, a population-based Finnish study on 3967 male twins aged 21–43 years found a 12-month-prevalence of 0.3% for sexual interest in children. Furthermore, 2.7% of the participants reported masturbation fantasies involving children below the age of 16, and 0.3% had sexual contact with children of that age group during the past 12 months (Mokros et al. 2012; Alanko et al. 2013). In an online survey of 8718 German men, 4.1% reported sexual fantasies involving prepubescent children, 3.2% reported sexual offending against prepubescent children and 0.1% reported a paedophilic sexual preference (Dombert et al. 2016).

Taking together the prevalence for paedophilia can be estimated to be around 0.3–3.8%, but when general fantasies were investigated, that prevalence may reach up to 5% among men in the general population (Tenbergen et al. 2015). Almost half of the general population reported sexual interest in at least one paraphilic activity.

3.5.2. Prevalence of sex offences in the general population

There are significant methodological biases in the surveys such as the definition of sex offending, the victims' age, the choice of the sample and the type of interview (self-questionnaire, face to face interview, phone interview, number and type of questions) and the response rate (Goldman Juliette and Padayachi 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 fell to 4% of women and 2% of men (Creighton 2002). In France,

11% of women aged 18–39 reported unwanted sexual relationships (Bajos et al. 2008). In 2016, the percentage increased, 15,556 women et 11,712 men aged 20–69 years were interviewed in France; 0.3% were raped during the past year while the lifetime prevalence of sexual aggression (excluding exhibitionism and sexual harassment) declared was 14.5% in women and 3.9% in men (in half of the cases before the age of 18 and in 75% of cases inside the family). In 2015, in total 62,000 women and 2700 men (20–69 years old) were victims of rape or of attempted rape in France among 60 million inhabitants (https://www.ined.fr/en/publications/population-and-societies/rape-sexual-assaults-in-france/). In a review, Hall and Hall (2007) found that 17–31% of women and 7–16% of males declared enduring an 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.

Sexual offences are underestimated, either because many sexual assaults are unreported, offenders were never apprehended or the offence did not result in a conviction (Elliott et al. 1995; Harris and Grace 1999). For example, men convicted of sexual offences against children claim 5 or more undetected sexual assaults for which they have never been apprehended (Elliott et al. 1995). In a study of 360 reported rape cases, less than 10% resulted in a conviction (Harris and Grace 1999).

3.5.3. Prevalence of sex offending and the prevalence of paraphilic disorders among sex offenders

In France, in 2011, 12% of prisoners were sex offenders. In British prisons, about 18% of the sentenced prison population were serving sentences for sex offences in 2017; in the USA, juveniles account for 17% of individuals arrested for sex offences (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/676241/offender-management-statistics-bulletin-q3-2017.pdf). In general, individuals with exhibitionism or paedophilic disorder make up the majority of apprehended sex offenders. Rape and indecent sexual assault of females by males constituted by far the majority of sex offences in the UK. However, the prevalence of sexual offences reported against children has increased. Of men born in England and Wales in 1953, 7 in 1000 had a conviction for a sexual offence against a child by the age of 40 years (Marshall 1997).

Using PPG in studies of men with sexual offence histories against children, the prevalence of paedophilia can jump from 30% for men with one offence to 61% for men with 3 or more sexual offences against children (Seto et al. 2009). In a French cohort of 100 male sex offenders under probation, 10% had a diagnosis of paedophilia or exhibitionism (Tesson et al. 2012).

3.6. Recidivism rate

Recidivism is a primary concern in the treatment of paraphilic disorders, especially in paedophilic disorders. Yet, most people recognise that incarceration alone will not solve sexual violence. In fact, incarceration may stop a person with paedophilic disorder from sexually assaulting children, but it does not change paedophilic sexual interest. Treating paedophilic disorder provides a more humane and lasting solution than incarceration and may at least be used concomitantly. Indeed, treating the offender is critical to preventing sexual violence and reducing victimisation.

The definition of the term recidivism needs clarification. According to Greenberg (1998) and Prentky et al. (1997), different definitions of recidivism may include sexual offences, nonsexual offences or both convictions and/or self-reported offences. Comparison between studies is difficult due to methodological differences: duration of follow up, type of paraphilias studied, definition of recidivism, type of victims, previous offences and previous convictions, retrospective or prospective design, outpatients or prisoners, type of treatment and compliance, dropout rates, short periods of active treatment or lengthy treatments, statistical analyses, etc. It remains challenging to identify those individuals at risk of relapse.

The mean number of victims per individual with the paedophilic disorder was estimated at 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 the case of intrafamilial paedophilia, the median number was 4.5 for those attracted to females and 5 for those attracted to males. In an anonymous survey involving 377 participants with self-admitted paedophilic interests, the mean number of victims reported by the participants who were attracted to females was 20, compared to 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).

3.7. Risk factors for sex offending

While some paraphilias can be associated with unusual sexual behaviours, they are not necessarily associated with offences. Patients may present for treatment because of associated distress to their personal lives. In contrast, other paraphilic behaviours may lead to sex offences and public health problems involving violations of established legal or moral codes of sexual behaviour. While few people with paedophilia ask for treatment before sex offending and arrest, this pattern is changing as people learn that treatment is available and effective and does not necessarily require an arrest.

A meta-analysis of twelve 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, 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 the best responders to pharmacological 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 a higher risk of sex offence recidivism (Hanson and Bussiere 1998). These data strongly suggest that the therapeutic management of paraphilic behaviours significantly reduces the recidivism rate. The mean estimated re-conviction rate for sexual offences was 13.7% (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 services suggest that 15% of CSO leaving prison are reconvicted for a further sexual offence within two years (Beech et al. 2002). Treated offenders had lower reconviction rates than untreated 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 meta-analyses have reported rates of recidivism and risk factors (Hanson and Morton-Bourgon 2005; Hanson et al. 2006; Craig et al. 2008). The cumulative recidivism rate increased from 15% at 5 years to 27% at 20 years of follow up. Men with paedophilia attracted to boys were more likely to re-offend (35% at 15 years) 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). In contrast, according to Cohen et al. (2018), minor-attracted persons with histories of sexual activity with children ($N = 342$) were significantly older than non-actors ($N = 223$), with longer duration of paedophilic attraction, more antisocial traits, more significant attraction to boys, greater difficulty controlling their attraction and more positive attitudes towards adult-child sexual activity, nonsexual offences as well as childhood sexual and nonsexual abuse. Self-reported paraphilic behaviour (exhibitionism, masochism, sadism or voyeurism, respectively) increased sexual offending risk (Baur et al. 2016; in a population of 5990 Finish male and female young adult twins).

Some dynamic risk factors were identified, such as psychopathy and antisocial behaviour. Denial, low self-esteem, addictive disorders (mostly alcoholism or drug abuse) and comorbid psychiatric disorders may also increase the risk of recidivism. Dynamic risks may be addressed, and psychotherapeutic or pharmacological treatments may help to improve these factors. Clinical factors, such as sexual sadism and 'hypersexuality' are now well documented in research studies as increasing the risk for sexual offence recidivism (Kingston and Bradford 2013; Kingston et al. 2010; Chagraoui and Thibaut 2016; Thibaut 2018).

The following static risk factors need accurate evaluation in sexual offenders in order to identify risk: previous sexual offences (especially rapes) and/or non-sexual offences (especially those with violence) increase the risk of recidivism (Hall and Hall 2007). Sex offenders with intellectual disabilities or sequelae of head injury are particularly susceptible to re-offend after treatment cessation. A past history of sexual abuse or physical violence during childhood may increase the risk (Hanson and Bussiere 1998; Jespersen et al. 2009). Early age of onset of paraphilic disorders is also associated with an increased risk (Barbaree et al. 2003). A high number of paraphilic interests reported by the offender increased the likelihood of reoffence (Hall and Hall 2007). In a recent study, the most reliable predictor for sexual re-offence was sexual interest in children as measured by plethysmography (especially when victims are strangers) (Stephens

et al. 2017: 656 men who had committed a sexual offence, mean duration of follow up 10 years). Finally, according to Mann et al. (2010), denial would increase the risk for sex offenders who remain committed to deviant lifestyles.

3.8. Assessment methods

Several actuarial instruments are available for adult male sexual offenders to help identify risks factors for recidivism as well as quantify recidivism risk in a given subject. In fact, there are three generations of risk assessment methods: unstructured professional judgement (first generation), actuarial methods using static predictors (second generation), and more recent methods that combine both static and dynamic factors (third generation). Hanson and Morton-Bourgon (2009) concluded that empirically derived actuarial approaches were more accurate than unstructured professional judgement in assessing the risk of sexual, violent recidivism and any recidivism. The use of third-generation risk assessment instruments that include both static and dynamic risk factors is becoming more prevalent. These latter instruments have the potential benefit of providing targets for treatment. Training and monitoring of evaluators are necessary to ensure that risk assessment procedures and instruments are used appropriately. During the last years, a fourth-generation risk assessment instrument was introduced. These new instruments integrate systematic intervention and monitoring of a broader range of risk factors and other personal factors important to treatment but further studies are needed before using them in sexual offenders (Andrews et al. 2006). (For review on this topic: Seifert et al. 2005; McGrath et al. 2010; Baldwin 2012).

3.8.1. Static risk assessment instruments

Some instruments include primarily or entirely static risk factors. Static risk factors are unchangeable historical variables, such as the number of prior sexual offence convictions, history of non-sexual criminal activity and victim gender. Static risk instruments are valuable in assessing the long-term reoffence risk of offenders. The Static-99 (Hanson and Thornton 2000; Harris et al. 2003) includes 10 static risk items. Scores fall into one of seven levels reflecting the probability of sexual and violent reoffending at five-, ten- and 15-year intervals, respectively. The SVR-20 (Sexual Violent Risk- 20) (Boer et al. 1997) was also designed to assess sexual reoffence risk among adult male sex offenders. It is composed of 20 static and dynamic risk items. Designed initially as an empirically guided risk-assessment instrument, research has found that scores on the instrument correlate with the probability that an individual will sexually re-offend. The Static-99 (now updated to Static 2002 R) is by far the most commonly used instrument in North America (http://www.Static99.org).

3.8.2. Dynamic risk assessment instruments

To identify targets for supervision and treatment intervention, as well as to measure the change in reoffence risk, assessment of dynamic risk factors also called criminogenic needs (e.g. Andrews and Bonta 2010), is required. Dynamic risk factors are potentially changeable offending-related aspects of an individual's functioning and are commonly reported as either 'stable' or 'acute.' Examples of acute dynamic risk factors include current access to potential victims and substance abuse. Acute risk factors potentially are more responsive to supervision and treatment interventions than are stable dynamic factors. The most commonly used instruments in North America are the Stable 2007 and the Acute 2007 (Hanson et al. 2006, 2007).

More recently the Violence Risk Scale-Sexual Offender Version (Olver, Mundt, et al. 2018; Olver, Neumann, et al. 2018; Olver, Sowden, et al. 2018; Sowden and Olver 2017) has been used to assess dynamic risk, for treatment planning and evaluation of treatment progress.

3.8.3. General risk assessment instruments

While previous instruments were primarily designed to assess the likelihood that a sexual abuser will commit another sexual offence, other instruments, such as the SORAG (Sexual Offence Risk Appraisal Guide) were designed to assess the risk of other types of criminal reoffending (Rettenberger et al. 2017).

Risk Matrix 2000 (Mann et al. 2010) is an actuarial instrument used to assess risk of further sexual or violent offending in sexual offenders.

Sexual sadism is associated with a high risk of recidivism and sexual violence.

The severe sexual sadism scale (SESAS), a dimensional instrument (11 items; cut off score: $\geq$4) was developed to assist in the diagnosis of sexual sadism (Nitschke et al. 2009). This scale is a file-based observer rating of pertinent crime-scene actions and has shown good psychometric properties.

3.9. Penile plethysmography (PPG)

Phallometry is an objective measure of men's sexual arousal, based on measurement of changes in penile volume or circumference during the presentation of sexual stimuli that may vary according to age or sexual interests (Fedoroff 2009, 2010). The circumferential method measures intra-individual changes in penile girth through a wire band around the base of the penis. The volumetric method uses a glass tube around the penis to measure calibrated air output as a result of erection. The latter method is more sensitive to small changes. Both measures are valid and reliable, producing sensitivities between 55 and 61% and specificities between 95 and 96% (Blanchard et al. 2001). In North America, PPG is considered as 'gold-standard' by several teams (Hanson and Morton-Bourgon 2005; Murphy et al. 2015) and as a predictor of sexual recidivism among identified CSO (Moulden et al. 2009). In contrast, in a study of 130 CSO, Wilson et al. (2011) found that DSM-IV-TR paedophilia diagnosis was not significantly correlated with phallometric results or with sexual recidivism. Yet, a report from the Canadian Agency for Drugs and Technologies in Health concluded in 2011 that evidence for the diagnostic accuracy of phallometric assessment was inconsistent (https://www.cadth.ca/sites/default/files/pdf/htis/sept-2011/RC0297_Phallometry_final.pdf). In the same way, Marshall and Fernandez (2000), Wilson et al. (2011) and Marshall (2014) advocate caution related to PPG responses (uninterpretable diminution under 10% of full erection) (lack of reliability among child molester subtypes, as well as in rapists and exhibitionists). Reliability issues, faking abilities to suppress an erection (McAnulty and Adams 1992; Adams et al. 1992) and ethical issues (e.g. connecting preserved penile erection and sexual recidivism) make PPG controversial in Europe (Meijer et al. 2008; Babchishin et al. 2013; Tenbergen et al. 2015). While penile plethysmography (PPG) is rarely used in most western European countries, in contrast, PPG is used routinely in Ontario-Canada (Murphy et al. 2015). The scientific discussion about whether polygraph testing adds to clinical diagnoses is ongoing in Canada (Meijer et al. 2008). Sexual arousal testing should not be used to determine guilt or innocence in criminal matters.

3.10. Other measures of sexual interest

3.10.1. Viewing time, eye tracking (ET) and other neurophysiological markers

One of the most well-validated tests is the viewing time paradigm measuring the length of time a participant spends looking at specific images as an indicator of sexual interest (Abel et al. 1998). It involves the presentation of pictures of clothed and semi-clothed children, adolescents and adults and the covert recording of relative viewing time or visual reaction time. Research assumes that all participants, including CSO, will look significantly longer at sexually arousing stimuli (Mokros et al. 2012). The effect of more extended viewing of relevant stimuli is associated with a task to evaluate the sexual attractiveness of the presented image, but not with the image itself. If the task to evaluate sexual attractiveness is removed, the differences in viewing time disappear (Imhoff et al. 2012; Pohl et al. 2016). A recent study found viewing time could also significantly predict sexual recidivism (Gray et al. 2015). For a review on this topic, see Schmidt et al. (2017).

Eye-tracking and pupil dilation may also indicate sexual interest. Men react more strongly in these studies than women; fixation latency is related to automatic attentional processes and relative fixation time to controlled attentional processes. In a group of people with paedophilia, Fromberger et al. (2012) demonstrated excellent sensitivity (86.4%) and specificity (90%) in discriminating between paedophiles and non-paedophiles. One study using eye-tracking aimed to understand cognitive strategies among people with paedophilia attempting to fake PPG measures (Trottier et al. 2014).

The association between eye-tracking and fMRI processing subliminal stimuli has also been tested. This method showed retention of automatic processes and change in control of attentional processes in a patient with paedophilia while receiving GnRH agonist therapy (Jordan et al. 2014).

3.10.2. Event-related brain potentials (ERPs)

ERPs have been used to investigate the time course of the specific processing of erotic pictures in 22 patients with paedophilia as compared to 22 healthy controls. An early frontal positive wave was reduced and slower in paedophilia. The reduced ability of erotic stimuli to elicit cortical activation at the early stages is suggestive of diminished automaticity, which may in part contribute to, or result from, the lack of sexual interest towards adults in patients with paedophilia (Knott et al. 2016).

3.10.3. Virtual reality (VR)

VR can be used to expose offenders to stimuli in order to train coping skills in virtual situations without endangering others. It may also be used for risk

assessment and therapy of CSO (for a review see Fromberger et al. 2018). In addition, it makes it possible to avoid a number of ethical and legal issues arising in connection with the use of stimuli involving children.

3.10.4. Polygraph

Polygraph techniques aimed at standardisation and reproducibility of physiological responses to questions of interest have been proposed as useful tools in the treatment and supervision of sex offenders (blood pressure, pulse, respiration and/or skin conductivity are measured, while a person answers a series of questions). Elliott and Vollm (2016) reviewed the current literature on this topic and concluded that, even if there was a significant increase in relevant disclosures, their impact on reported sex offence recidivism rates was not significant.

Presently, these methods are unlikely to provide a reliable assessment of treatment effectiveness. One study combined PPG, eye tracking, and immersive virtual reality (Renaud et al. 2010). Recently, Müller et al. (2014) described changes in sexual arousal pattern using PPG and ET (at least 6 months after the initial evaluation).

3.10.5. Implicit measures

A promising method to assess sexual preferences is an implicit measure. According to this theory, sexual preferences as well as personal attitudes implicitly affect memory and, therefore, affect and may even control attention, perception, thinking, decision making, affects and behaviour in an automatic and unconscious, immediate way. Several methods have been developed over the last few years to access implicit memory in general psychology. These have led to a better understanding of unconscious processes and their potential to objectively assess human attitudes in general (Greenwald and Banaji 2017).

The critical issue of faking-good in assessments in a forensic setting in general, suggests this methodology may be useful, but replication studies are needed to demonstrate validity in different populations. Babchishin et al. (2013) showed in a meta-analysis that Implicit Association Test (IAT) measures were able to distinguish CSO from non-CSO with the most significant group differences between CSO and non-offenders and moderate differences between COS and rapists. An application of implicit measures of sexual preferences regarding gender and different Tanner stages is the Explicit and Implicit Sexual Interest Profile (EISIP), a multimethod approach consisting of self-report, viewing time and IAT, developed by Schmidt et al. (2014): The EISIP delivers a graph depicting the self-evaluation of the proband index-values for all five Tanner-stages for both sexes (viewing time) as well as preferences between male vs. female, girl *vs.* women and boy *vs.* man (IAT). An adapted version examines the preference for sexualised violence (Larue et al. 2014).

3.11. Type of outcome measures reported in the literature used in these guidelines

The following outcome measurements were usually found in the literature.

3.11.1. Primary outcomes

Paraphilic and non-paraphilic sexual activity (fantasies, urges and behaviours) are evaluated using self-reports. Such urges may be assessed (for example) by questionnaires, diaries or scales of paraphilic fantasies and behaviours.

Sexual recidivism is measured by arrests, reconvictions usually for a combination of sexual offences and violent defences; or self-reports.

3.11.2. Secondary outcomes

Usually, self-report of the number of spontaneous erections and orgasms by any means, usually in a seven-day period is used. Plasma levels of free testosterone, total testosterone and in some centres, LH and FSH may be used as outcome measures and, in some cases, physiological sexual arousal patterns are measured using PPG.

4. Aetiology

Sexual arousal is dependent on neural, hormonal and genetic factors, together with the complex influence of culture and context. The aetiology of sexual interests, including paraphilic sexual interests, is still unclear. Various psychological, developmental, environmental, genetic and organic factors have been discussed, but none of the theories thoroughly explains paraphilic behaviours. The causes are multifactorial, meaning there are multiple possible treatment interventions.

Past history of sexual abuse

Prior history of sexual abuse is often reported as a risk factor correlated with paedophilia. The frequency reported for people with paedophilia, who were abused as children ranges from 28 to 93% *vs.* 15% for controls (Jespersen et al. 2009). The claim that sexual abuse 'causes' paedophilia, however, has been

disputed (Fedoroff and Pinkus 1996). Only a small proportion of sexually abused children develop paedophilia (Nunes et al. 2013). This association might be moderated by other genetic or environmental factors (e.g. experiences of neglect in childhood, lack of parental supervision, intrafamilial violence and poor parent–child attachment) (Marshall et al. 2000; Salter et al. 2003) and specific characteristics of the experienced abuse (duration, timing, use of violence, penetration, relationship to the perpetrator and having perpetrators of both sexes) (Burton et al. 2002). The exact mechanism by which history of being sexually abused increases the likelihood of developing paedophilia remains unknown (learned associations; imitation; anger, frustration, revenge; undoing; and a desire to be punished are mechanisms that have been proposed). In the case of child pornography, many offenders report 'research' as a motivation, sometimes including a need to check to see if images of their own abuse have been posted.

The next section focuses on the possible biological determinants of paraphilic behaviours.

4.1. Oestrogens

Oestrogens per se have little direct influence on sexual desire in males (Meston and Frohlich 2000). Oestradiol is involved in bone mineralisation in both males and females. In a recent case report, topical oestradiol was used to eliminate painful erections in a man suffering from Peyronnie's disease who was unable to tolerate other anti-testosterone medications (Thuswaldner and Fedoroff 2020).

4.2. Testosterone

The primary androgen produced by the testes, plays a significant 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 significant determinant of sexual desire, fantasies, and behaviour and basically, it controls the frequency, duration, and magnitude of spontaneous erections (Carani et al. 1992). The effects of testosterone (and of its metabolite 5α-dihydrotestosterone (DHT)) are mediated through their actions on the intracellular androgen receptor. Testosterone secretion is regulated by a feedback mechanism in the hypothalamic-pituitary gonadal 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 luteinising 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 a hypogonadal adult man with impaired nocturnal penile tumescence. A minimal level of testosterone is necessary for the sexual drive in males. However, the threshold remains questionable. Testosterone levels do not correlate with the intensity of sexual drive. The relationships between testosterone and aggressive behaviour are also complex (Batrinos 2012).

There is no clear evidence that subjects with paraphilias have higher basic testosterone levels, nor data indicating an increased androgen receptor activity (Kingston et al. 2012). In people with paraphilic disorders no difference in self-reported measures of sexual behaviour was reported with reference to baseline serum testosterone levels (below or above 300 ng/dL) (Kravitz et al. 1996). Marked hypersecretion of LH was reported in response to GnRH in men with paedophilic disorder, as compared to controls with other paraphilic disorders, whereas baseline LH and testosterone values were within the normal range. These data may indicate a hypothalamic-pituitary-gonadal dysfunction in men with paedophilic disorder (Gaffney and Berlin 1984). The benefit of suppressing testosterone to castration levels is associated with decreasing sexual arousal in general. More recently, LH levels have been noted to be associated with sexual offence recidivism. Although this is a preliminary scientific finding, it may point towards luteinising hormone levels being more critical concerning paraphilic disorders than testosterone levels (Kingston et al. 2012). The natural history of the paraphilic disorders follows the same pattern as the development of healthy human sexuality which is driven principally by biological factors but affected by psychological and environmental factors as well (Jordan et al. 2011; Bradford and Ahmed 2014).

4.3. Neurotransmitters

Serotonin and dopamine affect, to a lesser extent, sexual behaviour, as shown in animal and human studies (Bradford 1999, 2001; Kafka 2006). Dopamine agonist treatments may be associated with hypersexual behaviours and, in some cases, with sexual delinquency (see also Chapter 6.4.1.1). Levels of norepinephrine, dopamine, dihydroxyphenylalanine and dihydroxyphenylacetic acid were significantly higher and serotonin levels were lower in patients with paraphilias with

compulsive symptoms. Thus neurotransmitters levels seem to be more relevant to control on sexual behaviour but not on paraphilia itself (Kogan et al. 1995). Maes et al. (2001) have reported that paedophilia was accompanied by increased plasma concentrations of catecholamines. Nine men with paedophilia had higher cortisone and prolactin levels in response to meta-chlorophenylpiperazine (a serotonin (5HT) agonist) as compared to controls. This may be a marker of serotoninergic disturbance in paedophilia. The results suggest that there is a decreased activity of the serotoninergic presynaptic neuron and a 5-HT2 postsynaptic receptor hyperresponsivity in paedophilic subjects (Maes et al. 2001). Bradford (1996) has speculated that serotonin may be the most critical neurotransmitter in forensic mental health.

