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SEXUAL DISORDERS (G DWYER, SECTION EDITOR)

The Biological Treatment of Paraphilic Disorders: an Updated Review

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Abstract Paraphilic disorders are characterized by atypical sexual interests, fantasies, and behaviors that are subjectively distressing to patients or pose a risk of harm to others. By their very nature, some paraphilic disorders may predispose an individual to commit sexual offenses. The biological treatment of paraphilic disorders, then, is of paramount importance for psychiatry and society at large. Three categories of pharmacologic agents commonly used to treat paraphilic disorders are selective serotonin reuptake inhibitors, synthetic steroidal analogs, and gonadotropin-releasing hormone analogs. Each medication uses a different mechanism of action and has different effects on the physiological and psychological features of paraphilic disorders. In general, these medications have limited high-quality research to support their use. Despite this, some authors have proposed treatment algorithms for individuals with paraphilic disorders of varying severity. These guidelines offer clinicians potentially useful, rational approaches to assessing treatment need in individuals with paraphilic disorders. Recent neuroimaging research suggests that functional magnetic resonance imaging may offer further promise in effectively assessing paraphilic disorders to help direct treatment options.

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Introduction

Paraphilic disorders are a group of related conditions characterized by atypical sexual interest. In 1887, Richard von Krafft-Ebing published his seminal work on sexual deviancy, *Psychopathia Sexualis*, since which time psychiatrists have recognized that individuals may demonstrate a broad array of atypical sexual interests including fetishes, transvestism, among many others [1]. Though the majority of paraphilic behaviors would not result in an interpersonal offense, research has demonstrated a strong link between certain paraphilic disorders like pedophilic disorder and sexual offending [2]. In addition, the majority of clinical knowledge and available data on the treatment for paraphilic disorders comes from individuals who have presented due to criminal justice involvement or who are at risk of sexual offending. Recent meta-analytic data suggest that biological treatment for sexual offenders with paraphilic disorders is more effective than psychotherapies at reducing sexually violent recidivism [3]. A recent Cochrane review on psychological treatments for sexual offenders did not find evidence that any type of psychological intervention demonstrated a treatment benefit [4••]. Clearly, then, the pharmacological management of paraphilic disorders and their associated interests, fantasies, and behaviors is of paramount importance for both patients and society at large.

In this article, we provide an up-to-date review of the medical treatment of paraphilic disorders. We briefly define the diagnostic class of paraphilic disorders per contemporary psychiatric nosology. We then describe current available

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pharmacologic interventions for paraphilic disorders and the physiologic rationale for their use. To offer clinicians an informed approach to treating paraphilic disorders, we delineate recently proposed methods for evaluating a patient with a paraphilic disorder for treatment. Lastly, we summarize recent neuroimaging research into the neurophysiology of paraphilic disorders and describe how this may inform treatment in the future.

Defining Paraphilic Disorders

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* defines a paraphilia as "any intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners" [5, p. 685]. The Sexual and Gender Identity Disorders Work Group was tasked with updating this chapter of the text from its predecessor *DSM-IV-TR* [6] and "sought to draw a line between atypical human behavior and behavior that causes mental distress to a person or makes the person a serious threat to the psychological and physical well-being of other individuals" [7••]. The diagnostic criteria reflect this distinction and define a paraphilic disorder as "a paraphilia that is currently causing distress or impairment to the individual or a paraphilia whose satisfaction has entailed personal harm, or risk of harm, to others" [5, p. 685–6].

The criteria for the paraphilic disorders in the *DSM-5* indicate that the individual must have "recurrent and intense sexual arousal" from "fantasies, urges, or behaviors" related to the atypical sexual activity [5, p. 686–702]. This means that engaging in a paraphilic behavior is not required in order for a diagnosis of a paraphilic disorder. In addition, the *DSM-5* criteria were edited from *DSM-IV-TR* such that a behavior unaccompanied by recurrent and intense sexual arousal cannot qualify for a diagnosis of a paraphilic disorder [8]. *DSM-5* delineates the criteria for eight specific paraphilic disorders including voyeuristic disorder, exhibitionistic disorder, frotteuristic disorder, sexual masochism disorder, sexual sadism disorder, pedophilic disorder, fetishistic disorder, and transvestic disorder. The text also allows a diagnosis of "other specified paraphilic disorder" for individuals with rare types of paraphilic disorders such as zoophilic disorder and necrophilic disorder when the deviant arousal causes them qualitative life impairments.

