Drugs (2022) 82:663–681
https://doi.org/10.1007/s40265-022-01696-1

REVIEW ARTICLE

Pharmacological Treatment for Pedophilic Disorder and Compulsive Sexual Behavior Disorder: A Review

Valdemar Landgren[1] · Josephine Savard[2,3] · Cecilia Dhejne[2,4] · Jussi Jokinen[3,6] · Stefan Arver[2,4] · Michael C. Seto[5] · Christoffer Rahm[6]

Accepted: 2 March 2022 / Published online: 12 April 2022

Abstract

Guidelines for the pharmacological treatment of paraphilic disorders have historically been based on data from forensic settings and on risk levels for sexual crime. However, emerging treatment options are being evaluated for individuals experiencing distress because of their sexual urges and preferences, targeting both paraphilic disorders such as pedophilic disorder (PeD) and the new diagnosis of compulsive sexual behavior disorder (CSBD) included in the International Classification of Diseases, 11th Revision (ICD-11). As in other mental disorders, this may enable individualized pharmacological treatment plans, taking into account components of sexuality (e.g. high libido, compulsivity, anxiety-driven/sex as coping), medical and psychiatric comorbidity, adverse effects and patient preferences. In order to expand on previous reviews, we conducted a literature search focusing on randomized controlled trials of pharmacological treatment for persons likely to have PeD or CSBD. Our search was not restricted to studies involving forensic or criminal samples. Twelve studies conducted between 1974 and 2021 were identified regardless of setting (outpatient or inpatient), with only one study conducted during the last decade. Of a total of 213 participants included in these studies, 122 (57%) were likely to have PeD, 34 (16%) were likely to have a CSBD, and the remainder had unspecified paraphilias (40, 21%) or sexual offense (17, 8%) as the treatment indication. The diagnostic procedure for PeD and/or CSBD, as well as comorbid psychiatric symptoms, has been described in seven studies. The studies provide some empirical evidence that testosterone-lowering drugs reduce sexual activity for patients with PeD or CSBD, but the body of evidence is meager. There is a need for studies using larger samples, specific criteria for inclusion, longer follow-up periods, and standardized outcome measures with adherence to international reporting guidelines.

Key Points

Few randomized controlled trials (RCTs) for pedophilic disorder (PeD) or compulsive sexual behavior disorder have been conducted.

There is evidence that testosterone-lowering drugs reduce sexual activity in patients with PeD.

There is a need for RCTs that adhere to international reporting standards, and the field needs to develop standardized outcome measures.

Valdemar Landgren and Josephine Savard contributed equally to this work.

✉ Christoffer Rahm
christoffer.rahm@ki.se

1 Gillberg Neuropsychiatry Centre, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

2 Anova, Karolinska University Hospital, Stockholm, Sweden

3 Department of Clinical Sciences/Psychiatry, Umeå University, Umeå, Sweden

4 Department of Medicine, Karolinska Institutet, Stockholm, Sweden

5 Royal Ottawa Health Care Group, Ottawa, ON, Canada

6 Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, and Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden

1 Introduction

Pedophilic disorder (PeD) is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),* as a persistent sexual attraction to prepubescent children that results in distress or negative consequences [1]. PeD is one of several paraphilic disorders listed in DSM-5, all characterized by atypical sexual interests causing distress or impairment to the individual or risk to harm for others. Building on the clinical term 'hypersexuality' [2, 3], the conceptualization of hypersexual disorder was proposed in 2010 for the clinical phenomenon of increased sexual preoccupation and compulsive sexual behavior that was experienced as out of control and associated with significant distress or impairment [4]. Other terminology has also been used to describe this clinical condition, such as sexual addiction [5] and sexual compulsivity [6]. The current version of the International Classification of Diseases (11 Revision [ICD-11]) uses the term compulsive sexual behavior disorder (CSBD) [7] to describe a disorder characterized by a persistent pattern of failure to control intense, recurring sexual impulses or urges, resulting in sexual behavior over an extended period of time that causes marked distress or impairment.

There is an empirically strong association between CSBD and paraphilic disorders [3], especially PeD [8–10]. Recent data indicate CSBD symptoms to be highly prevalent among help-seeking individuals with PeD [11, 12]. Individuals with symptoms of both PeD and CSBD are at relatively higher risk of sexually offending, given evidence that pedophilia and compulsive sexual behavior are independently related to sexual recidivism among identified offenders [13].

A substantial proportion of individuals with paraphilic disorders, and PeD in particular, may be at risk for sexual crime perpetration, especially in conjunction with increased sexual drive [14, 15]. At least some of these at-risk persons are willing to seek professional help if it is offered [16–18]. As a result, clinical initiatives and helplines dedicated to the prevention of sexual violence and treatment of sexual disorders have been launched. Some examples are the German Dunkelfeld Project [19], Stop It Now UK and US [20], the Swedish Preventell Helpline [21], and Don't Offend India [22]. There is also an increased interest in evidence-based methods in forensic settings to treat individuals convicted of sexual crimes.

The recently published guidelines from the World Federation of Societies of Biological Psychiatry (WFSBP) provide a thorough overview of available treatments and provide recommendations for paraphilic disorders [17]. However, the WFSBP algorithm proposes that risk to sexually offend (specified as five levels, where a higher level indicates more risk of sexual violence) and potential 'level of severity' of any sexual offense (e.g. sexual sadism fantasies), should guide choice of treatment: selective serotonin reuptake inhibitors (SSRIs) and psychotherapy with a cognitive behavioral approach are recommended for individuals considered at low risk of offending, while psychotherapy and testosterone-lowering drugs are recommended for individuals at high risk of offending. Although the authors also discuss considerations regarding comorbidity, and recommend to diagnose and treat comorbid conditions (if any), these considerations are not directly part of the algorithm. While we concur that risk assessments should not be neglected when choosing intervention, especially when it comes to psychosocial intervention planning, clinical decision making regarding pharmacological treatment should emphasize medical considerations [23]. This includes medical and psychiatric comorbidity, adverse effect profiles, and patient preferences. For example, if a medical evaluation confirms the manic phase of a bipolar disorder to be the underlying cause of sexual offending, anti-mania treatment and maintenance treatment with mood stabilizers should be considered. As another example, a patient with CSBD deemed high risk for committing a sexual offense may need pharmacological treatment with antidepressants for associated suicidal thoughts. Furthermore, due to a lack of controlled trials in the field, the majority of publications on which the WFSBP guidelines are based are open-label, observational studies with a low level of evidence.

Reviews of this area have been previously published. A Cochrane review by Khan et al. [14] assessed treatments targeting offending risk but did not include trials targeting either PeD or CSBD per se, as the latter diagnosis was not included in either the DSM-5 or ICD-10 at the time. Other recent reviews by Lewis et al. [24] and Turner and Briken [18] focused on gonadotropin-releasing hormone (GnRH) analogs for recidivism prevention in male sexual offenders, and for paraphilic disorders in men at risk of sexual offending, respectively, but no other pharmacological agents were reviewed.

The aim of this review is therefore to expand on previous reviews [14, 18, 24] by identifying possible treatment targets, focusing specifically on randomized controlled trials (RCTs) of pharmacological treatment for PeD and taking into account the newly defined diagnosis of CSBD, as well as psychiatric comorbidity. More specifically, we examine studies of PeD, CSBD, or PeD coexisting with CSBD.

2 Methods

2.1 Literature Search

We considered the literature search by Thibaut et al. [17, 25] regarding the previous and current WFSBP guidelines to

be a large and comprehensive effort in identifying relevant research conducted in the years 1969–2018, and we therefore focused on more recently published studies. A literature search was restricted to the period 1 January 2010 to 17 December 2021 (Fig. 1), with 2010 being the year hypersexual disorder was first proposed as a diagnosis [4]. The search was designed and conducted by a Librarian at the biomedical library of Gothenburg University. Relevant studies were identified using searches of the PubMed, PsycINFO, and Scopus databases restricted to the English language. We chose a wide set of search criteria for the clinical phenomena but a restricted description of study design, as shown in Online Resource 1. Additionally, we screened for eligible studies in previously performed reviews of pharmacological treatments of paraphilic disorders [14–18, 24]. We also searched ClinicalTrials.gov and the EudraCT database for as yet unpublished studies. Eligibility assessment of search hits was performed independently by the two first authors, and disagreements were resolved by consensus.

