Double-blind, Controlled, Clinical Trial Planned in Germany to Investigate the Efficacy of Psychotherapy Combined with Triptorelin in Adult Male Patients with Severe Pedophilic Disorders: Presentation of the Study Protocol

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ABSTRACT

Background: The treatment of paraphilias, especially of pedophilia, centers upon cognitive-behavioral psychotherapy and pharmacologic interventions. Two open, uncontrolled clinical studies using the synthetic LHRH-agonist triptorelin suggested that, combined with psychotherapy, antiandrogen treatment reduced deviant sexual fantasies, urges, and behaviors in paraphilic patients. There is a need for further research using controlled, randomized trials to examine the effectiveness of sexual offender treatment including psychotherapeutic and pharmacologic interventions.

Objective: The aim of this pilot study is to evaluate the efficacy and tolerability of cognitive-behavioral psychotherapy together with intramuscular (IM) 3-monthly injections of triptorelin in adult men with severe pedophilia.

Study design and methods: In this multicenter, forensic psychiatric hospital-based, double-blind, controlled, parallel group phase IV trial conducted in Germany, convicted male sexual offenders aged ≥ 18 years with pedophilia, as defined by DSM-IV-TR criteria, will be randomized to receive study-specific psychotherapy together either with triptorelin or placebo for 12 months (total of 4 injections). This is a pilot study, therefore exploratory data analyses will be carried out of three different target parameters:

1. Changes in psychosexual characteristics using the Multiphasic Sex Inventory (scale: sexual abuse of children)
2. Changes in the risk of violent sexual behavior using the Sexual Violence Risk-20 total score
3. Changes in serum testosterone concentration

Treatment effects will be assessed by comparing baseline values with those at the final examination (month 12).

Limitations: The absence of real-life stimulants to test for actual recidivism limits possible findings.

The study will be conducted in agreement with the European GCP-guideline, all relevant legal requirements, and the legal framework for voluntary treatment of convicted sexual offenders in Germany.

BACKGROUND

Considering the seriousness of some paraphilias, in particular pedophilia, which may result in severe consequences for the individual and can lead to sexually

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offensive behavior with violation of established laws and unacceptable consequences for the young victims, there is an acute need for effective treatment. Currently-available and ethically-acceptable treatment options include cognitive-behavioral, psychotherapy and treatment with antiandrogens as well as other medications, such as selective serotonin reuptake inhibitors (1, 2). Data from randomized, controlled, clinical trials (RCTs) in men with severe paraphilias are still lacking. This can be explained by the difficulty in performing rigorous studies in the relevant patient population. Major reasons for the scarcity of data include legal impediments, ethical problems, and lack of reliable clinical endpoints; difficulties in standardizing sexually-deviant fantasies and behaviors; and difficulties in follow-up and reporting of endpoints which are criminal acts, such as sexual offences (1, 3).

Psychotherapy combined with antiandrogen medication in sex offenders is increasingly being used as a method to control paraphilic sexual urges, desires, and resultant behaviors (2). Since the implementation of luteinizing hormone-releasing hormone (LHRH)-agonist therapy, especially for the treatment of severe paraphilias, the number of sex offenders voluntarily treated with antiandrogens in some German forensic psychiatric clinics has increased (4). Results of uncontrolled studies performed with LHRH-agonists support the potential efficacy of such approaches (1, 3, 5-8).

Most of the data have been generated with the long-acting, synthetic analogues of LHRH, leuprorelin and triptorelin, which are generally delivered as depot injections on a 1-, 2-, 3-, or 6-monthly basis. These agents induce a transient rise in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. This, in turn, elevates testosterone production ("flare up" phenomenon) transiently, beginning within approximately 2-3 days of the first injection and lasting through the first one or two weeks of therapy (9). As use continues, gonadotrope responsiveness to endogenous LHRH is suppressed. The result is reduced LH and FSH secretion and testosterone production such that testosterone serum concentrations fall to castration levels usually within 2-4 weeks of therapy initiation (9). One of the main advantages of LHRH agonists is the reversibility of their hormonal effect. Testosterone recovery, however, is highly variable among patients and the time for serum testosterone concentrations to increase above castrate levels is highly dependent on the duration of androgen deprivation therapy (ADT) (10). Normalization is achieved in 73-100% of patients within six months of stopping ADT of ≤ one year in duration. However, normalization occurs in ≤ 18% of patients at six months after stopping ADT of three years duration. The period of attenuated serum testosterone concentrations in most patients who have received ADT for three years is approximately 18 months (10). The most commonly observed adverse events (AEs) related to LHRH-agonist treatment are due to their hormonal effects.