In the same way, Mincke et al. (2006) reported depletion of *n*-3 polyunsaturated fatty acids in 27 men with paedophilia, compared to controls, which may cause alterations in the serotoninergic turnover, which are related to impulse dyscontrol and aggression-hostility associated with sex offenders. Enhancing central serotonin activity in the hypothalamus may inhibit sexual behaviour in some mammalian species (Lorrain et al. 1999). Low 5-hydroxy-indol acetic acid concentrations in the cerebrospinal fluid were associated with severe aggression, which resulted from impaired impulse control in juvenile male primates while testosterone was more associated with competitive aggression (Higley et al. 1996). Selective 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; Bradford 2001). Although it is impossible to thoroughly review the many neuroscience developments related to serotonin in recent years, gender influences on a permanent increase in serotonin transporter function on cerebral metabolism raise some exciting differences between males and females (Dawson et al. 2009). Currently, we know that selective SSRIs have a range of effects associated with disorders linked to the endocrine system. It has been observed that some effects on hormonal levels and sexual functioning such as breast enlargement can occur as a result of treatment with SSRIs. What is not clearly understood is the mechanism of action of the SSRIs that results in these disorders related to the endocrine system. Evidence is accumulating that these effects may be due to interference with steroidogenesis (Jacobsen et al. 2015). Studies of the serotonin transporter related to gender and impulsivity show that generally, women are more impulsive than men, but the 5-HT system is more involved in the impulsivity of men than it is in women. This may again provide some insight into the differences between men and women in relation to their sexual behaviour (Marazziti et al. 2010). These findings suggest that the influence of a permanent increase in the human serotonin transporter gene transcription is higher in females than in males, which in this instance has an effect on affective responses, but at some stage in the future, effects on sexual behaviour might also be noted. Although this work is confined principally to studies of affective disorders, it is also promising concerning future research on the human serotonin transporter and how it is affected by, for example GnRH agonists (Frokjaer et al. 2015).

4.4. Brain regions involved in sexual behaviour; brain lesions and neuroimaging contribution

4.4.1. Brain lesions and paraphilic disorders

Paraphilias or conditions that look like paraphilias have been reported as the result of brain trauma, especially during childhood (Lehne 1984; Simpson et al. 1999; Langevin 2006). Any temporal or frontal lobe damage may be involved (Hucker et al. 1986; Langevin et al. 1989; Mendez et al. 2000; Bradford 2001) including: Kleine Levin and Klüver Bucy syndromes (50% of patients have inappropriate sexual behaviours) or epilepsy (Mitchell et al. 1954; Hill et al. 1957); dementia (especially frontotemporal dementia); Huntington's disease (10% of patients complain of inappropriate sexual behaviours) especially in men. Paraphilias can also occur in patients undergoing dopamine receptor agonist therapy (e.g. in Parkinson's disease). Mohnke et al. (2014) have reviewed all published cases of paraphilias and paraphilic disorders associated with neurological disorders. However, neurological disorders may also unmask a predisposition to sexual interest in children through different mechanisms (disinhibition or hypersexuality).

Evidence for impaired neurocognitive and executive functions has been repeatedly reported in paedophilia including lower processing speed, verbal deficits, diminished task switching and cognitive reasoning abilities as well as an increased rate of left-handedness and finally, reduced general IQ. These measures correlate with grey matter volume in both bilateral temporoparietal junction (TPJ) and left dorsolateral prefrontal cortex (DLPFC) (for review Tenbergen et al. 2015). From this review, Tenbergen et al. concluded that

paedophilia could result from neurodevelopmental abnormalities.

4.4.2. Structural neuroimaging studies

In neurological case reports, morphological alterations include the frontal and temporal lobes, the amygdala, non-motor basal ganglia, hypothalamus and septal nuclei. However, the anatomical location of impairment varied considerably between case studies (Mohnke et al. 2014).

Quantitative voxel-based morphometric studies conducted in larger samples have primarily been conducted in men with paedophilia with no a priori hypothesis. Reduced grey matter volumes in frontal, parietal and temporal lobes, especially in the right amygdala have been described in 31 men with paedophilic disorder compared to 39 healthy controls (Schiffer et al. 2007; Schiltz et al. 2007). Poeppl et al. (2011, 2013) did not confirm prefrontal cortex anomalies in offending paedophiles but replicated a decrease in the right amygdala volume (associated with face discrimination tasks). These latter authors also reported correlations between decreased grey matter volume in the left DLPFC and paedophilic sexual interest/sexual offence as well as a correlation between decreased grey matter volume in the orbitofrontal cortex (OFC) and preference for lower age children. Finally, Schiffer et al. (2017) reported a lower grey matter volume in the right temporal pole in CSO (58 cases) as compared with non-offending men with paedophilia (60 cases), as well as an association between lower grey matter volume in dorsomedial PFC and anterior cingulate cortex and increased risk of re-offending.

In an unreplicated study, using static MRI, Cantor et al. (2008) described white matter previously unpredicted reductions in fibres linking grey matter regions that respond to sexual stimulation, mostly located in the corpus callosum and bilaterally in the temporal and parietal lobes of 44 men with paedophilia as compared to 53 subjects convicted for non-sexual crimes (reduced white matter volumes were reported in the left superior fronto-occipital fasciculus, and right arcuate fasciculus).

Gerwinn et al. (2015) did not find any significant grey or white matter differences between 24 men with paedophilia and 32 non-paedophilic men matched for sexual orientation. They concluded that given the inconsistencies among studies, it is not possible to locate a macrostructural brain pathology related explicitly to paedophilia.

4.4.3. Electroencephalogram (EEG) and functional neuroimaging studies

In an EEG study of 19 controls compared with 19 patients with paraphilic disorders and 21 sex offenders without paraphilia, an increased activation in the right hemisphere involving the limbic structures was suggested in paraphilic disorders (Kirenskaya-Berus and Tkachenko 2003).

Several components were activated during visual sexual stimulation: autonomic (right insula, left ACC), emotional (amygdala), motivational (ACC, parietal cortex) and cognitive (right lateral OFC, parietal cortex) (for review Mohnke et al. 2014). More specifically, sexual interest is influenced by the anterior and preoptic area of the hypothalamus, the anterior and mediodorsal thalamus, the septal area, and the perirhinal parahippocampus, including the dentate gyrus. In contrast, sexual disinterest is regulated by the substantia innominate (Poeppl et al. 2016). However, the link between neuronal activity and paraphilic sexual behaviour remains unclear. Neurobehavioral models of paedophilia and CSO suggest a pattern of temporal and in particular prefrontal disturbances leading to inappropriate behavioural control and subsequently an increased propensity to sexually offend against children (Cohen et al. 2002). However, unambiguous empirical evidence for such mechanisms is still missing. Only a few functional magnetic resonance imaging (fMRI) studies have investigated abnormal brain activations during visual sexual stimulation in paedophilic disorders. Poeppl et al. (2014) and Mohnke et al. (2014) have published reviews on this topic. They concluded that anomalies were located predominantly to cortical and subcortical regions that are related to the generation of sexual arousal. More specifically, men with paedophilia showed abnormal neural activity in the left DLPFC and the hypothalamus (Walter et al. 2007), the right amygdala (Sartorius et al. 2008), thalamus, pallidum and striatum (Schiffer et al. 2008), cingulate and bilateral insular cortex (Poeppl et al. 2011), as well as in the OFC and right DLPFC (Schiffer, Paul, et al. 2008). OFC dysfunction may account for impaired response inhibition in paedophilia (Habermeyer, Esposito, Händel, Lemoine, Kuhl, et al. 2013). Interestingly, paedophilic subjects recruit similar networks during sexual excitement induced by child sexual stimuli as non-paedophilic subjects in response to adult sexual content (Schiffer, Paul, et al. 2008; Poeppl et al. 2011). In contrast, men with paedophilia who committed sex offences, compared with men without paedophilia, differentially activate DLPFC, hippocampus, thalamus, amygdala as well as superior

parietal lobule and superior temporal gyrus, when viewing child or adult stimuli, respectively (Poeppl et al. 2011). Moreover, failure to deactivate the TPJ (left precuneus, angular gyrus) during response inhibition has been observed in men with paedophilia (Habermeyer, Esposito, Händel, Lemoine, et al. 2013). Using a similar paradigm, Kärgel et al. (2017) reported heightened behavioural inhibitory control abilities in non-offending men ($n = 37$) compared to men with paedophilic offences ($n = 40$). In summary, there is considerable variability between studies.

Case reports point to the relevance of frontal and temporal brain areas, which are more likely to be implicated in behavioural control than in sexual interest. Controlled neuroimaging studies show a mixed picture. The small number of studies, the small sample sizes, comorbidities, variable sexual orientations, treatment effects and the difficulty of performing such studies may have contributed to these discrepancies. Another significant confounding factor is that almost all studies did not differentiate between paedophilia as an interest and child sexual offences. A notable non-independently replicated exception is Ponseti et al. (2012). Ponseti et al. (2012) suggest that functional imaging of brain response patterns during visual sexual stimulation might enable diagnostic classification of paedophilia with high sensitivity and specificity. In that study, paedophilic participants were all incarcerated or legally-involved. Kärgel et al. (2015) have shown that connectivity differences in resting state were associated with child sexual offences rather than paedophilia.

Until now, no consistent structural or functional alterations across studies could be identified for paedophilia. Encouraging results like a twofold replication of reduced amygdala volume in CSO and altered processing of the sexual arousal network in men with paedophilia have underlined the potential interest of neuroimaging in studies of paedophilia. Nevertheless, their functional significance remains to be further investigated.

4.4.4. Neuroimaging and treatment efficacy

In parallel, a few single fMRI case studies have aimed to assess treatment efficiency. Compared to untreated men with paedophilia, there was a significant decrease in neuronal responsiveness to visual sexual stimuli which has been described in subcortical areas (hypothalamus, hippocampus, insular cortex, substantia nigra) and anterior cingulate cortex in a man with paedophilia treated by a GnRH agonist (Schiffer et al. 2009). Habermeyer et al. (2012) compared neuronal responsiveness before and after 10 months of a GnRH agonist and found reduced activity in the right amygdala and gyri (superior frontal, right precentral, superior temporal). In addition, subliminal visual stimuli demonstrated a changed activation pattern in occipital and parietal regions, hippocampi and OFC after 4 months of GnRH agonist therapy (Jordan et al. 2014).

4.5. Genetics

Melnyk et al. (1969) and Dodson et al. (1972) estimated that the incidence of XYY in tall sexual offenders (>1.80 m) presenting with intellectual disabilities would be eight times higher than that observed in mental retardation without delinquency. According to Dodson et al. (1972), the frequency would be 1/6 among tall sexual offenders *vs.* 1–5/10,000 in the general population. In a retrospective investigation of the court reports about sexual homicide perpetrators, chromosome analysis had been carried out in 13/166 (7.8%) men. Three men (1.8%) with XYY chromosome abnormality were found (Briken et al. 2006). In rare cases, men with Klinefelter syndrome (XXY, prevalence in the general population: 1/600 among males) may engage in criminal sexual behaviour especially when initiating androgen therapy (O'Donovan and Völlm 2018). The overall risk of conviction was moderately increased in men with 47, XYY (934 cases) or XXY (161 cases) as compared to matched controls in a Danish population; however, it was similar to controls when adjusting for socioeconomic parameters (Stochholm et al. 2012).

The question of whether there is a genetic predisposition towards paraphilic disorders and/or paedophilic disorders has been recently studied. Gaffney et al. (1984), in a retrospective study, reported that paedophilia was significantly more prevalent in first-degree relatives of patients fulfilling DSM-III criteria for paedophilia ($n = 33$) compared to families of patients with non-paedophilic paraphilias ($n = 21$). A Finnish group published the first twin study (3967 twin pairs) investigating paedophilia. They have shown that genetic factors contribute to sexual interests, fantasies, or activity pertaining to children under the age of 16 years (Alanko et al. 2010). However, the heritability estimated in the study explained only 14.6% of the variance (Alanko et al. 2013). Given the apparently weak heritability of paedophilia together with the assumed significant effects of early environment (e.g. own sexual victimisation during childhood), and possibly an interaction among different factors, epigenetics (studying the dynamic changes in gene regulation) might represent a promising way to disentangle the biological substrates and possible markers

of paraphilic behaviour. Alanko et al. (2016) have focussed on 54 single nucleotide polymorphisms (SNPs) located on genes linked to androgen, oestrogen, prolactin, corticotrophin, serotonin and oxytocin in 1672 male paraphilic subjects. Functional polymorphisms in dopamine receptors genes (DRD1, DRD2 and DRD4), catechol-O-methyltransferase gene (COMT), dopamine transporter gene (DAT), serotonin transporter gene (SLC6A4), serotonin type 2 A receptor gene (5HTR2A), tryptophan hydroxylase 2 gene (TPH2), monoamine oxidase A gene (MAOA), and brain-derived neurotrophic factor gene (BDNF) were analysed in paraphilic disorders, specifically in people with paedophilic disorders and rapists (Jakubczyk et al. 2017). Although these association studies did not find any differences between controls and patients with paraphilic disorders, further research in this area is recommended.

Prenatal androgenisation was previously part of the speculation that it may be involved in the development of paedophilia from early studies on CPA (Bradford 1983a, 1983b). CPA blocks the intracellular androgen receptors including those in the anterior hypothalamus and, therefore, blocks foetal androgenisation or in theory when used in adults could impact on the androgen system in the hypothalamus (Bradford 1983a, 1983b). More recently, CSO have been evaluated in a 2×2 factorial design assessing the markers for prenatal brain androgenisation, genetic parameters of androgen receptor function, epigenetic regulation, and peripheral hormones; 194 clinical subjects consisting of CSO and 72 age-matched controls were evaluated. CSO showed signs of elevated prenatal androgen exposure compared to non-offending paedophiles and controls. Further, the methylation status of the androgen receptor gene was also higher in CSO, indicating lower functionality of the testosterone system, accompanied by lower peripheral testosterone levels. Notably, markers of prenatal androgenisation and the methylation status of the androgen receptor gene were correlated with the total number of sexual offences committed. This study showed alterations of the androgen system on a prenatal level, an epigenetic level, and an endocrine level. Although none of these results were specific to paedophilia, this may have to do with the selection/diagnostic process for paedophilia. It does, however, support that CSO possibly have testosterone linked abnormalities originating in prenatal androgenisation and the interaction of the testosterone receptor gene and peripheral hormones including plasma testosterone (Kingston et al. 2012; Kruger et al. 2019).

5. Evaluation of a subject with a paraphilic disorder/monitoring on treatment

5.1. Evaluation

Sexual offenders are a heterogeneous group. Standardised methods of assessment, including risk assessment tools, would probably help to facilitate treatment strategies. Such methods would include the assessment of intellectual and personality functioning or psychopathology and the assessment of sexual behaviour and minimisation or denial of the sex offence. Standardised assessment scales are also appealing to evaluate the potential risk of reoffending (Static-99 is the most frequently used in North America, McGrath et al. 2010). The use of direct measurement of sexual arousal using phallometric assessment is often used in North America but is not recommended in Europe (see Chapter 3.9). Visual Reaction time may be used as a less intrusive objective measure of sexual preference (see Chapter 3.10).

Motivational interviewing is not mentioned in the published studies, but lack of motivation is a significant factor of non-compliance, and it should also be routinely assessed and improved if necessary.

A psychiatric interview is necessary to identify and address environment stressors and potentially treatable neuropsychiatric conditions, which may contribute to aggressive and paraphilic behaviour.

A physical examination is also necessary which should focus on endocrinological (including genitals) and neurological status.

Demographic and clinical characteristics (from patient' self-report and medical file) must include:

- demographic characteristics of the subject: age, gender, education level, current and past marital status, number of children (age and gender if any), current and past employment status (with or without children), contacts with children;
- normophilic and paraphilic sexual fantasies and activity (frequency and type), exclusive or non-exclusive paraphilic behaviour, age at onset of paraphilic behaviour and fantasies, type and number of paraphilic disorders, gender and age of victims, intrafamilial or extrafamilial victim (known or unknown victim), internet or video use of pornography (paraphilic or non-paraphilic), use of violence in association with paraphilic disorders; previous convictions for sexual or non-sexual offences (history of records in police/justice systems (sexual and non-sexual offences); family and personal history of sexual disorders; previous treatment for paraphilic

disorders and compliance; alcohol or illicit drug consumption before paraphilic sexual behaviour; age of puberty, etc.;
- family and personal history of psychiatric disorders; a personal history of personality disorders, suicide attempts, brain trauma; current dementia, mental retardation, psychiatric or non-psychiatric diseases; previous history of sexual or physical abuse, etc.;
- empathy, coping with stress, impulsivity, interpersonal relationships, insight, motivation for treatment, cognitive distortions (concerning sexuality with children, mutual consent, the use of violence etc.), denial, hypersexuality, etc.

The aims of the baseline evaluation are to obtain:

- socio-demographic characteristics (age, gender, contact with children in case of paedophilic disorder …);
- diagnosis and assessment of the severity of the paraphilic disorder(s) (number and types of paraphilic disorders, age at onset, adult or child victims and age and gender if <18 years), intra- or extra-familial, exclusive or not);
- in case of sex offence: rape or sexual abuse/exhibitionism, sexual sadism, criminal versatility, adult or child victim (known or unknown victim);
- assessment of personality disorders;
- assessment of psychiatric disorders including addictive disorders;
- assessment of somatic comorbidities (in case of any concomitant medical condition, check for possible pathophysiological, metabolic or drug–drug interaction patterns; including hormone-producing tumours as well as drug-induced hypersexuality, agitation or impulsivity);
- assessment of hypersexuality, impulsivity, sexual and nonsexual violence;
- assessment of the trauma associated with a previous history of sexual abuse;
- assessment of IQ in case of mental retardation and of executive functions in case of brain lesions;
- assessment of treatment motivation and capacity;
- assessment of recidivism risk, actuarial assessment scales may be useful (see Chapter 3.8); past history of sentences (sexual and/or non-sexual offences);
- assessment of the need for treatment referral;
- past history of previous treatment of sexual disorders (efficacy, compliance and side effects);
- antiandrogens or GnRH agonists (when necessary) have to be prescribed with the help of an endocrinologist (if necessary), after appropriate medical assessment (see Table 1);
- Finally, freely given 'written' informed consent (with the help of his/her legal guardian if applicable) must be obtained from the subject if antiandrogen or GnRH agonist treatment is necessary.

5.2. Contra-indications

5.2.1. MPA treatment

MPA treatment must not be used without consent, prior to the completion of puberty, in cases of adrenal disease, pregnancy and breastfeeding or breast or uterine diseases (in case of a female subject), severe and untreated hypertension, previous history or risk of thromboembolic disease (smoking may increase the risk), diabetes mellitus, severe depressive disorder, allergy to MPA, active pituitary disease and meningioma.

5.2.2. CPA

CPA must not be used without consent, prior to the completion of puberty, in cases of hepatocellular disease, liver carcinoma, diabetes mellitus, severe and untreated hypertension, carcinoma except prostate carcinoma, pregnancy and breastfeeding (in case of a female subject), previous history or risk of thromboembolic disease (smoking may increase the risk), severe cardiac disease, adrenal disease, severe depressive disorder, tuberculosis, cachexia, epilepsy, psychosis, allergy to CPA, drepanocytosis, active pituitary disease, meningioma (Reilly et al. 2000; Hill et al. 2003; Huygh et al. 2015).

5.2.3. GnRH agonists

GnRH agonists must not be used without consent, prior to the completion of puberty, in cases of severe and untreated hypertension, pregnancy and breastfeeding (in case of a female subject), severe cardiac disease (cardiovascular risk factors such as smoking, hypertension, abnormal lipid profile or diabetes should be carefully controlled and treated if necessary), QTc prolongation, severe osteoporosis especially in case of prior fractures, severe depressive disorder, psychosis (Thibaut and Colonna 1992), allergy to GnRH agonists, active pituitary disease.

5.3. Medical monitoring is necessary during pharmacological treatment

In all cases, paraphilic and non-paraphilic sexual activity and fantasies (nature, intensity and frequency), as well as the risk of a sex offence, must be evaluated during the interview at least every 1–3 months through self-reports of the patient and, if useful and if possible by interviewing family members or caregivers.

In the case of CPA or MPA treatment, side effects are usually dose-related. See Table 1 for recommendations.

6. Therapeutic approaches

Treatment modalities currently used in the treatment of people with paraphilic behaviours fall into three categories: bilateral orchidectomy (surgical castration,

Table 1. Evaluation of a patient before pharmacological treatment of paraphilic disorders and medical survey during treatment.

Baseline	3rd month	6th month	12th month	24th month and thereafter every year
SSRIs[#] and antiandrogens[##] or GnRH agonists[##]				
Evaluation of sexual fantasies and behaviour (paraphilic and non-paraphilic)	×	×	×	× (at each consultation thereafter)
Weight, height, body mass index (BMI)	×	×	×	×
Blood pressure	×	×	×	×
Electrocardiogram	×	If any cardiac symptoms	If any cardiac symptoms	If any cardiac symptoms
Hepatocellular function	×	× if CPA	× if CPA or GnRH agonists	× if CPA or GnRH agonists (then every 3–6 months in case of CPA)
Kidney function	×	–	× if GnRH agonists	× if GnRH agonists
Thyroid function	×	–	–	–
Blood cell counts	×	–	–	–
Fasting blood glucose levels	×	–	×	×
Lipid profile	×	–	×	×
Antiandrogens or GnRH agonists				
Freely given 'written' informed consent	×	–	–	–
Calcium and phosphate blood levels	×	–	×	×
Physical examination including genitals	×	×	×	×
Risk of feminisation (especially gynaecomastia)	×	×	×	×
Depression, suicidal thoughts	×	×	×	×
Plasma hormone levels: testosterone***, testosterone-binding protein, LH, prolactin	×	–	–	–
Osteodensitometry*	×	–	×*	×
MRI brain scan**	×	–	–	× if CPA

[#]Be careful in case of adolescents; there is an increased risk of suicide.
[##]Puberty and especially growth must be completed.
*Necessary in case of an increased risk of osteoporosis: fractures or age > 50 years, an association of corticoids or anticonvulsants, alcohol use disorder, highly recommended in other cases. Calcium, vitamin D or biphosphonates must be prescribed in case of osteoporosis in order to avoid bone fractures.
**In case of CPA treatment only: brain structural MRI has to be checked at year 5th and then every 2 years in case of a long duration of treatment (>6 months) and high dosage. When CPA is withdrawn, there is no necessity for brain structural MRI follow up. In cases of GnRH agonist treatment, at baseline, check for active pituitary and hypothalamic disease or meningioma.
***Testosterone blood levels could be measured during treatment in case of uncontrolled breaks in the therapy, or in case of risk of masked testosterone supplementation
Special Warning: The FDA warned about the increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death and stroke) in men receiving GnRH agonist medications for the treatment of prostate cancer (https://www.fda.gov/Drugs/DrugSafety/ucm209842.htm). An increased risk of colorectal cancer was also reported with GnRH agonists.

for review, see Heim and Hursch 1979), psychotherapy, pharmacotherapy. Stereotaxic neurosurgery and oestrogen administration have been attempted but are not currently in use, due to the high risks displayed (respectively, those inherent to the invasive surgical technique, and severe 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, CBT. Most of the subjects included in the studies are CSO, rapists, exhibitionists and subjects with paedophilic disorders.

6.1. Methods and limitations

6.1.1. Methods

These guidelines are intended for use in clinical practice by clinicians who diagnose and treat male patients with paraphilic disorders. 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. We have evaluated the role of pharmacological agents in the treatment and management of paraphilic disorders, with a focus on the treatment of adult males. Because such treatments are not delivered in isolation, the role of specific psychosocial and psychotherapeutic interventions is also briefly covered.