Pharmacologic Treatments for Paraphilic Disorders

Pharmacologic treatments for paraphilic disorders fall into three main categories including selective serotonin reuptake inhibitors (SSRIs), steroidal antiandrogens, and gonadotropin-releasing hormone (GnRH) analogs. Numerous recent review articles have extensively summarized the body of literature on these various agents and their relevance in treating paraphilic disorders and sexual offenders [9••, 10, 11, 12•]. Below, we briefly review the medications, their proposed mechanisms of action, and their current standing in the treatment of paraphilic disorders. For a more extensive review of data on these agents, the World Federation of Societies of Biological Psychiatry's 2010 guidelines [10] for the treatment of paraphilias and the review article by Garcia and colleagues [12•] are recommended.

Selective Serotonin Reuptake Inhibitors

The use of SSRIs for the treatment of paraphilic disorders has become the standard of care [9••]. Treatment providers and researchers have predicated their usefulness on various grounds. First, SSRIs can impair libido, orgasm, and ejaculation via their activation of the $5HT_2$ receptors [13•]. Studies vary in the reported incidence of these sexual side effects with some reporting low rates and resolution of effects over time. This suggests that predicating treatment of paraphilic disorders with SSRIs on the basis of side effects may be misguided [14]. Second, some have likened paraphilic fantasies, urges, and behaviors to the intrusive thoughts and compulsive behaviors seen in obsessive-compulsive spectrum disorders, such that pro-serotonergic agents may reduce the intensity of paraphilic urges and "compulsive" paraphilic sexual behaviors [15]. Lastly, depressive and anxiety disorders are commonly comorbid with paraphilic disorders, such that SSRIs may address underlying affective symptoms that contribute to the distressing quality of paraphilic thoughts and behaviors [16].

Current available data on the use of SSRIs in the treatment of paraphilic disorders are limited. The most studied SSRIs for paraphilic disorders are fluoxetine and sertraline, which have demonstrated efficacy in reducing fantasies and paraphilic behaviors in pedophilia, exhibitionism, voyeurism, and fetishism [16]. In 2002, Adi and colleagues performed a systematic review of the use of SSRIs in sexual offenders, identified 9 case series with a total of 225 patients, and found that offenders with exhibitionism, compulsive masturbation, and pedophilia showed the most improvement with SSRIs [17]. The WFSBP guidelines [10] reviewed all available studies published up until 2010 and noted the lack of controlled, randomized studies evaluating the efficacy of SSRIs in the treatment of paraphilic disorders. They concluded that "the results of psychotropic interventions are not favourable" with a level C of evidence ("minimal research-based evidence to support the recommendation").

Despite the lack of research support for their use, various experts have provided some clinical recommendations regarding the use of SSRIs to treat paraphilic disorders and sexual offenders. Bradford has noted that sertraline appears to reduce deviant sexual behaviors while maintaining or improving normal sexuality [18]. Some have suggested that early use of

SSRIs between the ages of 12 and 18 could prevent the acting out of deviant sexual interests and fantasies that begin to form around those ages. For these reasons, SSRIs are recommended in the treatment of mild paraphilias, in juveniles with paraphilic disorders and in cases with comorbid obsessive-compulsive disorder and depression [19].

Antiandrogen Therapy

The mainstay of treatment of paraphilic disorders, especially in sexual offending populations, has been antiandrogen agents. This class of agents, comprised of synthetic steroidal analogs and GnRH analogs, acts by reducing levels of circulating, free testosterone. Testosterone is a hormonal steroid produced primarily in the male human testes. It is involved in various areas of psychological functioning including sexuality, aggression, cognition, and personality [20]. Elevated levels of testosterone were once considered to be related to deviant sexual interests and sexual offending [21, 22]. Though research no longer supports this premise [15, 23], some speculate that individuals with paraphilic disorders may respond atypically to normal levels of testosterone. Reductions in testosterone result in reductions in libido, erections, sperm count, and masturbation frequency, which explains why testosterone has become a primary target in the treatment of paraphilic disorders [24].

