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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

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Abstract

Background: Different pharmacological agents are used in the treatment of paraphilic disorders in sexual offenders or men with a risk of sexual offending, with Luteinizing-Hormone-Releasing-Hormone-Agonists (LHRH-agonists) being the agents introduced more recently into treatment regimes.

Aim: This systematic review aims at summarizing the relevant literature concerning the treatment of paraphilic disorders in sexual offenders with LHRH-agonists. The present manuscript is an update of the systematic review published in 2003 by Briken and colleagues.

Methods: The databases PubMed and Google Scholar were searched for literature published between January 2003 and October 2017 using the following key words: *LHRH-agonists, GnRH-agonists, antiandrogens AND paraphilia, pedophilia, sex offenders.*

Outcomes: Evaluation of the effectiveness and side effects of LHRH-agonist treatment in sexual offenders with a paraphilic disorder.

Results: After screening for duplicates and applying specific selection criteria the search revealed a total of 24 eligible studies reporting on a sample of 256 patients. There is still growing evidence that LHRH-agonists are more effective than steroidal antiandrogens in lowering paraphilic sexual thoughts and behaviors. Current research is now also based on methods that may be less susceptible to faking, for example eye-tracking, brain imaging and viewing time measures. Side effects occurring most frequently are fatigue, hot flashes, depressive mood, weight gain, high blood pressure, diabetes, gynecomastia, loss of erectile function, and a loss in bone mineral density.

Clinical Implications: Although LHRH-agonists seem to be the most effective drugs in the treatment of paraphilic fantasies and behaviors, they should be reserved for paraphilic patients with the highest risk of sexual offending because of their extensive side effects.

Strengths & Limitations: This systematic review considers all types of research about LHRH-agonist treatment in paraphilic disorders thereby providing a complete overview about the current state of research. However, most studies are case-reports or observational studies and randomized controlled clinical trials are completely missing so far.

Conclusions: LHRH-agonists are a useful treatment form when combined with psychotherapy in paraphilic patients with the highest risk of sexual offending. However, throughout treatment close monitoring of side effects is needed and ethical concerns always have to be kept in mind.

Key words: GnRH-agonists, LHRH-agonists, sexual offender, treatment, antiandrogens, paraphilia, pedophilia, paraphilic disorder, pedophilic disorder

Introduction

In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) paraphilic interests are defined as "any intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physiologically mature, consenting human partners".[1] To be differentiated from paraphilic interests are paraphilic disorders that additionally cause distress or impairments in normal, daily functioning to the patient or harm to others.[1] Although discussed controversially the distinction between paraphilic interests and disorders could lead to a destigmatization and depathologization of non-normative sexual interests.[2] Prevalence rates of a paraphilic disorder around 50% have been found in sexual offenders, with pedophilic disorder (between 40% and 47%) and sexual sadism disorder (between 6% and 13%) being among the diagnoses found most frequently.[3–5] A deviant sexual preference is one of the strongest predictors for sexual recidivism in adult as well as adolescent sexual offenders.[6]

Due to the crucial role testosterone plays in male sexuality, it may be one significant factor contributing to the etiology of paraphilic urges and behaviors.[7] Physiologically testosterone is produced in the Leydig cells of the testes and to a small amount also in the adrenal cortex and the brain.[8] Testosterone production in the brain is either de novo from cholesterol or through transformation of classical steroids such as progesterone that enter the nervous system through the blood stream.[9] Its production and secretion is controlled by the hypothalamic-pituitary-gonadal axis and follows a negative feedback mechanism. Testosterone receptors were found in different brain areas of humans or in animals, for example the corpora mammilaria, the hippocampus, the amygdala, the orbitofrontal cortex, the inferior temporal cortex, and hypothalamus. According to the four-component model of sexual arousal proposed by Stoleru

and colleagues these brain structures are involved in cognitive (e.g., the orbitofrontal cortex), emotional (e.g. the amygdala), and motivational (e.g. the hypothalamus) processes that take place during sexual arousal and overt sexual behaviors.[7,10–17] Alterations in these brain areas could lead to changes in sexual arousal patterns, including sexual arousal to non-normative objects or sexual practices. Underscoring this suggestion imaging studies have found structural and functional alterations in most of the above-mentioned brain areas in sexual offenders with a pedophilic disorder.[18–20] In structural imaging studies reduced gray matter volumes in the orbitofrontal and dorsolateral prefrontal cortex, insula, ventral striatum, cingulate gyrus, parahippocampal gyrus, and the right amygdala were found in pedophilic sexual offenders compared to healthy controls.[18,19] Furthermore, using functional magnetic resonance imaging (fMRI) decreased activity in the left dorsolateral prefrontal cortex, the right occipital and right parietal cortex, the hypothalamus, and the insula were reported in pedophilic sexual offenders during the presentation of sexual stimuli.[20]