To prepare these guidelines, we have brought together different views on the appropriate treatment of paraphilic disorders from experts representing different countries. An extensive literature search was conducted using the English-language-literature (as well as the French- and German-language-literature) indexed on MEDLINE/PubMed (1990–2018 for SSRIs) (1969–2018 for hormonal treatments), supplemented by other sources, including published reviews. The following search terms were used: antidepressants, SSRIs, androgen antagonists, hormonal treatment,

gonadotrophin-releasing hormone agonists and antagonists, CPA, medroxyprogesterone 17-acetate or MPA, paraphilic disorders, sex offences or sex offenders, sexual behaviour, incest. All available papers reporting treatment of paraphilic disorders in English, French, or German were considered. Few were controlled studies, and most of them have used a cross over methodology or were open studies. Additional publications or reviews were identified through the internet. Papers were analysed critically to assess the current state of research on this topic. The guidelines presented here are based on data from publications in peer-reviewed journals (according to previous WFSBP guidelines, Soyka et al. 2008). 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 to 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 good 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.

6.1.2. Limitations

Most reports on the treatment of paraphilic disorders are case reports or series.

In general, treatment efficacy studies are marked by some methodological biases and are extremely difficult to conduct for several reasons: small sample sizes leading to false-negative results; difficulties in conducting studies with forensic patients; sex offending is not socially acceptable, and until recently, those who suffer from paraphilic disorders have rarely sought treatment voluntarily or their motivation is low (many studies obtained their populations from prisons or legally mandated sexual treatment groups); people with paedophilia who are able to control their interests 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 abused children). The identification of standardised and reliable measures of sexual behaviour is difficult. Sex offenders' self-reports of their sexual activity and arrest record reports are usually used, but they do not constitute reliable indices of normal or paraphilic 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* PPG, which measures penile erectile responses to various visual or auditory erotic stimuli in a laboratory, are still a subject of debate. PPG is not often used to monitor response to treatment, but it has been used (Bradford and Pawlak 1987; Bradford and Pawlak 1993a, 1993b).

Finally, there are no pharmacological studies conducted in sexual murderers and, very few in women.

National or international collaborative studies, including large cohorts of well-defined paraphilic disorders with long duration of follow up, are needed to confirm these preliminary data on the efficacy of pharmacological treatments in paraphilias. Comparisons between studies are often difficult due to methodological differences: duration of follow up (long duration of follow up being necessary to determine the rates of recidivism), type of paraphilic disorders with high heterogeneity among samples, definition of recidivism, type of victims, previous offences and/or convictions, retrospective or prospective

designs, outpatients or prisoners, type of treatment and compliance, statistical analyses, treatment side effects or dropout rates are often not reported, etc.

In most countries, clinical trials are not allowed while patients are incarcerated (Briken et al. 2017); moreover, conducting controlled double-blind studies comparing antiandrogen or GnRH agonist treatment with placebo in outpatients with paraphilias and risk of sex offending raises ethical concerns. Marshall and Marshall (2007) have proposed alternative designs (incidental design and actuarially based evaluation) for future studies. 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/she can adapt treatment to the learning style and interpersonal approach of each subject and adjust therapy to the fluctuations in the subject's motivation and mood. The controlled study design does not allow many of the features of a productive therapist-subject relationship.

6.2. Psychological therapies

This treatment approach is beyond the scope of this study. Psychotherapy is an essential aspect of treatment, although debate exists concerning its overall effectiveness for long-term prevention of sexual offences. Several studies have reported that the best outcomes in preventing repeat sexual offences against children occur when pharmacological agents and psychotherapy are used together (McConaghy 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, CBT and supportive psychotherapies. There could be as many definitions of psychodynamic or psychoanalytic therapy as they are studies.

In a 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 definitions of psychotherapies used in sex offender populations. They suggested that 'well-defined' CBT occurred 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 the 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.

In North America, CBT is the standard treatment for paraphilic disorders, who are not at high risk of victimisation (Marshall et al. 2005; McGrath et al. 2010). However, the efficacy of this form of therapy has been questioned (reviewed in Fedoroff and Marshall 2010). The general strategy towards psychotherapy with people who have paedophilic disorders is a cognitive-behavioural approach (addressing their cognitive distortions) combined with empathy training, sexual impulse control training, coping with stress, relapse prevention and biofeedback (Hall and Hall 2007). Sex offenders employ distorted patterns of thinking which allow them to rationalise 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 programmes for sex offenders seek to tackle and change these distorted attitudes as well as other significant factors which can contribute to sexual offending, including the inability to control anger, inability to express feelings and communicate effectively, problems in managing stress, alcohol and drug abuse or paraphilic sexual arousal.

Research studies in the USA into different treatment programmes in prisons and in the community have identified reductions in re-offence rates (Grossman 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 most substantial 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 CBT. In a comprehensive meta-analysis of different treatment programmes (Hanson et al. 2002) ((CBT $n = 29$, 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 3 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 (3 studies and 237 subjects) and for institutional and community treatments. CBT and systemic treatments were associated with reductions in sexual recidivism (from 17.4 to 9.9%). Older forms of psychotherapy (prior to 1980) appeared to have little effect. Kenworthy et al. (2004) published a Cochrane meta-analysis of nine RCTs (500 adult sex offenders of whom 52% were diagnosed with paedophilic disorders, maximal duration of follow up of 10 years). Psychodynamic, psychoanalytic, behavioural or CBTs were compared with each other, drug treatment or standard care in institutional or community settings. Among all studies, the most interesting was 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 paedophilic subjects, exhibitionists or sex offenders. Re-arrest over 10 years was higher, 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 meta-analysis 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 programmes, 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 completely disappeared (11% in each group). 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 CBT 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 CBT was slightly smaller than that reported by Hanson et al. (2002) (OR = 1.45 *vs.* 1.67, respectively). Other approaches (insight-oriented treatment, therapeutic communities and other psychosocial programmes) did not significantly influence recidivism. In their updated meta-analysis (Schmucker and Lösel 2015) on 29 eligible comparisons containing a total of 4939 treated and 5448 untreated sexual offenders, the recidivism rates were 10.1% in treated *vs.* 13.7% in the untreated group. None of the comparisons evaluating biological treatments fulfilled the eligibility criteria. The mean effect size for sexual recidivism was smaller than in their previous meta-analysis but still statistically significant (OR = 1.41; $p < .01$). Specialised psychological treatment targeting sexual offences and treatment for adolescents produced stronger effects, as did treatment that was individualised (rather than purely group based).

A Cochrane review has shown that psychodynamic treatment was less effective in terms of prevention of sexual offending as compared to probation alone and failed to show significant efficacy of CBT compared to no treatment except for one study in which antiandrogen treatment was associated to CBT (Dennis et al. 2012). Walton and Chou (2015) have recently conducted a systematic review of the effectiveness of psychological treatment interventions in CSO. Studies were restricted to RCTs, controlled trials and cohort designs where recidivism had been used as the outcome variable. One RCT and nine cohort studies were included in the analysis, with a total of 2,119 participants. Among them, 52.1% received the intervention under investigation, and 47.9% did not. The reported recidivism rates were 13.9% for the treated CSO compared to 18.6% for the untreated CSO, respectively; only three studies reported statistically significant lower recidivism rates for treated child molesters but eight studies were assessed as weak. Grønnerød et al. (2015) have conducted a meta-analysis of publications in peer-reviewed journals in 1980 or later, including 14 studies coded according to Collaborative Outcome Data Committee criteria. In total, 1421 adult CSO in psychotherapy and 1509 untreated controls were included, with a minimum average follow-up period of 3 years. Recidivism was defined as rearrest or reconviction. Study quality was classified into strong, good, weak or rejected. They have found a treatment effect size of $r = 0.03$ for nine studies evaluated as good or weak, while all studies yielded an effect size of $r = 0.08$, including five studies classified as rejected. They cannot conclude on any effect of treatment on CSO. The authors concluded that despite a large amount of research, only a tiny fraction of studies met a minimum of scientific standards, and even fewer provided sensible and useful data from which it was possible to draw conclusions. Finally, Gannon et al. (2019), in a metaanalysis including 70 studies (11 additional studies as compared to Schmuker and Lösel 2015), described the recidivism of 55,604 offenders (22,321 treated, 33,283 untreated comparison subjects). Sexual recidivism was 9.5% for treated (CBT) and 14.1% for untreated individuals (mean duration of follow up: 76.2 months). A qualified licenced psychologist and supervision provided by psychologists as well as group-based treatments and programmes that incorporated some form of arousal reconditioning, were associated with the best results. Polygraph use was associated with lower treatment effect sizes.

Conclusion and recommendations

The efficacy of CBT for sex offenders is such as to indicate a modest reduction in recidivism (Losel and Schmucker 2005), but this is challenged by studies with more extended follow-up periods (Kenworthy et al. 2004; Maletzky and Steinhauser 2002) and recent reviews (Dennis et al. 2012; Walton and Chou 2015; Grønnerød et al. 2015; Gannon et al. 2019) (Level C/D of evidence). The other approaches (insight-oriented treatment, therapeutic communities and other psychosocial programmes) do not seem to reduce recidivism (Level E of evidence). Moreover, the more extended the observation periods, the higher the cumulative recidivism rates, leaving the impression that the durability of psychological therapies is limited. Furthermore, most of these studies were not conducted with sex offenders at high risk of sexual violence, which means that they cannot be generalised to all sex offenders. Well-conducted studies with longer follow-up durations are needed.

6.3. Bilateral orchidectomy

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.

In Europe, surgical castration was done for the first time in Switzerland in 1892, as an 'imbecile' was cured of his neuralgic pain of the testes and his hypersexuality.

In Europe, estimated recidivism rates, based on rearrest or conviction, were 2.5–7.5% in surgically castrated sex offenders *vs.* 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 sexual desire or sexual orientation. The effect on non-sexual crimes was less clear. About 40–50% 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 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). Štěpán et al. (1989) reported an increased risk of bone demineralisation in these castrated subjects.

In several American states, and in some European countries, surgical castration is legally permitted. In some countries (e.g. Germany and Czech Republic) the

'Law on Voluntary Castration' provided that voluntary castration could be proposed 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 or even surgical castration for repeat child molesters. Several other states have also passed or considered passing such laws (e.g. Florida, Louisiana, Iowa, Colorado, Massachusetts, Michigan, Texas and Washington state).

Although it has been shown that surgical castration reduces paraphilic fantasies and behaviours, there is an alternative, more effective and less invasive treatments are available. Surgical castration has now been abandoned in the vast majority of European countries. It is worthwhile to mention however, that post-castration recidivism rates are among the lowest rates among all forms of treatments. However, one physically castrated paedophile has restored its potency by taking exogenous testosterone and then abused again (Stone et al. 2000).

The working group positions itself clearly and unambiguously against surgical castration in paraphilic patients and sex offenders.

6.4. Pharmacotherapy

6.4.1. Psychotropic drugs excluding selective serotonin reuptake inhibitors

It is recommended that the common comorbid psychiatric disorders reported in subjects with paraphilic disorders should be diagnosed and treated as well. In these cases, psychotropic drugs are used to treat comorbid psychiatric disorders. The use of psychotropic medications in paraphilic disorders is not new. Yet, no randomised controlled trials have documented their efficacy.

6.4.1.1. Patients with paraphilic disorders and brain diseases. Neurological diseases may be confused with disorders of sexual behaviour or associated with them (for review: Krueger and Kaplan 2000). For example, in treating Parkinson's disease with dopaminergic agonists, such as pramipexole, ropinirole, pergolide, rotigotine, apomorphine or bromocriptine, it has been observed that a significant number of patients develop impulse control disorders, such as hypersexuality which may increase the risk of inappropriate sexual behaviour. There is a trend showing that the proportion of impulse control disorders is related to the selectivity for D3 receptors over D2 receptors, with pramipexole having the highest association with impulse control disorders. It was reported that impulsive, compulsive disorders are also associated with other disorders treated with dopamine agonists or levodopa, such as restless legs syndrome, multiple system atrophy, progressive supranuclear palsy, pituitary adenoma or fibromyalgia. Impulse control disorders were associated with higher dopamine agonist doses (Garcia and Thibaut 2010; for review, see Thibaut 2018). Few data are available regarding the treatment of dopamine-associated inappropriate sexual behaviours. Use of dopaminergic dose reduction or antidepressants has been proposed (for review: Witjas et al. 2012; Solla et al. 2015; Thibaut 2018). In patients with dementia, Ozkan et al. (2008) and Guay (2008) have published guidelines about the use of psychotropic drugs in order to decrease inappropriate sexual behaviours.

6.4.1.2. Anticonvulsants and lithium. Lithium carbonate (Ward 1975; Cesnik and Coleman 1989; Balon 2000; Zourkova 2000) (no controlled studies were conducted) has been sporadically used over the years. Bartova et al. (1978) evaluated lithium therapy in 11 patients treated with 900 mg/d for 5 months. Paraphilic sexual tendencies disappeared in six patients; nausea occurred in two cases. Anticonvulsants (carbamazepine, topiramate, divalproate or divalproex sodium plus quetiapine) (Nelson et al. 2001; Varela and Black 2002; Wang et al. 2014) have also been sporadically used. No prospective trials have documented topiramate effectiveness (an 'anti-impulsivity' medication) in paedophilic disorders but several case reports have described topiramate effectiveness in reducing unwanted sexual behaviours or hypersexuality (sex with prostitutes, compulsive viewers of pornography and 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).

In conclusion, no apparent efficacy was observed using lithium or anticonvulsants when no bipolar disorder was associated with paraphilic disorders.

6.4.1.3. Antipsychotics. Importantly, atypical neuroleptics (aripiprazole, amisulpride, olanzapine, risperidone, paliperidone or quetiapine) have been associated with hypersexuality in several case reports of psychotic patients, which may favour inappropriate sexual behaviour. This side effect may improve or cease when antipsychotic treatment is withdrawn or replaced with another antipsychotic (No authors listed 2014).

Antipsychotics (benperidol, thioridazine, haloperidol and risperidone) have been used in case reports (Tennent et al. 1974; Zbytovský 1993; Bourgeois and Klein 1996 (fluoxetine plus risperidone 6 mg/d: paedophilia and comorbid dysthymia); Zourkova 2000, 2002).

In a placebo-controlled cross over study (18 weeks: 3 × 6-week periods), chlorpromazine (125 mg/d), benperidol (1.25 mg/d) and placebo were compared in 12 paedophiles in a high-security hospital (Tennent et al. 1974). There were no statistically significant differences in most comparisons between the three groups. Extrapyramidal side effects were frequently observed with benperidol; drowsiness was more frequent with chlorpromazine. Ten patients (Bartova et al. 1978) were receiving fluphenazine decanoate (12.5–25 mg every 2–3 weeks i.m. for 3–4 months). Paraphilic sexual tendencies disappeared in five cases and were reduced in four cases. Extrapyramidal symptoms and orthostasis occurred in eight patients. Clozapine was proposed for dopaminergic-induced paraphilic disorders in patients with Parkinson's disease (Fernandez and Durso 1998).

However, it is also important to remember that GnRH agonist treatment may exacerbate delusions in schizophrenic patients with paraphilic sexual thoughts associated with delusions (Thibaut et al. 1991; Thibaut and Colonna 1992). In conclusion, in spite of rare cases of sex offences related to delusions in schizophrenic patients, no apparent efficacy was reported with the use of antipsychotics in paraphilic disorders whereas numerous and potentially severe side effects were observed.

6.4.1.4. Tricyclic antidepressants and mirtazapine. One double-blind crossover study showed that clomipramine and desipramine, as compared with placebo, equally reduced paraphilic behaviour in eight subjects (from 50 to 70% as compared to baseline scores). However, 7 subjects out of 15 dropped out of the study (Kruesi et al. 1992: 15 subjects with paraphilic disorders (paedophilic disorder: two cases, phone sex: seven cases, exhibitionism: four cases, sexual sadism: one case) and/or compulsive masturbation (4); mean age 31 years; treatment periods of 5 weeks; mean dose clomipramine: 163 mg/d (75–250); mean dose desipramine: 213 mg/d (100–250)). There was no preferential response to the more specific serotoninergic antidepressant. In two cases, treatment was restarted after paraphilic relapse.

The more common anticholinergic side effects observed with clomipramine as compared with SSRIs have limited its use in paraphilic disorders (Leo and Kim 1995).

Mirtazapine was successfully used in one case report (Coskun and Mukaddes 2008).

6.4.1.5. Naltrexone. Naltrexone is a long-acting opioid antagonist used clinically in the treatment of alcohol dependence or drug abuse, which inhibits dopamine release in the nucleus accumbens.

Firoz et al. (2014) reported naltrexone efficacy in one case of fetishism with comorbid substance use.

An open, prospective study reported on the efficacy of naltrexone (100–200 mg/d for at least 2 months) and CBT in 15 out of 21 juvenile males with paedophilic disorders and legally-adjudicated sexual offenders (in-patients) with sexual hyperactivity and compulsive masturbation (Ryback 2004). The outcome measures were the reduction in time spent in sexual fantasies and masturbation. Increasing dosage to $\geq$200 mg/d did not increase efficacy in partial responders or nonresponders. Five out of six nonresponders benefitted from leuprolide therapy after 3 months (the most severe cases). Relapse occurred in the 13 patients in whom naltrexone was decreased below 50 mg/d.

Conclusion and recommendations
The level of evidence for the use of psychotropic drugs (except for SSRIs) is very poor when there are no psychiatric comorbidities (case reports, small sample sizes, lack of power, lack of controlled studies) **(Level E of evidence)**.

6.4.2. Selective serotonin 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 increase sexual drive and associated 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 men with paedophilic disorders, decreased activity of the 5HT presynaptic neurons and up-regulation of postsynaptic 5HT2A receptors have been reported (Maes et al. 2001).

Another line of support comes from the clinical observation of the similarities of paraphilic fantasies, urges and behaviours with obsessive/compulsive symptoms. Similar brain abnormalities in corticostriatal circuits have been documented. As SSRIs have proven

to be efficacious in the treatment of obsessive-compulsive disorders (OCD), it seems logical to use them in people with paraphilic disorders and 'hypersexual' patients whose symptoms have a compulsive element.

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 have shown to decrease impulsivity. SSRIs can also increase affiliative behaviours secondary to an increase of vasopressin and oxytocin, and thus may produce additional beneficial effects (Gołyszny and Obuchowicz 2019).

Common psychiatric comorbidities or personality disorders have been reported in adults with paraphilic disorders and hypersexual subjects: mood and/or anxiety disorders; conduct and impulse control disorders; attention deficit hyperactivity disorder (ADHD); substance and alcohol use disorders as well as common borderline, avoidant, schizoid or antisocial comorbid personality disorders. It is recommended that these comorbid disorders be treated as well. Moreover, many patients with paraphilic disorders report high feelings of loneliness, fear of intimacy and isolation.

Increased knowledge about the secondary effects of SSRIs on sexual behaviour suggested the opportunity of using these side effects for the treatment of the paraphilic disorder. Indeed, a medication that enhances central serotoninergic transmission has been found to reduce fantasies and paraphilic behaviour (Jacobsen 1992). These side effects could be mediated by serotoninergic inhibition on dopaminergic tone in brain circuits involved in sexual behaviour (Bijlsma et al. 2014).

Lastly, chronic administration of SSRIs increases the level of the BDNF, which has neuroprotective effects on hippocampal, striatal and mesencephalic dopaminergic neurons (Björkholm and Monteggia 2016). BDNF serves as a transducer, acting as the link between the antidepressant drug and the neuroplastic changes that result in the improvement of the depressive symptoms. This results in increased neuronal plasticity and, consequently in an increased capacity for changing behaviour. In conjunction with CBT 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 is hypothesised to have a range of beneficial effects on the brain of sexual offenders (Bradford 1996; Bradford 2001; Saleh 2004). The aim of the use of SSRIs in the treatment of paraphilic disorders is to change sexual desire and sexual fantasies and to reduce paraphilic sexual behaviour as a result of the effect of these drugs on central serotoninergic transmission. SSRIs produce effects on sexual functioning in both males and females (though somewhat differently), which means that these drugs can be used for the treatment of paraphilic disorders and hypersexuality in both males and females. In fact, 95.6% of females and 97.9% of males showed impairment in one area of sexual functioning when treated with these drugs in a study of over 3000 patients (Clayton et al. 2006). The level and type of sexual dysfunction also vary between individuals with various SSRIs. Based on clinical experience, paroxetine (which has the highest potency for the 5 HT receptors as well as muscarinic cholinergic receptors) causes erectile dysfunction to a higher degree than fluvoxamine, fluoxetine or sertraline. From a clinical standpoint and based on clinical experience by one of the authors (Bradford), paroxetine should not be used for the treatment of paraphilic disorders as erectile dysfunction and inhibited orgasm in men increase non-compliance (Montejo et al. 1996).

In the past decade, numerous case reports have described the efficacy of SSRIs in the treatment of paraphilic disorders, as well as non-paraphilic hypersexuality (Steward and Shin 1997 (one case report of efficacy of paroxetine in sexual disinhibition in dementia)) (for a review see Gijs and Gooren 1996; Bradford and Greenberg 1996; Balon 1998; Garcia and Thibaut 2011).

Two meta-analyses on the effectiveness of all kinds of treatments for sexual abusers including only controlled randomised studies found that no controlled randomised studies have been published on antidepressants (White et al. 2000, Cochrane Library; Losel and Schmucker 2005, Campbell Collaboration Group). Adi et al. (2002) conducted a systematic review of the currently available evidence on the effectiveness of the use of SSRIs for the treatment of sex offenders. One hundred and thirty studies were found, but finally only nine studies were considered acceptable for the meta-analysis: (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. All of them were case series, reporting pre-post psychometric comparisons within subjects in a short time. Only one study had more than a 1-year follow-up, only one was prospective, and none of them included measures of recidivism reduction. The main problem was the

lack of control groups. The scales used in assessing the outcomes were subjective. The length of follow-up was insufficient to assess significant long-term consequences on re-offence. In many studies, heterogeneous groups of paraphilic disorders were included. Exhibitionism, compulsive masturbation, and paedophilic disorder were the most frequent paraphilic disorders in which treatment with SSRIs was associated to clinical improvement. In most cases, other psychiatric diagnoses were associated with paraphilic disorders (mostly affective disorders or OCD). In spite of these methodological limitations, the results were promising. Eight studies showed some significant reduction from baseline in the frequency of masturbation and in the intensity of paraphilic fantasies; depression, anxiety, sexual activity, penile tumescence and general adaptation in paraphilic interests and sexual compulsions were also decreased. One study conducted by Stein et al. (1992) showed only efficacy in compulsive patients. Adi et al. (2002) concluded that there was preliminary evidence of the potential value of SSRIs in the treatment of people with paraphilic disorders. Their economic analysis showed the potential for cost-effectiveness.

6.4.2.1. Fluoxetine. The efficacy of fluoxetine was reported (paraphilic fantasies and behaviours were reduced) in the treatment of: paedophilic disorders (Perilstein et al. 1991 [three cases]; Bradford and Gratzer 1995 [one case]; Greenberg et al. 1996 [a retrospective study comparing three SSRIs]; Bourgeois and Klein 1996 [one case: risperidone plus fluoxetine]; Aguirre 1999 (one case)); exhibitionism (Bianchi 1990; [one case]; Perilstein et al. 1991 [three cases]; Coleman et al. 1992; Yang and Liang 2010 [one case with paraphilia and comorbid schizophrenia]); fetishism (Lorefice 1991, one case); voyeurism (Emmanuel et al. 1991, one case); frotteurism (Bhatia et al. 2010, one case with hypersexual behaviour) as well as various paraphilic disorders (Kafka 1991 (one case of rapist); Kafka 1994 (fluoxetine or sertraline); Kafka and Prentky 1992a,1992b [open studies]; Fedoroff 1995 [open study]; Greenberg et al. 1996 [a retrospective study comparing three SSRIs]; Kafka and Hennen 2000 [fluoxetine and methylphenidate]).