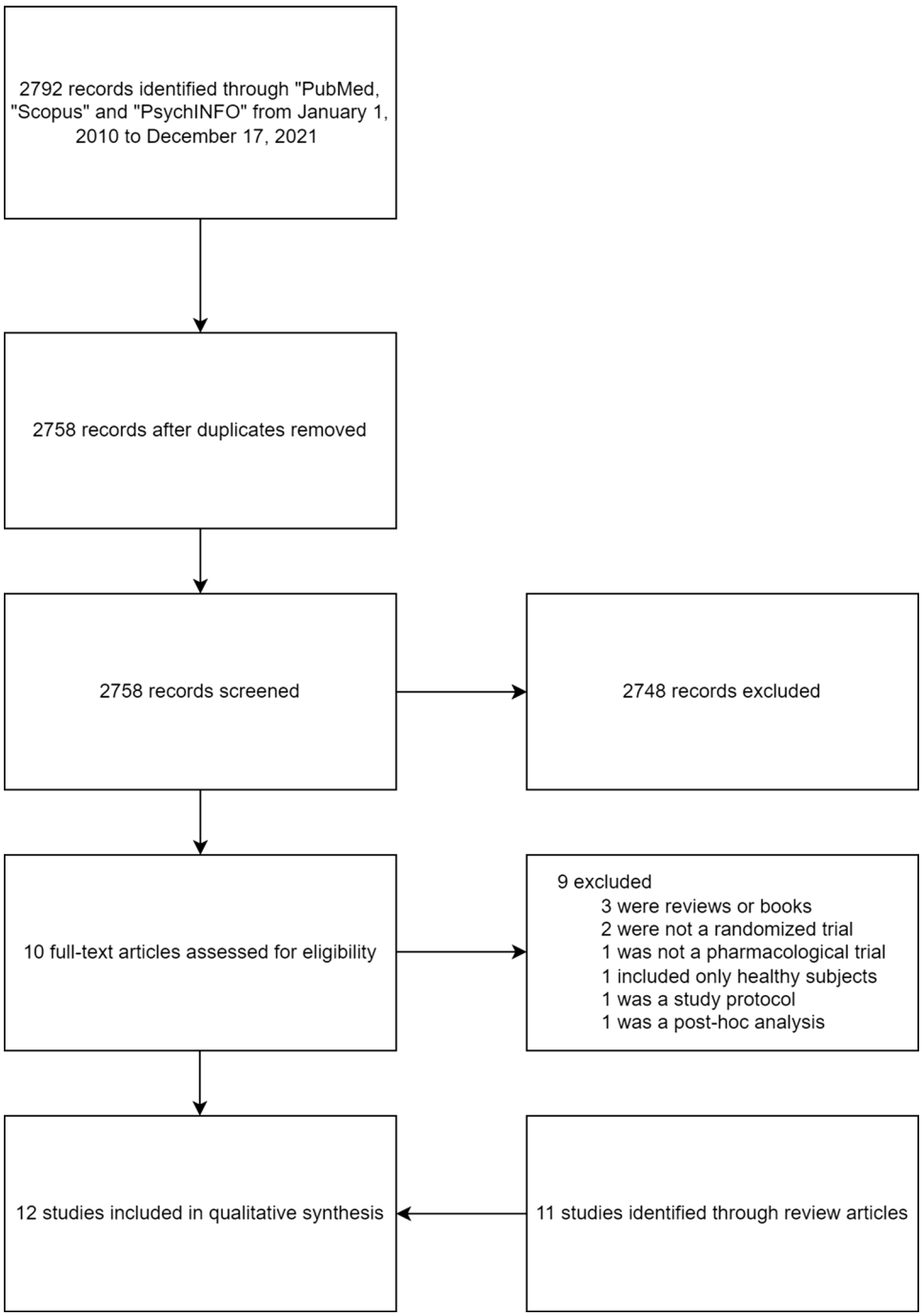

Fig. 1 PRISMA flow diagram. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

2.2 Study Inclusion Criteria

We included RCTs evaluating pharmacological treatment compared with a psychological intervention, another pharmacological treatment, or placebo. Open-label, single- or double-blinded studies were included, as were blinded single-subject reversal designs irrespective of setting (outpatient, inpatient, or correctional) or country. Studies with other designs (e.g. observational or case-control studies) were excluded. Study participants had to be adults and a majority were likely to have CSBD and/or PeD (or a history of sexual offenses implicating such sexual interest). Because studies spanned many years, we considered comparability of conditions rather than specific diagnostic criteria, because the criteria for PeD has changed over different iterations of the DSM and ICD systems and CSBD criteria were only introduced in ICD-11.

The clinical term 'hypersexuality' occurred in some studies and its interpretation is somewhat ambiguous. The current concept of CSBD is characterized by repetitive sexual behavior, loss of control, and adverse consequences, and not by an increase in sex drive per se (although this may co-occur with CSBD). Thus, to avoid an anachronistic interpretation of the term 'hypersexuality', we made our own consensus judgment about whether the described patient characteristics best fitted the modern concept of CSBD.

2.3 Quality Assessment

Risk of bias for the included studies was assessed independently by two assessors (VL, CR) using the Cochrane risk-of-bias tool [26], and disparities were resolved by consensus. According to the risk-of-bias tool, for a trial to be judged at low risk of bias, all five domains that were assessed, i.e. randomization process, deviations from intended interventions, missing data, outcome measurement, selective reporting, needed to be judged as low risk. Otherwise, the risk of bias was judged as high.

3 Overview of Relevant Studies

The literature search for RCTs published between 2010 and 2021 resulted in 2687 search hits, of which two reports from the same trial were eligible [10, 27] but only the primary report was included [10]. Other reasons for exclusion were not being clinical studies or RCTs, or the involvement of healthy participants. We excluded studies of impulse control disorder in Parkinson's disease because any problematic sexual behavior is likely an adverse effect of dopaminergic treatment and therefore does not meet the criteria for CSBD.

We found five additional trials on the ClinicalTrials.gov and EudraCT websites [28–32], one investigating an SSRI versus placebo, two investigating naltrexone versus placebo, one investigating SSRI versus naltrexone, and one investigating leuprorelin acetate versus cyproterone acetate (CPA), but none with any reported data.

From previous reviews, we included 11 additional studies [33–43]. Of these, we included five studies that were not part of the Cochrane review by Khan et al. [14], who excluded the work of Kruesi et al. [38] due to a lack of placebo control; Schober et al. [40] had no randomization of order; Cooper et al. [35] described treatment order as quasi-randomized, and neither Wincze et al. [43] (small sample size, $N = 3$) nor Wainberg et al. [42] (no outcome related to offending risk) were mentioned. We chose to include these papers because we found no evidence of bias in how treatment was assigned in the first three studies, the within-patient design of Wincze et al. [43] allowed for some comparison of treatments, and the Wainberg study [42] fitted the scope of our review (treatment of PeD and CSBD). We found clinical descriptions consistent with CSBD in three studies (i.e. 'compulsive sexual nature' in Kruesi et al. [38], 'non-paraphilic compulsive sexual behavior' in Wainberg et al. [42], and 'deviant hypersexuality with serious acting-out propensities with potential adverse social and legal sequelae' in Cooper [36]).

3.1 Study Settings and Participants

An overview of the 12 included studies is provided in Table 1. Eight studies were conducted in North America [34–38, 40, 42, 43], three in Europe [10, 33, 41], and one in Australia [39]. The median sample size was 13.5 (range 3–52) and the total sample size was 213. Of 213 participants, 122 (57%) were deemed to have PeD, 34 (16%) were deemed to have CSBD, and 2 (1%) were diagnosed with both disorders. The remainder had unspecified paraphilias (40, 21%) or sexual offense (17, 8%) as the treatment indication.

The 12 studies are further described in Table 2. The criteria for both inclusion and exclusion are clearly reported in eight studies, and the diagnostic procedure for PeD and/or CSBD or equivalent presenting conditions is clearly described in six studies [10, 34, 35, 37–40, 42]. Comorbidity (assessment of symptoms and/or diagnoses such as intellectual disability, anxiety, personality disorders, depression, substance abuse) is mentioned in six studies [10, 35, 38–40, 42] and thoroughly reported in three [10, 38, 42].

3.2 Quality Assessment

All studies except the two most recently published—one on CSBD [42] and one on PeD [10]—were deemed to be at high risk of bias (additional data are given in Online Resource 2). The most common reasons were bias in selection of the reported results (no prespecified plan for analysis was provided or described, lack of direct head-to-head analysis of

Table 1 Summary of included studies

	N (%)
No. of studies	12
Total sample size	213
Continent, no. of participants (%)	
North America	107 (50)
Europe	76 (36)
Australia	30 (14)
Forensic psychiatry/correctional setting[a]	90 (42)
Main treatment indication	
Sexual offense	6 (3)
Sexual offense against children	11 (5)
Unspecified paraphilia	15 (7)
Pedophilic disorder	58 (27)
Outpatient setting	123 (58)
Main treatment indication	
Pedophilic disorder	64 (30)
Unspecified paraphilia	25 (12)
Compulsive sexual behavior disorder/hypersexuality	34 (16)

[a]Although jurisdictions handle these participants differently, forensic psychiatry and correctional settings were collapsed because treatment indication arises in conjunction with criminal acts

treatment arms), and bias in outcome measurement (lack of blinding).