However, it is not clear in how far changed testosterone concentrations are associated with these changes in brain activation patterns and subsequently with paraphilic behaviors or sexual offending. Giotakos et al. found higher plasma testosterone levels in a sample of sexual offenders against adults but not in sexual offenders against children (not necessarily with a paraphilic disorder) compared to healthy controls. However, in all three groups the plasma testosterone level was still within the normal range. Studer and colleagues reported a positive association between higher serum testosterone levels and sexual recidivism in a sample of 501 sexual offenders (also not necessarily with a paraphilic disorder).[21,22] In their study 14.5% of the sexual offenders had testosterone concentrations above the normal range, while the authors estimated that a rate of 2.5% would be expected for the general population.[22] Other studies, however, did not find an association between serum testosterone concentrations and sexual

recidivism and some found even significantly higher serum testosterone levels in healthy controls compared to child sexual abusers.[23,24] A recent meta-analysis concluded that serum testosterone concentrations are not altered in sexual offenders, but sexual offenders against adults may tend to have higher serum testosterone concentrations than child sexual abusers, however, these are usually still within the normal range.[25] Furthermore, many studies did not distinguish between sexual offenders with a paraphilic disorder and those without a paraphilic disorder. The authors suggested that increased testosterone concentrations may lead to more violent and antisocial rather than more paraphilic behaviors and increased antisocial behaviors may in turn facilitate committing sexual offences in certain individuals.[21,25,26] Nonetheless, previous research has suggested that suppressed serum testosterone concentrations might not only cause decreased sexual functioning but also a reduced frequency of paraphilic fantasies and behaviors.[27,28]

Besides testosterone, dopamine and serotonin also play an important role in male sexuality. While dopamine is mainly involved in processes of sexual excitation, serotonin is associated with sexual inhibition processes.[29] Dopamine receptors relevant for sexual functioning can be found in mesolimbic, nigrostriatal, and hypothalamic brain structures[29]. Some case studies have found an association between the onset of paraphilic fantasies and behaviors and treatment with dopamine enhancing drugs in patients with Parkinson disease.[30] However, no differences in genetic polymorphisms in dopamine receptor or dopamine transporter genes were found between sexual offenders with a paraphilic disorder and healthy controls.[31]

After an extensive review of the literature published up until 2009 the current guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) came to the conclusion to use selective-serotonin-reuptake-inhibitors (SSRIs), steroidal antiandrogens (cyproterone acetate; CPA and medroxyprogesterone acetate; MPA), and Luteinizing-Hormone-Releasing-

Hormone-Agonists (LHRH-agonists) in the treatment of paraphilic disorders.[32] Although antipsychotics lead to alterations in dopamine metabolism and some small studies have shown that antipsychotics can lead to a reduction of paraphilic fantasies and behaviors, they should only be applied if comorbid diagnoses justify their use.[32] Furthermore, in patients with a comorbid depressive or obsessive-compulsive disorder SSRIs should be preferred over other agents.[32–37] In antisocial individuals a recent Cochrane review found that only the anticonvulsants phenytoin, carbamazepine, and valproate were more effective than placebo treatment and led to a reduction in aggressive behaviors, including sexually aggressive behaviors. However, all included studies were conducted with general rather than explicitly sexual offenders.[38] Concerning comorbid Attention-Deficit-Hyperactivity-Disorder there is evidence from one case series that psychostimulants combined with SSRIs show some efficacy in lowering paraphilic fantasies.[39] In paraphilic individuals with a comorbid bipolar disorder there is some evidence for the effectiveness of mood stabilizers.[40,41] Furthermore, in a retrospective study with bipolar sexual offenders it was found that divalproex sodium led to a significant decrease of manic symptoms, however, no changes in paraphilic symptoms were reported. Nevertheless, divalproex sodium could be considered in sexual offenders whose offending has been associated with manic symptoms.[42]

Steroidal antiandrogens and LHRH-agonists have in common that they suppress serum testosterone concentrations via different mechanisms and are thus summarized under the term androgen deprivation therapy (ADT). Cyproterone acetate binds to androgen receptors and competitively replaces testosterone and 5-α-dihydrotestosterone from androgen receptors thereby inhibiting their effect on sexuality and other body functions. Furthermore, CPA acts as a progesterone causing an inhibition of LHRH secretion from the hypothalamus leading to decreased plasma testosterone levels.[43] Medroxyprogesterone acetate also reduces LHRH

secretion from the hypothalamus via a negative feedback mechanism. Moreover, MPA leads to a decline in serum testosterone concentrations by inducing the production of the enzyme testosterone-α-reductase and by increasing the binding of testosterone to the testosterone hormone-binding globulin, reducing the amount of freely available testosterone in the body.[32] Different studies, including randomized controlled trials, have shown that CPA and MPA lead to a reduction of paraphilic urges, behaviors, and fantasies.[44–48] However, all controlled studies have been conducted more than 25 years ago.