✓ Open studies

Several open studies were published using a mean dose of 40 mg/d for 4–6 weeks. Treatment dosage was gradually increased until the efficacy was observed. Kafka and Prentky (1992a) (open study) have used fluoxetine for the treatment of 10 patients with paraphilic disorders, and 10 patients with non-paraphilic hypersexuality, 19 had comorbid dysthymia. In both groups, they have observed a significant reduction of paraphilic sexual behaviour, hypersexuality and depression. Typical sexual behaviour was not adversely affected. Kafka and Prentky (1992b) reported that fluoxetine (20–60 mg/d) for 12 weeks preferentially reduced the frequency of paraphilic behaviours in 20 male paraphilic subjects (exhibitionism, phone sex, sadism, fetishism and frotteurism) at week 4, and hypothesised that SSRIs might even facilitate normal sexual arousal. Men with paraphilias and/or 'hypersexuality' who did not respond to sertraline for at least 4 weeks were offered fluoxetine (mean dose: 50 mg/d; mean duration of treatment: 30 weeks), and six of the nine subjects showed clinical improvement (Kafka 1994). No men with paedophilic disorders were included in this study, and most study participants had comorbid mood disorders. Fedoroff (1995) reported a 95% remission of symptoms when fluoxetine was used in combination with psychotherapy as compared to psychotherapy alone ($n = 51$ cases). A retrospective study, conducted by Greenberg et al. (1996), in 58 subjects with paraphilic disorders, 17–72 years of age (mean age: 36 years), compared the effectiveness of fluoxetine ($N = 17$), fluvoxamine ($N = 16$) and sertraline ($N = 25$). Seventy-nine percent of subjects received concurrent psychotherapy. The primary paraphilias were paedophilia (74%), exhibitionism (14%) and sexual sadism (12%). Comorbid disorders were borderline personality disorder (31%), depression (28%) or alcohol dependence (17%). Results showed a significant decrease in paraphilic fantasy intensity and frequency from week fourth to eighth, but no further improvement at week 12. Fluvoxamine, fluoxetine and sertraline were found to be equally valid. Adverse effects were similar for the three drugs (insomnia, delayed ejaculation, headache, drowsiness, reduced sexual drive, diarrhoea, nausea). Finally, Kafka and Hennen (2000) reported a reduction of paraphilic total sexual outlet and time spent in paraphilic behaviours with fluoxetine in 22/26 men with paraphilic or paraphilia-related disorders and comorbid ADHD (see also below).

In contrast, fluoxetine (60–80 mg/d) did not improve paraphilic behaviours in three subjects after 2–10 months of treatment (Stein et al. 1992, retrospective open study). However, co-morbid non–sexual OCD symptoms improved in these patients. Similarly, one case report of an exhibitionist and another one of sexual sadism (Wawrose and Sisto 1992) were

associated with inconclusive results or lack of efficacy of fluoxetine (80 mg/d).

6.4.2.2. Sertraline. The efficacy of sertraline was reported (paraphilic fantasies and behaviours were reduced) in the treatment of paedophilic disorders (Bradford and Gratzer 1995, one case; Bradford 1999 and 2001, open studies:" see below); transvestic fetishism (Rubenstein and Engel 1996; one case with sertraline and lithium); frotteurism (Patra et al. 2013; one case with hypersexuality and depression and complete remission at 6-month); as well as various paraphilic or paraphilia-related disorders (Kafka 1994 open study; Greenberg et al. 1996 open comparative study see above; Kafka and Hennen 2000 see below).

✓ Open studies

Physiological measures of sexual arousal (PPG) showed a decrease in paedophilic arousal (by 53%) and improved or maintained normal arousal after 12 weeks of sertraline treatment (Bradford 1999, 2001). Kafka (1994) reported the efficacy of sertraline (mean dose 100 g/d; mean duration 17 weeks) in 24 men with paraphilic disorders and hypersexuality. Unconventional total sexual outlet and average time per day spent in unusual sexual behaviour were significantly reduced without affecting normal sexual behaviour in about half of the sample; however, 9/24 men failed to respond to sertraline. No subjects with paedophilic disorders were included in this study, and most subjects had comorbid mood disorders. A retrospective study, conducted by Greenberg et al. (1996, see above), in 58 paraphilic disorders, compared the effectiveness of fluvoxamine ($N = 16$), fluoxetine ($N = 17$) and sertraline ($N = 25$). A significant reduction of paraphilic fantasies was observed with sertraline. Finally, an open study conducted by Bradford (2000) in 20 subjects with paedophilic disorders for 12 weeks with sertraline has reported a reduction of paraphilic sexual fantasies and behaviour without affecting normal sexual behaviour.

Finally, a 23-year-old female with paedophilic disorder was treated with sertraline (50 mg/d) (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.

6.4.2.3. Fluvoxamine. The efficacy of fluvoxamine was reported (paraphilic fantasies and behaviours were reduced) in the treatment of exhibitionism (Zohar et al. 1994, one case with compulsive masturbation) as well as various paraphilic or paraphilia-related disorders (Greenberg et al. 1996, open comparative study see above; Kafka and Hennen 2000, see below). In contrast, fluvoxamine (200–300 mg/d) did not improve paraphilic behaviours in one case after 2–10 months of treatment (Stein et al. 1992, retrospective open study). This may have been due to a higher incidence of delayed orgasm at the higher doses used (1994). However, co-morbid nonsexual OCD symptoms improved in this patient.

✓ Open study

A retrospective study, conducted by Greenberg et al. (1996, see above), in 58 paraphilic disorders, comparing the effectiveness of fluvoxamine ($N = 16$), fluoxetine ($N = 17$) and sertraline ($N = 25$) has shown a significant reduction of paraphilic fantasies with fluvoxamine.

6.4.2.4. Paroxetine. The efficacy of paroxetine was reported (paraphilic fantasies and behaviours were reduced) in the treatment of sexual disinhibition in dementia (Steward and Shin 1997) and compulsive voyeurism or exhibitionism (Abouesh and Clayton 1999, two cases).

6.4.2.5. Citalopram.

✓ Controlled study

The only double-blind study by Wainberg et al. (2006), compared 20–60 mg of citalopram *vs.* placebo in 28 homosexual men with compulsive sexual behaviour in a 12-week trial. Efficacy was measured using the Yale-Brown OCD scale. Positive treatment effects were seen on sexual desire/drive ($p = .05$), frequency of masturbation ($p = .01$) and pornography use ($p = .05$). However, no paraphilic disorders were observed in these subjects.

6.4.2.6. Several authors have compared the effectiveness of SSRIs to other treatments.

✓ Open studies

Greenberg and Bradford (1997) compared 95 patients receiving SSRIs plus psychosocial intervention *vs.* 104 subjects having only psychosocial treatment. Both strategies reduced paraphilic behaviours, but only the SSRIs reduced fantasies and desire within 12 weeks. Kraus et al. (2006) reported a marked reduction of paraphilic symptoms in an open, uncontrolled retrospective study of 16 men with paraphilias receiving SSRIs in combination with psychotherapy. Bradford and Greenberg (1996) reported that psychotherapy plus SSRIs were more effective than psychotherapy alone.

Kafka and Hennen (2000) added amphetamine, methylphenidate (40 mg/d for a mean duration of 9.6 months), pemoline or bupropion to SSRIs to counteract tolerance effects and to treat residual depressive or ADHD symptoms (open study, 26 male patients with paraphilic disorders). The addition led to a significant additional decrease in paraphilic or paraphilia-related disorders.

6.4.2.7. SSRIs' side effects. The majority of people will only experience a few mild side effects with SSRIs. Some of the main side effects of SSRIs are described below, but this is not an exhaustive list (National Health Service, UK, www.nhs.uk).

Common side effects of SSRIs can include: feeling agitated, shaky or anxious, feeling or being sick, indigestion, diarrhoea or constipation, loss of appetite and weight loss, dizziness, blurred vision, dry mouth, excessive sweating, insomnia or drowsiness, headache, low sex drive, difficulty achieving orgasm during sex or masturbation, and in men, difficulty obtaining or maintaining an erection (erectile dysfunction).

Less common side effects of SSRIs can include: bruising or bleeding easily, including vomiting blood or, blood in their stools, confusion, problems with movement, such as stiffness or shaking, hallucinations, being unable to pass urine.

Serotonin syndrome is an uncommon but potentially severe set of side effects linked to SSRIs. It is usually triggered when an SSRI is used in combination with another medication (or substance) that also raises serotonin levels, such as another antidepressant, lithium or St John's Wort. Symptoms of serotonin syndrome can include confusion, agitation, muscle twitching, sweating, shivering, and diarrhoea. Symptoms of severe serotonin syndrome include a very high temperature (fever), seizures (fits), irregular heartbeat (arrhythmia) and loss of consciousness. It is a potentially fatal disorder.

Hyponatraemia: elderly people who take SSRIs may experience hyponatraemia. Mild hyponatraemia can cause symptoms similar to depression or side effects of SSRIs, such as: feeling sick, headache, muscle pain, reduced appetite and confusion. More severe hyponatraemia can cause the following symptoms: feeling listless and tired, disorientation, agitation, psychosis, seizures, loss of consciousness and confusion.

Suicidal thoughts: young people under 25 seem at higher risk (for review: http://www.nimh.nih.gov/health/topics/child-and-adolescent-mental-health/antidepressant-medications-for-children-and-adolescents-information-for-parents-and-caregivers.shtml).

6.4.2.8. Conclusion and clinical recommendations. The only double-blind study by Wainberg et al. (2006), was conducted in males with compulsive behaviour and cannot be generalised to males with paraphilic disorders.

Rösler and Witztum (2000) suggested that SSRIs might be an effective treatment only in men with a specific OCD component to their sexual behaviour. Indeed, the one proposed mechanism of action relates the anti-obsessional effects of SSRIs to the hypothesis that hypersexuality and some paraphilias may be related to OCD, or to impulsive control disorders (Stein et al. 1992). Yet, the use of SSRIs to treat paraphilic disorders has been shown not only to be successful in reducing paraphilic interests but also well tolerated with a high level of patient satisfaction despite the onset of some sexual dysfunction (Kraus et al. 2007). Some researchers conclude that many reasons exist for the lack of research on antidepressant treatment of sexual offenders: (1) lack of interest by governments to promote their use in these patients and to fund research; (2) ethical barriers preventing double-blind studies in men with paraphilic disorders associated with criminal acts to be carried out; (3) sexual offenders constitute a highly stigmatised 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 or fluoxetine reduces paraphilic sexual behaviours independent of their antidepressant effect without affecting or even with improving non-paraphilic sexuality (Bradford et al. 1995; Bradford 2000). Due to better tolerability, compliance should be improved (Fedoroff 1995).
- Paraphilias usually start at adolescence and are limited to paraphilic fantasies related to masturbation between 12 and 18 years. SSRIs given at this stage may help prevent acting on paraphilic interests (Bradford and Fedoroff 2006).
- Taking into account clinical data, Bradford (2000), Bradford and Fedoroff (2006) and Kafka (personal communication), Thibaut et al. (2010): WFSBP guidelines, recommend SSRIs prescription in mild paraphilic disorders such as exhibitionism or paedophilia (without CSO) in cases with high levels of paraphilic arousal that cannot be controlled with CBT and that have comorbidity with OCD, impulse control disorders and depression, as well as in maintenance treatment.

Informed and motivated patients are good candidates (ATSA Practice Standards and Guidelines for the Evaluation, Treatment, and Management of Adult Male Sexual Abusers 2004, Oregon).

SSRIS can also be used in association with antiandrogen or GnRH agonist treatment in order to improve depressive symptoms, which are frequently observed in the first months of antiandrogen or GnRH agonist treatment.

Conclusion and recommendations
Though not formally approved, SSRIs have already been included in clinical practice 'off label' for the treatment of paraphilic disorders with specific indications, although more research demonstrating efficacy is also needed. Despite a lack of controlled studies, there is some clinical evidence that at least sertraline and fluoxetine reduce paraphilic sexual behaviour in mild cases of paraphilic disorders such as exhibitionism or paedophilia without CSO with a reasonable benefit/risk ratio **(Level C of evidence)**.

6.4.3. Oestrogens

The first study was published in 1949 (Golla and Hodge). Despite its efficacy (Whittaker 1959; Bancroft et al. 1974), numerous side effects were reported (nausea, weight gain, feminisation, breast cancer, cardiovascular and cerebrovascular ischaemic disease, thromboembolism) (Field 1973). Breast carcinoma was also reported in transsexual individuals during the use of oestrogenic treatment (Symmers 1968).

Conclusion and recommendations
Oestrogens must not be used in the treatment of paraphilic disorders and/or sex offenders (Level D of evidence and severe side effects).

6.4.4. Hormonal treatments (or androgen deprivation therapy): Antiandrogens or GnRH analogues

Not every sex offender is a candidate for hormonal treatment, even if it has the benefit of being reversible once discontinued.

6.4.4.1. Antiandrogens: MPA and CPA.

6.4.4.1.1. Medroxyprogesterone acetate (MPA).

✓ MPA characteristics

MPA is a progesterone derivative that acts as a progestogen and, like testosterone itself, exerts negative feedback on the hypothalamic-pituitary axis, resulting in a decrease 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 prostate cancer. MPA was the first drug studied in the treatment of paraphilic disorders. MPA may be prescribed as an intra muscular (i.m.) depot preparation (150 or 400 mg/mL) or per os (2.5, 5 or 10 mg); 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 (1968) and has since been used in the USA.

✓ Studies

More than 600 cases have been reported among different studies including 13 case reports (24 subjects), 13 open or controlled studies (including 3 double-blind cross-over studies).

• Case reports

Thirteen case reports including 24 subjects were found (Berlin and Coyle 1981; Berlin and Meinecke 1981; Cordoba and Chapel 1983; Bourget and Bradford 1987; Cooper 1987; Cooper et al. 1990; Ross et al. 1987; Cooper 1988; Weiner et al. 1992; Stewart 2005; Light and Holroyd 2006; Krueger et al. 2006; Rea et al. 2017). All participants were males, aged from 17 to 85 years (in 13 cases, subjects were aged above 65 years, and exhibitionism or hypersexuality was associated with dementia). Paedophilia was observed in five cases (in association with exhibitionism, mental retardation, or schizophrenia in 4/5 cases). In one case, the patient's testosterone level was elevated before treatment to 880 ng/100 mL (Berlin and Meinecke 1981). MPA (100 mg/4 weeks to 750 mg/week i.m. or 100–300 mg/d per os) was used for 2 months to 4 years. PPG (using audio stimuli or nocturnal PPG) was used as an outcome measurement in two cases. In all cases, except for two, paraphilic sexual behaviour and fantasies disappeared within 3 weeks; in the remaining cases, erectile response to audio sexual stimuli was increased with MPA (Cooper 1987) or treatment was not successful (one case of exhibitionism with intellectual disability, duration of follow up 31 months) (fluoxetine plus MPA) (Rea et al. 2017). 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. 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 paraphilic behaviours in

older patients with dementia. The beneficial effects of MPA (300 mg/week for 1 year) on compulsive masturbation, exhibitionism or, rape attempts were reported in four patients (75–84 years old) with dementia (Cooper 1987). Exhibitionism and attempted rape by two men with dementia (71 and 84 years old) were also successfully treated with MPA (150–200 mg/2 weeks) (Weiner et al. 1992).

- Open and controlled studies (13 studies, see Table 2)

Among 13 studies, three were double blind cross over studies (comparing MPA and placebo) including 51 subjects with paedophilic disorders and 8 sex offenders (Wincze et al. 1986; Hucker et al. 1988; Kiersch 1990), 9 were open studies and one was a retrospective study (275 sex offenders, Maletzky et al. 2006).

✓ Efficacy, dosage, duration of treatment

Paedophilia or exhibitionism was reported in 27% and 15% of about 600 cases, respectively. Participants were males aged from 14 to 85 years. 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 intra-muscular (i.m.), long-acting preparation (100–900 mg/week) or, per os (60–300 mg/d). Gottesman and Schubert (1993) reported no paraphilic sexual behaviour with 60 mg/d of MPA. These authors recommended a low dose when side effects were observed and when there was a low risk of a sex offence. Reduction of sexual behaviour and complete disappearance of paraphilic sexual behaviour and fantasies was observed after 1–2 months in the majority of cases in spite of maintained erectile function during PPG in four studies. Cooper (1986) recommended a minimum duration of MPA treatment of 2 years. Money et al. (1975), using MPA in a few cases, reported no reduction in non-sexual crimes in sex offenders with antisocial behaviour.

The re-offence rate for 334 individuals taking depot MPA was higher 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). In 12 cases, recidivism of paraphilic sexual behaviour was reported during MPA treatment using different criteria (Langevin et al. 1979; Money et al. 1981; Cooper 1987; McConaghy et al. 1989; Kiersch 1990; Kravitz et al. 1995, 1996). Some studies reported increased recidivism after MPA was stopped (Money et al. 1981; Meyer et al. 1992; Meyer, Wiener, et al. 1992; Gottesman and Schubert 1993). Drug abuse, previous head trauma, learning disabilities, single marital status, personality disorders, and higher initial testosterone levels increased the recidivism risk (Meyer et al. 1992). Early treatment interruption was also a risk factor. Finally, McConaghy et al. (1989) reported a lower efficacy of MPA in juveniles.

Interestingly, Langevin et al. (1979) reported no reduction of sexual behaviour in healthy controls with MPA treatment (100 mg/d). Indeed, during MPA treatment, three pregnancies were observed in the intimate female partners.

✓ Side effects

The adverse effects of MPA included: hot flushes, gynaecomastia, spermogram abnormalities, erectile dysfunction, decrease in testicular volume, weight gain (18%, max 9 kg), headache (9%), nausea, asthenia, lethargy, insomnia, leg cramps (<1%), increased blood pressure, diabetes mellitus (<1%), gallstones (1%) (Meyer, Wiener, et al. 1992), transient increased levels of hepatic enzymes, gastrointestinal symptoms, depressive symptoms or disorders, adrenal suppression (in 1 case and MPA was replaced with a GnRH agonist), Cushing syndrome (in a 30-year-old male with paedophilia treated with MPA, 300 mg/d 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).

Conclusion and recommendations

Many subjects received MPA treatment in North America, and some biases were observed in the literature (small size of samples, short duration of follow up, cross over study design, open studies or retrospective study design). In addition, severe side effects were observed with MPA.

The low benefit/risk ratio did not favour the use of MPA, which was abandoned in Europe (Level C of evidence).

6.4.4.1.2. Cyproterone acetate (CPA).

✓ CPA characteristics

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 robust progestational action, which causes an inhibition of GnRH

secretion and a decrease in both GnRH and LH release (Neuman 1977; Jeffcoate et al. 1980).

A search on Google Scholar with a keyword CPA resulted in 28,900 articles. 11,000 articles were written since 2010, and in 2017 and 2018 there are 183 articles listed. By far, the majority of them are directed towards the treatment of prostate carcinoma, gender identity disorder and hirsutism. There are no recent articles related to the treatment of paraphilic disorders. Because of the long history of the use of CPA from 1960 and its continued use, there is a large amount of documentation related to adverse effects and side effects of this medication. The antiandrogen effect and the impact on sexual behaviour, which are well documented, are used to treat paraphilic disorders. It is an effective treatment both when given orally and intramuscularly. There is also documentation of its use in combination with the GnRH agonists or its use after treatment with the GnRH agonists. This provides essential clinical information related to the use of CPA.

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. It is also used as a treatment for precocious puberty or hirsutism. CPA may be given either by injection (long-acting form (100 mg/mL) or as tablets (50 and 100 mg)). In the USA, it is only available in a low dosage form in a combination product with ethinylestradiol. The first clinical use of CPA in sex offenders (predominantly exhibitionists) occurred in Germany (Laschet and Laschet 1967, 1971), in an open study, which showed an efficacy of CPA in 80% of paraphilic sexual behaviour.

✓ Studies

- Case reports

Twenty-one patients were reported in 11 case reports (Cooper et al. 1972; Lederer 1974; Bradford and Pawlak 1987; Grinshpoon et al. 1991; Thibaut et al. 1991; Thibaut and Colonna 1992; Byrne et al. 1992; Cooper, Cernovsky, et al. 1992; Eriksson and Eriksson 1998; Gooren et al. 2001; Panesar et al. 2011, no information available; Amelung et al. 2012 no information provided on the type of antiandrogen therapy in six paedophiles). Two paedophilic subjects 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 disinhibition) were receiving CPA (50–200 mg/d or 275–300 mg i.m. every 2 weeks), from 4 weeks to 10 years. In some cases, PPG was used. In most cases, paraphilic 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, Cernovsky et al. (1992) reported a better efficacy with 200 mg/d of CPA as compared with 100 mg/d. Thibaut et al. (1991) and Thibaut and Colonna (1992) reported a concurrent decrease in nonsexual aggressiveness while CPA was used. In most cases, testosterone levels decreased.

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

- Open and controlled studies (11 studies, see Table 3)

Among the 11 studies, 2 were double-blind cross over comparative studies (CPA *vs.* ethinyl oestradiol, 12 sex offenders, Bancroft et al. 1974) (CPA *vs.* MPA, seven subjects with paedophilic disorders, Cooper et al. 1992b), 2 were double-blind cross over studies including respectively 9 sex offenders and 19 subjects with paraphilias and comparing CPA with placebo (Cooper 1981; Bradford and Pawlak 1993a), one was a single-blind study (five paedophiles, CPA *vs.* placebo, Cooper and Cernovsky 1992) and the six remaining studies were open studies.

✓ Efficacy, dosage, duration of treatment

About 900 male subjects were included in 11 open and double or single-blind cross over studies. Approximately 20% of the cases were patients with paedophilic disorders. The most frequent comorbidities observed were mental retardation and psychopathy. CPA (50–200 mg/d per os or 300–600 mg i.m. every 1 or 2 weeks) was associated with a significant decrease of self-reported sexual fantasies or activity and frequency of masturbation and disappearance of paraphilic sexual behaviour in about 80–90% of cases within 4–12 weeks. Morning erections, ejaculation, and spermatogenesis were decreased. In most cases, 100–200 mg/d was sufficient, moreover, in 80% of the cases, 100 mg/d oral CPA was sufficient. Depending on the dosage, the authors suggested that CPA could be used as a chemical castration agent or as a reducer of sexual drive, permitting the ability to achieve and

Table 2. Changes in paraphilic behaviours in male patients treated with medroxyprogesterone acetate (open and controlled studies).