Medroxyprogesterone Acetate

Medroxyprogesterone acetate (MPA) is a synthetic derivative of progesterone, a female steroidal hormone involved in pregnancy, the menstrual cycle, and embryogenesis. Most commonly used for contraception and hormone replacement therapy, MPA has been shown to reduce free testosterone levels by the following mechanisms: (1) activation of the hepatic enzyme testosterone-alpha-reductase, which catabolizes testosterone; (2) suppression of the hypothalamic-pituitary-gonadal axis via activity at androgen receptors with resultant reduction in luteinizing hormone (LH) release and androgen production and release; (3) increased testosterone binding to testosterone-binding globulin with resultant decrease in functional "free" testosterone levels; and (4) reduction in the cellular uptake of androgens via binding to androgen receptors [25, 26]. Through these multiple mechanisms of action, MPA suppresses sexual drive and reduces the intensity and frequency of sexual urges and cravings in individuals with paraphilic disorders [27]. MPA has numerous reported side effects including weight gain (18 %), headache (9 %), gallstones (1 %), thromboembolism (1 %), as well as transient elevation of hepatic enzymes, hot flashes, insomnia, depressive symptoms, and adrenal suppression [28].

The WFSBP guidelines reviewed available literature on the use of MPA, including 13 open and controlled studies with a total of approximately 600 paraphiliac subjects, with pedophilia present in 15 % of the cases [10]. In most cases, the administration of MPA resulted in the reduction of sexual behavior and the complete disappearance of deviant sexual behavior and fantasies after 1 to 2 months of treatment. A recent Cochrane review that examined studies on pharmacological interventions in sexual offenders found only seven small studies that met their inclusion criteria, all of which utilized MPA, and noted that data remain poor with regard to evidence of the effectiveness of MPA in reducing sexual recidivism and tolerability [29••]. It is not surprising, therefore, that the WFSBP guidelines noted a level C of evidence for their recommendation against MPA due to its unfavorable risk/benefit ratio [10].

Cyproterone Acetate

Cyproterone acetate (CPA), like MPA, is a synthetic steroid similar to progesterone that acts as an antiandrogen by directly binding to androgen receptors and reducing the intracellular uptake and metabolism of testosterone. It inhibits GnRH secretion and LH release, resulting in decreased testosterone production and release [30]. CPA is not available in the USA at doses used for the treatment of paraphilic disorders, but it is available as an oral contraceptive pill in combination with ethinyl estradiol. It is more commonly used as an antiandrogen in Canada, Europe, and the Middle East. Like MPA, it is also available as an injectable intramuscular formulation or a pill.

The WFSBP guidelines reviewed 10 open and controlled studies with approximately 900 male subjects, of whom about 20 % had pedophilia. Eighty to 90 % of subjects experienced a significant decrease in sexual fantasies or activity, frequency of masturbation, and disappearance of deviant sexual behavior within 4 to 12 weeks [10]. Side effects from CPA include hot flashes, hair loss, gynecomastia, weight gain, and osteoporosis [31]. A review of studies comparing the use of CPA and MPA found that individuals taking CPA sexually reoffended at a rate of 6 % and that many reoffended if they did not comply with treatment protocols or after discontinuing treatment. Those individuals on CPA offended less frequently than those on MPA [32]. The WFSBP guidelines again noted a level C quality of evidence to make recommendations on the use of CPA [10].

GnRH Analogs

The GnRH analogs are another form of antiandrogen treatment whose mechanism of action is to suppress the physiologic, pulsatile release of luteinizing hormone (responsible for stimulating testicular production of testosterone) from the pituitary gland. Originally developed for use in individuals with prostate cancer [33], these agents reduce testosterone to levels

of surgically castrated individuals within 1 month [34]. The three GnRH analogs that have been studied as antiandrogen treatment are triptorelin, leuprorelin, and goserelin. All three agents can be administered in long-acting injectable formulations, and both leuprorelin and goserelin have daily intramuscular formulations. Most studies on these agents have involved small sample sizes. Pooled data from two prospective open studies, two retrospective studies, and one case report involving 75 male paraphiliacs, among whom were 33 pedophiles and 8 exhibitionists, saw the disappearance of deviant sexual fantasies and a reduction of nondeviant sexual behavior between 1 and 3 months after the initiation of treatment with triptorelin. With one exception, there were no observed deviant sexual behaviors or sexual offenses committed during treatment [10, 35]. Similar findings have been observed for leuprorelin [36]. One retrospective study comparing GnRH analogs and CPA in 58 subjects found that these agents showed the same efficacy [37]. The 2015 Cochrane review on pharmacologic treatments for sexual offenders identified no studies on the use of GnRH analogs of sufficient quality that met the inclusion criteria for their review [29••].