LHRH-agonists are the agents introduced most recently into treatment regimes of paraphilic disorders in sexual offenders. Initially, they were developed for the treatment of prostate cancer and are still used for this indication.[49] Currently, buserelin, goserelin, leuprolide, and triptorelin are available. The first three agents have specific amino acid substitutions in positions six and ten in the natural LHRH decapeptide structure, while triptorelin has a single amino acid substitution at position six.[49] Usually LHRH-agonists are given as a depot via intramuscular or subcutaneous injections every one to six month, whereby concentrations differ between preparations (buserelin: 6.3mg s.c./2-month; 9.45mg s.c./3-month; goserelin: 3.6mg s.c./1-month, 10.8mg s.c./3-month; leuprorelin: 7.5mg i.m./1-month; 22.5mg i.m./3-month; 30mg i.m./4-month; 45mg i.m./6-month; triptorelin: 3.75mg i.m./1-month; 11.25mg i.m./3-month; 22.5mg i.m./6-month).[32,50] In 2007, triptorelin (3-month formulation/i.m.) has received official approval in the European Union for the treatment of paraphilic disorders. Although not officially approved for the treatment of paraphilic disorders by the Federal Drug Administration of the U.S., in clinical practice LHRH-agonists are applied in the U.S. and Canada as well.[51] As hormonal agonists these agents mimic the function of LHRH in the pituitary gland and initially lead to a rapid increase of LH and serum testosterone levels during the first two weeks of treatment ("flare-up effect"). The permanent stimulation subsequently causes a desensibilization

and down regulation of LHRH receptors in the pituitary gland followed by a decreased testosterone synthesis. This mechanism ultimately leads to serum testosterone concentrations below castration level (usually defined as serum testosterone concentrations below 20 – 50ng/dl).[49] Through these mechanisms LHRH-agonists have proven to be able to reduce the frequency of paraphilic as well as non-paraphilic fantasies and behaviors.

In a previous systematic review, summarizing the relevant literature on LHRH-agonists in the treatment of paraphilic disorders in sexual offenders or men with a risk of sexual offending between 1980 and 2002 Briken and colleagues identified 13 studies reporting on 118 patients.[52] The authors inferred that due to the more intense suppression of serum testosterone concentrations following LHRH-agonist treatment, these agents may be more effective in lowering paraphilic fantasies and behaviors than steroidal antiandrogens and SSRIs. Thus, LHRH-agonists could be considered in cases in which steroidal antiandrogens and SSRIs have failed or were accompanied by too many side effects. Briken et al. concluded that more systematic studies are needed and future research should use more objective methods to assess clinical outcomes (e.g. penile plethysmography; PPG).[52] However, it has to be noted that PPG is a highly invasive measure and it is unclear in how far PPG outcomes can predict sexual recidivism in men with paraphilic disorders under LHRH-agonists.[53–55] Just recently, Schmucker and Lösel as well as Khan and colleagues attempted to meta-analyze the relevant literature on the effectiveness of pharmacological agents in sexual offender treatment, however, they failed in so far as both did not find any studies evaluating the use of LHRH-agonists meeting their inclusion criteria.[56,57] Thus, a systematic review including all types of published studies is needed to provide an overview about the current state of research concerning the treatment effectiveness and side effects of LHRH-agonists in sexual offenders with a paraphilic disorder. The present systematic review updates the review conducted by Briken and colleagues.[52]

Method

The databases PubMed and Google Scholar were searched for studies published between January 2003 and October 2017 using the following key words: *LHRH-agonists, GnRH-agonists, antiandrogens AND paraphilia, pedophilia, sex offenders.* This search revealed a total of 7910 publications in the two databases (see figure 1). All publications in English or German language were included if they contained original data on the treatment effectiveness or on side effects of LHRH-agonist treatment in sexual offenders with a paraphilic disorder. If two or more articles reported comparable findings on the same sample only the more recent study was considered.

*** Please insert figure 1 about here ***

Results

Our search revealed 24 original studies: $n = 17$ case reports, $n = 5$ cross-sectional studies, $n = 1$ quasi-experimental study, and $n = 1$ repeated measures, non-randomized, masked clinical trial.[43,58–80] In total, these studies reported about 256 patients who were treated with either leuprorelin, goserelin or triptorelin for different paraphilic disorders, mainly a pedophilic disorder. One, so far unpublished study was identified through personal contacts of the authors.[80]

Information on the number of patients, their diagnoses, the applied dose of the LHRH-agonist, as well as any side effects occurring under LHRH-agonist treatment can be found in table 1. Furthermore, it is noteworthy that in the meanwhile the World Federation of Societies of Biological Psychiatry (WFSBP) have published clinical guidelines on the pharmacological treatment of adolescent and adult sexual offenders.[32,81]

*** Please insert table 1 about here ***

Evaluation of effectiveness and side effects of LHRH-agonist treatment in adolescent (or young adult) sexual offenders

Leuprolide

Bussmann and Finger reported about five pedophilic sexual offenders from a forensic-psychiatric hospital in Berlin, Germany.[61] Two of the patients were previously treated with CPA, however, treatment had to be stopped because of side effects, especially osteoporosis. Signs of osteoporosis were reversible to some amount under LHRH-agonist treatment. All five patients reported a decrease of sexual urges and deviant sexual fantasies, increased behavioral control, and increased victim empathy.[61]

