

IN REVIEW

The Neurobiology, Neuropharmacology, and Pharmacological Treatment of the Paraphilias and Compulsive Sexual Behaviour

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There has been increasing interest in the treatment of sexual disorders in recent years. Sexual disorders are classified in DSM-IV as sexual dysfunctions, paraphilias, and gender identity disorders. The sexual dysfunctions are nondeviant or nonparaphilic. The sexual dysfunction disorders should include "hyperactive sexual desire disorder" under sexual desire disorders. Further, there should be a specifier for paraphilias of "with hypersexuality" or "without hypersexuality." There is still incomplete understanding of the neurobiology of sexual disorders although functional neuroanatomy and neuropharmacological research has exposed the neurotransmitters, receptors, and hormones that are involved in sexual desire. Various pharmacological agents including serotonin reuptake inhibitors, antiandrogens, LHRH agonists, and others have been documented as reducing sexual desire. An algorithm for the use of these drugs in the treatment of the paraphilias as well nonparaphilic hypersexuality is outlined. The modes of action, dosages, aims of treatment, and usual methods of prescribing these agents is reviewed in this article. Some future directions of research in pharmacological treatment is also discussed.

(Can J Psychiatry 2001;46:26–34)

Key Words: sexual desire disorders, paraphilias, hypersexuality, compulsive sexual behaviour, antiandrogens, specific serotonin reuptake inhibitors, LHRH agonists

Although it would be premature to say that the neurobiology and neuropharmacology of sexual behaviour is understood, there clearly have been major advances in recent years. There has been significant research on the serotonin receptors and their function in the brain. Serotonin (5-HT) is involved in the neurobiology of many psychiatric disorders, particularly mood disorder, and specifically depression, anxiety, schizophrenia, eating disorders, and obsessive-compulsive disorder (OCD). It also plays a role in migraines. Although the etiology of these disorders is not understood, pharmacological treatments that modulate levels of 5-HT have shown to be effective in all of them. Further, sexual disorders, both paraphilic (sexual deviation) and nonparaphilic (compulsive sexual disorder or nonparaphilic hypersexuality), have also responded to pharmacological treatments modulating serotonin levels (1). This has led to the speculation that a group of disorders could be classified together as obsessive-compulsive spectrum disorders (1,2). This is based not only on the diagnostic characteristics of these disorders as outlined in DSM-IV but also on the fact that

they respond to pharmacological treatment affecting the central nervous system level of 5-HT (1,2).

In general, the assessment and treatment of all types of sexual disorders have been neglected by psychiatry. In recent years, however, advances in psychiatric research have focused general psychiatry on these important clinical entities. OCD spectrum disorders include OCD, eating disorders, somatoform disorders, impulse control disorders, and neuropsychiatric disorders such as Tourette syndrome (TS); they may also include the sexual disorders (1,2). There are clinical similarities between OCD and sexual disorders that can be summarized as follows (1):

- Obsessions are similar to sexual fantasies, both paraphilic and nonparaphilic.
- Compulsions are similar to compulsive sexual behaviour (CSB), which can be paraphilic or nonparaphilic.
- There is a cross over of comorbidity between OCD and the sexual disorders, with depression and anxiety disorders being common in both groups.
- At a neurobiological and neuropharmacological level, there is a significant overlap between these disorders.

There is no consensus at this time as to whether the paraphilias and compulsive sexual behaviour (nonparaphilic hypersexuality) should be included in the OCD spectrum disorders.

Manuscript received and accepted December, 2000.