4 Pharmacological Interventions

Of 12 studies, six evaluated an active drug versus placebo; two used CPA [34, 36] (13% of participants), two used medroxyprogesterone acetate [39, 43] (MPA; 10% of participants), one used an SSRI [42] (13% of participants), and one used a GnRH antagonist [10] (24% of participants). Four studies compared two active drugs, [33, 33, 35, 38] (23%) and two compared a pharmacological treatment with psychotherapy [39, 40] (16%). Two studies made no statistical analysis of active treatment versus control/placebo treatment [35, 40].

Study durations ranged from 10 to 56 weeks (median 15 weeks). Adverse effects (predominately sexual adverse effects) were reported to some extent in most studies, but were systematically reported in only five studies [10, 33, 33, 34, 37].

An overview of the reviewed interventions and their putative mechanisms of action is provided in Table 3.

4.1 Ethinylestradiol

Bancroft et al. [33] reported on 12 men previously convicted of a sexual offense who were treated in an inpatient setting. They received ethinylestradiol or CPA in a crossover, double-blind design. Outcome measures were the sexual interest score, sexual activity score, and sexual attitude score, as well as responses to visual stimuli measured by penile erection and subjective ratings of sexual interest. The drugs significantly reduced both the sexual interest score and the sexual activity score compared with baseline. There were no significant differences between the two drugs on any measure. Adverse effects were not systematically reported.

4.2 Cyproterone Acetate

The study by Cooper et al. [36] included nine men with severe sexual acting out that had resulted in legal and social consequences. Four patients were referred to as 'hypersexual' and two with attraction to 'juveniles', making it difficult to distinguish pedophilia from hebephilia (attraction to pubescent children) or even older adolescents. Clinical details of one participant indicate only homosexuality, raising ethical considerations of the treatment aims of the study (while recognizing that homosexuality was a diagnosable condition at the time of this study if it was ego-dystonic). However, as it concerned only one participant, and it was not possible to exclude this individual from the results, this study was retained for analysis.

Participants acted as their own control, as they were allocated to randomly receive CPA or placebo in a balanced design for a total of 20 weeks. The main outcomes were measures of sexual interest and arousal, number of daytime erections, and results of a programmed masturbation intervention. The results indicated a significant effect for CPA compared with placebo in reducing libido and sexual behaviors.

Cooper et al. [35] performed a 28-week crossover trial of CPA, MPA, and placebo in 10 men with pedophilia. Self-reported measures of sexual fantasies, masturbations, morning erections, and sexual frustration, as well as observations of deviant sexual behaviors and phallometry were registered. Due to the slow recruitment of participants and only seven participants fulfilling the protocol, the statistical analysis plan could not be carried out. However, the authors reported a reduction on most outcome measures for both CPA and MPA. Adverse effects were assessed but were not systematically reported beyond a statement that there were no clear adverse effects (apart from ejaculate being more watery and of reduced volume) in the study.

Bradford and Pawlak [34] treated 19 men charged with a sexual offense and diagnosed with paraphilia. In a crossover fashion, participants were randomly allocated to receive placebo or CPA for 3 months, followed by a 3-month period of alternative treatment, with this alternation occurring four times over a total study period of 13 months. The main outcomes included subjective assessments of sexual interest and

Table 2 Study details

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
Bancroft et al. [33]	Sexual offenders, $N = 12$ Age of victims specified, of whom $n = 6$ were ≤14 years Mean age 26 years Forensic setting	Refers to earlier paper for selection criteria Details on subjects' offenses are reported No reports of psychiatric assessments or diagnostic procedure	Crossover RCT; ethinylestradiol 0.01 mg twice daily, CPA 50 mg twice daily Active treatment for 5 weeks and no treatment for 1 week, repeated once for a total of 12 weeks	Not specifically reported	Ratings of sexual interest, activity, and attitudes, as well as physiological responses to erotic stimuli	The drugs significantly reduced both the sexual interest score and the sexual activity score compared with no treatment ($F = 9.44$, $p < 0.001$; $F = 6.87$, $p < 0.01$). No difference between the two drugs. No formal placebo comparison CPA produced a weak effect in reducing erectile and subjective responses to erotic stimuli ($F = 4.45$, $p < 0.025$; $F = 6.68$, $p < 0.01$)	Assessed and the authors concluded that neither drug produced troublesome adverse effects	One participant became so depressed after 3 days of cyproterone acetate that he was excluded and replaced Pedophilia not systematically reported
Tennent et al. [41]	Child sexual offenders, $N = 12$ Mean age 33 years Correctional setting	Scope for change on measurements assessing erectile response to stimuli and meeting defined cut-off on sexual interest/activity score or on the sexual attitude score	Double-blind crossover RCT; four phases of six 6 weeks each Benperidol 1.25 mg from day 14; chlorpromazine 125 mg from day 14	Not specifically reported, however one participant became so severely depressed that he was excluded, however at what point was not revealed	Ratings of sexual behaviors and fantasies, measurements of sexual attitudes and physiological responses to sexual stimuli Measurements at the end of each 6-week period	Benperidol was significantly more effective than both chlorpromazine and placebo in reducing the sexual interest self-rating score (frequency of sexual thoughts; $F = 5.67$, $p < 0.025$) and sexual attitude score ($F = 5.1$, $p < 0.025$)	Patients' reports of adverse effects were recorded and reported for each case. No statistical analysis for comparisons	Two participants withdrew their consent during the first week; those and a participant who became depressed were replaced by three other volunteers Total study period should have been 18 weeks, however the authors had to change from a syrup preparation to tablets, meaning a no-treatment period while waiting for the preparation, of which the duration is not stated

Table 2 (continued)

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
Cooper et al. [36]	Hypersexuality and paraphilic disorders, $N = 9$ Mean age 43 years Outpatient setting	Participants presented with problems of severe sexual acting-out, with social and legal consequences Type of sexual deviant behavior is reported but a definition of hypersexuality or juveniles is lacking, as are other inclusion criteria	20-week single-blind crossover trial of CPA 50 mg and placebo	Not reported	Sexual interest score, sexual activity score, and reports of spontaneous daytime erections, and effect of programmed masturbation	Significant reduction of all domains compared with the placebo period ($p < 0.05$)	Not systematically reported ('virtually absent'). Testosterone levels returned to baseline within 30 days of cessation of CPA	Patient satisfaction and efficacy regarding criminal behavior not reported
Wincze et al. [43]	Pedophilic sexual offenders, $N = 3$ Mean age 44 years Forensic setting	'Participants were screened by a psychologist', unclear for what Type of offense is stated (child sexual offense), diagnostic procedure otherwise unclear No other treatment	Single-subject reversal design Baseline (7 days)—placebo (14 days)—MPA 160 mg/day (at least 30 days)—placebo (at least 21 days)	Not stated	Self-reports of sexual urges, sexual arousal, and phallometry response to erotic material Nocturnal penile erection Testosterone levels	Subjective decrease in urges during all drug phases Subjective decrease in arousal during the MPA phase compared with the initial placebo phases, with arousal not returning to baseline in the follow-up placebo phase Only slight decrease in genital response during the MPA phase	Not reported	Not a proper randomization, but the design with each individual being his own control motivates inclusion Small study. No formal statistical analysis
Hucker et al. [37]	Pedophilic disorder and charged or convicted of child sexual offense, $N = 18$ Mean age 37 years Forensic setting	Attraction to children confirmed by phallometric testing	Double-blind trial of MPA 200 mg or placebo for 3 months	Contraindicated medical condition	Sexual urges and sexual desires during the preceding 2 weeks at study termination (Urges Questionnaire) and assessment of adverse effects	Of the 10 items in the questionnaire, only decline in sexual fantasies was significant in those receiving MPA compared with placebo ($F = 7.91$, $p < 0.01$)	MPA led to significantly more depression	Thorough evaluation at baseline High dropout rate ($n = 11$ completed the study)

Table 2 (continued)

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
McConaghy et al. [39]	Sexual offenders $N = 30$, of whom pedophilic disorder = 15 Previous sexual offense, $n = 19$ Mean age 30 years Forensic setting	"All men who sought treatment were accepted" Paraphilia according to DSM-III	Randomly allocated to three parallel groups: MPA administered as injections for 6 months, imaginal desensitization therapy administered for 5 days, or both	Active psychosis	Main outcome not clearly specified Relapse rate, Spielberger State Trait Anxiety Inventory, questions on estimation of reduction in sexual urges and general tension on a percentage scale Hormone levels at 1 month follow-up Evaluation after 1 month (compared with the preceding month) and 1 year compared with the preceding year)	No significant differences across treatments in self-ratings of urges or tension 25 patients reported a marked reduction in or no anomalous desire at 1 month, 26 at 1 year. No significant difference between groups Significant correlations between testosterone decline and patients' and assessors' rated reduction of tension and anxiety in all groups Significant correlation between testosterone decrease and anomalous sexual urges was seen only for MPA-treated participants. No correlation to behavior observed Main finding stated as a significant correlation between reduced testosterone levels in the two groups receiving MPA and a reduction in their sexually anomalous urges ($r = 0.83$ at 1 month, $r = 0.82$ at 1 year, both $p < 0.001$)	20% ceased the injection treatment after 3–5 injections due to adverse effects	No measures of possibly co-occurring compulsive sexual behavior as indicated by patients being 'unable to control' sexual urges No specific data on the pedophilic disorder group, such as age or specific treatment outcome Imaginal desensitization is no longer in use. Allocation method not reported Blinding not possible, high risk of biased, subjective reports Some clinical characteristics are presented in the text, e.g. two participants with low intelligence needing help to fill in assessments