For the first time the rate of recidivism was compared between a group of sexual offenders being treated with LHRH-agonists and cognitive behavioral therapy (CBT; $n = 25$) and a group of sexual offenders being treated with CBT only ($n = 22$).[80] All sexual offenders receiving LHRH-agonists were diagnosed with a paraphilic disorder and they had a significantly higher risk measured with the Static-99R compared to the CBT only group.[80,82] All sexual offenders were treated in a community treatment program. Minimum LHRH-agonist treatment duration was 12 month, and average follow-up time after release from prison was 7.1 years. Despite their higher risk, sexual offenders treated with LHRH-agonists had a lower rate of recidivism than the CBT only group, at least concerning violent recidivism. None of the sexual offenders from the LHRH-agonist group and also only one of the CBT-only group recidivated with a sexual offence.[80]

In a prospective, cross-sectional study Koo et al. compared the treatment effectiveness and the kinetics of serum testosterone recovery in a sample of 56 paraphilic sexual offenders.[76] Of the included patients 38 were treated with LHRH-agonists for 3 month, while the remaining were treated for 6 month. In both groups more than 70% of the paraphilic sexual offenders reported a reduction of the frequency and intensity of paraphilic sexual thoughts and fantasies. No differences in the frequency of side effects were found between the groups. Terminating treatment led to an immediate upsurge of serum testosterone levels in the group being treated for only three month. Two month after treatment was stopped serum testosterone levels were even higher than at the beginning of treatment. In contrast, serum testosterone concentrations increased only gradually in patients who were treated for six month. In month five, after treatment was terminated, a rapid upsurge in serum testosterone concentrations was observed in these patients as well and testosterone concentrations were higher compared to baseline.[76] In the group treated for three month scores on the Wilson's sex fantasy questionnaire were comparable to the baseline scores one year after therapy was ended, while the scores remained reduced in the group being treated for six month. This accounted also for the sadism subscale of the questionnaire.[76]

In another cross-sectional study Ahn et al. found significantly reduced scores in the Wilson's sex fantasy questionnaire in nine paraphilic sexual offenders after three month of LHRH-agonist treatment.[78] However, scores in the Rape Myth Acceptance Scale and the Endorsement of Violence Scale remained unchanged.

Schober et al. included five male pedophilic patients in a prospective, repeated measures, nonrandomized, masked study.[79] All patients received a LHRH-agonist depot injection at baseline and repeated injections at months 1, 4, 7, and 10. After one year LHRH-agonist treatment was stopped and exchanged to placebo treatment without informing the patients.

Placebo was given for 12 month. Treatment effectiveness was measured using self-report, Abel Assessment, PPG, and psychological testing at baseline, and in three-month intervals throughout the whole study period. During LHRH-agonist treatment all patients reported decreased sex drive, decreased pedophilic sexual urges, and decreased masturbation frequencies. In two patients pedophilic sexual urges reoccurred after three month and in one patient after six month on placebo. These patients were put on LHRH-agonist treatment again. The remaining two patients stayed on placebo for the whole 12 months. In all five subjects the Abel Assessment as well as the PPG measure generally indicated no change in pedophilic sexual interests while being treated with LHRH-agonists. However, penile responses to pedophilic stimuli were lower under LHRH-agonist treatment compared to baseline or during placebo treatment.[79]

Different authors studied brain activation patterns in pedophilic sexual offenders under LHRH-agonist treatment. Schiffer et al. evaluated the brain activation pattern of a pedophilic sexual offender using functional magnetic resonance imaging (fMRI) in response to sexually arousing visual stimuli (images of nude girls and women) and to neutral visual stimuli (images of dressed girls and women) after being treated with a LHRH-agonist for three years.[65] The patient reported a 90% decrease of deviant sexual fantasies and masturbation frequency after nine-month of treatment. Viewing images of dressed girls led to a significantly stronger activation in the right prefrontal cortex, the left subgenual anterior cingulate, and the bilateral superior temporal cortex in comparison to viewing pictures of nude girls. Furthermore, viewing images of undressed girls led to a stronger activation in the dorsolateral prefrontal cortex, the superior parietal lobule, both middle occipital gyri, and the superior temporal cortex in contrast to the activation pattern found while viewing undressed women. Compared to a group of unmedicated pedophilic sexual offenders from a previous study of Schiffer and colleagues a weaker activation of the

hypothalamus, the amygdala, insula, substantia nigra, or the hippocampus was found in the patient from the present study while viewing undressed children.[83]

Using a similar paradigm Habermeyer and colleagues reported on a 43-year old sexual offender who was diagnosed with a non-exclusive pedophilia (attracted to men and boys). After LHRH-agonist treatment was initiated the participant reported about a reduction of sexual fantasies and sexual arousal and rated images of boys in bathing suits as significantly less sexually attractive compared to the pre-treatment ratings. Comparing the brain activation patterns while viewing images of boys in bathing suits pre- and post-treatment, a stronger activation of the right amygdala, the right superior frontal gyrus, the right precentral gyrus, and of the right superior temporal gyrus was found pre-treatment.