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There has been considerable recent progress in mapping out 5-HT receptor subtypes (3). Many pharmacological treatments acting on the central 5-HT system, such as selective serotonin reuptake inhibitors (SSRIs), antidepressants acting presynaptically to serotonergic neurons, and 5-HT receptor antagonists used in the prophylaxis of migraine, have mostly nonselective effects on postsynaptic 5-HT receptor subtypes (3). The initial work on 5-HT receptor subtypes was based on pharmacological tools. Since that time, receptor binding profiles, common second messenger coupling, and functional activity of ligands have isolated further receptor types (3). Based on this work, 4 main subgroups of 5-HT receptors have been identified, specifically 5-HT₁, 5-HT₂, 5-HT₃, and 5-HT₄. This classification has been confirmed by the sophisticated techniques of molecular biology, but the latter have also led to the identification of "novel" 5-HT receptors, specifically 5-HT_{1F}, 5-HT₅, 5-HT₆ and 5-HT₇(3). Various subtypes have also been identified. The 5-HT₁ receptor has 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} subtypes. The 5-HT₂ system has been shown to have 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes. There do not yet appear to be any subtypes of 5-HT₃ and 5-HT₄ receptors, but 5-HT₅ has 2 subtypes, 5-HT_{5A} and 5-HT_{5B}. No subtypes have been identified for the 5-HT₆ and 5-HT₇ receptors (3). All of the 5-HT receptors belong to a family of G protein-coupled receptors (3). Pharmacological research is establishing selective ligands for the various receptor subtypes, facilitating the development of subtype-specific agonists and antagonists. This will help elucidate how 5-HT receptor subtypes affect behaviour, including sexual disorders. It is also possible that other 5-HT receptor subtypes will be isolated or that further variations in receptor subtypes will be found. Perhaps mutations of the 5-HT receptor or subreceptor structures will be found to play a role in a variety of psychiatric disorders (3). Neuropharmacological research into 5-HT receptors is likely to continue to be of significant interest to general psychiatry and to the evaluation and treatment of sexual disorders.

There have been several studies on the neurobiology of hypersexuality. Broadly, the research literature shows that lesions in certain parts of the brain can lead to disinhibition of sexual behaviour that may result in compulsive sexual behaviour (3). In the neurological and neuropsychiatric literature, there are references to disinhibited sexual behaviour as a result of frontal lobe lesions. The caution here is that this is most likely part of a general behavioural disinhibition rather than being specific to sexual behaviour. The clinical presentation of certain elderly patients with dementia and disinhibited behaviour including paraphilic behaviour (exhibitionism) and nonparaphilic hypersexuality (inappropriate sexual advances to women) is mostly reported. A more detailed clinical evaluation would usually show that this is more clinically obvious disinhibited behaviour among a spectrum of other disinhibited behaviours (4,5). Paraphilic behaviour has been reported secondary to a wide variety of neuropsychiatric

disorders. These include temporal lobe epilepsy, postencephalitic neuropsychiatric syndromes, septal lesions, TS, frontal lobe lesions, tumours in various sites, bilateral temporal lobe lesions, and multiple sclerosis (5). Both nonparaphilic hyposexuality and hypersexuality have been reported in association with various brain lesions. Interestingly, OCD has also been observed secondary to various neurological disorders, and the sites of the lesions causing OCD overlap considerably with the ones that are associated with sexual disorders (5). There has also been research showing that corticostriatal circuits are most likely involved in OCD and TS (4,6,7). It has also been noted that there is comorbidity between sexual disorders and TS, including exhibitionism, other paraphilias, and nonparaphilic hypersexuality (8). It is interesting that coprolalia and copropraxia in TS clearly have a sexual behaviour component (8). Other research shows that these symptoms are related to the degree of Tourette syndrome gene-loading that is present (7). These sexual symptoms decrease with treatment using SSRIs and dopamine blockers (4,6,7). These observations support a relation between paraphilic behaviour, compulsive sexual behaviour, and a neurobiological abnormality; paraphilia and CSB appear to be a behavioural response to that abnormality. At the same time, there is possibly an overlap of the neurobiological abnormality and OCD spectrum disorders.

The exact nature of hypersexuality is difficult to define. The total sexual outlet (TSO), originally defined by Kinsey as the number of orgasms per week, is one measure of hypersexuality. Kafka has attempted to address this problem in a study of men presenting for treatment with compulsive sexual behaviour, which he describes as "paraphilia related disorders" (PRD) (9). In individuals with PRD were found in a small study to have 5 or more sexual outlets (or gasms) per week for long periods of their adult lives, while the average man would have 3 (9). Although this is simple and attractive in clinical terms, it does not define hypersexuality in empirical terms. What is needed is a large study of paraphilic and nonparaphilic men and women in whom typical patterns of sexual drive are examined. In addition, in my opinion, there would have to be some degree of social or occupational or other dysfunction coupled with it, rather than simply a quantitative measure of total orgasms per week. Various levels of sex drive could be established and defined as hyposexuality, normosexuality, and hypersexuality, based on ranges of sexual outlet measures. What is important conceptually, however, is that there are some men who have hypersexuality, some of whom may be paraphilic and some who are not. Testing for the presence or absence of paraphilia would be replicated at all levels of sexual drive, as men and women who have a paraphilia may be hypersexual, normosexual, or hyposexual. In addition, some individuals exhibit compulsive sexual behaviours (CSB) which are nonparaphilic. These include compulsive masturbation, compulsive use of pornography, and