Table 2 (continued)

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
Cooper et al. [35]	Men with pedophilic disorder who had committed sexual offenses, $N = 10$ Mean age 30 years Forensic setting	"History of pedophilia", other criteria not specified Associated clinical characteristics are presented, but the diagnostic procedure is not stated	Double-blind, placebo-controlled, two-dose comparison of CPA 100–200 mg vs. MPA 100–200 mg Seven periods of 4 weeks, total 28 weeks Phase 1: placebo Phase 2: CPA/MPA 100 mg Phase 3: CPA/MPA 200 mg Phase 4: placebo Phase 5: MPA/CPA 100 mg Phase 6: MPA/CPA 200 mg Phase 7: placebo The drug order was determined quasi-randomly; four received CPA first and three received MPA first	Not reported other than 'no other drugs allowed'	Self-reported measures of sexual fantasies, masturbations, morning erections, and sexual frustration. Observations of deviant sexual behaviors, phallometry, hormonal levels	Equivalent results of the drugs—reduced sexual thoughts and fantasies, frequency of morning erections, frequency and pleasure of masturbation, level of sexual frustration. The authors discuss the dosage of the drugs to have an impact on suppressing sexual arousal Reduction of testosterone, follicle-stimulating hormone, luteinizing hormone. Variable results of phallometry	Weekly assessments, however not systematically reported other than "there were no clear side effects" apart from impact on ejaculate	$N = 7$ fulfilled the study and 3 dropped out during the initial placebo phase, providing a sample too small for statistical analyses

Table 2 (continued)

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
Kruesi et al. [38]	Paraphilic disorders with a compulsive nature, $N = 15$ Mean age 31 years	DSM-III-R criteria for paraphilia and/or compulsive masturbation Semi-structured questionnaire was used to assess paraphilic behavior	Two-week single-blind placebo phase followed by double-blind crossover treatment with desipramine and clomipramine until symptoms decreased, reaching a maximum dose of 250 mg/day Note: participants with 50% improvement ($n = 4$) in the placebo phase were withdrawn from the study	OCD, psychosis, need for other medications, and/or other medical or neurological illness	Rating of paraphilic behavior through semi-structured interview (= paraphilic severity), obsessional symptoms (Leyton Obsessional Inventory), anxiety and depression (NIMH Global Assessment Scale)	Decrease in paraphilic symptoms during drug phases compared with baseline and placebo phases No significant differences between the agents	Only sexual adverse effects were assessed; delayed ejaculation (five taking clomipramine, one taking desipramine); erectile dysfunction (five taking clomipramine, three taking desipramine); painful ejaculation (one taking each drug)	Only eight participants completed the study, of whom four were clinically depressed No double-blinded treatment to placebo comparison entails high risk of rater bias
Bradford and Pawlak [34]	Paraphilic disorder with a history of sexual offense, $N = 19$, 12 with pedophilic disorder Mean age 31 years Outpatient setting: self-referrals, referrals from lawyers, and from the courts, as well as from communities	DSM-III criteria for paraphilic disorder, and charged for previous offense	Double-blind, single-subject crossover design of CPA 50–200 mg/day Total study period 13 months	Medical illness or medication History of a malignancy, cardiovascular disease, deep vein thrombosis or embolism, chronic liver disease, diabetes mellitus, chronic alcoholism, active psychosis, severe chronic depression, sickle cell anemia, or organic brain disease Patients taking medication were excluded	Several questionnaires, including the Sexual Interest Score and reported frequency of orgasms in the past week, as well as penile response	Significant reduction in number of orgasms and result on the sexual activity score (number of orgasms in the past week) compared with baseline; only the sexual activity score decreased significantly compared with placebo (Friedman's ANOVA Chi-square = 2.58)	Adverse effects and biochemical laboratory tests were monitored No significant change in the general condition of subjects was noted except for an average weight gain of 3.1 kg during the study protocol	

Table 2 (continued)

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
Schober et al. [40]	Men with pedophilic disorder and antisocial personality disorder convicted of sexual offense, four with lengthy sentences, $N = 5$ Forensic setting	Adults 'out of denial' with pedophilic disorder (according to DSM-IV) convicted of sexual abuse, fair to good health and normal testosterone levels	Repeated measures, non-randomized study of CBT + leuprolide for 12 months, followed by CBT + placebo for 12 months. Patients and data collectors were blinded to treatment duration and sequence of administration	IQ < 70, subnormal testosterone levels, contraindicated medical condition or drug interaction, unresponsive to child stimuli on plethysmography	Abel Assessment of self-report and visual reaction time to visual child stimuli converted to z-scores Monarch penile plethysmography calculating an area under the curve of penile erection for each category Polygraph interview about sexual thoughts, behaviors, and urges in the past 3 months	No consistent change in pedophilic interest according to Abel Assessment. Post hoc one-tailed tests of means of individual PPG to child stimuli decreased at some time points "Polygraph results of the question, 'Since your last polygraph, have you had strong urges to initiate sexual contact with anyone under 18?,' revealed 100% non-deceptive responses on leuprolide and 0% non-deceptive responses on placebo" Blinding broken after 3 months for two participants and leuprolide reinstated on their own initiative due to increased self-rated risk; blinding broken in a third participant due to worsening polygraph test results. No formal analysis comparing active and placebo phases	Injection site reaction (4), Mean weight gain of 10 kg after 12 months. Transient hot flashes ($n = 3$). Gynecomastia ($n = 1$). Partial or complete loss of erection ($n = 5$). Decrease in penile ($n = 2$) and testicular ($n = 1$) size. No muscle pain, decreased hair, or asthenia was reported. Two participants had 'bone scan' at baseline and 12 months with no significant change	"Almost all subjects had polygraph evidence of deception at baseline and on placebo, indicating discordance with self-report. Because of these results at baseline and on placebo, we concluded self-report alone was insufficient and thus a poor outcome measure to evaluate responses to treatment." Severe cases Extensive testing

Table 2 (continued)

References	Patient characteristics	Inclusion criteria/ diagnostic procedure	Methods and intervention	Exclusion criteria	Outcome measures	Effectiveness	Adverse effects	Comments
Wainberg et al. [42]	Gay and bisexual men with non-paraphilic compulsive sexual behavior, $N = 28$ Mean age 37 years Outpatient setting	Age >18 years Sex with two or more male partners within 90 days, and at least moderately ill on the CGI scale adapted for compulsive sexual behaviors	Double-blind Parallel group Citalopram or placebo for 12 weeks	Severe psychiatric disorder, such as suicidality, major depression, bipolar disorder, substance dependence. Abnormal physical or laboratory results, or ongoing SSRI treatment	Main outcome: Yale–Brown Obsessive-Compulsive Scale-Compulsive Sexual behavior. Other assessments included questions on desire level and frequency of sexual behaviors	No significant difference in main outcome measure Significant decrease in desire for sex ($F = 7.8$, $p < 0.05$), frequency of masturbation ($F = 7.9$, $p < 0.01$) and hours of pornography use per week ($F = 4.3$, $p < 0.05$) in the group assigned to citalopram compared with placebo	Not systematically reported, other than sexual adverse effects; significantly more often delayed ejaculation in the citalopram group Two dropouts from the citalopram group	Well-defined eligibility criteria High adherence to study protocol Short study period, no follow-up
Landgren et al. [10]	Help-seeking men with pedophilic disorder, $N = 52$ Mean age 36 years Outpatient setting	Males aged 18–65 years and diagnosed with pedophilic disorder (according to the DSM-5)	Double-blind, placebo-controlled, parallel groups for 10 weeks	Contraindications to magnetic resonance imaging, severe suicidality or psychosis, interfering treatment with hormonal therapies, or medical conditions stated as contraindications to treatment	Main outcome: composite measure of four risk factors for committing child sexual abuse, and self-rated risk	Compared with placebo, degarelix significantly reduced the composite score after 2 weeks (−1.8, (95% CI −3.2 to −0.5; $p = 0.01$) and 10 weeks (−2.2, 95% CI −3.6 to −0.7), as well as in the domains of pedophilic disorder (2 weeks: −0.7, 95% CI −1.4 to 0.0; 10 weeks: −1.1, 95% CI −1.8 to −0.4) and sexual preoccupation (2 weeks: −0.7, 95% CI −1.2 to −0.3; 10 weeks: −0.8, 95% CI −1.3 to −0.3) in the degarelix group compared with the placebo group. No significant improvement in low empathy, impaired self-regulation, or self-rated risk	Systematic reporting of mild to moderate adverse events. Two serious adverse events of increased suicidal ideation in the group receiving degarelix	Detailed description of recruitment methods and clinical characteristics. Short study period Novel outcome measures