In 2007, triptorelin received approval for "the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations" in the European Union (11, 12). Approval for the drug in this indication is based on two open, uncontrolled studies (13-15). The first open-label trial in males with severe paraphilias, treated with triptorelin 3.75mg IM once monthly for up to seven years, showed that most patients (83%) responded with a cessation of deviant sexual behaviors and markedly reduced sexual fantasies/activities during the follow-up period (7 months to 7 years) (14, 15). In the other uncontrolled observational study, 30 "treatment-resistant" paraphilic outpatients were treated with monthly IM injections of 3.75mg of triptorelin and supportive psychotherapy for 8 to 42 months (13). The efficacy of therapy was evaluated by the Three Main Complaints Questionnaire and the Intensity of Sexual Desire and Symptoms Scale. No sexual offenses were committed during triptorelin therapy. The severity of paraphilia as measured by self-reports and serum testosterone concentrations decreased significantly. Six men stopped treatment after 8 to 10 months, three because of intolerable AEs, two emigrated, and one wanted to father a child. Adverse events occurring during treatment included erectile failure, hot flashes, and decrease in bone mineral density.

Professionals agree that there is a need for further research with randomized, controlled trials using appropriate sample sizes and standardized methodology to investigate the utility of pharmacotherapy, including LHRH-agonists, in paraphilias (1, 3). This proposed 12-month pilot study will be the first randomized and placebo-controlled study investigating the efficacy and tolerability of cognitive-behavioral psychotherapy with/without antiandrogen treatment (3-monthly injections of triptorelin) in adult men with severe pedophilia. The analyses will focus on objectively quantifiable

parameters which measure changes in psychosexual characteristics from baseline to the final visit.

METHODS

STUDY DESIGN

This is a multicenter, forensic psychiatric hospital-based, double-blind, placebo-controlled, parallel-group, phase IV trial in which convicted sexual offenders will be randomized to receive psychotherapy together with either triptorelin or placebo.

ETHICAL AND LEGAL CONSIDERATIONS

This study will be in agreement with the European Good Clinical Practice (GCP) guideline (2005/28/EG), all relevant legal requirements, and the legal framework for voluntary antiandrogen treatment of convicted sexual offenders in Germany. The study has been planned by a national Advisory Board in cooperation with the sponsor (Dr. R. Pfleger GmbH, Bamberg, Germany). Members of this board include professionals of forensic psychiatry, urology/andrology, osteology, biometrics, medical ethics, and a judge experienced in supervision of sex offenders. During the study, the Advisory Board will meet regularly and as required. A national independent Ethics Committee and national authorities will be asked to approve the study protocol, the patient's information sheet, and the patient consent form before initiation of the study.

The study will be conducted in locked wards in about six German forensic psychiatric hospitals in accordance with the principles set out in the legal framework of the German Maßregelvollzug §63 Penal Code. All investigators will be psychiatrists experienced in treating patients with severe pedophilia. They will be trained in advance in all aspects of GCP and in performing all study-relevant procedures.

Eligible participants will be males aged ≥ 18 years with complete legal competence (Civil Code) exhibiting severe sexual behaviors which led to arrest by order of either judicial or administrative authorities and subsequent forensic commitment. They will have been sentenced to mandatory hospital treatment (German Maßregelvollzug) for psychiatric criminals intended to treat the offender and thus prevent subsequent reoffense. If the investigator decides, on the basis of the study protocol, that an individual may be a potential study candidate an external forensic psychiatrist unaffiliated with the study will assess the individual's competence to consent to participate in the study. This independent psychiatrist will be experienced with treatment of sexual offenders and will be responsible for all study centers. This psychiatrist will inform the offender about all relevant legal and medical aspects of this study, based on a study conversation guideline which will ensure that all individuals are provided with identical information. The potential participant will also receive a detailed information sheet about the benefits and risks of antiandrogen therapy. If he is willing to take part, the independent psychiatrist will then obtain his written consent to participate in this study and potentially receive antiandrogen therapy. The study consent will not be connected to any conditions for prematurely leaving forensic commitment (or avoiding further prosecution) or granting privileges from custody during the study. A second study-independent person at each center (e.g., a cleric) will act as ombudsperson for the patient in all relevant concerns.