		Methods		Results	
Reference	Characteristics of the patients	Treatment conditions	Outcome measures	Efficacy	Side effects/treatment interruption
Double-blind studies					
Wincze et al. (1986) USA Double-blind cross over-controlled study	*N* = 3 Males Aged: 36–60 years Sex offending? Paedophilia (3)	MPA 160 mg/d per os Or **Placebo** (No treatment 7 d Placebo 14 d MPA 160 mg/d for 42–56 d Placebo for 21–42 d) Duration of follow up: 1–3 months	Self-reports of spontaneous sexual activity Testosterone plasma levels **PPG** (visual erotic paraphilic stimuli), Nocturnal PPG	Reduction of sexual activity (self-report) Less obvious with PPG Reduction of testosterone levels with MPA	None *Treatment interruption*: No increase in sexual behaviour at the end of the placebo period
Hucker et al. (1988) Canada Double-blind cross over study	*N* = 48 Males Sex offending? Paedophilia (48) Comorbidity: Mental retardation	MPA (5) 300 mg/d per os Or **Placebo** (6) 18 subjects gave their consent for treatment 11 remained in the study until the end of follow up	Self-reports	Paraphilic sexual fantasies disappeared MPA > Placebo	Depression and excess salivation MPA > placebo
Kiersch (1990) USA Double-blind cross over study	*N* = 8 Males Aged: <40 years Sex offenders with previous convictions No comorbidity	MPA 100–400 mg/week i.m. (16 weeks) Or, **Placebo** (saline i.m.) (16 weeks) Duration of follow up: 22–64 weeks (4 cases)	Self-reports of paraphilic and non-paraphilic sexual stimuli Testosterone plasma levels **PPG** (audio)	Reduction of testosterone levels with MPA Reduction of response to paraphilic and non-paraphilic sexual stimuli (6) Effects maintained while on placebo treatment Reduction of masturbation frequency (6) *In 1 case increase of* paraphilic *sexual fantasies with MPA* *In 1 case sex offending while on placebo* No change in sexual orientation	Erectile dysfunction(1) Glaucoma (1) Headache (1)
Open studies					
Langevin et al. (1979) Canada	*N* = 37 Males Exhibitionists (37) *N* = 8 Males Exhibitionists (8) *N* = 10 heterosexual male subjects without paraphilic disorders	MPA (100–150 mg/d per os) + Psychotherapy (*n* = 15) (assertiveness training 15 h) or Psychotherapy alone (*n* = 17) or MPA alone (*n* = 5) Duration of follow up: 15 weeks MPA (100 mg/d per os) Or **Placebo**	Clinical interviews Recidivism rate Testosterone plasma levels Self-reports Testosterone plasma levels, **PPG**	After 2 years: *n* = 3 no paraphilic sexual behaviour High drop out rate in both groups: 20/37 early interruption Psychotherapy alone: 6/12 relapse MPA + Psychotherapy: 1/5 relapse MPA: significant decrease of testosterone levels, reduction of paraphilic sexual fantasies PPG: Placebo = MPA MPA = placebo in controls	Nausea (1) Weight gain (1) Nausea None None

(*continued*)

Table 2. Continued.

Reference	Characteristics of the patients	Methods: Treatment conditions	Methods: Outcome measures	Results: Efficacy	Results: Side effects/treatment interruption
Money et al. (1981) USA	*N* = 20 Males Aged 26–56 years Paedophilia (11) Exhibitionism (5) Sexual Sadism (1) Voyeurism (1) Sexual Masochism (1) Transvestism (1) Incest (1)	MPA (150–600 mg i.m. per week) Duration of follow up: 3 months to 5 years	Clinical interviews	*N* = 17 No paraphilic sexual behaviour *N = 3 relapse (1 with alcohol)*	Not reported *Treatment interruption*: At the end of the study, *n* = 11 stopped MPA and relapsed
Gagné (1981) Canada	*N* = 48 Males Previous convictions for sex offences (39) Paedophiles (27) Exhibitionism (6) Voyeurism (1) Incest (3) Rape (4) Others (2) Transvestism (2) Comorbidity: Alcoholism (7) Psychopathy (7)	MPA (200 mg i.m. 2–3 times per week for 2 weeks then 1–2 times per week for 4 weeks then 100 mg or 200 mg every 2 weeks for 12 weeks then 100 mg every 1–4 weeks for 8 months) + Psychotherapy Duration of follow up: 12 months	Clinical interviews (2/month) Testosterone plasma levels (1/month)	*N* = 40 Improvement within 10 d to 3 weeks Reduction of paraphilic sexual activity and fantasies and arousal Reduction of testosterone levels (25% of baseline levels) Improvement of social functioning within 2 to 3 months Similar efficacy between those with or without previous convictions	Asthenia for 3 d after injection (40) Weight gain (max 9 kg) (28/48) Headache (10) Insomnia (7) Hot flushes (14) Nausea (1) Thrombophlebitis (1) Impotence *Treatment interruption*: 1 case (thrombophlebitis) 5 cases against medical advice : no relapse
Meyer et al. (1985) USA	*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)	No evaluation of treatment efficacy Testosterone, LH, FSH plasma levels Spermograms Testis volume (every 6 months) MPA plasma levels	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 insulin levels (3) Headache (1) (decrease of MPA dosage) Sedation Decreased testis volume Transiently increased levels of hepatic enzymes (3) 3 Pregnancies (while MPA treatment of male partners)
McConaghy et al. (1989) Australia	*N* = 45 Males Aged 14–72 years (mean 32 ; 6 cases < 19) Sex offenders (45) Paedophilia Exhibitionism Fetishism Voyeurism Comorbidity: Mental retardation (1)	MPA (150 mg i.m. fortnightly for 4 injections then monthly) **1st Study** Psychotherapy alone (20) (Covert sensitisation, Imaginal desensitisation) **2nd Study** MPA (4 juveniles, 12 adults, 7 required MPA later) or Psychotherapy (10) (imaginal desensitisation (ID)) or MPA + ID (10) Duration of follow up: 1 year	Self-reports Testosterone plasma levels	**1st study** covert sensitisation < imaginal desensitisation **2nd Study** Same efficacy between the 3 groups, reduction of paraphilic sexual behaviour Less efficacy in juveniles 3 cases without MPA : sex offences *3 juveniles while receiving MPA: sex offences*	None

(*continued*)

Table 2. Continued.

Reference	Characteristics of the patients	Methods: Treatment conditions	Methods: Outcome measures	Results: Efficacy	Results: Side effects/treatment interruption
Meyer et al. (1992) and Meyer, Wiener, et al. (1992) USA	*N* = 40 Males (MPA treatment) Aged 16–78 years Sex offenders (40) Paedophilia (23) Rapist (7) Exhibitionism (10) *N* = 21 Males (Psychotherapy) Sex offenders (21) Paedophilia (14) Exhibitionism (6) Voyeurism (1) Comorbidity: Head trauma (5) Drug or alcohol abuse (*n*:?) Personality disorders or depressive disorders (33%) no psychopathy Micropenis (2)	MPA (400–800 mg/week i.m.) Versus Psychotherapy alone Duration of follow up: 6–12 years	Recidivism rate of paraphilic sexual behaviour Testosterone, LH, FSH plasma levels	Reduction of testosterone levels with MPA Recidivism decreased with MPA (7/40) *versus* 12/21 with psychotherapy alone	Weight gain (13) Gastrointestinal symptoms (2) Dizziness (1) Headache (1) Increased blood pressure (3) Diabetes mellitus (3) Gallstones (4) Leg cramps (2) *At the end of MPA treatment 10 relapsed:* Risks factor for recidivism: single, drug abuse, previous head trauma, learning disabilities, personality disorders, higher initial testosterone level
Gottesman and Schubert (1993) USA	*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	MPA (60 mg/d) (10–18 months) + Psychotherapy No previous pharmacological treatment, in 4 cases previous psychotherapy failed	Self-reports of paraphilic and non-paraphilic sexual behaviour per week Testosterone, LH, FSH plasma levels (1/month)	Reduction of paraphilic sexual fantasies and morning erections No paraphilic sexual behaviour in 6 cases Reduction of testosterone levels (50–75%) *Increase of sexual desire in 2 cases at treatment onset* *1 case of treatment resistance at week 3*	Headache 1st week (1) Weight gain (2) *Treatment interruption*: In 2 cases early treatment interruption (10 and 12 weeks) 1 lost to follow up, 1 recidivism (rape)
Kravitz et al. (1995) USA	*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 of paraphilic and non-paraphilic sexual fantasies and sexual activity Recidivism Testosterone plasma levels (every 3 months) Blood pressure and weight **PPG** (before MPA and every 6 months)	No paraphilic sexual behaviour Reduction of nonparaphilic 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

(*continued*)

Table 2. Continued.

Reference	Characteristics of the patients	Methods: Treatment conditions	Methods: Outcome measures	Results: Efficacy	Results: Side effects/treatment interruption
Kravitz et al. (1996) USA	*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) Subjects divided into 2 groups: Normal pre-treatment testosterone levels (9) Low pre-treatment testosterone levels (4) Duration of follow up: 6–12 months (*n* = 5)	Id above	Reduction of testosterone levels in most cases No paraphilic 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*	Not reported *Treatment interruption*: Testosterone levels returned to normal levels after treatment interruption (longer duration in older subjects)
Retrospective study					
Maletzky et al. (2006) USA (hospital records)	*N* = 275 Males (clinical files) Sex offenders, prisoners Paedophilia Exhibitionism Rapist Comorbidity?	**Group 1:** MPA (200–400 mg/week i.m.) (*N* = 79) (mostly paedophilic disorders) **Group 2:** MPA recommended but not used (*N* = 55) Depo-Provera Scale score >7 or Static 99 score >4) **Group 3:** MPA not recommended (*N* = 141) + Behavioural therapy	Recidivism of sexual paraphilic behaviour	MPA > no treatment : no paraphilic sexual behaviour with MPA *versus* paraphilic sexual behaviour observed in respectively 30% and 26% of subjects in groups 2 and 3	Not reported

MPA: medroxyprogesterone acetate; PPG: penile plethysmography; d: day.

maintain erectile function during non-paraphilic sexual behaviour.

Five comparative double (or single) blind cross over studies (Table 3) have compared CPA with placebo, MPA or ethinylestradiol in 52 sex offenders. Bancroft et al. (1974) compared the effects of CPA with those of 0.01 mg ethinylestradiol twice a day. Both treatments equally decreased sexual interest and sexual activity with no significant side effects (except for one case of early depressive disorder). Only CPA decreased responses to erotic stimuli (using PPG). 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, Sandhu, et al. 1992). In all studies, CPA, MPA and ethinylestradiol 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 PPG, 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 Sandhu, et al. 1992; Bradford and Pawlak 1993b). These results are in accordance with the view that erections in response to visual stimuli, are less androgen-dependent. By contrast, a consistent trend towards preferential suppression of paraphilic arousal using phallometric measures was observed during CPA treatment in a group of subjects with paedophilic disorders 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 paraphilic sexual activity (CPA > placebo and CPA > no treatment). The treatment effects of CPA or MPA were fully reversible, 1 or 2 months after medication interruption.

Cooper and Cernovsky (1994) compared CPA and leuprolide acetate using PPG in one man with paedophilic disorder. The following treatment sequences were used: placebo (32 weeks in total), no treatment (52 weeks in total), CPA 100 mg/d (36 weeks), CPA 200 mg/d (42 weeks), and 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-report of sexual arousal were superior to CPA efficacy (100 or 200 mg/d). No treatment and placebo sequences shared the same lack of effect on all measurements.

Some studies have reported reduced anxiety and irritability with CPA in their patients (Cooper, Cernovsky, et al. 1992; Cooper, Sandhu, et al. 1992; Bradford and Pawlak 1993b, Thibaut et al. 1991; Thibaut and Colonna 1992).

Since our previous guidelines, there is one new open study using CPA (case series). Seventy-six male sex offenders involved in a forensic programme in South Africa were studied. Changes in sexual functioning were measured in 13 individuals treated with CPA (±antipsychotics) as compared to 63 cases who were receiving only psychotropic drugs for comorbid schizophrenic disorders (treatment duration: 1–5 years). With the use of CPA, lower levels of sexual desire and frequency of sexual activity were observed, but the difference was not significant (Lippi and Van Staden 2017).

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 follow-up duration 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.

The efficacy was maintained while on treatment for up to 8 years in a sample of 300 males with paraphilic disorders (Laschet and Laschet 1975). 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 paraphilic disorders. According to Cooper (1986), a minimum 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 CPA administration. Plasma testosterone levels were only moderately decreased (for review, Guay 2009).

✓ Side effects related to hypoandrogenism

Erectile dysfunction, hot flushes, pilosity changes, hair loss, decreased sebum excretion rate, spermatogenesis reduction (reversible), impotence, decrease of sexual activity and fantasies, reduced ejaculate volume,

asthenia (in one case, treatment was stopped at week 2; Byrne et al. 1992), sleep disorders, depressive symptoms or disorders (Cooper Cernovsky, et al. 1992; Cooper, Sandhu, et al. 1992), leg cramps, and osteoporosis (Gijs and Gooren 1996; Grasswick and Bradford 2003) were reported. One hip fracture due to the bone mineral loss was observed in a 52-year-old man after 10 years of CPA treatment (300 mg/2 weeks) (Gooren et al. 2001).

- Or related to CPA itself

Headache, dyspnoea, weight gain, gynaecomastia (20% of cases, reversible; in 1 case radiotherapy was used), thrombo-embolic phenomena (Czerny and Briken 2002), increased level of prolactin, 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 or adenoma (Huygh et al. 2015), anaemia (Hill et al. 2003), local pain at the injection site (depot formulation), nausea, hepatocellular damage (especially when CPA dosage is > to 200–300 mg/d, after several months of treatment) it may be fatal, but severe hepatotoxicity is uncommon <1%) (Heinemann et al. 1997; Friedman et al. 1999: two cases of fatal fulminant hepatitis). According to animal research data, CPA is suspected of inducing liver cell carcinoma (Neumann et al. 1992; Kasper 2001).

In patients with prostate cancer, CPA increased the risk of venous thromboembolism more often as compared to flutamide or GnRH agonist monotherapy (3.5 fold). 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).

The hormonal dependency of cerebral meningioma is well known, but CPA seems to have a stronger influence on tumour growth. Several recent epidemiological studies have shown an increased risk of meningioma in people who have received CPA at high doses for at least 6 months (incidence rate of 60 per 100,000 person-years as compared to 7 in nonusers (Gil et al. 2011)). In patients with meningioma, the risk was only significantly increased among male users of a high-dose of CPA (OR 6.3 CI: 1.37–28.92) (3/745 patients were currently using CPA) compared with nonusers (Cea-Soriano et al. 2012). In 12/12 cases, a growth stabilisation and regression were reported after CPA treatment withdrawal with no regrowth during a mean follow up period of 1 year (Bernat et al. 2015). In some countries such as France, a structural MRI is recommended before treatment in case of planned prolonged treatment (>6 months with a high dose > 100 mg/d). Then, MRI has to be checked at the 5th year and thereafter every 2 years if CPA is maintained. When CPA is stopped, no additional follow up is required. Rare cases of prolactinomas or somatotrophinomas were reported in transsexual receiving oestrogens in combination with CPA (García-Malpartida et al. 2010; Nota et al. 2018). Yet, regular screening of prolactin levels or MRI is not recommended by these authors.

Conclusion and recommendations

In some countries, the oral form is the only form available, and treatment compliance may be erratic. Furthermore, the plasma testosterone level is not systematically decreased, and measurements of plasma levels of CPA are not available in many countries. Thus, poor treatment compliance is a significant concern with oral CPA.

In conclusion, many subjects received CPA treatment, and some biases were observed (small size of samples, short duration of follow up in most cases, cross over study design, open studies, retrospective study) (Level C of evidence). The risk/benefit ratio was moderate.

6.4.4.2. Gonadotrophin hormone-releasing hormone (GnRH) analogues or agonists.

✓ GnRH agonist characteristics

In fact, MPA and CPA have shown inconsistent results in the treatment of sex offenders. In addition, poor treatment compliance is a significant concern with oral CPA. Because of a substantial number of side effects, including gynaecomastia, weight gain, thrombo-embolic phenomena and hepatocellular damage, there was a need for other effective treatments with fewer side effects. The results obtained, using surgical castration, have motivated further research with GnRH analogue treatments.

GnRH agonists act initially at the level of the pituitary to stimulate LH release, resulting in a transient increase in serum testosterone levels (flare-up effect). After an initial stimulation, continuous administration of GnRH agonists causes rapid desensitisation of GnRH receptors, resulting in a 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). In many studies, an antiandrogen is used during the first week to prevent any increase in paraphilic sexual behaviour in relationship with this flare up effect. GnRH agonists do not interfere with the action of androgens of adrenal origin. Fourty percent of healthy controls reported a 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 also be 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 GnRH agonists are available. They were approved in many countries for the treatment of advanced prostate cancer (Vance and Smith 1984), endometriosis, precocious puberty, uterine fibromyomas and female infertility (*in vitro* fertilisation).

Triptorelin is a synthetic decapeptide agonist, an analogue of the GnRH. Triptorelin was developed as a pamoate salt (3 mg – 1-month formulation or 11.25 mg – 3-month formulation, there is also a 6-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 long-acting 11.25 mg).

Leuprorelin is a synthetic analogue of GnRH. It was developed as a daily i.m. or, monthly depot injections (3.75 or 7.5 mg – 1-month formulation or 11.25 mg – 3-month formulation) (leuprolide acetate). Leuprolide acetate is not approved in this indication.

Goserelin is also a synthetic analogue of GnRH. It was developed as a daily i.m. or, monthly depot injections (3.6 or 10.8 mg subcutaneously). Goserelin is not approved in this indication.

✓ Studies
• Case reports

Triptorelin

Hoogeveen and Van der Veer (2008) reported one case of a man with paedophilia, mental retardation and alcoholism treated with triptorelin (3.75 mg/month) for 37 months with respectable efficacy. Previous treatment with SSRI and antipsychotic treatment or psychotherapy had failed. Triptorelin was withdrawn at month 37th (osteoporosis), and paraphilic sexual fantasies returned. Testosterone levels decreased: from 22.8 before treatment to 1.3 nmol/L during treatment.

Since 2010, four studies reporting the efficacy of triptorelin treatment in six patients were published (Huygh et al. 2015 (one case); Mayrhofer et al. 2016 (two cases); Jordan et al. 2014 (one case); Amelung et al. 2012 (two cases)) (for an overview Turner and Briken 2018) (triptorelin 3-month formulation was used in 3/6 cases). A formal diagnosis of paedophilic disorder was reported in three cases, and four had been convicted for sexual offences mainly against children. One study presented results from self-identified paedophiles ($n = 3$; Amelung et al. 2012) and reported less sexual preoccupation and better sexual self-control.

Leuprorelin (leuprolide acetate)

Allolio et al. (1985) successfully treated with leuprorelin a homosexual man with a paedophilic disorder. Rousseau et al. (1990) reported the case of a man with exhibitionism (35 years old) who received a combination of short-acting leuprorelin and the antiandrogen flutamide with no side effects reported during 26 weeks. Concurrently with the decrease of testosterone, a sharp decline in the paraphilic sexual activities and fantasies was observed. The paraphilic activities totally ended after 2–4 weeks. Dickey (1992, 2002) reported the case of a male patient (28 years old) with multiple paraphilias and 'hypersexuality' successfully treated for six months (1992) and 10 years (2002) with leuprolide acetate (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 testicular origin alone was sufficient for treatment. Testosterone levels decreased: from 28.9 to 0.8 nmol/L. In a man with paedophilic disorder, a significantly more significant 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/d with a dose effect) or placebo. The study design was an elaborate cross over trial of successive 16-week-periods and then, 36 and 42 weeks with CPA 100 and 200 mg/d, respectively, leuprolide acetate for 24 weeks after a 10-week washout period. The testosterone level was reduced to castration levels with leuprolide acetate (Cooper and Cernovsky 1994). Single case reports of successful leuprolide acetate treatment (7.5 mg/month) of a patient with exhibitionism and Huntington's disease (Rich and Ovsiew 1994) or of a 43-year-old male patient with exhibitionism, 'hypersexuality', fronto temporal dementia and Klüver-Bucy syndrome (Ott 1995) were also published. Efficacy was reported at third month.

Nineteen case reports were published since 2010 (Briken et al. 2004, one case with paedophilic disorder; Saleh et al. 2004, six cases; Saleh, 2005, one case [in total five paedophilic disorders]; Bussmann and Finger 2009, five sex offenders [four paedophilic disorders; in two cases previous CPA treatment was stopped due to side effects including one case of osteoporosis];

Table 3. Changes in paraphilic behaviours in male patients treated with cyproterone acetate (CPA) (open and controlled studies).

		Methods		Results	
Reference	Characteristics of the patients	Treatment conditions	Outcome measures	Efficacy	Side effects/treatment interruption
Double-blind studies					
Bancroft et al. (1974) USA Double-blind cross over study	*N* = 12 Males Aged 22–34 years Sex offenders in high-security setting (12)	CPA (100 mg/d) or **Ethinyl-oestradiol** (0.02 mg/d) 3 periods of 6 weeks (No treatment, CPA or oestradiol)	Self-report of sexual and non-paraphilic sexual interest and activity Recidivism not reported Testosterone plasma levels **PPG**	CPA or ethinylestradiol: Both drugs significantly decreased sexual interest and activity Only CPA decreased responses to erotic stimuli (PPG)	Depressive disorder: 1 case on day 3 of CPA (treatment interruption needed)
Cooper (1981) Canada Double-blind cross over study	*N* = 9 Males Sex offenders (7) Exhibitionism (4), Voyeurism (2), Fetishism (1) Incest (1) Comorbidity: Hypersexuality (4)	CPA (100 mg/d) Or **Placebo** 5 periods of 4 weeks (No treatment, CPA 100 mg/d/ Placebo, No treatment, Placebo/CPA, No treatment),	Sexual fantasies and activity for the last 7 d (rating scale 0–100) Testosterone plasma levels	With CPA, reduction of testosterone levels (485 to 365: 30%); 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) ($p<.05$) *Dramatic antiaggressive effect of CPA*	Loss of energy 4/9 *Treatment interruption*: Reversible within 30 d of CPA interruption
Cooper and Cernovsky (1992) Canada Single blind cross over study	*N* = 5 Males Aged 21–31 years Paedophilia (5) Comorbidity: Psychopathy (2) Alcoholism (1) IQ 75–89 (3 cases)	CPA (100 mg/d) or **Placebo** (Placebo 4 weeks, CPA 100 mg/d 8 weeks,-placebo 4 weeks) Duration of follow up: 16 weeks **No statistical analyses**	Testosterone, LH, FSH, prolactin plasma levels 1/month **PPG** (1 per sequence) with audio and visual paraphilic and non paraphilic sexual stimuli Nocturnal penile PPG	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	Not reported *Treatment interruption*: Returned to baseline 4 weeks after CPA interruption
Cooper, Sandhu et al. (1992) Canada Double-blind cross over study	*N* = 10 Males Mean age: 30 years (23–37) Paedophilia (10) (3 dropped out during the initial placebo period) ≥2 paraphilias Exhibitionism 1 Sexual sadism 4 Rapist 1 Fetishism 2 Zoophilia 1 Transvestism 2 Comorbidity: Psychopathy 3 Alcoholism 2 Drug abuse 1 Mental retardation 1 In 3 cases denial and patients were excluded	CPA (100–200 mg/d) Or **MPA** 7 periods of 4 weeks (Placebo-MPA or CPA 100 mg/d- MPA or CPA 200 mg/d- Placebo-MPA or CPA 100 mg/d- MPA or CPA 200 mg/d- Placebo) **No statistical analyses**	Self-report of paraphilic and nonparaphilic sexual fantasies and activity Testosterone FSH, LH plasma levels **PPG** (audio and visual paraphilic and non-paraphilic sexual stimuli)	CPA and MPA: same efficacy dose-dependent (max effect at week 8th) Decrease of sexual fantasies, masturbation, morning erections, penile response to erotic stimuli (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	Reduced ejaculate volume

(*continued*)

Table 3. Continued.