promiscuity. In individuals with CSB may also be hypersexual, normosexual, or hyposexual. As compulsive sexual behaviour becomes more defined conceptually and diagnostically, a specific pharmacological approach to hypersexuality (paraphilic or nonparaphilic), in contrast to normosexuality or hyposexuality, would be developed. Hypersexuality would be recognized as distinct from CSB and paraphilic behaviour. What is not clear from research to date is whether hypersexuality is an aggravating factor in paraphilias. A consistent diagnostic formulation for hypersexuality must be developed, and it should be included in DSM-V.

Animal research and clinical studies have shown that the monoamines 5-HT and dopamine affect sexual behaviour (1,10). Further, manipulations of 5-HT and dopamine can either decrease or increase sexual behaviour, depending on which neuropharmacological intervention occurs (1,10). Any discussion of the effects of neurobiology on sexual behaviour has to take into account the neuropeptides in the brain that are significantly involved with the regulation of hormones (10). A neuropeptide, by definition, is a chain of 2 or more amino acids linked by peptide bonds and differs from other proteins only in the nature of the peptide links (10). Over 100 unique, biologically active peptides, ranging in size from 2 to about 40 amino acids, have been found, including gonadotropin-releasing hormone (GRH) and prolactin (10). GRH stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, which drive the production of testosterone in the testes and estrogen and other hormones in the ovaries (11). The behavioural effects of neuropeptides have been observed after their injection directly into the central nervous system—the preferred method of administration because most of the peptides can not penetrate the blood-brain barrier in amounts sufficient to be active (10). These neuropeptides are similar to monoamine neurotransmitters in having receptors on neurons, which they can excite or inhibit (10). One difference, however, is that the rate of activity for neuropeptides is slow compared with that of the monoamine neurotransmitters, and the duration of their activity can be extended for substantially longer periods of time (10).

Neuropeptides are found throughout the central nervous system as well as in peripheral organs such as the gastrointestinal tract, the pancreas, and the adrenal glands (10). The hypothalamic regions contain considerable amounts of these neuropeptides, including, among others, GRH, corticotropin-releasing hormone (CRH), and thyroid-releasing hormone (TRH) (10). Clearly, the role of the neuropeptide transmitter GRH is critical to an understanding of human sexual behaviour (11). Although research in rats has shown that the effects of neuropeptides on sexual behaviour are mediated solely through certain serotonergic receptor subtypes (12), the assumption that either 5-HT or dopamine independently have a dominant neurobiological role in