CBT cognitive behavioral therapy, *CGI* Clinical Global Impression, *CPA* cyproterone acetate, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *MPA* medroxyprogesterone, *RCT* randomized controlled trial, *SSRI* selective serotonin reuptake inhibitor, *ANOVA* analysis of variance, *CI* confidence interval, *OCD* obsessive compulsive disorder, *NIMH* National Institute of Mental Health, *PPG* penile plethysmography

Table 3 Interventions and their putative mechanisms of action

Pharmacologic group	Substance	Putative mechanism of action
Estrogen derivative	Ethinylestradiol	A potent orally administered estrogen derivative that mitigates the hypothalamic-pituitary-gonadal axis by suppressing gonadotropin secretion and thereby lowering testicular testosterone production [44]
Gestagen	CPA	A synthetic gestagen that acts as a competitive inhibitor on the androgen receptor, both peripherally and in the brain. It also decreases the release of luteinizing hormone and follicle-stimulating hormone, mediated through gestagen receptors, thereby blunting the effects of GnRH [45]
Gestagen	MPA	A gestagen with a similar structure to progesterone. The mechanism of action involves binding to progesterone receptors and inhibition of the secretion of GnRH via negative feedback, which eventually suppresses luteinizing hormone and follicle-stimulating hormone secretion, thereby reducing testosterone levels 10–14 days after oral ingestion [46]. Both MPA and CPA act as androgen receptor antagonists
Synthetic peptide	GnRH analog	GnRH analog stimulate GnRH receptors, causing a distinct rise in luteinizing hormone and follicle-stimulating hormone. Continuous stimulation causes a downregulation of the GnRH receptor that suppresses luteinizing hormone and follicle-stimulating hormone synthesis and secretion [47]
Synthetic peptide	GnRH antagonists	GnRH antagonists act by competitively blocking GnRH receptors, causing immediate blockage of luteinizing hormone and follicle-stimulating hormone secretion. This results in a rapid suppression of testosterone, with no initial testosterone surge as seen with GnRH analogs [47]
TCAs	Desipramine and clomipramine	TCAs block the reuptake transporter for norepinephrine and also act as antagonists at histaminergic, adrenergic, and muscarinic cholinergic receptors. Some TCAs, such as clomipramine, also inhibit the serotonin reuptake transporter [48]
SSRIs	Citalopram	SSRIs are a class of drugs with a wide range of clinical applications, including affective disorders and obsessive-compulsive disorder. The link between the serotonin system and sexual functions is complex and depends on receptor-type activation/inhibition [49]
Antipsychotic agents	Chlorpromazine and benperidol	Chlorpromazine, an aliphatic phenothiazine, is a first-generation antipsychotic drug. It not only blocks α1, 5HT2A, D2 and D1 receptors but also exerts effects on muscarinic, serotonin, and H1-receptors [50] Benperidol is a butyrophenone derivate, with high D2 receptor blockage potency [51]

TCAs tricyclic antidepressants, *SSRIs* selective serotonin reuptake inhibitors, *CPA* cyproterone acetate, *MPA* medroxyprogesterone acetate, *GnRH* gonadotropin-releasing hormone

frequency of orgasms and penile erection. There was a significant difference in the sexual activity score between CPA and placebo (a decrease in masturbation in the past week in the former). Sexual fantasies decreased significantly only between active phases and baseline, but not versus placebo. The authors speculated that arousability in the placebo phase at 10 months was inflated due to rebound from the active phase.

The fourth study of CPA used estrogen as a comparison (Bancroft et al. [33]) and is presented above in Sect. 4.1, wherein CPA produced a weak effect in reducing erectile and subjective responses to erotic stimuli.

4.3 Medroxyprogesterone Acetate

Wincze et al. [43] included three men convicted of a child sexual offense serving as their own controls in a single-subject reversal design in which MPA was compared with placebo, administered for a minimum of 3 months. The main outcome measures included subjective assessments of desire and arousal as well as penile erection. There was a decrease in subjective measures compared with baseline, but no statistical analysis was performed.

Hucker et al. [37] reported on sexual urges and desires in participants with attraction to children, charged with sexual offenses, and treated with MPA or placebo for 3 months. Of the recruited 18 participants, 7 dropped out, and reasons for discontinuation were not reported for 5 participants. The analysis included only treatment completers. Of the 10 items in the questionnaire, only reduction of sexual fantasies was significant in those receiving MPA compared with placebo. Adverse effects were presented thoroughly, with depressed mood being significantly more common in the MPA group. MPA also had a significant effect on blood tests, including rise in fasting glucose and creatinine and decline of testosterone and estrogen. McConaghy et al. [39] investigated the effect of MPA in 30 men who sought treatment for 'anomalous sexual urges' and behaviors they felt unable to control. The only exclusion criterion was active psychosis. Participants were randomly allocated to receive

MPA as injections for 6 months ($n = 10$), imaginal desensitization ($n = 10$), or both ($n = 10$). Imaginal desensitization was given for 5 days in a psychiatric hospital. The authors describe the logic of imaginal desensitization being that compulsive sexual behaviors are driven by tension and the therapy acts by reducing the participant's level of arousal so that failure to complete the behavior no longer results in compelling tension. Outcome measures included analogous scales with questions on sexual urges, desire and behaviors, general tension, and the Spielberger State Trait Anxiety, as well as hormonal levels. Fifteen of the 20 participants allocated to receive MPA or MPA plus imaginal desensitization completed the course of injections; four ceased after three to five injections due to adverse effects (painful urination, headache and reduced heterosexual interest) and one was lost to follow-up.

Twenty-five participants (nine receiving imaginal desensitization, eight receiving MPA, and eight receiving MPA plus imaginal desensitization) reported changes in anomalous sexual desire after 1 month, with no significant differences between the groups with regard to sexual desire, urges, or behaviors. It should be noted that the definition of 'changes' is not clearly stated. There were significant correlations between reduced testosterone levels following MPA or MPA plus imaginal desensitization treatment and mean reduction in anomalous sexual urges.

The fourth study of MPA was a comparison with CPA [35] and is presented in the section on CPA.

4.4 Gonadotropin-Releasing Hormone Analogs

Schober et al. [40] reported a crossover study of pharmacological augmentation therapy with leuprolide or placebo plus psychotherapy that included five men with PeD, multiple paraphilias, and antisocial personality disorder with extensive histories of sexual convictions. Participants and raters were blinded to treatment sequence and participants acted as their own controls. They received 12 months of injections with leuprolide, a GnRH analog (commencing with 2 weeks of 'sequestering' involving hospitalization and the administration of flutamide against any initial testosterone flare), followed by a planned placebo phase of 12 months. The main outcome measures included assessments of sexual response to children involving self-report, reaction time to visual stimuli, and genital arousal to child stimuli. Results showed no consistent change in pedophilic interest according to visual stimulus reaction time during leuprolide treatment compared with baseline. While on active treatment, all subjects self-reported a decrease in pedophilic urges and masturbation to thoughts of children. Post hoc one-tailed tests of means of individual penile erection measures to child stimuli decreased at most time points (measures at 10 months may have increased due to rebound following a 1.5-week delay in drug administration). Polygraph interview results were considered reliable during the active treatment phase and unreliable during the placebo phase. Blinding was broken after 3 months of placebo treatment and leuprolide was reinstated on patient initiative due to increased self-rated risk for two participants and in a third participant due to worsening polygraph test results. There was no formal analysis comparing leuprolide with placebo. Common adverse effects were injection site reactions, hot flushes, sexual dysfunctions, and weight gain.

4.5 Gonadotropin-Releasing Hormone Antagonists

Landgren et al. [10] reported a double-blind parallel-group trial of 52 men with PeD. Participants were recruited via a national telephone helpline followed by face-to-face evaluation. They received two consecutive injections with degarelix, a GnRH antagonist, or placebo at baseline and had follow-up assessments at 2 and 10 weeks. The primary outcome measure was a novel composite score of four operationalized risk factors (PeD, sexual preoccupation, impaired self-regulation, and low empathy) and self-rated risk for committing child sexual abuse. Degarelix significantly reduced the composite score at 2 and 10 weeks. In separate analyses, active treatment significantly reduced scores in the domains PeD and sexual preoccupation, but not self-rated risk, impaired self-regulation, or low empathy. Post hoc analyses revealed that 15 of the 26 participants (58%) in the degarelix group and 3 of the 26 participants (12%) in the placebo group denied sexual attraction to minors at 10 weeks, and 15 (58%) of those assigned degarelix wished to continue treatment. Adverse events were systematically assessed and reported; there were two serious adverse events of increased suicidal ideation in the group receiving degarelix. Injection site reaction (88%) and increased hepatobiliary enzyme levels (44%) were also reported in the degarelix group.