GnRH analogs may have advantages over steroidal antiandrogens like MPA and CPA. First, they may be used in situations where steroidal medications are contraindicated or ineffective. Second, they can be coadministered with CPA or MPA in patients in whom there is concern for covert androgen use [38]. Third, GnRH analogs appear to have a better side effect profile than the steroidal agents and may be better tolerated by patients [15]. Overall, the WFBSP guidelines note with a level C quality of evidence that GnRH analogs have demonstrated a very high efficacy, notably in cases where subjects have previously failed treatment with psychotherapy and other antiandrogens [10].

Treatment Approach

While some guidelines and review articles inform an approach to the treatment of paraphilic disorders, the WFSBP guidelines provide an algorithm to assist clinicians in determining appropriate treatments for individuals with paraphilic disorders [10]. These guidelines, developed prior to the publication of *DSM-5*, refer to the treatment of "paraphilias" as opposed to "paraphilic disorders," but remain useful because the algorithm is based on the severity of impairment and risk of harm. Consisting of six levels of treatment need, the algorithm recommends escalating degrees of medical intervention with the aims "(1) to control paraphiliac fantasies and behaviors in order to decrease the risk of recidivism, (2) to control sexual urges, and (3) to decrease the level of distress of the paraphiliac subject" [10, p. 645]. Level 1 treatment is designed for patients with paraphilias that do not have an impact on conventional sexual activity and desire; the associated treatment recommendation is psychotherapy, preferably cognitive behavioral therapy. Level 2 treatment is to be used in patients with paraphilias that have a minor impact on conventional sexual activity and desire or minor, "hands off" paraphilias; the associated treatment recommendation is an SSRI at the same dose as prescribed for obsessive-compulsive disorder. Level 3 treatment is for patients with paraphilias resulting in moderate reduction of conventional sexual activity and desire, "hands on" paraphilias with fondling but without penetration, and paraphilic sexual fantasies without sexual sadism; the associated treatment recommendation is to add a low-dose antiandrogen steroidal analog (MPA or CPA) to the SSRI therapy. Level 4 treatment is recommended for patients with paraphilias that substantially reduce conventional sexual activity and desire and create a moderate or high risk of sexual violence without sexual sadism; the associated treatment recommendations include a full-dose antiandrogen steroidal analog, including the intramuscular formulation if the patient is noncompliant. Level 5 treatment is for patients with paraphilias that almost completely suppress normative sexual desire and activity, pose a high risk of sexual violence, or involve sexual sadism fantasies, behavior, or physical violence; the associated treatment recommendation is to treat with a long-acting GnRH agonist. Level 6 is reserved for the most severe paraphilias, or "catastrophic cases," that result in the complete suppression of normative sexual desire and activity; the associated treatment recommendation is to use either CPA or MPA in combination with a GnRH agonist. To date, there have been no prospective studies on the effectiveness of using this algorithm in patients with paraphilic disorders to prevent sexual offending.

In 1999, the Oregon state legislature passed House Bill 2500, the first law nationwide that established a plan to evaluate sexually offending inmates prior to their release to determine if they were appropriate for medical treatment with MPA. An inmate would be referred for medical evaluation to determine the suitability of treatment with MPA based on his score on the depo-Provera Scale (see Table 1). Items on the depo-Provera Scale were selected based on research and experience that suggested their utility in determining an offender's need for treatment with MPA. An inmate would be considered strongly in need of MPA treatment if he had three or more factors, two or more factors marked with an [a], or a score exceeding 6 on the depo-Provera Scale, though ultimately clinical judgment was the decisive factor in referral [39]. During the first 4 years of the program, 275 inmates were evaluated. One hundred thirty-four inmates were deemed appropriate for MPA, of whom 79 received the medication and 55 did not. Inmates who received MPA were significantly less likely to reoffend than those who did not, and they were also less likely to violate the conditions of parole. Of the 134 individuals referred for treatment, a substantial portion had a diagnosis or pattern of abuse consistent with pedophilia (37 heterosexual pedophiles and 59 homosexual pedophiles), but there was also

Table 1 The depo-Provera Scale (adapted from Maletzsky et al. 2006)

1. Multiple victims	1
2. Multiple paraphilias	1
3. Preferential/obligatory deviant sexuality—by official or offender history[a]	1
4. Deviant sexual interest, by plethysmograph or Abel Screen[a]	2
5. Not living with victim(s)	1
6. Use of force in sexual crime(s)	1
7. Any male victim(s)[a]	2
8. Age under 30 at time of projected release	1
9. CNS dysfunction (developmental disability, CNS injury, etc.)[a]	2
10. History of psychiatric illness	1
11. Sexual violations while under community supervision	1
12. Sexual violations in an institution	1
13. History of sexual offender treatment failure(s)	2

An inmate would be considered strongly in need of MPA if he had three or more factors, two or more factors marked with an [a], or a score exceeding 6

a large group ($n = 34$) who were convicted of rape [40]. It is unclear from the study whether or not these individuals carried paraphilic diagnoses. Despite this, the depo-Provera Scale's items may serve clinicians as a tool for determining which paraphilic patients have a greater need for treatment with antiandrogen therapy, particularly those with a history of sexual offending or those at a high risk of sexual offending.