controlling sexual behaviour in humans is most likely completely inaccurate. The situation in humans is much more complicated (11). However, both animal research and research on the human male have shown that sexual behaviour declines following surgical castration and that this occurs at different rates in different species. The first element that disappears is ejaculation, followed by intromission, and then mounting behaviour (11). These responses are restored in the reverse sequence with an androgen replacement (11). The sites of action of androgens in the male animal are known to a certain degree. These are in the limbic system of the brain, the spinal cord, and the penis (11). In the spinal cord, the reflexes controlling erection and ejaculation are androgen-dependent and in the penis, tactile sensitivity is androgen-dependent (11). Studies of hormone replacement in hypogonadal men as well as studies of the effects of hormone levels in men with sexual dysfunction have all contributed to our knowledge of the role of androgens in male sexual behaviour (11). Studies of hyperprolactinemia show that it causes a decline in sexual desire, as seen in certain prolactin-producing tumours (11). The behavioural effects of the principal androgens in the human male, testosterone (T) and dihydrotestosterone (DHT), are mediated through T receptors and DHT receptors in the brain, particularly in the septal region, the pituitary, and the hypothalamus (11–13). Testosterone can also be aromatized to estradiol. Aromatization occurs in the hypothalamus and elsewhere and is also related to sexual drive in humans (11). Thus, the neurobiology of human sexual behaviour is extremely complicated and involves not only the monoamine transmitters 5-HT and, to a lesser extent, dopamine but is also regulated by neuropeptide neurotransmitters, located principally in the hypothalamus. In addition, circulating androgens and intracellular DHT and T receptors, specifically in the septal area and hypothalamus, also play a very important role. Clearly, complicated mechanisms both facilitate and inhibit sexual behaviour and involve all of these neurobiological systems—and probably others as well. It is obvious that these mechanisms are not fully understood at this time and it is therefore extremely premature to talk about a “monoamine hypothesis of compulsive sexual behaviour.” At the same time, certain pharmacological agents, by their actions on monoamine neurotransmitters and their effects on androgen receptors and circulating hormone levels, can have very significant and lasting effects on sexual behaviour (1, 14–16). A reduction in sexual behaviour, whether nonparaphilic or paraphilic, can be achieved.

The etiology of the paraphilias or sexual deviations is unknown (17,18). Further, the actual incidence and prevalence of the paraphilias is unknown (18,19). What is known is that the level of victimization of males and females in the general population is fairly consistent. As initially reported by Kinsey in the late 1940s, 24% of females had been victims of sexual abuse when they were 14 years of age or younger (20). A national survey in Canada in 1984 found that 23.5% of females

and 12.8% of males were victims of childhood sexual abuse (21), which is quite consistent with Kinsey's data. This may assist in gauging the prevalence of one paraphilia, specifically, pedophilia. For example, it is known that among identified pedophiles, approximately 35% were victims of sexual abuse as children. The average number of victims per pedophile is also known. It may therefore be possible to estimate the prevalence of pedophilia in the general population through extrapolation. In one study of sexual fantasies, two-thirds of males reported heterosexual pedophilic fantasies and about one-third of males had rape fantasies (22). As the presence of deviant sexual fantasies is an indication of the presence of a paraphilia at a mild level, this implies that mild pedophilia is prevalent at a staggeringly high rate in men in the general population. Further, assuming that the presence of rape fantasies indicates the presence of another paraphilia, specifically sexual sadism, then mild sadism would also be highly prevalent in the population at large. In my opinion, these are gross overestimates of the prevalence of mild pedophilia and sexual sadism. However, even if these figures were overestimated by a factor of 10, and the real levels are 6% and 3%, these disorders would still have a vastly higher prevalence than most other psychiatric disorders. At this time, the prevalence of paraphilias in the general population is unknown, and the prevalence of compulsive sexual behaviour is also unknown.

There are a number of pharmacological interventions that are available for the treatment of CSB and the paraphilias. These agents appear to have a direct impact on sexual drive. Sexual drive consists of various components, including a psychological component of subjective desire to engage in sexual activity (the sexual equivalent of hunger); the presence of sexual fantasies which may be nonparaphilic or paraphilic; a state of sexual arousal that provides motivation for seeking out sexual activity; and finally, the actual sexual activity itself, which ultimately results in an orgasm (23). Pharmacological agents have been identified that can affect all of the components of sexual drive. Ideally, however, one would want pharmacological agents that could affect deviant sexual interests in the case of paraphilias but not affect nondeviant sexual behaviour. As discussed later in this paper, there is at least some evidence that this might occur with the specific antiandrogen cyproterone acetate and the SSRI sertraline (24). In the case of CSB, the ideal treatment would result in a general reduction of sexual drive without extinguishing it—but giving the individual more control over his or her sexual behaviour.