4.6 Tricyclic Antidepressants

Drawing on evidence of the efficacy of clomipramine in treating obsessive compulsive disorder (OCD), Kruesi et al. conducted a trial comparing desipramine and clomipramine, two tricyclic antidepressants, in 15 patients with compulsive masturbation and/or paraphilia deemed to have a 'compulsive nature' [38]. Trialists speculated that a superiority of clomipramine would support the hypothesis that some paraphilic presentations are symptoms of OCD. Outcome measures included a semi-structured questionnaire of paraphilic behavior severity and obsessional features rated using the Leyton Obsessional Inventory. After a 2-week single-blind placebo phase, four placebo responders (> 50% improvement) were excluded. Of 11 participants, 8 completed two treatment phases of 5 weeks on each drug. Only per-protocol

results from the eight completers were reported, in which paraphilic severity was significantly lower for both drugs compared with baseline and the placebo phase, but with no difference between the two compounds. Notably, there was no double-blind placebo phase for comparison, thus increasing the rater bias.

Adverse effects noted were delayed ejaculation (five of eight patients taking clomipramine, one of eight patients taking desipramine) and erectile dysfunction (five of eight patients taking clomipramine, three of eight patients taking desipramine). No relation between improvement in paraphilic symptoms and adverse effects was noted.

Prevalence of psychiatric comorbidity was high, with 80% of patients having at least one other diagnosis (depression, anxiety disorder, or substance use disorder).

4.7 Selective Serotonin Reuptake Inhibitor

We found one RCT of citalopram, an SSRI, for CSBD [42]. The 28 participants were men who have sex with men and who received either citalopram or placebo in a double-blind design for 12 weeks. The main outcome measure was an adapted form of the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS-CSB). Other outcome measures included were frequency of masturbation and time spent viewing pornography. There were no significant differences between those assigned citalopram and those assigned placebo for the main outcome measure Y-BOCS-CSB. Significant effects seen in the treatment group were decrease in sex drive, frequency of masturbation, and hours of pornography use per week. Only sexual adverse effects were reported; delayed ejaculation was significantly more often reported by participants receiving citalopram.

4.8 Antipsychotic Agents

Tennent et al. [41] investigated two antipsychotic agents (chlorpromazine and benperidol) and placebo in a crossover RCT design in 12 men treated in a hospital setting who had committed child sexual offenses. Each drug was administered for a 6-week period. Outcome measures were the sexual interest score, sexual activity score, and sexual attitude score, as well as penile response to sexual stimuli. Benperidol was significantly more effective than chlorpromazine and placebo in reducing the sexual interest score and sexual attitude score, although the effect was considered 'weak'. The authors concluded that benperidol is insufficient to control severe forms of problematic sexual behaviors, but can be of value if the objective is a reduction in sexual thoughts. Adverse effects were reported for each individual as extrapyramidal, drowsiness, and 'others'. Extrapyramidal adverse effects were reported by eight participants taking benperidol, two taking chlorpromazine, and one taking placebo. Drowsiness was reported by five participants receiving benperidol, six receiving chlorpromazine, and four receiving placebo.

5 Discussion

This review aimed to identify and examine RCTs of pharmacological treatments for PeD and/or CSBD. Remarkably, our literature search covering the years 2010–2021 revealed only one eligible study, and when the search was extended to include RCTs conducted during the last 50 years, 11 additional studies were identified. Given the high priority of prevention of sexual violence and high degree of distress in this patient population, this is an understudied area.

We acknowledge that studies included in this review are pioneering work in the understanding and treatment of these disorders as they are the first such studies. The overarching rationale has been to minimize overt behavior through the reduction of sexual drive/desire. However, there is a problematic heterogeneity in methodology and outcomes in the trials. Recruitment methods and participant characteristics have been mixed and included few voluntarily help-seeking participants, reducing generalizability for non-forensic populations. The low prevalence of PeD and CSBD comorbidity in the identified studies is somewhat surprising given data in recent studies indicating a much higher rate [11, 12]. With these biases in mind, results need to be validated with methodology adhering to modern clinical trial standards.

The studies we reviewed demonstrate the meager basis for current clinical decision making. There is no gold standard biological marker for diagnosis, risk to sexually offend, or treatment outcome [52]. Furthermore, small samples, different inclusion/exclusion criteria, different clinical characteristics, unclear diagnostic procedures, non-uniform reporting of adverse effects, high risk of bias, and the absence of actual between-group comparisons in two studies preclude any firm conclusions on actual efficacy on clinically meaningful outcomes.

Despite the wide heterogeneity and bias of the included studies, there are nevertheless a few conclusions to be drawn. The main finding of this review is that several studies using different samples, methodologies, and pharmaceuticals indicate that testosterone-lowering drugs reduce sexual activity in PeD [10, 34, 36, 37], although one study, using MPA, showed no difference to control treatment [39]. There is therefore some empirical support that CPA, MPA, and the GnRH antagonist degarelix reduce sexual activity in patients with PeD or CSBD. There are insufficient data to compare the efficacy of these agents. Examining specific studies for each drug, CPA appears to reduce both sexual interest and behavior, while MPA reduced only sexual fantasies. Degarelix has the fastest documented onset of action, with effect on

pedophilic interest and compulsive sexual behavior already at 2 weeks, and also in individuals rated as high risk. The difference in onset of effect between these drugs may be due to different methods of measurement (studies on CPA and MPA compared the mean across treatment phases, while the primary outcome for degarelix was measured after 2 weeks) and/or differences in mechanism of action (CPA reduces circulating testosterone and competes as an androgen receptor antagonist, whereas degarelix rapidly and effectively suppresses testosterone and gonadotrophin levels in the circulation). It remains to be explored if reduced sexual activity translates into a reduction in criminal sexual behavior for PeD, improved quality of life, or improvement or worsening of concurrent psychiatric disorders.

There was one trial each supporting the use of benperidol [41] for the reduction of sexual desire in men convicted of child sexual offenses, and citalopram for the reduction of sexual desire and activity in CSBD [42]. With no RCT replication studies, these agents still need pivotal trials before firm conclusions can be drawn. Since both drugs appear to reduce sexual desire and activity through other mechanisms than testosterone suppression, further studies of these agents may increase the pharmacological arsenal for treatment of paraphilic disorders. This may be of particular interest in patients who do not respond to suppression of testosterone or in whom it is contraindicated. Although it may also be of interest in women, it needs to be demonstrated whether sexual drive plays a similar role in paraphilic disorders in women as in men.

Although a rationale for this review was examining treatment effects on issues other than risk (such as comorbidity), we conclude that the data are too limited to draw any firm conclusions. Concerns have been raised regarding the long-term adverse effects of testosterone-lowering agents. In Europe, two compounds were approved for the treatment of paraphilic disorders—CPA and the GnRH analog triptorelin (as a 3-month formulation). Depletion of testosterone (and reducing its subsequent metabolization to estrogen) is responsible for vasomotor instability, reduced bone mineral density and muscle mass, as well as increased weight gain, insulin resistance and cardiovascular risk [53–56]. Additionally, the European Medicines Agency has issued a recommendation to restrict the use of CPA, the second-line drug in the WFSBP guidelines, due to a dose-response association with developing meningioma, stating that "The medicine should only be used for reduction of sex drive in sexual deviations in men when other treatment options are not suitable" [57]. Other testosterone-lowering agents than CPA may therefore be preferable. Degarelix was approved for prostate cancer by the US FDA in 2008 [55] and is the most recent drug used for the treatment of paraphilic disorders; data on safety/tolerability are still lacking in paraphilic disorders. GnRH analogs have been available for the treatment of advanced prostate cancer for over 30 years. Triptorelin, a synthetic GnRH analog, was, on the basis of observational studies, recently approved in Europe (3-month formulation) for the reversible decrease in plasma testosterone to castration levels in order to reduce drive in sexual deviations of adult men. Given its widespread use, including the addition of CPA, supportive RCTs would be preferable to confirm efficacy.

Other agents reviewed have adverse effects that need to be taken into account. TCAs are regarded as effective antidepressant agents, but use is limited due to adverse effects and risk of death by overdose [48]. Sexual dysfunctions caused by SSRIs appear to be attributable to activation of postsynaptic 5-HT2 receptors, and include orgasmic delay, anorgasmia, and decreased libido [58]. Benperidol has been associated with a high risk of adverse events, including extrapyramidal adverse effects, and its use is limited to a few countries [51].

More data on adverse effects and tolerability in this patient group are much needed, although some clues may be inferred from studies using the agents for other indications. Remarkably, studies of testosterone suppression in CSBD, hallmarked by high sexual activity, are virtually absent, as are treatment studies targeting other features of the disorder (e.g. loss of control, and repetitive sexual behavior despite little or no satisfaction).