Insights From Imaging

Recent studies suggest that neuroimaging may one day be a useful modality to aid in the assessment, categorization, and treatment of paraphilic disorders. Imaging methods (primarily functional magnetic resonance imaging) have been utilized to identify the neural substrates associated with sexual interest and response, including the cognitive, emotional, motivational, and autonomic domains of sexual behavior. Specifically, the orbitofrontal cortex and superior parietal cortex have been implicated in the cognitive role of categorizing sexual stimuli; the secondary somatosensory and insular cortices and amygdala play a role in an individuals' emotional arousal to sexual stimuli; the left anterior cingulate gyrus has been implicated in the motivational aspect of sexual behavior; lastly, activity in the hypothalamus, insula, and rostral anterior cingulate cortex influences the autonomic arousal experienced during sexual response [41–43].

Numerous studies have demonstrated radiographically significant differences in brain matter volumes in various cerebral structures between nonpedophilic and pedophilic subjects. In addition, studies have demonstrated atypical neural activity in pedophilic subjects [44••]. These findings are not solely of academic interest. Researchers have found that aberrant neural signals can be modified by patients using neurofeedback, and the changes in the neural activity of particular brain regions may be viewed on a screen during real-time fMRI imaging. Neurofeedback may be used to augment cognitive strategies to control deviant sexual thoughts [45••]. This modality may be the first use of functional neuroimaging to treat paraphilic disorders [46].

Our improved understanding of the neural substrates of paraphilic disorders may also help improve our ability to classify patients in greater need of treatment. Kärgel and colleagues [47••] compared resting state functional connectivity (RSFC), a measure of interaction between brain regions when one is not performing a specific task, in cortical circuits between a sample of pedophiles who engaged in child sexual abuse ($n = 12$), a sample of pedophiles who did not engage in child sexual abuse ($n = 14$), and normal controls ($n = 14$). They found that the sample of pedophiles who engaged in child sexual abuse demonstrated decreased RSFC between the left amygdala and orbitofrontal cortex and anterior prefrontal regions, brain regions that are implicated in motivational and socio-emotional processes. They postulated that such a functional deficit may account for an increased propensity to engage in child sexual abuse. With further study and validation, such findings may prove clinically useful as a measure predictive of a pedophile's proneness to act on his sexual interest. Clinically, such a finding could be used to identify patients who might benefit from more aggressive treatment or monitoring.

To date, the vast majority of neuroimaging research in paraphilic disorders has focused on pedophilic disorder. Relatively little is known about the generalizability of findings from pedophilic disorder to other paraphilic disorders. Furthermore, there are very few neuroimaging studies that assess the impact of pharmacologic or psychological interventions on the deficits seen in individuals with pedophilic disorder. Future research may help delineate the similarities and differences in functional deficits seen in pedophilic disorder and the other paraphilic disorders and elucidate the functional changes indicative of a response to treatment.

Conclusion

The paraphilic disorders form a heterogeneous collection of diagnoses based on deviant sexual interest. These disorders predispose some individuals to engage in behaviors that may result in sexual offending and therefore represent an important target of intervention for psychiatrists and society at large. Treatment options are few and research into their efficacy and effectiveness is limited. Currently utilized biological agents include selective serotonin reuptake inhibitors and antiandrogen medications like synthetic steroidal analogs and gonadotropin-releasing hormone analogs. Despite the limited evidence available to support the use of these medications in individuals with paraphilic disorders, there have been recent attempts to develop practical guidelines for their use

and rational treatment approaches. Generally, these approaches recommend more aggressive treatment for individuals with more severe paraphilic disorders that risk greater danger to themselves and to society. Neuroimaging research provides the hope that as our knowledge of the neural substrates of aberrant sexual interest and behavior grows, we might be able to identify those individuals most at risk for offending and most in need of treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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