SELECTION OF STUDY PATIENTS

Participants will be convicted males aged ≥ 18 years with pedophilia, as defined by DSM-IV-TR criteria (16), who are kept in institutions for mandatory treatment in forensic psychiatric hospitals. Eligibility criteria for the study will be determined by an experienced forensic psychiatrist. Results of physical and psychiatric examinations will provide information necessary to decide whether or not the potential patient fulfils all study inclusion criteria and does not meet any exclusion criteria.

STUDY PROCEDURES AND ASSESSMENTS

After consenting to participate in the study, but before any trial-related procedures/assessments are performed, a medical and psychiatric history will be completed at the baseline visit (T0). All potential patients will undergo a physical examination and a number of laboratory parameters (blood chemistry including Prothrombin time [Quick value], serum testosterone, LH, FSH, prolactin, and sex hormone-binding globulin [SHBG]; urinalysis) will be measured. In order to maintain the blindness of the study, information about individual's serum testosterone concentrations will be provided to the investigator only at the baseline visit. During the course of the study, serum testosterone concentrations will be directly reported to the responsible data monitor. Bone mineral density (BMD) of the proximal femur and the lumbal spine will be determined by dual-energy X-ray

absorptiometry at baseline and at final visit. Patients with pre-existing osteopenia (WHO criteria: T-score between -1.0 and -2.5 SD) will also be monitored by dual-energy X-ray absorptiometry for changes in BMD after 6 months. In order to describe the individual's current and dynamic risk factors and sexual interests and behaviors, the following tests will be performed at the baseline visit: basic documentation including the Kinsey Scale (17, 18), and the STATIC-99 as a current risk-assessment tool (19); the Sexual Violence Risk-20 (SVR-20) which includes dynamic risk factors (20, 21) will be performed at baseline and at final visit; the Multiphasic Sex Inventory (MSI) (22), a modification of the total sexual outcome (TSO) (23-25), and eye-tracking tests (26) will be carried out at baseline (preliminary tests) and at different visits during the course of the study. The German version of the Beck Depression Inventory Revision (BDI-II) for measuring the severity of depression will be applied at the baseline visit, after 3, 6, 9, and 12 months (27). Participants will be advised to refrain from smoking and alcohol use. All inclusion and exclusion criteria will be checked. Any signs and symptoms of potentially occurring AEs will be documented.

Fourteen days after the baseline visit T0 (visit T0+14), eye-tracking tests (visual orientation paradigm; mental rotation paradigm) will be performed. Again, all inclusion and exclusion criteria will be checked, serum testosterone concentrations will be measured, and signs and symptoms of potentially occurring AEs will be documented. Eligible patients at this time will randomly be assigned to one of the two therapy arms according to the randomization schedule and will receive the first psychotherapy session together with the study medication at the end of this visit.

Each patient will subsequently attend six visits (T1, T2, T3, T4, T5-14, T5) at 1, 3, 6, 9, 11.5, and 12 months after baseline visit T0+14 (in addition to the weekly psychotherapy sessions). The study will end for each patient at the final visit (T5) after 12 months. Follow-up treatment will be carried out according to the usual approach implemented at each clinic.