The evaluation of sexual behaviour requires expertise and training in sexology and a specialized sexual behaviours clinic. In such a clinic, there is typically a detailed psychiatric and physical examination and an assessment of sexual behaviour, using various psychological and physiological tests. As various neuropsychiatric problems can have a significant effect on sexuality, neuropsychiatric expertise should be

available and should be used to complete the evaluation. The evaluation includes a sex hormone profile, consisting of free and total testosterone, FSH, LH, estradiol, prolactin, and progesterone. This sex hormone profile will also provide the baseline for any treatments involving antiandrogens or hormones. In addition, sex drive abnormalities and certain high-risk cases for sexual violence may involve hormone abnormalities. Various questionnaires are used to provide a structured sexual history and measure the nature and degree of sexual fantasies, the nature and degree of cognitive distortions and how they relate to paraphilias, components of sexual drive and of nonparaphilic sexual behaviour, and the presence and extent of substance abuse. The last component of the evaluation is physiological testing of sexual arousal to establish whether a deviant sexual preference is present or not.

This author has recently established an algorithm for the treatment of paraphilias (24) that is based on an enhanced classification of paraphilias described in the DSM-III-R (23). The new classification scheme has 4 categories (24):

1. Mild
2. Moderate
3. Severe
4. Catastrophic

The last category, catastrophic, has been added to the original 3 described in DSM-III-R. The full version of this classification is available in a recent publication by this author (23). The newly-developed algorithm encompasses 6 levels of treatment for the 4 categories of paraphilia.

Level 1: Regardless of the severity of the paraphilia, cognitive-behavioural treatment and relapse-prevention treatment would always be given.

Level 2: Pharmacological treatment would start with SSRIs. This would be indicated in all cases of mild paraphilia.

Level 3: If the SSRIs were not effective in 4 to 6 weeks at adequate dosage levels, a small dose of an antiandrogen would be added. A typical pharmacological regime would be sertraline 200 mg daily with 50 mg of medroxyprogesterone acetate (MPA) or 50 mg of cyproterone acetate (CPA). This would be used in mild and moderate levels of paraphilia.

Level 4: The full antiandrogen or hormonal treatment would be given orally. This would involve 50 to 300 mg of MPA daily or 50 to 300 mg of CPA daily. This regimen would be used in most moderate cases and in some severe cases.

Level 5: The full antiandrogen treatment or hormonal treatment would be given intramuscularly (IM). This would

involve 300 mg of MPA given IM each week with 200 mg of CPA given IM every 2 weeks. This regimen would be used in severe cases and some catastrophic cases.

Level 6: A complete suppression of androgens and sex drive would be sought by giving CPA 200 to 400 mg IM weekly or providing a luteinizing hormone–releasing hormone (LHRH) agonist. This regimen would be used for some severe cases of paraphilia and would be the treatment of choice in catastrophic cases.

The aims of treatment using this algorithm would be the suppression of deviant sexual fantasies, urges, and behaviours, with a minor impact on sexual drive at Levels 2 and 3. Suppression of deviant sexual fantasies, urges, and behaviour, with a moderate reduction in sexual drive, would be seen at Levels 3 and 4, but this would be dose-dependent. Suppression of deviant sexual fantasies, urges, and behaviour, and a severe reduction of sexual drive (depending on the dose of medication) would occur at Levels 4 and 5. A complete or near-complete suppression of sexual drive would be seen at Level 6.

In general, the aims of pharmacological treatments would be to suppress deviant sexual fantasies, to suppress deviant sexual urges and behaviour, and to reduce the risk of recidivism and further victimization. With regard to nonparaphilic hypersexuality (NPH), a mild, moderate, and severe classification would apply following the outline in DSM-III.

Pharmacological Treatment

There are 3 main categories of pharmacological intervention in the paraphilias, and to a certain degree, they could also be used for the treatment of nonparaphilic hypersexuality. These pharmacological treatments are (24):

- The specific serotonin reuptake inhibitors (SSRIs)
- The antiandrogens and hormonal treatments
- The LHRH agonists