		Methods		Results	
Reference	Characteristics of the patients	Treatment conditions	Outcome measures	Efficacy	Side effects/treatment interruption
Bradford and Pawlak (1993a) Canada Double-blind cross over study	*N* = 19 Male outpatients Mean age: 30 years (19–45) Paedophiles (12) Frotteurism (1) Rapists (2) Fetishism (1) Incest (2) Exhibitionism (1)	CPA 50–200 mg/d or **Placebo** Four 3-month treatment periods (No treatment 1 month-CPA 50–200 mg/d or placebo double-blind 3 months-CPA 50–200 mg/d or placebo for 3 months double-blind successively) (CPA dosage could be changed every month during the last period) **Statistical analyses performed** Duration of follow up: 13 months	BPRS, Buss Durkee Inventory, Rating scales for sexual interest and activity Testosterone, LH, FSH, prolactin plasma levels **PPG** (visual stimuli)	Significant decrease of sexual arousal, fantasies, and activity (5.65 ± 4.7 to 3.59 ± 4.2) and a decrease of BPRS scores No decrease in hostility CPA > Placebo and CPA > No treatment on sexual fantasies and desire Significant reduction of testosterone (50%) and FSH (30%) levels No change for LH No statistical difference observed using PPG	No significant difference for side effects Mean weight gain with CPA: 1.3 kg Significant increase in prolactin levels (X2) *Treatment interruption*: 2 drop out (excellent efficacy): 1 recidivism within 6 months
Open studies					
Laschet and Laschet (1971) Germany	*N* = 110 Males Sex offenders (80%) Paedophiles (29) Exhibitionism Sexual sadism	CPA (50–200 mg/d) Duration of follow up 4 months-4 years	Not reported	Decrease of sexual activity in 80% of cases if CPA >100mg/day Decrease of number of erections and orgasms Maximal effect at 20-25th day CPA In 20% cases dosage must be increased up to 200mg/d	Asthenia Sleep disorders Depressive symptoms Weight gain Pilosity changes Gynecomastia 20% after 6–8 months
Mothes et al. (1971) Germany	*N* = 352 Males Paedophiles (30%)	CPA (100–300 mg/d) Duration of follow up : max 3 years	Self-report of sexual activity (1/year)	Improvement in 90% of cases within 1–3 years of CPA	Not reported
Davies (1974) USA (case reports)	*N* = 50 Males 3 elderly subjects with sexual disorders Sex offenders (16) (women or children; 4 violent sexual fantasies) Exhibitionism Comorbidity: Mental retardation 13 Hypersexuality (10) Chromosomal aberrations (4)	CPA (50–100 mg/d) In *n*? cases: 200 mg/d Duration of follow up: max 3 years	Clinical observation No rating scales	Reduction of paraphilic sexual behavior (16 sex offenders)	Blood tests: no change Gynecomastia (2) Increased severity of diabetes mellitus (1) *Treatment interruption:* No relapse after 3 years

(*continued*)

Table 3. Continued.

		Methods		Results	
Reference	Characteristics of the patients	Treatment conditions	Outcome measures	Efficacy	Side effects/treatment interruption
Laschet and Laschet (1975) Germany Open study	*N* = 300 Males	CPA: (50–200 mg/d oral or i.m. 300–600 mg every 1 or 2 weeks) Duration of follow up: 8 years	Testosterone plasma levels	Improvement in 90% of cases	At onset: A decrease in the number of erections and ejaculation and spermatogenesis Asthenia Depressive symptoms Weight gain After 6–8 months: Gynecomastia (20%) Decreased pilosity Decreased sebum
Bradford and Pawlak (1993b) Canada	*N* = 20 Males Aged 18–60 years Paedophiles (15) Incest (3) Paedophilia (2) Exhibitionism	CPA (50–200 mg/d (mean 85)) Duration of follow up: 9–12 weeks	Testosterone plasma levels **PPG** (audio paraphilic and non-paraphilic sexual stimuli) before CPA and after 2 to 3 months	Maximal efficacy within 8-12 weeks Decrease of penile tumescence depends on the type of visual stimuli (paraphilic > nonparaphilic) Decrease of spontaneous erections and of nonparaphilic sexual fantasies Decrease of testosterone levels mostly in patients with higher (7/17) (but normal > 28 nMol/L) baseline levels	No side effects reported
Lippi and Van Staden (2017) South Africa (case series)	*N* = 76 Males Aged 22–69 Sex offenders (76) (rape: 67) Paedophile (1) 1 Exhibitionism (1) Voyeurism Comorbidity: Intellectual disability (13) SCZ or SCZ spectrum (66)	**CPA** (13 cases)+antipsychotics (6) (2 were on a monthly i.m. dose of 150 mg, 11 were on 300 mg) Treatment duration: 1–5 years Psychotropic drugs, no CPA (63) Antipsychotics (69) SSRIs (3)	Changes in sexual functioning questionnaire male clinical version (CSFQ-M-C):	No differences between CPA or antipsychotics (66/76 had comorbid psychotic disorders)	Not reported

CPA: cyproterone acetate; MPA: medroxyprogesterone acetate; PPG: penile plethysmography; d: day.

Schiffer et al. 2009, one case; Habermeyer et al. 2012, one case; Moulier et al. 2012, one case and 1 healthy control; Park et al. 2014, one case; Mayrhofer et al. 2016, one case; Fosdick and Mohiuddin 2016) (one case – 3-month formulation). Male subjects (17 sex offenders) with paraphilic disorders (exhibitionism, paedophilic disorder (14 cases), sexual sadism or paraphilia not specified) were receiving leuprolide acetate (7.5 mg/month or 11.25 mg every 3 months in 9 cases) for several months to one and a half year. Psychotherapy was associated with hormonal treatment. In several cases, psychiatric comorbidities were associated. In two cases, there was an initial increase in sexual impulses (flare-up effect?) (Bussmann and Finger (2009). In seven known cases, flutamide was used for 15 d to 6 weeks in association with leuprolide acetate. Using self-report of sexual activity or PPG, paraphilic sexual behaviour and fantasies disappeared within 1–3 months after treatment introduction, concurrently to the decrease of testosterone levels. In one case (Saleh et al. 2004), MPA has to be added to GnRH agonists to reduce paraphilic sexual fantasies. One relapse occurred while the paedophilic patient was receiving leuprolide acetate (3-month formulation) after 1 year with a suicide attempt (Briken et al. 2004); there was comorbidity with mental retardation and addictive disorders. In most cases, side effects were not reported. Park et al. (2014) reported the efficacy of leuprolide acetate (1-month formulation) in a patient with exhibitionism, frotteurism, and severe mental retardation. Finally, Fosdick and Mohiuddin (2016) have described the case of a patient with autism and inappropriate sexual behaviour towards children. He received leuprolide acetate (3-month formulation). While on treatment, no more incidents of sexual aggression occurred.

Goserelin

Brahams (1988) reported on the efficacy of goserelin acetate in a homosexual male sex offender with paedophilic disorder. Previous MPA (800 mg i.m. per week) or CPA (600 mg/d) treatments were unsuccessful. The efficacy of goserelin was reported in five additional cases of sex offenders (Beier et al. 2010, one case of paedophilic disorder with no effect of the former CPA treatment; Polak and Nijman 2005, four sex offenders).

- Open and controlled studies (Tables 4a and b).

No RCTs were published.

Triptorelin: Among the four studies, there were three open, prospective studies (48 subjects with paraphilic disorders) and one retrospective study (30 sex offenders).

Leuprolide acetate: Among the four studies, there were three open studies (28 subjects with paraphilic disorders).

Since 2010, additional cases were published in prospective, open, or retrospective studies (see Tables 4a and b).

One retrospective study compared different GnRH agonist treatments with CPA (58 subjects with paraphilic disorders).

In most of the studies, CPA or flutamide was used in combination with GnRH agonists during the first weeks of GnRH agonist treatment.

✓ Efficacy, dosage

Triptorelin

In addition to the seven previous case reports, three open, prospective studies using triptorelin (1-month formulation or 3-month formulation) were conducted in sex offenders and/or subjects with paraphilic disorders (Thibaut et al. 1993, 1996, 1998; Rösler and Witztum 1998, 2008; Ho et al. 2012). The data are summarised in Tables 4a and b. Thibaut et al. (1993) reported the first open study of triptorelin in six patients with paraphilic behaviours. Rösler and Witztum (1998) reported another open, uncontrolled study of triptorelin in 30 patients with paraphilic behaviours using a similar design. In 2008, Rösler and Witztum reported an update of their cohort including 100 men (70 additional cases) with severe paraphilia treated over a period of 15 years with a long-acting analogue of GnRH. Czerny and Briken (2002), in a retrospective study, compared different GnRH agonist treatments with CPA and three patients were receiving triptorelin in this study. Finally, Ho et al. (2012) reported the efficacy of triptorelin (1-month formulation in four cases and 3-month formulation in three cases) in seven sex offenders (5 CSO). PPG was used in two cases. In general, the duration of treatment varied from several months to 7 years. The data are summarised in Tables 4a and b.

Among the 48 male subjects (aged from 15 to 57 years), the most common paraphilic disorders observed, whenever reported, were paedophilic disorders ($n = 38$) and exhibitionistic disorders ($n = 8$) (29 were sex offenders). In six cases, at least two paraphilic disorders were observed in the same patients. In some cases, comorbidities were associated with paraphilic disorders (mental retardation, schizophrenia or, in most cases, personality disorders). In Rösler's study, two scales were used: 'Intensity of sexual desire and

symptoms scale', and the 'Three main complaints questionnaire'. In Thibaut et al.'s study (1993), CPA was concurrently used for the first weeks of triptorelin in order to prevent the behavioural consequences of a theoretical flare-up effect. During triptorelin treatment, no paraphilic 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 sexual behaviour was observed with a maximal effect after 1 or 3 months, and paraphilic sexual fantasies disappeared. One-third of cases (13 cases) have previously received CPA without efficacy. These studies were only open studies without any comparison with placebo. However, in all cases, but one, triptorelin was successful, and the paraphilic sexual behaviour completely disappeared during GnRH agonist treatment. Moreover, triptorelin efficacy was superior to CPA efficacy in 13 out of 41 cases. In the Czerny and Briken's study, similar efficacy was observed with CPA and triptorelin (three cases). In most cases, concurrent psychotherapy was used.

Since the new sustained-release triptorelin pamoate 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 actively improve the treatment compliance, on which long-term control of the paraphilic behaviours largely depends. Indeed, in Ho et al.'s study (2012), triptorelin 1-month (four cases) and 3-month formulation (three cases) similarly decreased paraphilic sexual behaviour.

In conclusion, 85 paraphilic subjects were successfully treated with triptorelin (99% efficacy). In all studies (48 paraphilic subjects of whom 75% were sex offenders, and two-third had a diagnosis of paedophilic disorder) and in seven additional case reports, during triptorelin treatment, no paraphilic sexual behaviour was observed, and no sex offence was reported in 54/55 cases (max. follow up duration: 7 years). Moreover, Hansen and Lykke-Olesen (1997) published a retrospective study on 30 male sex offenders confirming the excellent efficacy of triptorelin, but the duration of the follow up was not reported. In one additional unpublished case, triptorelin was more efficient than leuprolide acetate; in another case of exclusive paedophilic disorder, CPA (200 mg/d) was added to triptorelin in order to entirely suppress paedophilic fantasies and behaviour (F. Thibaut). Rösler and Witztum (2008) confirmed these positive results by extending their study to 70 additional paraphilic subjects (including 80% of men with paedophilia and/or non-paedophilic child molesters and 45 sex offenders, duration of follow up of 15 years). Finally, Sauter et al. (2020) reported that paraphilic patients with problems in self-regulatory abilities seem to profit most from pharmacological sex-drive-reducing treatment (triporelin in 35/38 cases) in combination with psychotherapy *vs.* psychotherapy alone (22 cases).

Leuprorelin or leuprolide acetate

Four studies (39 cases in total) using leuprolide acetate (1- or 3-month formulations) were performed in patients with paraphilic behaviours (Briken et al. 2001; Briken 2002; Krueger and Kaplan 2001; Czerny and Briken 2002 (retrospective study, 11 cases with leuprolide acetate treatment); Schober et al. 2005, 2006 (cross over study)). The last of these studies was a double-blind study; 25 case reports were also previously described. The data are summarised in Tables 4a and b. In total, 64 male participants (20–61 years old) with paraphilic disorders, including 60% of paedophilic disorders, half were sex offenders, were receiving leuprolide acetate (1- or 3-month formulation). In some cases, paraphilias were not specified. Mental retardation, alcohol abuse and personality disorders were the most frequently observed comorbidities. PPG was used in Schober et al.'s study. In most studies conducted before 2010, CPA or flutamide was concurrently used for the first weeks of treatment in order to prevent the behavioural consequences of a possible 'flare-up effect' which was reported by urologists. The maximal duration of follow up was 57 months (mean duration 1 year). In most cases, concurrent psychotherapy was used. Concurrent to the rapid decrease of testosterone levels, a reduction of sexual behaviour was observed, and paraphilic sexual fantasies disappeared. However, in one case report (Briken et al. 2004), the patient relapsed while being treated with leuprolide acetate treatment and committed a sex offence. The Schober et al.'s study was a 'masked' cross over study (*vs.* placebo) ($n = 5$ sex offenders) but unfortunately was not intended for the study of leuprolide acetate efficacy. They 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, paraphilic sexual fantasies returned and testosterone levels returned to baseline levels.

Since 2010, three prospective studies from Korea (Ahn et al. 2013; Koo et al. 2014; Choi et al. 2018) and one retrospective study (Gallo et al. 2019) have been

published. Ahn et al. (2013) reported about a small sample of nine males (three with paedophilic disorders) with different paraphilic disorders and assessed effects using the Wilson Sexual Fantasies Questionnaire where a significant decrease in sexual fantasies was observed. Koo et al. (2014), in 56 sex offenders with different paraphilic disorders (29 with paedophilic disorders and 5 with exhibitionistic disorders) divided into two groups compared a 3-month formulation and a 6-month formulation. The expected upsurge of testosterone (flare-up effect) after the termination of medication in both groups was compared and was faster in the first group (3-month formulation) (within 2 months) as compared to the second group (6-month formulation). Choi et al. (2018) have reported the efficacy of a 1-month formulation of leuprolide in seven sex offenders for 12 months. Finally, Gallo et al. (2019), in a retrospective study, have compared leuprolide acetate (25 cases, 1-month formulation) plus psychotherapy with psychotherapy alone (22 cases) in 47 sex offenders with paraphilic disorders. GnRH agonists were superior to psychotherapy in preventing recidivism (no recidivism *vs.* 1, despite a higher risk using the Static 99 observed in the GnRH agonist treatment group) (treatment duration $>$ 1 year, mean follow up duration 7 years).

In conclusion, about 160 paraphilic subjects (75% were sex offenders and half had a diagnosis of paedophilic disorders) were successfully treated with leuprolide acetate (99% efficacy (one recidivism while treated and in another case, MPA was added to GnRH agonists (Saleh et al. 2004))).

GnRH agonists (triptorelin or leuprolide acetate) were compared with CPA or between them

Czerny and Briken (2002), in a retrospective study, compared the efficacy of GnRH agonists and CPA in 58 subjects with paraphilic disorders, including 16 paedophiles. In 19 cases with data available, 11 received leuprolide acetate, 3 triptorelin and, 5 goserelin acetate as compared with CPA alone in 29 cases. CPA and GnRH analogues showed the same efficacy with no effect on paraphilic 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 aggressive sexual impulses under CPA. In these latter cases, the intensity of sexual desire and symptoms was notably reduced with GnRH analogues as compared with previous CPA treatment.

In a study using a comparative observational study method, Turner et al. (2013), 10 years later, found that for most of the 65 sex offenders in forensic hospitals in Germany treated with GnRH agonists, a lower frequency and intensity of sexual thoughts were reported. However, no difference was observed with CPA, but experts reported more often side effects with CPA treatment.

Finally, Cooper and Cernovsky (1994), using PPG in a male subject with a paedophilic disorder, 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/d (36 weeks), CPA 200 mg/d (42 weeks), and 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-report of sexual arousal were superior to CPA efficacy (100 or 200 mg/d). No treatment and placebo sequences shared the same lack of effect on all measurements.

Finally, in a population of 100 sex offenders, SSRIs (75 cases), CPA (16 cases) or triptorelin (2 cases), in association with a sex offending treatment programme, significantly reduced sexual preoccupation and 'hypersexual' behaviours one month after starting treatment. Interestingly, at 3-month and 6-month, the reductions levelled off with SSRIs but continued to show a steady decline with CPA and GnRH agonists (Winder et al. 2017).

Interestingly, in men with advanced prostate cancer, triptorelin (3.75 mg/month) reduced testosterone concentrations less rapidly, but maintained castration as effectively as leuprolide (7.5 mg/month) (the percentage of men with castrate levels of serum testosterone was lower at day 29 for triptorelin than for leuprolide (91.2% *vs.* 99.3%), but equivalent at day 57 (97.7% *vs.* 97.1%)). The 9-month survival rate was significantly higher for triptorelin than for leuprolide (97.0% vs 90.5%; p=.033). Both treatments were well tolerated (Heyns et al. 2003). There are no controlled comparison studies between triptorelin and leuprolide in paraphilic disorders.

✓ Duration of GnRH agonist treatment

The duration of treatment necessary to achieve a complete disappearance of paraphilic sexual behaviour and the conditions of treatment interruption remains an open question. Efficacy was maintained for years in 99% of cases and as long as the GnRH agonist treatment was maintained (for example the maximal follow

up duration reported was 15 years for triptorelin and 10 years for leuprolide acetate).

In numerous cases where GnRH agonist treatment was stopped, paraphilic sexual behaviour reoccurred.

In the Rousseau et al.'s study (1990), the authors reported recidivism when a successful treatment with leuprorelin and flutamide was abruptly stopped at the 26th week. In Thibaut et al.'s study (1996), the authors described a recurrence of paraphilic 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 paraphilic fantasies disappeared again. By contrast, in a third case ('serial rapist'), 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 paraphilic sexual behaviour after abrupt interruption of GnRH agonist treatment). When the combination of triptorelin and testosterone was stopped after 10 months of concurrent prescription (as soon as the testosterone level was back in the normal range), the paraphilic sexual behaviour did not return, and this lack of paraphilic sexual fantasies or behaviour was maintained for 3 years. However, GnRH agonist treatment was restarted after 3 years upon the patient's request, his paraphilic sexual fantasies reoccurred, and he was afraid of committing a new rape (F. Thibaut). In Rösler and Witztum's study (1998), in eight cases, triptorelin was interrupted after 8–10 months, paraphilic interests resumed in five cases, in which follow-up was possible (in three cases because of GnRH agonist side effects). In 2 cases, triptorelin was resumed with good efficacy and in three cases, CPA (200 mg/d) was introduced, but without efficacy in 2/3 cases. In Hansen and Lykke-Olesen's retrospective study (1997), five subjects stopped triptorelin when they left prison, and in one case, paraphilic sexual behaviour returned. In one additional case report, paraphilic sexual behaviour resumed when triptorelin was stopped because of bone mineral loss (Hoogeveen and Vander Veer 2008). In the Krueger and Kaplan' study (2001), in one case leuprolide acetate was stopped, and paraphilic sexual behaviour reappeared. In the Schober'study (2005), when leuprolide acetate was replaced with placebo, in 3/5 cases, paraphilic sexual behaviour returned within 2 months and, in one case, there was a 'high risk of a sex offence'. In Koo et al.'s study, when leuprolide acetate was abruptly stopped, a fast increase in plasma testosterone levels was observed within 2 months with the 3-month formulation, which was expected. Paraphilic sexual fantasies returned, but the follow-up duration (14 months) was too short of concluding the absence of recidivism. Fosdick and Mohiuddin (2016) stopped a 3-month leuprolide acetate treatment after 7 years of efficacy in one autistic CSO, which immediately led to sexually abusive behaviours towards his younger brother. Finally, in a prospective observational study, Voß et al. (2016) reported about the treatment of 30 patients with different paraphilic disorders. In 15 patients, medication was withdrawn; in 9 patients, testosterone levels normalised after 3–7 months without treatment; paraphilic fantasies reoccurred without any recidivism, but the follow-up duration was also short.

In conclusion, in 60–90% of cases (10/17 with triptorelin and 71/79 with leuprolide) in which GnRH agonist treatment was stopped, paraphilic sexual fantasies reappeared. In most cases, the duration of the follow up was too short (<2 years) to conclude to an absence of recidivism. In order to avoid a flare-up effect due to a surge in testosterone levels when GnRH is stopped, CPA treatment may be prescribed in order to help to control paraphilic sexual fantasies, which might be associated to this flare-up effect. The surge in testosterone level was higher when the 3-month formulation was stopped as compared with the 6-month formulation.

In the author's experience, a minimum 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. However, severe side effects or spouse's pressure may make it necessary to change or stop the medication. Recently, Briken et al. (2018) have described 'The Change or Stop Testosterone Lowering Medication (COSTLow)- Scale' that presents 15 factors that may be helpful in structured professional judgement process when it is necessary to stop the GnRH agonist treatment (see also in Chapter 7, Table 7).

✓ (Markers) of efficacy

Several authors have used functional imaging with the visualisation of images of children in paedophilic subjects and reported changes in brain activation patterns while patients were treated with leuprolide acetate. Schiffer et al. (2009) showed suppression of neural processing of sexual stimuli in subcortical areas. Habermeyer et al. (2012) showed a different brain

activation pattern using fMRI while viewing images of boys and adult men. Moulier et al. (2012) compared cerebral activations in a treated patient with paedophilic disorder (1-month formulation leuprolide acetate) before and after several months of treatment with a non-paraphilic control. The levels of brain activation (images of young boys) undergoing treatment became equivalent in the patient and the control and, an absence of paedophilic interest was also observed on treatment using PPG. Although these modifications were associated with a decrease in paraphilic sexual fantasies, they cannot be used to predict the risk of recidivism in case of treatment interruption.

Jordan et al. (2014) ($n = 1$) used eye-tracking and fMRI to validate pre-post changes under triptorelin (shorter relative fixation time for images of girls as compared to before treatment; a different brain activation pattern was also observed as compared to before treatment) in a sex offender diagnosed with paedophilic disorder and antisocial personality. Eye pursuit measures have suggested that the paedophile subject receiving triptorelin could better control its attraction for children whereas the automatic processes remained unchanged even if patterns of brain activation were reduced (Jordan et al. 2014).

Finally, several case studies (Schober et al. 2005 (leuprolide acetate, five cases), Saleh (2005) (leuprolide acetate, 1 case) and Ho et al. (2012) (triptorelin, 2 cases)) have used PPG to test the penile response of GnRH agonist-treated patients. They reported a reduced excitation. Cooper and Cernovsky (1994), using PPG in a man with a paedophilic disorder, have compared CPA and leuprolide acetate. Leuprolide efficacy on phallometric data and self-report of sexual arousal was superior to CPA efficacy (100 or 200 mg/d). No treatment and placebo sequences shared the same lack of effect on all measurements. Although PPG is widely used in Canada, it is less used in more recent studies (as compared to previous studies with CPA and MPA) and remains a matter of controversies in Europe for several reasons (mainly reliability and ethics (visualisation of sexual violence or naked children) (see Chapter 3.9 for further discussion)).

✓ Side effects

Bone mineral loss

In Thibaut et al.'s study (1993), six young men (aged from 15 to 39) with paraphilic behaviours were receiving triptorelin 3.75 mg per 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. Triptorelin was stopped after 4.5 months due to bone demineralisation (Thibaut et al. 1996). It is to be noted that pubertal development was complete in the 15-year-old subject, 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 paraphilic behaviours were prescribed triptorelin 3.75 mg per 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 standard, except for fourteen 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 time points. The decrease was significant only in the lumbar spine ($p < .05$ after 6 and 12 months of treatment *vs.* the previous months). Two patients, who had progressive demineralisation, were given oral calcium and vitamin D supplements after completing 24 months of triptorelin therapy. Hoogeveen and Van der Veer (2008) reported bone demineralisation in one patient aged 35 years after 37 months of triptorelin treatment in spite of bisphosphonates and calcium treatment from 2nd to 37th month. Triptorelin had to be stopped. Ho et al. (2012) also reported one case of bone loss among seven sex offenders treated with triptorelin (monthly or quarterly).