Moulier et al. compared the brain activation patterns of a 46-year old man diagnosed with pedophilia and a 47-year old heterosexual male healthy control.[69] Both participants viewed images of male and female children and of female adults wearing swimsuits as well as images of dressed female children and adults. Functional magnetic resonance imaging and PPG measurement was performed before and again five months into therapy. After five month of treatment the patient reported no more pedophilic sexual fantasies and desires and penile responses to images of boys and girls in swimsuits had decreased markedly. Before treatment the patient showed a stronger activation in the left calcarine fissure, the left anterior insula, the caudal anterior cingulate cortex and the left cerebellar vermis while viewing images of boys compared to the control subject. Five month into treatment no differences in brain activation patterns could be observed between the patient and the control subject.[69]

Triptorelin

In a case report of a male pedophilic sexual offender with comorbid cocaine and opiate dependence, alcohol abuse, and borderline intellectual functioning Briken et al. reported for the first time a relapse with a sexual offence in a patient treated with LHRH-agonists.[60] Although the patient himself described that he had better control over his paraphilic urges, his sexual interest in male juveniles remained unchanged and even increased during the course of therapy. This finally resulted in another sexual offence against a boy after one year of therapy. After disclosure to the police and in therapy the patient tried to attempt suicide but survived.[60]

In a male patient with mild mental retardation who had been convicted for child sexual abuse (no paraphilic disorder diagnosis), previous treatment approaches using antipsychotics and SSRIs did not have an influence on the patient's sexual behavior. The patient reported a marked decrease in sexual preoccupation after LHRH-agonist treatment was initiated.[63] Despite being treated with bisphosphonates and vitamin D the patient's bone mineral density steadily decreased, so that LHRH-agonist treatment had to be stopped after 37 month. After ending treatment pedophilic sexual fantasies almost immediately returned.[63]

Huygh et al. described the case of a 48-year-old pedophilic man who was convicted because of multiple child sexual abuse offenses. Before treatment was started a full blood count revealed a serum testosterone level at the lower end. [64] After LHRH-agonist treatment was commenced serum testosterone levels remained unusually high and LH and FSH levels were also above the norm. A MR scan of the brain showed a large adenoma of the pituitary gland that had to be resected because of the risk of pituitary apoplexy under LHRH-agonist treatment. After resection testosterone levels fell to castration level.[64]

A research group reported their experiences with treating self-identifying, help-seeking pedophiles (actually not accused, convicted or under probation because of sexual offending) from

the German Dunkelfeld project between 2005 and 2010.[58,84] Of the 111 men fulfilling the criteria for pedophilia or paraphilia NOS seven were treated with LHRH-agonists at any time throughout the program. Only three men took the medication for more than eight weeks. Two patients reported fewer empathy deficits, better sexual self-control, and less deviant sexual fantasies. The third patient did not report any changes in the frequency of pedophilic sexual fantasies.[58]

Thirty sexual offenders with a paraphilic disorder (mainly pedophilia) were treated with LHRH-agonists at a forensic outpatient center in Berlin, Germany.[68] Three patients developed osteoporosis and all three patients had to be treated because of calcium oxalate-monohydrate urinary stones.[68] Voß et al. described their experiences concerning treatment withdrawal trials in 15 of these 30 patients.[77] In all cases LHRH-agonist withdrawal was supported by psychotherapy and supervised by an experienced clinician. The mean follow-up time after ending LHRH-agonist treatment was 18 month (SD = 9 month). In nine patients serum testosterone concentrations normalized after ending LHRH-agonist treatment, however, the duration to normalization of serum testosterone levels varied between 2 and 18 month. Body hair, physical strength, and testicle volume increased immediately after LHRH-agonist therapy was ended, however, erectile functioning remained suppressed despite normal testosterone concentrations. Most patients also described an increase of paraphilic fantasies and urges after treatment was ended.[77]

Ho et al. reported on seven sexual offenders (not necessarily with a paraphilic disorder) treated with LHRH-agonists at a maximum-security hospital.[74] In all patients a reduction of sexual and violent incidents at the hospital was observed and all patients reported decreased sexual fantasies, desire and arousal. Two of the seven patients underwent additional PPG recordings. Both patients displayed significantly reduced levels of arousal.[74]

In a case study of a 47-year old pedophilic sexual offender Jordan et al. examined the effect of LHRH-agonist treatment using eye tracking and fMRI.[66] After three month of treatment the patient reported no more pedophilic sexual fantasies. Eye-tracking measurements were conducted three weeks before LHRH-agonist treatment and four month after treatment start, while fMRI scans were performed two month before and four month after treatment start. During eye-tracking the patient was confronted with either a girl together with an adult female or a boy together with an adult male image on a computer screen, while eye movements were recorded. During the fMRI sessions the same images were subliminally presented to the patient for 16.7ms followed by a neutral mask stimulus for 483.3ms. Before treatment the patient had a significantly longer relative fixation time (controlled attentional processes) for girl images than for women images in the eye-tracking experiment. Four month into treatment he showed longer fixation times for adult females than for girl stimuli. Furthermore, the patient showed a lower fixation latency (automatic attentional processes) for images of girls compared to images of females at least before treatment. After four month of treatment this difference was not significant anymore. Concerning the patient's brain activation patterns he showed a stronger activation in the bilateral cerebellum, bilateral fusiform gyrus, lingual gyrus, calcarine gyrus and the left inferior temporal gyrus to subliminally presented images of girls before as compared to four month into treatment. The bilateral superior and middle occipital gyrus, the superior parietal lobule, and the right lingual gyrus and precuneus showed stronger activations during the second as compared to the first measurement.[66]

Goserelin

In a case-report Beier et al. described a 39-year old self-identified pedophilic patient with an exclusive pedophilic disorder sexually attracted to boys. The patient worked as a teacher for

young boys in the sexually preferred age range at a youth center. Although he had sexually abused several young boys, he was so far not convicted for any sexual offence. The patient clearly suffered from his pedophilic sexual desires and chose to be treated with a LHRH-agonist, after treatment with CPA did not lead to any reduction in pedophilic sexual desire. After LHRH-agonist treatment was initiated the patient reported about a significant reduction of his sexual urges and stated that the risk of sexually abusive behaviors had vanished.