The SSRIs

The SSRIs have long been documented as causing a reduction in sexual desire. They have also been an important advance in the treatment of the paraphilias because they are well-known to the average psychiatrist (15,25). Decreasing brain 5-HT in animals resulted in sexual drive increases as measured by increased mounting behaviour. In contrast, increasing brain levels of 5-HT reduced sexual drive and sexual behaviour. Therefore drugs that increase 5-HT levels in the brain have been used to treat paraphilias (15, 25). Starting in 1990, treatment successes for various paraphilias, such as exhibitionism, using fluoxetine hydrochloride and sertraline, have been reported (25–36). Fluoxetine and sertraline have been the

most commonly used pharmacological agents for the treatment of the paraphilias and nonparaphilic hypersexuality. Kafka reported on 4 patients treated for NPH with fluoxetine hydrochloride (30). Significant reductions in sexual drive were observed. He also reported on 3 cases of paraphilia treated with fluoxetine hydrochloride, where considerable clinical improvement was observed (30). Kafka and Prentky completed an open-label outpatient study on one group of men with paraphilia and another group suffering from NPH. Both groups were treated over a 12-week period with a mean dose of 30 mg fluoxetine hydrochloride daily. Clinical improvement in all cases was noted (31). Stein and others reported a failure of treatment of sexual disorders with fluoxetine hydrochloride (32). Coleman and others completed a study of 13 men with paraphilia treated with fluoxetine hydrochloride and reported improvement in all aspects of deviant sexual behaviour but, specifically, a reduction in deviant sexual fantasies, urges, and behaviours (33). Kafka reported on an open-label clinical trial of men suffering from paraphilia and NPH using sertraline (34). The subjects showed a significant reduction in deviant sexual fantasies, urges, masturbation, and deviant and nondeviant sexual behaviour. The clinical response rate was 50%. The treatment nonresponders were offered fluoxetine hydrochloride, and about 60% of this group showed some clinical improvement. The mean dosage of sertraline in Kafka's study was 100 mg daily, and for fluoxetine hydrochloride it was 51.1 mg daily. The mean duration of treatment was 30.5 weeks (SD 16.8 weeks).

Bradford and others reported on a 12-week open-label dose study of pedophilia treated with sertraline (35). There were 20 subjects in the study. Two subjects dropped out. The mean effective dosage of sertraline was 131 mg daily. None of the patients discontinued the sertraline due to inadequate treatment response. The study looked at various sexual behaviours, including sexual arousal patterns. All of the deviant sexual behaviours were reduced by the sertraline and, in addition, heterosexual intercourse showed a slight increase over the course of the study. This indicated some improvement in normophilic behaviour. Physiological measures of sexual arousal showed deviant arousal was reduced, while at the same time, comparative levels of normophilic arousal—arousal to consenting sex with adults—was maintained or in fact increased. Greenberg and others treated a variety of paraphilias using 3 different SSRIs, specifically sertraline, fluoxetine, and fluvoxamine (36). The final sample ($n = 58$) showed that the 3 SSRIs were equal in their effectiveness in reducing deviant sexual fantasies, urges, and behaviour. The principle effect was on deviant sexual fantasies (36). In a similar study, Greenberg and others looked at a sample ($n = 95$) of paraphilic men treated with SSRIs compared with a control group ($n = 104$) who received only

cognitive-behavioural treatment (25). Over the initial 12-week period of treatment, the frequency and severity of sexually deviant fantasies and urges were significantly reduced in the SSRI-treated group compared with the control group. These studies provide evidence that SSRIs reduce deviant sexual fantasies, urges, and behaviour. This would make them the drug of choice in the treatment of paraphilias as well as nonparaphilic hypersexuality. The number of studies completed to date is still small, however, and no double-blind studies have been reported.

Antiandrogens and Hormonal Agents

The initial hormonal treatment for the paraphilias used estrogens. The effectiveness of these treatments, however, was reduced because of their various side effects, specifically nausea, vomiting, weight gain, and feminization (37–41).

Medroxyprogesterone acetate (Provera) has been the most common form of pharmacological treatment for sexual deviation in the US. This is partly due to studies started at Johns Hopkins, but has also been dictated by the lack of alternatives such as CPA. Several clinical studies have been completed (42–58).