Krueger and Kaplan (2001) observed three cases of demineralisation at 35 and 57 months, respectively,

among 12 patients aged from 20 to 48-year-old, receiving leuprolide acetate. Czerny and Briken (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 demineralisation after 3 years of leuprolide acetate treatment in a 28-year-old patient. Calcium and vitamin D were used. Grasswick and Bradford (2003) focussed their study on bone mineral survey in seven male subjects with paraphilic disorders (36–61) years (paedophilic disorder in five cases, sexual sadism in one case) and reported demineralisation in 2/4 cases with CPA, one case with leuprolide acetate (plus CPA 300 mg/d) and two of two with surgical castration (plus CPA), the follow-up duration was 4 years. Vit D and calcium were used. Briken et al. (2009) reported two cases of osteoporosis among 26 imprisoned sex offenders treated with different GnRH agonists. Turner et al. (2013) reported bone demineralisation in 8 among 65 sex offenders treated with different GnRH agonists. In the study by Koo et al. (2014), 4 cases out of 56 showed worsening of pre-existing bone demineralisation after 3 months of leuprolide acetate. Finally, Mayrhofer et al. (2016) reported a bone loss in three cases with monthly leuprolide or quarterly triptorelin. In total, 26 cases of bone loss were reported among 250 published cases treated with GnRH agonists (10% of cases).

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 GnRH agonist treatment (except for Hoogeveen and Van der Veer 2008), 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, corticoids or anticonvulsant concomitant use. A class of drugs, the bisphosphonates (e.g. oral alendronate or risedronate, and parental pamidronate or zoledronic acid is 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 GnRH agonists. Alendronate was found to reduce the incidence of vertebral fractures in men in randomised, double-blind trials, but as yet there have been no randomised trials of reduction in fracture rates in men treated with androgen deprivation therapy for paraphilic disorders. Nevertheless, the use of bisphosphonates 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 GnRH agonist treatment. Considering the role of oestrogens in male bone health, selective oestrogen receptor modulators are also being investigated (for review Giltay and Gooren 2009).

Other side effects

Most patients reported progressive erectile dysfunction and decreased libido after 1–3 months of treatment. The lack of sexual interest towards adult partners, with an inability to achieve or maintain an erection or perform sexual intercourse, was proportional to age, occurring in some younger men (40% of healthy controls) but in almost all men older than 35 years.

The patients included in the studies complained of additional side effects such as: hot flushes (37–50%), asthenia, feminisation including mild gynaecomastia (10%) (one patient had severe gynaecomastia under previous CPA treatment, which did not reoccur under triptorelin), decreased facial and body hair growth (2–23%), hair loss, decreased testicular volume (4–25%) or episodic painful ejaculation (one case); blood pressure variations; nausea; weight gain (2–30%); transient pain or site reaction at the site of injection (granulomas were observed with leuprolide (11%); cephalalgias; sleep disorders; diffuse muscular tenderness or myalgia; excessive sweating; calcium oxalate urinary stones (three cases with osteoporosis, triptorelin or leuprolide acetate was used) (Mayrhofer et al. (2016)); and finally depressive symptoms (20%) (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)).

In contrast, in all patients in whom standard blood biochemistry was checked, the results remained within the normal ranges.

As noticed in our first guidelines, psychiatrists using hormonal suppression in treating paraphilic disorders should be aware of the risk of pituitary apoplexy in case of a pre-existing tumour and be able to recognise the symptoms. Pituitary apoplexy revealing gonadotroph or non-secretive adenoma was reported in two case reports (Chanson and Schaison 1995; Huygh et al. 2015); an unusual case of a prolonged flare-up of testosterone after administration of triptorelin and CPA caused by a pituitary tumour was described by Huygh et al. (2015).

Koo et al. (2014) (56 cases) did not find any differences in terms of side effects by comparing quarterly leuprolide acetate or its semi-annual formulation.

Finally, Czerny and Briken (2002) compared CPA with GnRH agonists in 58 subjects (29 in each treatment group) and reported more frequently with CPA as compared with GnRH agonists: weight gain (14/29 *vs.* 4/29), gynaecomastia (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 10th month) and blood pressure variations (2/29 *vs.* 0/29) were more frequent with GnRH agonists as compared with CPA. Hypogonadism was observed in one case with CPA and one case with GnRH agonists.

Some additional side effects were reported in elderly patients treated with GnRH agonists *for prostate cancer:* Urinary incontinence or retention, dysuria, pollakiuria, kidney pain, abnormal kidney function, thrombophlebitis, pulmonary embolism, rarely myocardial infarction, dyspnoea, rhinitis, abdominal pain, diarrhoea, constipation, vomiting, gastroesophageal reflux, abnormal liver function and cholestatic hepatitis, epilepsy, vertigo, paresthaesia, loss of consciousness, hyperuricaemia, diabetes, allergy to triptorelin (3-month formulation), increase in lymphocytes count, rarely anaphylactic shock, QTc prolongation is expected with long term androgen deprivation. No interaction with cytochromes is known. In the case of pre-existing abnormal kidney or liver function, the GnRH agonist dosage remains the same.

Decreased glucose tolerance, changes in LDL, cholesterol and triglycerides have been reported in elderly patients treated with GnRH agonists, but these patients had additional cardiovascular risk factors. These recent data need to be validated in younger subjects with paraphilic disorders.

In 2010, the American Food and Drug Administration (FDA) reported that patients undergoing treatment with GnRH agonists for the treatment of prostate cancer were at a 'small increased risk for diabetes, heart attack, stroke, and sudden death'. Recently, the FDA requested that new warnings be added to the labels of GnRH agonists to inform patients and healthcare professionals of the potential risks of heart disease and diabetes (https://www.fda.gov/Drugs/DrugSafety/ucm209842.htm). Moreover, Gillessen et al. (2010) have reported an increased risk of colorectal cancer in long term use of GnRH agonists for prostate cancer.

Conclusion and recommendations

A previous Cochrane analysis concluded that 'the efficacy and the tolerability of the testosterone-suppressing drugs were uncertain given that all studies were small and of limited duration', which is not consistent with current routine clinical practice, and that 'further research is required using larger sample sizes, longer duration of treatment and evaluating the most often used medications (particularly SSRIs which are used "off label" or GnRH agonists)' (Khan et al. 2015). Yet, there are thousands of studies, using CPA and the GnRH agonists for the treatment of other conditions, in particular, prostate carcinoma. All studies consistently document their effects on the sexual drive as well as their tolerability and safety, even in debilitated patients with prostate carcinoma. These data need to be taken into consideration in our task force report as well as the fact that the relationship between testosterone levels and the sexual drive was clearly established in preclinical as well as clinical research. Moreover, surgical castration recidivism studies with hundreds of individuals included in the various studies and follow-up periods for up to 20 years have shown a dramatic decrease in sexual reoffence.

Despite the lack of controlled studies and the difficulty to conduct such studies in these populations, the efficacy observed in many open studies in patients with the most severe paraphilic disorders allows us to conclude to a Level B/C of evidence. Most of these patients were previously treated with other antiandrogens, SSRIs, or psychotherapy without efficacy or with low compliance (in case of oral forms).

6.4.5. Gonadotrophin releasing hormone (GnRH) antagonists

Degarelix is a third-generation gondadotrophin-releasing hormone antagonist approved for the treatment of prostate cancer. It binds directly to GnRH receptors without causing the initial testosterone surge associated with GnRH agonists. It is available as a 1-month depot injection (degarelix acetate). Urologists and oncologists consider they are at least non-inferior to the GnRH agonists regarding efficacy and safety in the treatment of prostate cancer while there is a potential benefit in terms of cardiovascular morbidity (e.g. atherosclerosis and QTc prolongation). Interestingly a 3-month depot degarelix is currently evaluated (Dellis and Papatsoris 2017; Olsson et al. 2017).

7. Guidelines

Most paraphilic disorders are chronic, lasting for many years if not a lifetime. However, there is no evidence that paraphilic interests cannot change and/or respond to therapy (Fedoroff 2018). Sexual orientation (hetero, homo or bisexuality) is never the subject of treatment. Merely having a paraphilia is obviously not illegal. Acting in response to paraphilic urges may be associated with sexual offences and may subject the person with paraphilia to severe sanctions. Treating offenders is critical in an approach to preventing sexual violence and reducing victimisation. However, treatment is also delivered to paraphilic patients to

Table 4a. Changes in paraphilic behaviours in male patients treated with triptorelin (open and controlled studies).

Reference	Characteristics of the patients	Previous treatment	Methods		Results		
			Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Open studies							
Thibaut et al. (1993, 1996, 1998) France	$N = 11$ Males Aged 15 to 57 years (mean: 25) Previous sex offences (7) Paedophilia (7) Exhibitionism (1) Sexual sadism and exhibitionism (1) Rapists (2) Comorbidity: Mild mental retardation (6) Bipolar disorder (1) Borderline personality disorder (1) AIDS (1)	CPA ($N = 4$) 150–300 mg/d Lack of efficacy (3 cases) Gynaecomastia (1 case) Duration of follow up: 6 months–3 years	Triptorelin 3.75 mg/month + CPA 200 mg/d (10 d to 1 yr, one week before GnRHa to prevent a flare-up effect) + Psychotherapy Duration of follow-up: 7 months–7 years	Self-report of paraphilic and non-paraphilic sexual activity and fantasies (Intensity of sexual desire and symptoms scale) Recidivism Hormonal levels (Testosterone, FSH, LH, TeBG, Oestradiol) Testis volume Osteodensitometry	Decreased levels of testosterone (22.9 to 1.2 nMol/L $p<.1$) and of LH and oestradiol but not TeBG Paraphilic sexual fantasies and behaviour disappeared in 10/11 cases Sexual activity decreased from 40 +/ 10 to 0.6 +/ 0.2 per week after 1st month ($p<.01$) Sexual fantasies decreased from 57 +/ 13 to 0.2 +/ 0.1 after 1st month ($p<.01$) In 4 cases nonparaphilic sexual activity and erectile capacities were maintained **Relapse 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	Erectile failure (2) Decreased libido (11/11) No change in testis volume Hot flushes (1) Asthenia (1) Pain at the injection site (1) Depressive syndrome with a suicidal attempt (1) Vertebral bone loss after 3 years (1)	*Treatment interruption*: (3 cases) at 12th, 34th and at 58th months In the first 2 cases, relapse of paraphilic behaviour within 8–10 weeks In the 2nd case, the patient asks for treatment reintroduction (recurrence of paraphilic sexual fantasies) In the 3rd case no relapse but a 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 (HIV infection) 1 lost to follow up

(*continued*)

Table 4a. Continued.

Reference	Characteristics of the patients	Previous treatment	Methods		Results		
			Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Rösler and Witztum (1998) Israel	$N = 30$ Males Mean age 32 ± 8 years Sex offenders (16) Paedophilia (25) Exhibitionism (7) Voyeurism (2) Frotteurism (2) Sexual hyperactivity (30) $\geq$1 paraphilia: 5 cases Comorbidity: (22) Schizophrenia (5) Personality disorders (9)	CPA ($N = 9$) 150–300 mg/d Stopped at least 1 year before the study SSRIs (7 cases) withdrawn at least 2 months before the study Lithium (2) Antipsychotics (9) Duration of follow up: 4–10 years	Triptorelin 3.75 mg/month + Psychotherapy + Psychotropic drugs (7 cases and in 2 cases two drugs) No CPA Duration of follow-up: 8–42 months	Self-report of paraphilic and nonparaphilic sexual activity and fantasies Three main complaints questionnaire scale before treatment and at 12 months (severity of the 3 problems ascertained to most affect the subject) Recidivism FSL LH testosterone plasma levels (1/month) Testis volume (every 3 months) Osteodensitometry (2/year) **Statistical analysis conducted on 24 cases** (>/1-year treatment)	No paraphilic sexual behaviour Decrease of self-report incidents of paraphilic sexual behaviour from baseline (5+/2 (range 2 to 8) to 0 during treatment Decrease in sexual behaviour (intensity of sexual desire and symptoms scale: 8+/0.2 to 2.7 +/ 2.3 at 6 months ($p<.05$) and to 1.7 +/ 0.9 at 12 months and to 1.4 +/ 0.15 at 42 months) Maximal effect after 3–10 months (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 $p<.001$) Decrease in LH levels (10.6 +/ 5.3 to 0.8 +/ 0.4) and testosterone levels (545 +/ 196 ng/dl to 26 +/ 14 ng/dl at 6 months $p<.05$)	Hot flushes (6) Decreased testicular volume up to 50% after 36 months ($p<.05$) Decreased facial and body hair growth (3) Asthenia and myalgia (2) Muscular pain and at the injection site Erectile failure (21) Decreased lumbar bone mineral density (11/18): Vitamin D + Calcium if necessary after 2 yrs (2)	*Treatment interruption*: 5/8 relapses (in 3 cases due to side effects) (Testosterone levels returned to baseline levels within 2 months) Replacement with CPA in 3/8 cases (200 mg/day): relapse in 2 cases and reintroduction of triptorelin in 2/8 cases

(*continued*)

Table 4a. Continued.

Reference	Characteristics of the patients	Previous treatment	Methods		Results		
			Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Rösler and Witztum (2008) Israel Follow up of the study (Abstract 850184: Endocrine Society 90th Annual Meeting, USA)	$N = 100$ Males (70 additional cases) Mean age 35 ± 13 years Sex offenders: 45 Paedophilia and/or non paedophilic child molesters: 80 Past history of sexual abuse: 25%	No information	Triptorelin 3.75 mg/month + Psychotherapy	Self-report of paraphilic and non-paraphilic sexual activity and fantasies (monthly) Three main complaints questionnaire scale before treatment and at 12 months (severity of the 3 problems ascertained to most affect the subject) Recidivism Testosterone plasma levels Testis volume (every 3 months) Osteodensitometry (2/year)	Decrease in deviant sexual fantasies and desire: Mean ± SD: 45 ± 10 per week before therapy to 0 ($p<.001$) on triptorelin Decrease in the number of abnormal behaviour incidents: 6.2 to 0 ($p<.001$) on triptorelin therapy Effects were age dependent, evident after 3 to 10 months and persisted in all men as long as triptorelin was administered continuously Testosterone concentrations: 18.7 ± 2.4 nmol/L before therapy to 1.0 ± 0.1 nmol/L ($p<.001$) after one year of triptorelin, and remained low thereafter	Main side effects: erectile failure, hot flashes, and decrease in bone mineral density, effectively treatable with bisphosphonates	*Treatment interruption*: For more than 6 months resulted in recurrence of the paraphilic manifestations with repeated convictions in 10 men
Retrospective study							
Hansen and Lykke-Olesen (1997)	$N = 30$ Males Previous sex offences Psychopathy (? cases)	No information	Triptorelin (dosage?) + CPA (dosage?) + Psychotherapy	Self-report of paraphilic and non-paraphilic sexual activity and fantasies Recidivism	No follow up clearly reported No relapse and decrease of paraphilic sexual fantasies while treated Only 5 cases maintained long term treatment	Gynaecomastia Hot flushes Urinary incontinence (1) Increased sweating Weight gain	*Treatment interruption*: (7 cases): Reasons: 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
Case series							
Ho et al. (2012) UK	$N = 7$ Males Mean age: 42 years Sex offenders: 7 (child 5, women 2)	No information	Triptorelin 3-month formulation (3 cases) 1-month formulation (4 cases)	Self-report of paraphilic and non-paraphilic sexual activity and fantasies Recidivism **PPG (2 cases)**	No relapse and decrease of paraphilic and nonparaphilic sexual fantasies and behaviours (also observed with PPG in 2 cases)	Gynaecomastia (2) Hot flushes (1) Smaller testicles (1) Bone mineral loss (1)	

Table 4b. Changes in paraphilic behaviours in male patients treated with leuprolide acetate (open and controlled studies).

			Methods		Results		
Reference	Characteristics of the patients	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Open studies							
Briken et al. 2001 and 2002 Germany	$N = 11$ males Aged 19–57 years Previous sexual offences (11) Paedophilia (7) Incest (1) Sadism with (3) or without paedophilia (1) Comorbidity : Sexual impulsivity (3) Mental retardation (5)	CPA ($N = 6$) 300 mg (form?) for 2–14 months SSRIs (4 cases) Antipsychotics (2 cases)	Leuprolide acetate 3-month formulation + CPA (300 mg depot for 2 weeks) + Psychotherapy Duration of follow up: 1 year	Self-report (Likert scale) of paraphilic and nonparaphilic sexual activity and fantasies Testosterone plasma levels	No paraphilic 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 the injection site Suicide attempt (1)	
Krueger and Kaplan 2001 USA	$N = 12$ Males Aged 20–48 years (mean age 35.5) Paedophilia (6) Exhibitionism (5) Voyeurism (3) Sexual Sadism (1) Paraphilias NOS (2) Comorbidity: Mental retardation (1) Brain trauma (2) Frontal lobectomy, Personality disorders Addictions, Depressive disorders, Chromosomal aberrations(1), Psychosis	MPA ($N = 2$) 120 mg/day SSRIs (9) (high dosages) Other psychotropic drugs (7) No effect of previous MPA in 1 case or SSRIs (6 cases)	Leuprolide acetate (3.75 or 7.5 mg/month) + Flutamide 250 mg TID for 30 days + Psychotherapy (CBT or individual supportive) Duration of follow up: 6 to 57 months	Self-report of paraphilic and nonparaphilic sexual activity and fantasies Testosterone FSH, LH plasma levels Osteodensitometry	No relapse 12/12 cases Marked reduction of paraphilic and non-paraphilic sexual arousal and interest depending on pre-treatment frequency and intensity Mean testosterone level ($n = 8$) decreased from 493 ng/dL (baseline) to 22 while treatment	Mild gynaecomastia (3) Decrease of erections except for one case (20 years old) Nausea (1) Depressive disorder (1) Bone mineral loss (3) >35 months treatment	*Treatment Interruption:* One relapse In two cases, the effect was maintained after treatment interruption for 2–4 years

(*continued*)

Table 4b. Continued.

Reference	Characteristics of the patients	Previous treatment	Methods		Results		
			Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Schober et al. 2005 and 2006 USA Prospective, repeated measures, nonrandomized masked cross over study Not designed to evaluate GnRH efficacy	*N* = 5 Males Mean age 50 years (36–58) Sex offenders convicted (5) Paedophilia (5) Comorbidity: Alcoholism (2) Depressive disorders (1) Personality disorders Psychopathy (5) At inclusion: Minnesota 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 a low risk Y BOCS : in 3 cases severe sexual compulsions, in 2 cases moderate sexual compulsions	No information None	Leuprolide acetate (7.5 /month, then 3-month formulation) + Flutamide tid 250 mg for 14 days Then **Placebo** for 12 months + Behavioural therapy for 2 years Duration of follow up: 2 years	Self-report of paraphilic and nonparaphilic sexual activity and fantasies Other Scales: Hare psychopathy check list revised Minnesota Sex Offender Screening tool revised Y BOCS Static 99 (sexual offender risk assessment) Testosterone plasma levels **PPG** (erotic visual stimuli) (Abel assessment)	No change in sexual interest No paraphilic behaviour **No statistical analysis of GnRH analogues efficacy *vs.* placebo** **Leuprolide acetate:** Reduction of paraphilic and non-paraphilic sexual activity (masturbation rate decreased from 1.7/ week at baseline to 0.1 at 12 months) with leuprolide acetate > placebo **PPG**, $p<.05$ Decreased testosterone levels **Placebo:** Increased sexual activity, fantasies, and paraphilic fantasies with placebo after 2 months in 3 cases including a high risk of recidivism in one case Testosterone levels returned to baseline levels	Decrease in flaccid penile circumference Hot flushes (3) Gynaecomastia (1) Erectile dysfunction (5) No hair loss Weight gain (mean 22 lbs) (5) Pain at the injection site (4) No asthenia No muscular pain In 1 case prostatic nodule at baseline decreased with GnRH	
Ahn et al. 2013 Korea	*N* = 9 Males Paedophilia (3) Voyeurism (1) Fetishism (1)	No information	Leuprolide acetate	Self-report of paraphilic and nonparaphilic sexual activity and fantasies	A significant decrease in sexual fantasies	Not reported	
Turner et al. 2013 Germany	*N* = 65 Males Sex offenders (65)	No information	GnRH agonist or CPA	Self-report of paraphilic and nonparaphilic sexual activity and fantasies	CPA = GnRH agonists: >65% of patients reported lower frequency and intensity of sexual thoughts	Gynaecomastia (7), Hot flushes (27), Decreased body hair (17), Smaller testis volume (2), Weight gain (11), Pain at the injection site (19) Bone mineral loss (8) More side effects with CPA	

(*continued*)

Table 4b. Continued.

			Methods		Results		
Reference	Characteristics of the patients	Previous treatment	Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Koo et al. 2014 Korea	*N* = 56 Males Mean age: 34,9 years Sex offenders (56) (in prison) Paedophilia (29) Exhibitionism (5) Voyeurism (3) Other paraphilias (15)	No information	Leuprolide acetate 3.75 mg/month Group A: 3-month formulation (*N* = 38) Group B: 6-month formulation (*N* = 18)	Wilson's Sex Fantasy Questionnaire (SFQ) scores Psychobehavioral assessments and serum T levels were serially measured during the on-cycle and the following observational 12-month off-cycle	Most men in groups A and B reported decreased frequency and intensity of sexual thoughts (76% and 78%) and masturbation frequency (74% and 83% respectively) The median Wilson's Sex Fantasy Questionnaire (SFQ) scores were significantly reduced in both groups.	No differences in the frequency of side effects Group A: hot flushes (17), testis reduction (9), decreased body hair (2), weight gain (11), depression (8), pain at the site of injection (7), myalgia (4), loss of bone mineral density (4) Group B: hot flushes (11), testis reduction (2), depression (3), pain at the site of injection (5), myalgia (2), weight gain (3), diaphoresis (2) loss of bone mineral density (2)	*Treatment interruption:* In group A: upsurge of serum T during the first 2 months In group B: serum T gradually recovered to the baseline level and upsurge beyond baseline levels at month 5. SFQ scores: group A returned to pre-treatment levels following the observational period. Group B remained suppressed
Voß et al. 2016 Germany	*N* = 30 Males Age : 36–72 y Paedophilia (21), fetishism (1), sadomasochism (2), multiple paraphilia (2), paraphilia NOS (2	No information	GnRH agonist	Self-report of paraphilic and nonparaphilic sexual activity and fantasies		Not reported	*Treatment interruption:* (15 cases) in 9/11 patients testosterone levels normalised within 3–7 m; First erections occurred several months after testosterone levels normalised; paraphilic fantasies returned, but there were no new sexual offences
Choi et al. 2018 Korea	*N* = 7 Males Mean age: 46.6 years Sex offenders (7) Paraphilic disorders	No CPA No flare up effect	Leuprolide acetate (1-month formulation) Duration of treatment: 12 months		Significant improvement in paraphilic sexual activity from 1st to 12th month	Mild feminisation, Fatigue, Hot flushes	

(*continued*)

Table 4b. Continued.