In view of these limitations, the research field would benefit from conducting RCTs adhering to international standards for reporting, such as the Consolidated Standards of Reporting Trials (CONSORT) checklist [59]. RCTs are the gold standard for assessing causal effects of treatments and their magnitude [60]. Random allocation minimizes risk for confounding due to selection bias [61]. Blinding of outcome assessors, and optimally also participants, reduces bias in outcome assessments, of special importance for subjective outcomes such as self-reports and qualitative assessments that are otherwise prone to bias [59, 62]. Whether RCTs are unfeasible to conduct due to practical issues (hard-to-reach patient population) and due to the perceived ethical issue of assigning control treatment in the form of placebo or no treatment has been subject to debate [63, 64]. Although observational studies may reveal clues about large and/or rare positive or negative effects, we argue efficacy cannot reliably be demonstrated without RCTs [60]. Because large treatment effects are rare in medicine [65] and many practices are abandoned after proper trials have proved them to be harmful [66], clinical equipoise as to whether interventions are beneficial or not is genuine and generally warrants evaluation in an RCT. Not all control conditions are equal in an RCT, and some, such as waiting lists, may even be harmful [67]. With the completion of RCTs where treatment outperforms a placebo comparator, which are underway for the conditions at study here, active comparators are established

for future interventions to compete against [10, 68]. From a research ethical perspective, too many risks are involved for patients, their relatives, and potential victims, as well as for the responsible prescriber, in the treatment of patients at risk of crime acting out sexual impulses, to accept the current status quo [60].

The WSFBP guidelines proposed risk levels (likelihood and severity of offending) to guide treatment choice, but risk of offending has not been assessed in the RCTs reported here. Studies included in this review have focused on reduction of risk through reduction of sexual desire, however this assumption has not been tested by a comparison between high- and low-risk individuals. In addition to multimodal measurement of offending (self-report, collateral information, legal records), future studies would benefit from reviewing other risk domains identified in sexual offending research, such as impulsivity and low empathy [13, 69], as well as concurrent treatment needs, such as psychosocial circumstances and co-existing conditions.

It would also be important for future research to control for opportunity to act on sexual impulses, because situational factors play an important role in explaining sexual offending [70]. Access to children is relevant to PeD, as is access to sexual services for CSBD. Nuances about these conditions should also be considered. For example, the distinction has been made between exclusive (attraction only to children) and non-exclusive (attraction to both children and adults) forms of PeD, where the minority with the exclusive form might face more difficulty in managing their sexual urges and are at higher risk to sexually offend than those who can legally express their sexual desires (desires related to adults in non-exclusive individuals) [71]. One suggestion would be to consider patient-centered care, prioritizing patient-oriented goals and shared decision making, as in other fields of psychiatry.

5.1 Limitations

Limitations of this review include the literature search covering the years 2010–2020 and relying on previous reviews for earlier years, based on the assumption that the review by Thibaut et al. [17] was comprehensive and accurate. Another limitation is that our review was conducted in English only, therefore RCTs reported in other languages might not have been captured. Furthermore, we could only review studies that have been completed and reported, and thus a limitation of our review is the limitations of the studies that were included, which includes small sample sizes, relatively short follow-up periods, and heterogeneity in outcome measures. Some of the studies we reviewed had additional methodological concerns, such as the study by Hucker et al. [37], which only analyzed data of treatment completers, and the report by Kruesi et al. [38], which could be seen as tipping the scale towards finding a positive treatment effect by eliminating those with strong placebo responses and only considering those who had completed treatment. Both of these biases have led to recommendations for intent-to-treat analyses that include all participants assigned to either treatment or placebo conditions [72].

Finally, as we explained in the Methods section, we did not rely on specific diagnostic criteria as criteria for PeD have changed over time and CSBD was first introduced in ICD-11, which has only recently been launched. The advantage of this approach is that we could include studies that included equivalent clinical conditions. However, the limitation is that we introduced subjective judgment in which studies were included and the different operationalizations of the condition introduced heterogeneity in who was included in this review. We attempted to limit the influence of subjective judgment by screening studies by consensus.

6 Conclusion

More research on pharmacological treatment of PeD and CSBD is clearly needed. We recommend using large samples, reliable study designs (preferably double-blind RCTs), specific criteria for inclusion, long follow-up periods and intent-to-treat analyses. As already noted, we need RCTs that adhere to international reporting standards, and the field needs to develop standardized outcome measures.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01696-1.

Acknowledgements The authors thank Helen Sjöblom at the Biomedical Library of Gothenburg University for assistance in performing the literature search.

Declarations

Funding Open access funding provided by Karolinska Institute.

Conflict of interest Valdemar Landgren, Josephine Savard, Cecilia Dhejne, Stefan Arver, Michael C. Seto, and Christoffer Rahm report no conflicts of interest. JJ has participated in Advisory Boards for Janssen regarding esketamine for MDD with current suicidal ideation.

Availability of data and material Not applicable.

Code availability Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable

Authors' contributions JS, VL, and CR conceived and designed the analysis. JS and VL performed the literature search. JS, VL and CR

undertook the revisions. JS, VL, MS, CD, SA, JJ, and CR wrote the paper, approved the final version of the manuscript for submission, and agree to be accountable for the work.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596
2. Stein DJ, Black DW, Shapira NA, Spitzer RL. Hypersexual disorder and preoccupation with internet pornography. Am J Psychiatry. 2001;158:1590–4.
3. Kafka MP. Hypersexual desire in males: an operational definition and clinical implications for males with paraphilias and paraphilia-related disorders. Arch Sex Behav. 1997;26:505–26.
4. Kafka MP. Hypersexual disorder: a proposed diagnosis for DSM-V. Arch Sex Behav. 2010;39:377–400.
5. Carnes P. Out of the shadows: understanding sexual addiction. San Francisco: CompCare Publications; 1983.
6. Coleman E. Sexual compulsivity: Journal of Chemical Dependency Treatment. New York: Taylor & Francis; 1987. p. 189–204.
7. World Health Organization. International Classification of Diseases 11th Revision. https://icd.who.int/en. Accessed 2 Sept 2020.
8. Gerwinn H, Weiß S, Tenbergen G, Amelung T, Födisch C, Pohl A, et al. Clinical characteristics associated with paedophilia and child sex offending—differentiating sexual preference from offence status. Eur Psychiatry. 2018;51:74–85.
9. Klein V, Schmidt AF, Turner D, Briken P. Are sex drive and hypersexuality associated with pedophilic interest and cHild sexual abuse in a male community sample? PLoS One. 2015;10:e0129730.
10. Landgren V, Malki K, Bottai M, Arver S, Rahm C. Effect of gonadotropin-releasing hormone antagonist on risk of committing child sexual abuse in men with Pedophilic disorder: a randomized clinical trial. JAMA Psychiatry. 2020;77(9):897–905. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2764552. Accessed 29 Apr 2020.
11. Adebahr R, Söderström EZ, Arver S, Jokinen J, Öberg KG. Reaching men and women at risk of committing sexual offences—findings from the national Swedish telephone helpline PrevenTell. J Sex Med. 2021;18:1571–81.
12. Wittström F, Långström N, Landgren V, Rahm C. Risk factors for sexual offending in self-referred men with pedophilic disorder: a Swedish case–control study. Front Psychol. 2020;11:571775.
13. Hanson RK, Morton-Bourgon KE. The characteristics of persistent sexual offenders: a meta-analysis of recidivism studies. J Consult Clin Psychol. 2005;73:1154–63.
14. Khan O, Ferriter M, Huband N, Powney MJ, Dennis JA, Duggan C. Pharmacological interventions for those who have sexually offended or are at risk of offending. Cochrane Database Syst Rev. 2015;18(2):CD007989.
15. Långström N, Enebrink P, Laurén E-M, Lindblom J, Werkö S, Hanson RK. Preventing sexual abusers of children from reoffending: systematic review of medical and psychological interventions. BMJ. 2013;347.
16. Assumpção AA, Garcia FD, Garcia HD, Bradford JMW, Thibaut F. Pharmacologic treatment of paraphilias. Psychiatr Clin N Am. 2014;37:173–81.
17. Thibaut F, Cosyns P, Fedoroff JP, Briken P, Goethals K, Bradford JMW, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) 2020 guidelines for the pharmacological treatment of paraphilic disorders. World J Biol Psychiatry. 2020;21:412–90.
18. Turner D, Briken P. Treatment of paraphilic disorders in sexual offenders or men with a risk of sexual offending with luteinizing hormone-releasing hormone agonists: an updated systematic review. J Sex Med. 2018;15:77–93.
19. Troubled desire. Global Prevention Dunkelfeld. https://troubled-desire.com/en/. Accessed 23 Sept 2020.
20. About Us. Stop It Now. https://www.stopitnow.org/about-us. Accessed 23 Sept 2020.
21. Preventell—Help Line for Sex Addiction and Unwanted Sexuality. http://preventell.se/?lang=en. Accessed 23 Sept 2020.
22. Don't Offend India. https://dontoffendindia.org/. Accessed 23 Sept 2020.
23. Kendler KS. Toward a philosophical structure for psychiatry. Am J Psychiatry. 2005;162(3):433–40.
24. Lewis A, Grubin D, Ross CC, Das M. Gonadotrophin-releasing hormone agonist treatment for sexual offenders: a systematic review. J Psychopharmacol. 2017;31:1281–93.
25. Thibaut F, Barra FDL, Gordon H, Cosyns P, Bradford JM, WFSBP Task force on sexual disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of paraphilias. World J Biol Psychiatry. 2010;11:604–55.
26. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
27. Landgren V, Olsson P, Briken P, Rahm C. Effects of testosterone suppression on desire, hypersexuality, and sexual interest in children in men with Pedophilic disorder. World J Biol Psychiatry. 2022. https://doi.org/10.1080/15622975.2021.2014683.
28. Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004984-11/FR. Accessed 11 Jan 2021.
29. Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002161-56/PL. Accessed 11 Jan 2021.
30. Institut National de la Santé Et de la Recherche Médicale, France. Comparative Controlled Clinical Trial of Two Pharmacological Treatments of Pedophilia. ClinicalTrials.gov; 2009 Jul. Report No.: NCT00601276. https://clinicaltrials.gov/ct2/show/NCT00601276.
31. University of Minnesota. A Double-Blind, Placebo-Controlled Study of Naltrexone in Compulsive Sexual Behavior. ClinicalTrials.gov; 2012 Apr. Report No.: NCT00467558. https://clinicaltrials.gov/ct2/show/NCT00467558.
32. Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001049-15/SE. Accessed 6 Jan 2022.
33. Bancroft J, Tennent G, Loucas K, Cass J. The control of deviant sexual behaviour by drugs: I. Behavioural changes following oestrogens and anti-androgens. Br J Psychiatry. 1974;125:310–5.
34. Bradford JMW, Pawlak A. Double-blind placebo crossover study of cyproterone acetate in the treatment of the paraphilias. Arch Sex Behav. 1993;22:383–402.