Polak and Nijman reported about four sexual offenders, not necessarily with a paraphilic disorder, treated with LHRH-agonists. In these patients the number of sexual and non-sexual aggressive acts decreased markedly.[71] One patient was previously treated with CPA, however, treatment had to be terminated due to severe side effects. After changing medication to a LHRH-agonist serum testosterone concentrations dropped even further and the patient experienced no more side effects.[71]

Type of LHRH-agonist not specified

Of all 79 sexual offenders who were placed in a forensic-psychiatric hospital in Berlin, Germany, between 1998 and 2005, 32.9% were treated with LHRH-agonists at any time during the observed period.[75] All of the sexual offenders treated with pharmacological agents were diagnosed with a paraphilic disorder. In 58% of the patients side effects were observed with fatigue, headache, sleep disorders, hot flashes, depression and loss of bone mineral density being observed most frequently. Patients being treated with LHRH-agonists or CPA were considered for home leave steps earlier than unmedicated patients.[75]

In an observational study Turner et al. assessed the frequency of LHRH-agonist prescription for sexual offenders in German forensic psychiatric institutions.[43] Of the 611 sexual offenders included in the study 65 were treated with LHRH-agonists. Paraphilic disorder

diagnoses were not evaluated in that study. Of those being treated pharmacologically, 75.4% reported a reduction of the frequency of sexual thoughts. A loss of bone mineral density was only observed in those patients being treated with LHRH-agonists and not during treatment with CPA. Side effects occurring most frequently during LHRH-agonist treatment were: hot flashes, pain at the site of injection, decreased body hair, and weight gain.[43]

Evaluation of effectiveness and side effects of LHRH-agonist treatment in adolescent (or young adult) sexual offenders

Park and colleagues as well as Fosdick and Mohiuddin each reported about one patient with autistic disorder and mental retardation who was treated with LHRH-agonists due to sexually aggressive behaviors.[62,70] The patients in both studies were not diagnosed with a paraphilic disorder. The patient of Park et al. was described as showing a high frequency of masturbatory behavior (4-5 hours/day), repeated genital exposure and sexually aggressive behavior against different family members beginning at 18 years of age.[70] Treatment with valproate and olanzapine led to an initial improvement of symptoms but was accompanied by a variety of side effects, especially weight gain. After changing the antipsychotic medication sexual and aggressive symptoms increased again and a LHRH-agonist was given additionally. This dual treatment led to a complete decline in masturbatory and significantly less sexually aggressive behaviors. Besides a further weight gain the patient showed no other side effects.[70] The patient described by Fosdick and Mohiuddin was 11 years of age when sexually aggressive behaviors towards other children started.[62] Different pharmacological agents (e.g. different antipsychotics, benzodiazepines, fluoxetine, methylphenidate) had no effect on sexual aggression, while LHRH-

agonist treatment led to a clear decrease of sexual aggression. At 19-years of age therapy was terminated; however, sexually aggressive behaviors immediately reoccurred.[62]

In six patients under 20-years of age diagnosed with pedophilia or a paraphilia NOS and mild to moderate mental retardation Saleh et al. found a decreased frequency of paraphilic thoughts and better control of paraphilic fantasies during LHRH-agonist treatment.[73] Side effects were not observed in any of the six patients. In one patient pedophilic sexual fantasies returned after 12 month of treatment. This patient was additionally given MPA leading to a complete disappearance of pedophilic sexual fantasies. No side effects occurred under this dual treatment.[73]

Saleh described a 19-year-old hypersexual patient who was diagnosed with a paraphilia NOS and was charged for indecent exposure and public masturbation.[72] Prior to treatment and two times during LHRH-agonist treatment the patient was examined using PPG. Prior to treatment the patient showed the highest arousal to stories of adult female rape and exhibitionism. After one as well as after five month of treatment and consistent with the patient's hormonal profile and self-description he did not show sexual arousal in the PPG recordings to any of the stories he listened to (adult female or male consensual sex, sex with female or male child, adult female rape). The patient reported no side effects while taking the medication.[72]