Reference	Characteristics of the patients	Previous treatment	Methods		Results		
			Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Retrospective studies							
Czerny et al. 2002 Germany	*N* = 58 Males Mean age: 38 years Paedophilia (16), Sadomasochism (3), Exhibitionism, Fetichism, Voyeurism Comorbidity: Mental retardation (24), alcoholism(8), personality disorders (26)	No data	Leuprolide 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 agonists) and 22.6 months (CPA)	Self-report of paraphilic and nonparaphilic sexual activity and fantasies Testosterone, LH, FSH plasma levels	Efficacy: CPA = GnRH agonists Reduction in sexual activity and fantasies **No efficacy in three cases in each group** In one case with CPA treatment, paraphilic sexual fantasies increased In two cases CPA was unsuccessful and replaced with GnRHa with good efficacy	Hypogonadism CPA (1) GnRHa (1) Hair loss CPA (4) Gynaecomastia CPA (10) GnRHa (4) Hot flushes CPA (2) GnRHa (4) Weight gain CPA (14) GnRHa (4) Asthenia CPA (3) GnRHa (4) Thromboembolism CPA (1) Depressive disorder CPA (2) Blood pressure variations GnRHa (2) Bone demineralisation GnRHa (1)	
Briken et al. 2009 Germany	*N* = 26 Males Age: 41.5 years Sex offenders (26) in prison Paedophilia or sadomasochism	9% previously received CPA	GnRH agonist	Home leave steps	Before GnRHa: 91.7% of sexual offenders had sexual violations during incarceration Under GnRHa: no more violations; considered for home leave sooner than not treated	No side effects (11), Hot flushes (3), Testes pain (1) Fatigue (8), Headache (8), Sleep disorders (8), Depression (2), Weight gain (1), Dry skin (1), Pain at the injection site (Nausea and constipation (1) Osteoporosis (2)	
Gallo et al. 2017 Canada	*N* = 47 Males Age: 28–83 y Sex offenders (47) Paraphilic disorders? *N* = 81 control group (untreated, non-violent offenders)	No information	Leuprolide acetate + CBT; *n* = 25) or only CBT (*n* = 22)	Sexual offenders treated with GnRH agonists + Psychotherapy had significantly higher risk according to the Static-99R vs. psychotherapy-only group	Sexual offenders receiving GnRH agonists had a significantly lower rate of recidivism Both treated groups of sexual offenders recidivated at substantially lower rates than predicted by the Static-99R	Not reported	

(*continued*)

Table 4b. Continued.

Reference	Characteristics of the patients	Previous treatment	Methods		Results		
			Treatment conditions	Outcome measures	Efficacy	Side effects	Treatment interruption
Case reports							
Saleh et al. 2004 USA	$N = 6$ Males Aged 19–20 years Paedophilia (1) Frotteurism (1) Sexual Sadism (1) Paraphilia not specified (3) Comorbidity: ADHD (2) Drug abuse (2) Bipolar disorders (5) Mental retardation (2) Psychopathy (2) Borderline disorder (1) Conduct disorder (2) Klinefelter syndrome (1)	None	Leuprolide acetate 7.5 mg/month + Flutamide for 14 days + Psychotherapy Duration of follow up: 10–16 months	Self-report of paraphilic and nonparaphilic sexual activity and fantasies Testosterone, oestradiol FSH, LH plasma levels	Sexual activity decreased Paraphilic sexual behaviour and fantasies disappeared **In one patient, no change in the content of paraphilic fantasies**	Retrograde ejaculation (1) Erectile failure (1)	

GnRHa: GnRH agonists; CPA: cyproterone acetate; PPG: penile plethysmography; CBT: cognitive behavioural therapy; SSRIs: selective serotonin reuptake inhibitors; d: day; yr: year; T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; AIDS: acquired immunodeficiency syndrome; ADHD: attention-deficit hyperactivity disorder; SSRIs: selective serotonin reuptake inhibitors; NOS: not otherwise specified.

reduce distress associated with paraphilic fantasies, urges, or behaviours.

Guidelines for the pharmacological treatment of people with paraphilic disorders (including sex offenders) were developed by a Task Force of the World Federation of Societies of Biological Psychiatry (Thibaut et al. 2010) and updated in this article. The new WFSBP treatment algorithm distinguishes five levels of treatment for different categories of paraphilic disorders (see Table 5).

Neurodevelopmental and trauma models that posit being neglected or sexually abused as a child are significant factors mainly associated with paedophilic disorder and the risk for sexual abuse. Psychological treatment of physical or sexual trauma is an essential component of the treatment plan.

Preventing sexual trauma through media campaigns and school programmes (education of parents, teachers, and youths) is also very helpful as well as creating a free hotline for people who want to anonymously seek help for their paraphilic sexual fantasies before acting out (as implemented in Germany) (Thibaut 2015; Briken 2018).

The aims of the treatment of paraphilic disorders are:

1. to control paraphilic fantasies and behaviours in order to decrease the risk of a sex offence;
2. to control paraphilic sexual urges;
3. to decrease the level of distress of persons with paraphilic disorders;
4. to enhance non-paraphilic sexual interests and behaviours.

According to numerous reviews or meta-analyses (Gijs and Gooren 1996; Bradford 2000; Rösler and Witztum 2000; Thibaut 2003; Maletzky et al. 2006; Hall and Hall 2007; Guay 2009; Thibaut et al. 2010; Garcia and Thibaut 2011; Bradford et al. 2013; Assumpção et al. 2014; Holoyda and Kellaher 2016), the combination of pharmacological and CBT coupled with provision of care under close legal supervision appears to reduce the risk of repeated offences. Moreover, reducing libido seems to make some offenders more responsive to psychotherapy (Murray 2000). Only cognitive and behavioural therapy has shown a modest degree of effectiveness among sex offenders (Lösel and Schmucker 2005; Dennis et al. 2012 Cochrane Review) (for review, see also Chapter 6.2). In paraphilic subjects at high risk of offence, pharmacological treatment must be used in addition to psychotherapy.

Table 5. WFSBP algorithm of pharmacological treatment of paraphilic disorders.

Level of severity	Treatement
Level 1 • Aim: control of paraphilic sexual fantasies, compulsions, and behaviours without impact on conventional sexual activity and on sexual desire. May be used in cases of voyeurism, fetishism, frotteurism disorders without any risk of rape or child abuse	• Psychotherapy (preferentially **CBT** if available **(Level C/D)**, no level of evidence for other forms of psychotherapy)
Level 2 • Aim: control of paraphilic 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[1] paraphilic disorders with low risk of sexual violence, i.e. exhibitionism disorder without any risk of rape or child abuse • No satisfactory results at level 1	• Psychotherapy (preferentially CBT if available **(Level C/D)**, no level of evidence for other forms of psychotherapy) • **SSRIs:** increase the dosage at the same level as prescribed in OCD (e.g. fluoxetine 40–60 mg/d or sertraline 200 mg/d) **(Level C)**** ○ Onset of efficacy: 1–3 months ○ Efficacy: 70% if no sexual violence
Level 3 • Aim: control of paraphilic sexual fantasies, compulsions, and behaviours with a substantial reduction of sexual activity and desire • Moderate risk of sexual violence (intellectual disability, neurological comorbid disorders such as dementia) • No sexual sadism fantasies and/or behaviour (if present: go to level 4) • Compliant patient, if not: use i.m. formulation or go to level 4 • If CPA and/or MPA are not available in your country or if there are associated with severe side effects, skip level 3 and go to level 4 • No satisfactory results at level 2	• Psychotherapy (preferentially CBT if available **(Level C/D)**, no level of evidence for other forms of psychotherapy) • **CPA***: oral, 50–200 mg/d (maximum 300) or i.m., 200–400 mg once weekly and then every 2–4 weeks **(Level C)**; • or **MPA***: oral, 50–400 mg/d or i.m., 400 mg weekly and then monthly if CPA is not available **(Level C)** ○ No markers of compliance if oral form ○ Efficacy 80–90% (mean recidivism rate: 6%) ○ Onset of efficacy: 1–3 months ○ If co-morbidity with anxiety, depressive or obsessive-compulsive symptoms, SSRIs may be associated with CPA
Level 4 • Aim: control of paraphilic sexual fantasies, compulsions, and behaviours with almost complete suppression of sexual desire and activity • Moderately high to high risk of sexual violence and severe paraphilic disorders • Paedophilic disorder or sexual sadism fantasies and/or behaviour or physical violence • No compliance or no satisfactory results at level 3	• Psychotherapy (preferentially CBT if available **(Level C/D)**, no level of evidence for other forms of psychotherapy) • Long-acting **GnRH agonists***, i.e. triptorelin or leuprolide acetate 3 (or 3.75) mg/month or 11.25 mg i.m. every 3 months **(Level B/C#)** ○ Efficacy $>$ 90% (recidivism rate $<$5%) ○ Onset of efficacy: 1–3 months ○ Testosterone levels measurements may be easily used to control GnRH agonist treatment compliance if necessary ○ CPA* must be associated with GnRH agonists (one week before and during the first month of GnRH agonists) to prevent a flare-up effect and to control the relapse risk of paraphilic sexual behaviour associated with this flare up effect
Level 5 • Aim: control of paraphilic sexual fantasies, compulsions, and behaviours with complete suppression of sexual desire and activity • Most severe paraphilic disorders (catastrophic cases) • No satisfactory results at level 4	• Psychotherapy (preferentially CBT if available (Level C/D), no level of evidence for other forms of psychotherapy). • **In addition to GnRH agonists***: ○ **Use antiandrogen treatment***, i.e.: CPA*: oral, 50–200 mg/d (maximum 300) or i.m. 200–400 mg once weekly and then every 2–4 weeks; or MPA*: 50–400 mg/d or 400 mg i.m. weekly and then monthly if CPA is not available **(no level of evidence)** ○ **SSRIs may also be added (no level of evidence)**
Treatment duration/treatment interruption • If sexual violence: violent sexual fantasies reappeared in 90% of cases, months or years after treatment withdrawal • Usually, there is no change of sexual orientation or paraphilia content with the treatment	Treatment duration/treatment interruption • At least 2 years in case of mild paraphilic disorder • At least 5 years or longer if necessary (if high risk of sexual violence) • A scale is proposed for treatment change or interruption (Briken et al. 2018) • Avoid abrupt GnRH agonist treatment withdrawal if 1-or 3-month formulation (CPA might be used to prevent the risk of recidivism associated with the rebound of testosterone levels in case of GnRH agonists withdrawal) • In case of severe osteoporosis: calcium, vitamin D and/or bisphosphonates must be prescribed and osteodensitometry must be checked yearly • In case of severe side effects (thromboembolism or severe liver dysfunction) CPA or MPA treatment must be replaced with GnRH agonists • After treatment withdrawal, hormonal treatment can be resumed in case of recurrence of paraphilic sexual fantasies and/or behaviour

General comments: CPA and triptorelin 3-month formulation (in Europe) were approved in the indication of the treatment of paraphilic disorders in adult males. In April 2020, the French drug agency specified that, given the risk of meningioma, cyproterone acetate can be used only when other treatments are deemed inappropriate. The patient receiving CPA must sign each year with his doctor a mandatory information certificate. Other compounds are used 'off label'. The Depo-Provera scale may be used for the evaluation of sex offenders to guide hormonal treatment use in paraphilic subjects. Psychological treatment of physical or sexual trauma (if any) is an essential component of the treatment plan

*Freely given 'written' informed consent is mandatory

**In some countries, due to a low risk of meningioma, CPA is recommended only in patients with a contraindication to GnRHa or in those who have treatment resistance. However, if the patient is informed on the risk of meningioma and signs a written consent renewed annually, CPA can be used.
#Cumulative evidence from open studies for GnRH agonists
[1]Hands-off paraphilic disorder includes: exhibitionism, voyeurism. Hands-on paraphilic disorder includes: sadism, masochism, frotteurism, zoophilia, necrophilia. Hands-off paedophilic disorder (no physical contact with the victim) includes: undressing the victim, the offender himself undressing, giving instructions to perform sexual activities in the presence of the offender, filming and/or photographing intimate scenes and viewing pornography. Hands-on paedophilia includes: touching above the clothing, touching beneath the clothing, vaginal and/or anal penetration, oral penetration by the offender and oral penetration by the victim (Rosner 2003).

The treatment choice will primarily depend on:

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

Prior to treatment, each individual should be carefully examined by at least one mental health professional, in order to identify and evaluate the patient (especially number and type of paraphilic disorders, motivation, compliance 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 (see Chapter 5: baseline evaluation before treatment). In the case of psychiatric comorbidities, pharmacological treatment such as antipsychotics, SSRIs, mood stabilisers or specific types of psychotherapy or CBT must be used (see also Chapters 3.3. and 6.4.1.). Hormonal treatment may be co-prescribed in case of lack of efficacy of adequate treatment of the psychiatric disease in order to control paraphilic behaviour. However, hormonal treatment may increase psychotic symptoms if any (Thibaut et al. 1991, 1992).

The diagnosis of a paraphilic disorder must be carefully established, and clinical characteristics of the patients listed. Specific clinical assessment is recommended before the start of androgen deprivation therapy and during follow-up (see Chapter 5 for initial assessment and monitoring of treatment). Although PPG is widely used in the USA and Canada, it remains a matter of controversies in Europe for several reasons (mainly reliability and ethics) (see also Chapter 3.9). Modification of patterns of brain activation or visual reaction time does not allow to confirm the diagnosis or to estimate the recidivism risk (see also Chapters 3.3 and 3.4).

Treatment should follow the principles of the Risk-Need-Responsivity model developed by Andrews and Bonta (2010). These authors suggested that effective therapy has to focus on the risk of a single offender for committing new offences. The higher the risk, the more intensive the intervention should be. Specific criminogenic needs, like paraphilic disorders, should be considered in therapy goals as well as responsivity factors like intellectual disability or comorbid psychiatric or personality disorders (see Chapters 3.3 and 3.4).

Pharmacological interventions include:

✓ SSRIs (for review, see Chapter 6.4.2.)

SSRIs are useful in the treatment of paraphilic disorders associated with anxiety and OCD, impulse control disorders, or depressive disorders. Some paraphilic subjects suffer from a pattern of not-controlling their sexual urges, which have a robust compulsive element and often cause considerable subjective distress. SSRIs can be useful in these cases, which are usually not associated with severe sex offending, especially in exhibitionists without comorbidities. The dosage must be increased to the doses used in OCD, in case of insufficiency or lack of efficacy of usual dosage. However, the efficacy of SSRIs in treating paraphilic interests decreases when a patient acquires delayed orgasm. They are used 'off label.' For a medical survey, while patients are on SSRIs, see Chapter 5.

✓ Hormonal treatments or androgen deprivation therapies (for review, see Chapter 6.4.4)

Not every sex offender is a candidate for hormonal treatment, even if it has the benefit of being reversible once discontinued. For paraphilic disorders characterised by intense and frequent paraphilic sexual desire and arousal, which highly predispose the patient to severe paraphilic behaviours (such as paedophilic disorders or rape), a hormonal intervention using GnRH agonists is needed. The Depo-Provera scale may be used to help in treatment decision (Maletzky et al. 2006; Turner et al. 2014; Table 6). Moreover, patients may ask for it even though they are not at high risk (Murphy et al. 2014). When properly administered, with an appropriate protocol to detect and treat side effects should they develop, GnRH agonist treatments constitute no more or less of a risk than most other forms of frequently prescribed psychopharmacological agents (Berlin 2009). Androgen deprivation therapies may also be used in the treatment of sex offenders

Table 6. Depo-Provera scale (Maletzky et al. (2006) revised by Holoyda and Kellaher (2016)).

Definition of the items	Score if present
Multiple paraphilic disorders	1
Preferential/obligatory paraphilic sexuality by official or offender history[a]	1
Paraphilic sexual interest (PPG)[a]	2
Any male victim(s)[a]	2
Multiple victims	1
Not living with the victim(s)	1
Use of force in sexual crime(s)	1
CNS dysfunction (developmental disability, CNS injury, etc.)[a]	2
History of psychiatric illness	1
Age under 30 at time of projected release	1
Sexual violation(s) in an institution	1
Sexual violation(s) while under community supervision	1
History of sexual offender treatment failure(s)	2

a: factors marked with an[a];
PPG: penile plethysmography; CNS: central nervous system

with mental retardation or cognitive dysfunctions associated with brain diseases. This has to be discussed with the patient's family and/or caregivers and legal guardian if any (Cooper 1995; Sherak 2000; Cosyns and Thibaut 2017). GnRH agonists have to be prescribed by a physician after freely given 'written' informed consent is obtained. GnRH agonists, by inducing castrate testosterone levels within one month, 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 paraphilic behaviour in more than 95% of patients with severe paraphilic behaviours. In addition, GnRH agonists produced less variable results in the treatment of paraphilic behaviours than MPA or CPA with less severe side effects except for those related to hypoandrogenism (Rösler and Witztum 1998; Thibaut et al. 1998, 2010; Czerny and Briken 2002; Turner et al. 2013; Cosyns and Thibaut 2017). For a medical survey, while patients are on 'antiandrogens', see Chapter 5.

Efficacy was maintained throughout the treatment duration in all responders. In men who interrupted treatment, testosterone levels progressively returned to baseline, but in 60–90% of published cases, paraphilic sexual fantasies reappeared, and in few patients, recidivism occurred. The studies did not support the specificity of GnRH agonists in reducing sex drive for paraphilic *vs.* conventional 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. Finally, the use of long-acting GnRH agonists, administered parentally, once every one- to three- or six months, excluded the uncontrolled breaks in the therapy often observed with oral CPA treatment. In addition, in the case of low compliance, plasma testosterone levels can be measured, in contrast with CPA and MPA treatments where there is no reliable marker of compliance. GnRH agonist treatment probably constitutes the most promising treatment for sex offenders at risk of sexual violence, such as those with paedophilic disorders or serial rapists. In addition, these hormonal treatments should be considered for all patients who wish treatment to decrease their paraphilic interests.

In spite of these new treatments, which induce reversible chemical castration, in several states of the USA and in some European countries, surgical castration is still allowed in place of chemical castration for repeat child molesters. However, the task force is clearly against surgical castration.

There is a theoretical risk that patients could antagonise their GnRH agonist treatment or even surgical castration effects with testosterone supplementation, but we could not find data in the existing literature concerning this risk. This may be because hormonal treatment decreases sex drive and therefore, the interest in taking testosterone. If there is any doubt, plasma testosterone levels should be checked.

The WFSBP treatment algorithm distinguishes five levels of treatment for different categories of paraphilic disorders (see Table 5).

Maletzky et al. (2006) proposed a scale (the Depo-Provera Scale revised by Holoyda and Kellaher (2016)) intended for determining which subjects with paraphilic disorders have a greater need for treatment with antiandrogens or GnRH agonists, particularly those with a history of sexual offending or those at high risk of sexual offending (Table 6). A score superior or equal to 6 (maximum 17) on this scale of 13 items or the presence of three factors or two or more factors marked with an[a,] could be an indication for hormonal treatment. Though ultimately, clinical judgement must remain the decisive factor in antiandrogen deprivation therapy decision.

Table 7. Factors of the 'Change of stop testosterone-lowering medication (COSTLow)-scale' (from Briken et al. (2018)).

Factor
1. Compliance for monitoring effects and side effects
2. Openness relating to sexual interest and activity before treatment, increase in openness under treatment
3. A substantial decrease in the severity of paraphilic disorders (from level >3 to level 2 of the WFSBP guidelines (Thibaut et al. 2020)) or from level 2 to 1 in the sexual deviance subscale of the STABLE 2007 (Hanson et al. 2007)
4. No hypersexual disorder (definition Kafka 2010) or sexual preoccupation (definition STABLE 2007)
5. The desire for non-paraphilic sexuality related to seeking intimacy that is not against the consent or interest of another person (also willing to have children)
6. Willing to switch to another medication (GnRH -> CPA oral -> SSRI)
7. Psychotherapeutic treatment was possible before treatment
8. Trustful relationship between treatment provider and patient before treatment
9. Duration of treatment with a sufficient effect for a minimum of 3 years
10. Age > 45 years
11. Low degree of violence in paraphilic symptomatology (e.g. no sadistic homicidal fantasies)
12 Psychopathy CheckList-Score (PCL) (Hare 2003) <16
13. No acute severe psychopathology (psychosis, mania, high level of impulsivity)
14. Sufficient level of supervision and control (if necessary) or absolute lack of access to victims
15. No acute high-risk (definition, e.g. according to the ACUTE 2007) Hanson et al. 2007

With increasing duration of experience and number of treated patients as well as aging patients, change of or withdrawal from antiandrogen deprivation therapy has become an important issue. The 'Change or stop testosterone-lowering medication' (COSTLow)- scale can be used to structure the process of changing or discontinuing antiandrogen deprivation therapy in patients with severe paraphilic disorders (Briken et al. 2018) (Table 7). Every factor of the COSTLow-Scale is rated using a 3-point ordinal rating scale with 2 = definitely present, 1 = possibly or partially present or 0 = absent. Scores are added to a sum score and an overall assessment. The higher the sum score, the better substantiated is the overall assessment in which the change or cessation of testosterone-lowering medication (TLM) can be considered. There is no cut-off. In the case of non-consent or severe side effects that are untreatable (e.g. severe osteoporosis, thromboembolism), the medication has to be changed or stopped independently of the achieved score.

Management of erectile dysfunction:
Antiandrogens, as well as GnRH agonists and antagonists, are associated with a high rate of erectile dysfunction. In the case of nonexclusive paraphilic disorders, patients and their intimate partners may complain about this side effect, which might be associated with low compliance. We could not find any data in the literature related to the treatment of this side effect in patients with paraphilic disorders receiving antiandrogen deprivation therapy. In non-paraphilic subjects, phosphodiesterase type 5 inhibitors (PDE5i) (sildenafil, vardenafil, tadalafil, avanafil) on demand or daily are an efficient symptomatic treatment in patients with all forms of erectile dysfunction. Intracavernous injections of PGE1 or vacuum pump provide second-line treatment (for review see Füllhase et al. 2014; Yafi et al. 2018, about their tolerance). Helping convicted sex criminals to overcome erectile dysfunction raises major legal and ethical issues. The case 'Evrard' was a multirecidivist sex offender convicted for several rapes and sexual assaults on children in France who was prescribed sildenafil before being released from prison. Immediately after his release from prison, he was apprehended and found in possession of sildenafil after kidnapping and raping a six-year-old boy in the North of France.

8. Conclusion

SSRIs have been used 'off label' in half of the community-based treatment programmes in North America; antiandrogens and/or GnRH agonists have been used in 30% of cases in the US and 42–60% of cases in Canada (McGrath et al. 2010). CPA and 3-month triptorelin have marketing authorizations in most European countries in this indication. In Germany, among 611 sex offenders (rape of adults or children in 90% of cases) present in 32 forensic services, 11% were treated with GnRH agonists, 5% with CPA, 11.5% with SSRIs and 10% received antipsychotic therapy due to psychiatric comorbidities (Turner et al. 2013). In France (preliminary results of the French cohort of 343 paraphilic sex offenders coordinated by F. Thibaut), about 25% of the subjects benefitted from SSRIs, 15% received CPA and 14% GnRH agonists.

A period of time of provision of care under legal supervision can help to establish and secure a treatment plan in sex offenders with severe paraphilic disorders. The new hormonal state created by GnRH

agonist treatments indisputably leads to a decrease of the uncontrollable sexual impulses. Given the long timeframe in CBT effectiveness and the uncertainty of their results, when combined with antiandrogen or GnRH agonist treatments, they are undertaken with more serenity and are less likely to be interrupted by transgressive recidivism. Antiandrogen and GnRH agonist treatments are particularly recommended in repeat sex offenders with paedophilic disorders, especially those interested in male victims, as well as in serial rapists; or in profoundly immature or intellectually disabled CSO. This type of treatment contributes to their social reintegration. National Consultative Ethics Committee recommended in all cases of hormonal treatment, a freely given 'written' informed consent which can be renewed. This medical prescription assumes a minimal awareness of the paraphilic disorder by the patient. In case of family, social or judicial pressure, a trusting relationship between the patient and his health care provider is crucial, where the primary goal is to provide care to the person while decreasing recidivism risk. It should also be remembered that, in most cases, prescribing hormonal treatment does not change the content of paraphilia (e.g. in case of exclusive paedophilia), and that the therapeutic action is mainly symptomatic, only the biological effect of the hormonal treatment can be guaranteed. In 60–90% of cases of treatment withdrawal, during the months or years following treatment cessation, there was a recurrence of paraphilic sexual fantasies. In contrast, during hormonal treatment (as with surgical castration), there have been rare cases of reoffence (1–2% of published cases receiving GnRH agonists, which is considerably less than the recurrence rate observed without treatment or in those who benefit from psychotherapy alone, with the same level of severity of paraphilic disorders). Interestingly, a 3-month depot degarelix (a GnRH antagonist) is currently used in the treatment of prostate cancer and could be considered in the future for the treatment of paraphilic disorders at risk of sexual violence.

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