STUDY TREATMENTS

All patients will receive cognitive-behavioral psychotherapy according to the study-specific manual in German, based on the Core Sex Offender Treatment Programme (SOTP), the Offending Behaviour Programme Unit, the SOTP Rolling Programme, and the explanations set out in the manual "Treating Sexual Offenders" (28). Study-related psychotherapy includes 13 thematic blocks, with each block consisting of a variable number of sessions. To be included in the evaluation of the study each patient will have to attend psychotherapy blocks 1-12 with a minimum of 28 and a maximum of 44 sessions. Psychotherapy will be provided on a regular basis (one session per week; minimum duration: 40-50 minutes) over a period of 12 months by a psychiatrist/psychotherapist experienced in treating patients with pedophilia. Each psychiatrist/psychotherapist involved in this study will be trained in advance to perform the study-related psychotherapy. Each will complete a checklist of the actual progress of the patient in the structured program, ensuring adequate quality and monitoring of psychotherapy. One of the psychotherapists/psychiatrists who developed the psychotherapy manual will supervise and audit the treatment program every 2 to 3 months. Psychotherapy can be continued following the end of study.

At visit T0+14, drug therapy will start. Patients randomized to the test group will begin treatment with triptorelin (triptorelin embonate) suspension 11.25mg/2mL administered every 12 weeks as a single intramuscular injection for a period of 12 months (total of 4 injections). Patients randomized to the reference group will begin treatment with 2mL placebo suspension administered every 12 weeks as a single intramuscular injection for one year (total of 4 injections). Blinding will be achieved by packaging the test product (trademark: Salvacyl®, distributor: Dr. R. Pfleger, Bamberg; manufacturer: Ipsen Pharma Biotech, France) and the reference product (placebo suspension; manufactured by Ipsen Pharma Biotech, France) in identical vials with identical printing (identical batch number) and supplied in identical folding boxes with identical labelling. Thus, the study medications (including packaging) will be indistinguishable. They will be kept in boxes labelled with the respective patient number as determined by the randomization procedure. Study medication and sealed emergency envelopes containing information for unblinding the study will be given to the investigators.

In order to minimize treatment-related bone loss, adequate calcium (1.000 mg/day) and vitamin D (1.000 IU/day) supplementation will be maintained according to recent recommendations (29).

ASSESSMENT OF EFFICACY

Changes in three target parameters will be used to assess therapeutic outcome:

1. Psychosexual characteristics using the MSI (in German), scale: sexual abuse of children (SMK) (22)
2. Risk of violent sexual behavior using the SVR-20 total score (in German) (20, 21)
3. Serum testosterone concentration (total testosterone)

All instruments used for therapy assessment have been validated. Treatment effects will be assessed by comparing baseline values with those at the final examination (month 12).

Co-variables and all other variables will only be used to describe the patient population. The scales sexual compulsivity (SZ) and lying-scale regarding sexual abuse of children of the MSI (22) will be used as co-variables of the scale sexual abuse of children. During the study, changes in total sexual outcome will be described using a modified version of the manual originated by Kafka (23-25). Two eye-tracking methods (Visual Orientation Paradigm, Mental Rotation) will be used to examine selective attention processes to sexual preferred stimuli before and after therapy (26). A final judgement (low, moderate, or high) about the risk of future sexual violence will be made at the end of study by SVR-20 summary risk rating.

ASSESSMENT OF TOLERABILITY

The tolerability of treatment will be monitored throughout the study based on reported AEs and results of physical examination, BDI, routine laboratory measurements, urinalysis, and BMD examinations. Information on AEs will be collected by the investigator by questioning the patients, spontaneous reports and observation, and will be reported on the appropriate case report form (CRF) pages. Occurrence of any serious AE will lead to notification of the drug safety officer of the sponsor within 24 hours.

STATISTICAL ANALYSIS

This is a pilot study and, therefore, exploratory data analyses will be carried out. Nevertheless, data analyses will focus on defined therapeutically-relevant outcomes, i.e., the changes of psychosexual characteristics from baseline to final examination. Three different target parameters (see Assessment of Efficacy) will be evaluated in order to substantiate and elucidate the mechanisms underlying study results. All other variables will only be used to describe the patient population.

As valid information from RCTs is still lacking, a precise calculation of sample size is not possible. Furthermore, there is only limited access to a restricted pool of patients. Therefore, the ultimate sample size will be defined by the number of suitable patients present at the study centers.

Those individuals whose eligibility is confirmed will be randomly allocated to one of the two treatment arms in a 1:1 ratio stratified by center to rule out factors involving centers, investigators, and settings. The allocation schedule will be produced by persons who will not be involved in any subsequent aspect of the study.