Discussion

Applying LHRH-agonists usually leads to serum testosterone concentrations below castration level. In contrast, low dose CPA or MPA treatment (e.g., 50 – 100mg/day) is typically followed by a moderate reduction of serum testosterone concentrations. Because serum testosterone concentrations below castration level lead to a pronounced reduction not only of paraphilic fantasies and behaviors but also of conventional, non-paraphilic sexual activity and desire, LHRH-agonists should be used in most severe cases of (paraphilic) sexual offenders only

as is suggested in current treatment guidelines.[32,52] In less severe cases it would be ethically and even legally questionable to prevent the possibility of having a conventional sexual life as such an approach would be in conflict with Article 12 of the European Convention on Human Rights and Article 16 of the Declaration of Human Rights of the United Nations ("the right to found a family").[85] Factors that could indicate a high risk in patients that are typically considered in clinical practice, include a history of sexual offender treatment failures, sexual violations while under community supervision or in an institution, use of force in sexual crimes, and CNS dysfunctions.[86] Furthermore, LHRH-agonists should preferably be restricted to sexual offenders with a paraphilic disorder. Treating those without a disorder would be a mere punishment and would not be compatible with medial ethics.[87]

Studies applying self-report measures are rather promising concerning the effectiveness of LHRH-agonists. However, the findings of recently published studies employing indirect or psychophysiological measures such as viewing-time, eye-tracking, or PPG were less clear. While all patients in the study of Schober et al. indicated a clear decrease of pedophilic sexual fantasies on the self-report measure, no consistent decrease was found in the PPG measurements.[79] This discrepancy could be due to the self-report measures being more susceptible to a social desirable answering style and impression management strategies. Although it is obvious that using PPG or other indirect or psychophysiological measures on a regular basis is not possible due to the high temporal, technical and monetary expenditure, it could still be requested that relying solely on self-report is also not a preferable solution, at least in diagnostically challenging cases. These include, for example, patients with lacking introspective abilities, e.g. those with mental retardation, patients who present with a high likelihood of a social desirable answering style, or patients in complete denial of their paraphilic fantasies and urges.

Current brain imaging studies found reduced activations of brain structures involved in the visual processing of sexual stimuli (e.g., the calcarine fissure, and calcarine gyrus, the anterior insula, the lingual gyrus, and the inferior temporal gyrus), involved in motivational processes (e.g., caudal anterior cingulate cortex, frontal gyrus, precentral gyrus), and most importantly involved in the emotional appraisal of sexual stimuli (e.g., amygdala, insula, cingulate cortex, and hypothalamus) following LHRH-agonist treatment in paraphilic sexual offenders.[65–67] Furthermore, subcortical brain areas that lead to a suppression of the cortical processing of preferred sexual stimuli were also modulated by LHRH-agonists, suggesting that LHRH-agonists alter top-down as well as bottom-up processes.[65] Furthermore, these findings show that LHRH-agonists might influence most components relevant to sexual behavior according to the model of Stoleru and colleagues.[17] As LHRH-agonists seem to have a significant effect on brain structures involved in the emotional evaluation of sexual stimuli, this could be a hint that LHRH-agonists do not simply lead to a decline in sexual desire and functioning but might also lead to a changed appraisal of paraphilic stimuli. However, this suggestion has so far not been tested empirically.

Although LHRH-agonists usually lead to a more pronounced reduction of serum testosterone concentrations than steroidal antiandrogens, they are not necessarily accompanied by more side effects. Some uncontrolled studies have even found less side effects during LHRH-agonist treatment.[43,61,71] Nevertheless, LHRH-agonists still have a broad spectrum of side effects, for example fatigue, headache, sleep disorders, hot flashes, depressive mood, pain at the site of injection, hepatocellular dysfunctions, testis size reduction, gynecomastia, loss of erectile function, and a loss in bone mineral density. Furthermore, LHRH-agonist treatment is associated with an increased risk for cardiovascular events.[88] An increase in LDL and triglyceride levels, an increase in insulin resistance, a decrease in glucose tolerance, and the weight gain usually observed following LHRH-agonist treatment, enhance the likelihood to develop atherosclerosis

and coronary artery disease, predisposing the individual to suffer a myocardial infarction or stroke.[89] However, it has to be taken into consideration that these findings stem from studies with prostate carcinoma patients. To identify patients at risk for cardiovascular events a comprehensive medical evaluation should be conducted before treatment and at regular intervals during treatment, at least every three to six month. Examinations should include full blood counts, blood pressure measurements, electrocardiogram, and regular weight measurements.

As shown by current research a loss of bone mineral density can be found especially during LHRH-agonist treatment.[43,68] Thus, bone mineral density should be measured at baseline and in the following at least every two years. As suggested by a recent case report osteopenia or osteoporosis following LHRH-agonist treatment might also cause the development of calcium-oxalate urinary stones that could ultimately lead to acute or chronic post renal kidney failure.[68] Furthermore, in patients that do not show a decrease in serum testosterone, serum LH and FSH levels after the first four weeks of LHRH-agonist treatment, conducting a brain MR scan should be considered to identify structural abnormalities, especially anomalies of the pituitary gland due to the risk of pituitary apoplexy under LHRH-agonist treatment.[64] Importantly, pituitary apoplexy can occur in hormone-active but also in hormone-inactive adenomas, underlining that measurements of serum hormone concentrations might not be sufficient to detect patients at risk (the patient described in the present review had normal TSH, T4, Prolactin, LH, FSH, Testosterone, ACTH, and Cortisol serum concentrations before LHRH-agonist treatment was initiated).[64,90] Pituitary apoplexy is a clinical syndrome characterized by sudden headache, visual impairment, and opthalmoplegia caused by the enlargement or hemorrhage of a pituitary adenoma.[90] Although pituitary apoplexy following LHRH-agonist treatment is a very rare condition and only a few case reports have been published so far (mainly in patients with prostate

cancer but now also in a patient who has been treated with LHRH-agonists for reduction of paraphilic behaviors), it is a possibly life threatening condition.[90]