35. Cooper AJ, Sandhu S, Losztyn S, Cernovsky Z. A double-blind placebo controlled trial of medroxyprogesterone acetate and cyproterone acetate with seven pedophiles. Can J Psychiatry. 1992;37:687–93.
36. Cooper AJ. A placebo-controlled trial of the antiandrogen cyproterone acetate in deviant hypersexuality. Compr Psychiatry. 1981;22:458–65.
37. Hucker S, Langevin R, Bain J. A double blind trial of sex drive reducing medication in pedophiles. Ann Sex Res. 1988;1(2):227–42.
38. Kruesi MJP, Fine S, Valladares L, Phillips RA, Rapoport JL. Paraphilias: a double-blind crossover comparison of clomipramine versus desipramine. Arch Sex Behav. 1992;21:587–93.
39. McConaghy N, Blaszczynski A, Kidson W. Treatment of sex offenders with imaginal desensitization and/or medroxyprogesterone. Acta Psychiatr Scand. 1988;77:199–206.
40. Schober JM, Kuhn PJ, Kovacs PG, Earle JH, Byrne PM, Fries RA. Leuprolide acetate suppresses pedophilic urges and arousability. Arch Sex Behav. 2005;34:691–705.
41. Tennent G, Bancroft J, Cass J. The control of deviant sexual behavior by drugs: a double-blind controlled study of benperidol, chlorpromazine, and placebo. Arch Sex Behav. 1974;3:261–71.
42. Wainberg JP, et al. A double-blind study of citalopram versus placebo in the treatment of compulsive sexual behaviors in gay and bisexual men. J Clin Psychiatry. 2006;67(12):1968–73.
43. Wincze JP, Bansal S, Malamud M. Effects of medroxyprogesterone acetate on subjective arousal, arousal to erotic stimulation, and nocturnal penile tumescence in male sex offenders. Arch Sex Behav. 1986;15:293–305.
44. Finkelstein JS, O'Dea LS, Whitcomb RW, Crowley WF. Sex steroid control of gonadotropin secretion in the human male. II. Effects of estradiol administration in normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 1991;73:621–8.
45. Knuth UA, Hano R, Nieschlag E. Effect of flutamide or cyproterone acetate on pituitary and testicular hormones in normal men. J Clin Endocrinol Metab. 1984;59:963–9.
46. Warriar N, Pagé N, Koutsilieris M, Govindan MV. Antiandrogens inhibit human androgen receptor-dependent gene transcription activation in the human prostate cancer cells LNCaP. Prostate. 1994;24:176–86.
47. Boccon-Gibod L, van der Meulen E, Persson B-E. An update on the use of gonadotropin-releasing hormone antagonists in prostate cancer. Ther Adv Urol. 2011;3:127–40.
48. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge: Cambridge University Press; 2013.
49. Pfaus JG. Pathways of sexual desire. J Sex Med. 2009;6:1506–33.
50. Saha KB, Bo L, Zhao S, Xia J, Sampson S, Zaman RU. Chlorpromazine versus atypical antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews. New York: Wiley; 2016. https://doi.org/10.1002/14651858.CD010631.pub2/full.
51. Schwarz C, Hartung B, Leucht S. Benperidol for schizophrenia. Cochrane database of systematic reviews. New York: Wiley; 2005. https://doi.org/10.1002/14651858.CD003083.pub2/full.
52. Jordan K, Wild TSN, Fromberger P, Müller I, Müller JL. Are there any biomarkers for Pedophilia and sexual child abuse? A Review. Front Psychiatry. 2019;10:940.
53. Russell N, Cheung A, Grossmann M. Estradiol for the mitigation of adverse effects of androgen deprivation therapy. Endocr Relat Cancer. 2017;24:R297-313.
54. Finkelstein JS, Lee H, Burnett-Bowie S-AM, Pallais JC, Yu EW, Borges LF, et al. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med. 2013;369:1011–22.
55. Finkelstein JS, Lee H, Leder BZ, Burnett-Bowie S-AM, Goldstein DW, Hahn CW, et al. Gonadal steroid–dependent effects on bone turnover and bone mineral density in men. J Clin Investig. 2016;126:1114–25.
56. Taylor AP, Lee H, Webb ML, Joffe H, Finkelstein JS. Effects of testosterone and estradiol deficiency on vasomotor symptoms in hypogonadal men. J Clin Endocrinol Metab. 2016;101:3479–86.
57. Dimitrova EK. Restrictions in use of cyproterone due to meningioma risk. European Medicines Agency. 2020. https://www.ema.europa.eu/en/news/restrictions-use-cyproterone-due-meningioma-risk. Accessed 2 Sept 2020.
58. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. Prim Care Companion J Clin Psychiatry. 2001;3:22–7.
59. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869–c869.
60. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. N Engl J Med. 2020;382:674–8.
61. Zhao W, Berger V. Imbalance control in clinical trial subject randomization—from philosophy to strategy. J Clin Epidemiol. 2018;101:116–8.
62. Catalogue of Bias. Catalog of Bias. 2017. https://catalogofbias.org/. Accessed 2 Sep 2020.
63. Marshall WL, Marshall LE. The utility of the random controlled trial for evaluating sexual offender treatment: the gold standard or an inappropriate strategy? Sex Abuse. 2007;19:175–91.
64. Seto MC, Marques JK, Harris GT, Chaffin M, Lalumière ML, Miner MH, et al. Good science and progress in sex offender treatment are intertwined: a response to Marshall and Marshall (2007). Sex Abuse. 2008;20:247–55.
65. Pereira TV, Horwitz RI, Ioannidis JPA. Empirical evaluation of very large treatment effects of medical interventions. JAMA. 2012;308:1676–84.
66. Herrera-Perez D, Haslam A, Crain T, Gill J, Livingston C, Kaestner V, et al. A comprehensive review of randomized clinical trials in three medical journals reveals 396 medical reversals. Elife. 2019;8:e45183.
67. Michopoulos I, Furukawa TA, Noma H, Kishimoto S, Onishi A, Ostinelli EG, et al. Different control conditions can produce different effect estimates in psychotherapy trials for depression. J Clin Epidemiol. 2021;132:59–70.
68. ISRCTN Registry. ISRCTN76841676: Prevent it: Can internet-delivered psychotherapy reduce usage of online child sexual abuse material? https://www.isrctn.com/ISRCTN76841676. Accessed 15 Sept 2021.
69. Savard J, Hirvikoski T, Öberg KG, Dhejne C, Rahm C, Jokinen J. Impulsivity in compulsive sexual behavior disorder and pedophilic disorder. J Behav Addict. 2021;10(3):839–47.
70. Seto MC. The motivation-facilitation model of sexual offending. Sex Abuse. 2019;31:3–24.
71. Seto MC. Pedophilia and sexual offending against children: theory, assessment, and intervention. 2nd ed. Washington, DC: American Psychological Association; 2018.
72. Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials. 2000;21:167–89.