MPA is a progestagen and has a motive action through the induction of testosterone reductase in the liver, thereby decreasing circulating levels of testosterone. In addition, its action as a progestagen blocks the secretion of the gonadotropins (FSH and LH), although the mechanism of action is not fully understood (15). Studies have shown that it does not compete with androgens at the androgen receptor level and therefore by definition is not a true antiandrogen (15). MPA can be given both orally or IM. A number of side effects have been described, including weight gain, decreased sperm production, a hyperinsulinic response to a glucose load, and the potential to aggravate or precipitate diabetes mellitus, headache, deep vein thrombosis, hot flashes, nausea or vomiting, and feminization. Clinical studies show that MPA has a significant impact on deviant sexual fantasies and deviant sexual urges and behaviour. MPA has been used primarily in open clinical trials and most commonly is given IM at a dosage level of 300 to 400 mg weekly as part of an initial treatment, with the reduction to 100 mg weekly as part of a maintenance program. MPA can be given orally in dosages ranging from 50 to 300 mg daily (15, 24). Two open clinical studies of note were completed in 1981. In the first, Berlin and Mienecke treated 20 paraphilic men (42). They showed that MPA was an effective treatment in reducing deviant sexual fantasies and urges. At the same time, they observed that there was a significant relapse rate if treatment were discontinued. The dosage of MPA was 200 to 400 mg IM given weekly. In the second study, Gagne treated 48 patients (45) and reported effects similar to those of Berlin and Mienecke. He also

extensively documented various side effects, as outlined above. Wincze and others completed a double-blind study on 3 pedophiles using MPA (58). They noted that sexual arousal, as measured by penile tumescence in a laboratory setting, showed significant reduction in response to erotic stimuli. Self-reported arousal outside of the laboratory setting, however, was unreliable and inconsistent. Nocturnal penile tumescence was also measured and was reduced in all cases with active treatment. Meyer and others completed a study of 40 men treated with both MPA and group psychotherapy (49). The MPA was given at a dosage of 400 mg weekly by IM injections and the duration of treatment ranged from 6 months to 12 years. They included a control group of treatment refusers who received only group psychotherapy over the same period. This study also assessed treatment outcome. The MPA-treated group had an 18% recidivism rate while the treatment-refuser group had a 35% recidivism rate. Gottesman and Schu bert used a low dosage of MPA (60 mg daily) given orally for a period of 15 months in an open-label trial involving 7 subjects (46). They reported a significant reduction in deviant sexual fantasies and positive treatment outcome in all of these patients. The significant feature of this study is that it is the only one to examine systematically the effects of orally administered MPA.

Cyproterone acetate is a true antiandrogen as well as having progestinic and antigonadotropic effects (15). CPA is by far the most extensively studied antiandrogen in terms of its effects as a treatment for sexual deviation (15). It was originally used in Germany in the mid-1960s and since then has been used extensively in various parts of the world (59–71; and Ortmann J, 1984, unpublished observations).

As a true antiandrogen, CPA is active at androgen receptors throughout the body. It blocks the intracellular molecular receptors. The block of androgen receptors decreases all types of sexual behaviour, including sexual fantasies, deviant sexual behaviour, masturbation, and sexual intercourse, and it also has an impact on erections. CPA also has strong progestational activity, reducing the levels of FSH and LH. It is the acetate radical that gives it the progestinic effect. Cyproterone without the acetate radical has no antigonadotropic effects. CPA is a competitive inhibitor of testosterone and dihydrotestosterone at androgen receptors throughout the body (15, 24).

The first clinical studies using CPA were conducted in Germany (66, 67). In 1971, Laschet and Laschet reported on more than 100 sexually deviant men who were treated with CPA. They were mostly exhibitionists and pedophiles, as well as sexual sadists. About 50% of the subjects were also sexual offenders. This was an open-label clinical trial with a treatment duration of 6 months to 4 years (67). In 80% of cases, CPA

given orally at 100 mg daily and significantly reduced sexual drive, erections, and orgasms. CPA was also administered IM at levels of 300 mg every second week. With this approach, 20% of exhibitors had a complete elimination of all deviant sexual behaviour and, in some cases, these behaviours did not return even after the treatment was discontinued. Side effects of weight gain, depression, and feminization were noted. Laschet and Laschet reported on a similar study on 300 men treated for up to 8 years with excellent treatment outcome (66). Several other studies have since then been completed, all of which show that CPA is generally an effective treatment for sexual deviance. This author completed 2 studies on CPA, one a double-blind study and the other an examination of the sexual arousal patterns of pedophiles (59,60). The double-blind crossover study used 19 subjects, all of whom met DSM-III-R criteria for pedophilia. This sample also included sexual offenders, principally with high pre-treatment recidivism rates and a mean of 2.5 previous convictions for sexual offences per subject. CPA was administered orally in 3-month active-treatment phases alternating with 3-month placebo phases. There was a reduction in sexual arousal responses by active drug treatment that did not quite reach statistical significance. Self-reported urges of sexual arousal were all reduced, as was psychopathology as measured by various writing styles. Other measures of sexual behaviour, including sexual fantasies and masturbation, were all significantly reduced by CPA. In the study of CPA effects on the sexual arousal patterns of pedophiles, it was noted that deviant sexual arousal was affected differently from normophilic arousal in the same subjects. This differential effect on sexual arousal is a very important clinical observation that requires further research.