Besides physical examinations all patients should be evaluated on regular time intervals by a trained (forensic) psychiatrist and/or expert in sexual medicine. Although it was shown that psychiatric evaluations are already conducted on a regular basis, time intervals seem to vary considerably.[87] Besides evaluating frequently occurring psychiatric side effects of LHRH-agonists, like for example depressive mood or sleep disturbances, one current case report has shown that suicidal ideations and attempts can also occur.[60] Another advantage of regular psychiatric evaluations would be the possibility to closely monitor therapeutic success and would guarantee that the right time point to end ADT would not be missed. In some patients paraphilic symptomatology might return soon after terminating LHRH-agonist treatment. This seems to account especially for patients with mental retardation and for those who have been treated with LHRH-agonists for just a short time period. It was shown that terminating LHRH-agonist application after only three month of treatment leads to a rapid and even overshooting increase of serum testosterone concentrations and to an increase of paraphilic symptomatology at least one year after therapy was ended. This increase in paraphilic fantasies was not observed in patients treated for six month.[91] There are also recent reports of successful treatment withdrawal trials.[77] Briken and colleagues have developed a scale that could assist treatment providers in the decision whether or not treatment should be terminated (The Change or Stop Testosterone Lowering Medication-scale [COSTLow-scale]). This scale is currently under validation and if validated successfully, treatment providers could use the scale on a regular basis (the current so far unvalidated version of the COSTLow-scale can be requested from the authors).

First studies were published indicating that LHRH-agonists seem to be a useful treatment option not only in adult sexual offenders with a paraphilic disorder but also in adolescents and young adults, especially in those less susceptible for psychotherapeutic treatment, for example with deficits in cognitive functioning.[62,70,73] In 2016, the WFSBP also published guidelines for the treatment of adolescent sexual offenders with paraphilic disorders.[81] Recognizing the above said and comparable to the treatment guidelines of adults, psychological treatment is considered as the first-line treatment in all cases. Depending on the risk of the patient pharmacological agents can be added to the treatment. In adolescents with a low to moderate risk for sexual violence SSRIs can be given and ADT should be added to SSRIs only in those with a high or very high risk. Thereby, the treatment provider can choose between CPA, MPA or LHRH-agonists. It has to be noted though that ADT should be used only in adolescents with completed puberty and growth, and the initiation of ADT requires adolescents to be at least in Tanner stage V and to have completed bone development.[32]

Conclusions

Current studies suggest that LHRH-agonists might be the most effective drugs to decrease paraphilic sexual fantasies, urges, and behaviors. This accounts for adult, adolescent, and sexual offenders with a mental retardation. Although current results from brain imaging studies suggest that LHRH-agonists might have an influence not only on sexual drive per sé but explicitly on the emotional appraisal of paraphilic stimuli, LHRH-agonists should be reserved for most severe cases of (paraphilic) sexual offenders because they frequently lead to a complete decline of all sexual behaviors, thereby inferring with fundamental human rights. This clarifies that LHRH-agonists should not be used with the intention of lifelong treatment and the possibility of ending treatment when adequate should be closely monitored. Furthermore, psychotherapy should

always be carried out alongside pharmacotherapy. Psychotherapy should enable paraphilic sexual offenders to gain better control over their paraphilic fantasies and urges, however, in some individuals paraphilic urges might be so intense that treatment with psychopharmacological agents is needed to increase susceptibility to psychotherapeutic interventions. Although LHRH-agonists seem to be quite effective, the claim for randomized, placebo-controlled clinical studies has to be renewed. However, at the moment it seems not very realistic that in the near future such controlled studies will be implemented due to ethical concerns.[92,93] Current studies used different kinds of LHRH-agonists, in different formulations, some did not mention the precise agent they used, or did not specify the treatment duration. Moreover, sample characterizations were inconsistent between studies with some evaluating paraphilic sexual offenders, some assessing sexual offenders without a paraphilic disorder and even others assessing paraphilic individuals who have not sexually offended so far. Treatment settings differ between studies and it can be inferred that treatment effects differ between inpatient and outpatient settings. Finally, legal statutes concerning pharmacological sexual offender therapy differ between countries as was shown by a recent study and it is unclear in how far these differences in legal prerequisites influence treatment effectiveness.[87] All these points complicate the integration of current research results. To increase comparability, future studies about the treatment effectiveness of LHRH-agonists should definitely consider reporting these points. Nevertheless, a precise systematic review and evaluation of the current state of research is crucial to provide an up-to-date overview about current treatment guidelines and settings and their empirical basis.

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Twitter statement: LHRH-agonists should be combined with psychotherapeutic interventions in sexual offenders with a high risk and intense paraphilic urges.

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Figure captions

Fig. 1: Prisma flow diagram: Overview of search strategy.