LHRH Agonists

Luteinizing hormone-releasing hormone agonists have also been used to treat paraphilias. They have the specific treatment effect of overstimulating the hypothalamus. There is initially an increase in GRH secretion and then a reduction to almost zero. Consequently, there is no gonadotropin secretion and the circulating levels of T and DHT drop to castration levels (15, 24). The LHRH agonists are given IM and have a prolonged action. They were first flagged as potential treatment by this author in 1985 (14). There have been limited clinical studies on the use of LHRH agonists (72–75). A study by Rouseau and others in 1998 documented changes in sexual behaviour in prostate cancer patients treated with flutamide as well as an LHRH agonist. There was a significant impact on sexual functioning compared with a pre-treatment phase. Thibaut and others reported on the treatment of 6 men who suffered from a paraphilia, principally pedophilia. Two of them had previously been treated with oral CPA at dosages ranging from 150 to 300 mg daily, but they did not appear to respond; however, their compliance was in

question. The patients were treated with triptorelin 3.75 mg IM monthly concurrently with CPA 200 mg daily for 5 months. In 5 out of the 6 patients, a marked decrease in sexual behaviour was noted (75). A very important study was published by Rosler and Witztum (73). This was an uncontrolled open study of 30 men with a mean age of 32 years who were treated with triptorelin. They received monthly injections of 3.75 mg of triptorelin and supportive psychotherapy for a follow-up period of between 8 and 42 months. Treatment outcome was measured by questionnaires. All of these men showed a decrease in deviant sexual fantasies and deviant sexual urges. Plasma testosterone levels fell to castration levels.

Conclusion

There are several pharmacological treatments available for the treatment of the paraphilias and nonparaphilic hypersexuality. These treatments are based on established neurobiological principles. Future research on serotonergic receptors and polypeptidic neurotransmitters is likely to lead to new pharmacological treatments. Hypersexuality should be included as a separate sexual dysfunction (sexual deviance disorder) in DSM-V.

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Résumé—La neurobiologie, la neuropharmacologie et le traitement pharmacologique des paraphilies et du comportement sexuel compulsif

Ces dernières années, on constate un intérêt accru pour le traitement des troubles sexuels. Les troubles sexuels sont classés dans le Manuel diagnostique et statistique des troubles mentaux (DSM IV) comme étant les dysfonctions sexuelles, les paraphilies et les troubles de l'identité sexuelle. Les dysfonctions sexuelles sont non déviantes ou non paraphiliques. Les dysfonctions sexuelles devraient inclure « le trouble du désir sexuel hyperactif », dans la catégorie des troubles du désir sexuel. En outre, on devrait spécifier si les paraphilies sont « avec hypersexualité » ou « sans hypersexualité ». On ne comprend pas encore complètement la neurobiologie des troubles sexuels, bien que la neuroanatomie fonctionnelle et la recherche neuropharmacologique aient exposé les neurotransmetteurs, les récepteurs et les hormones responsables du désir sexuel. Les études indiquent que divers agents pharmacologiques, y compris les inhibiteurs de recaptage de la sérotonine (IRS), les antiandrogènes, les agonistes LHRH et d'autres réduisent le désir sexuel. Un algorithme pour l'utilisation de ces médicaments dans le traitement des paraphilies et de l'hypersexualité non paraphilique est présenté. Les modes d'action, les dosages, les cibles du traitement et les méthodes usuelles de prescription de ces agents sont recensés dans cet article. On y présente aussi certaines orientations futures de la recherche en traitement pharmacologique.