Data will be analyzed by an intention-to-treat approach. All analyses will be performed and all tables, figures and data listings will be prepared using SAS version 9.2 or subsequent versions. Categorical variables will be presented as ratios and percentages. If the assumption of normal distribution for continuous variables of interest cannot be confirmed, the distribution will be described by the median, minimum and maximum and interquartile range. If variables are normally distributed (if required, after transformation) mean and standard deviation will also be calculated. Data summaries and listings will be separated by center and treatment group. All patient data will be included in data listings. Further approaches to data analyses are still to be determined in detail by the final statistical analysis plan.

QUALITY ASSURANCE

Quality assurance and quality control systems will be implemented and maintained using written standard operating procedures to ensure that the trial is conducted and data are generated, documented, analyzed, and reported in compliance with the study protocol, the GCP-rules, and other applicable regulatory requirements.

Monitoring will be performed by the sponsor or a representative of the sponsor. The monitor will get in touch with the study centers at regular intervals to request information on the progress of the study. Dependent on patient recruitment the monitor will visit the study centers to check study procedures and to review study documents. The sponsor will supervise study progress and will organize internal and external audits of the study, as well as meetings of the Advisory Board at regular intervals.

DISCUSSION

We are convinced that this pilot study will provide a platform for a critical debate of selected legal, ethical and methodological aspects. Some controversial points are emphasized in advance.

Several in-depth review articles have focused on the legal and ethical issues of antiandrogen pharmacotherapy in sex offenders with particular reference to the European Convention of Human Rights and the concept of human dignity (30-33). The design and methods of this study follow the recommendations of these articles. The legal requirements in Germany for antihormonal treatment of patients with severe sexual deviations, especially those regulating information to be provided and voluntary consent, are described in the German castration law (34). This law does not exclude convicted sexual offenders who are kept in institutions for hospital treatment enforcement (30). To what extent and under which conditions these sexual offenders can participate in clinical trials is currently under discussion (35, 36). In the present case this will be decided by the independent Ethics Committee and national authorities. The present trial protocol is explicit with regards to all aspects concerning genuinely independent study-related information and the voluntary decision-making of these patients.

The fact that the patients of this proposed study are to be treated in forensic psychiatric hospitals (the German Maßregelvollzug) complicates the treatment process both legally and scientifically. On the one hand in Germany this is the typical setting where antiandrogen medication is prescribed to patients with a high-risk for sexual offending related to a paraphilic disorder. On the other hand treatment has to be offered in a locked ward setting until the risk is reduced markedly. That means that risk has to be reduced before home leave steps are possible.

Antiandrogen treatment can be justified if it is medically and/or criminally necessary (30). Treatment has to be in the best interest of the offender to control his paraphilic thoughts and to decrease the risk for recidivism and, thus, in turn, to protect the general public. Several uncontrolled studies with LHRH-analogues have suggested that testosterone suppression to castrate levels can reduce the sexual drive and urge in men with paraphilias (3, 5, 6, 13-15). Through this, it may be possible to also open a wider window for the success of concomitant psychological treatment approaches.

The first purpose of the present study is, therefore, to investigate the efficacy of cognitive-behavioral therapy in the management of males with pedophilia. All patients will receive intensive psychotherapy according to the study-specific manual. Through this, it can be guaranteed that all patients who have voluntarily given their consent will be treated in a comparable manner. Attendance at psychotherapy sessions offers a real opportunity to each motivated sexual offender who truly desires to control his paraphilic behavior to have access to the currently most reliable risk management approach and through this to give the offender maximal help to effect a real change.

The second purpose of this study is to evaluate the efficacy of pharmacotherapy in addition to psychotherapy. Proof of clinical efficacy and safety of a drug should be based on randomized, double-blind, controlled clinical studies. Therefore, patients in the trial will be randomly assigned to antiandrogen treatment and placebo reference groups. This means that only approximately half of the study population will be treated with the active drug. Moreover, a transient increase in the concentration of circulating testosterone can occur following the initial injection of triptorelin, which theoretically could be detrimental in terms of deviant sexual behaviors. However, serum testosterone concentrations will subsequently decline dramatically over a reasonably short period of time and remain significantly lowered with repeated injections. Based on these facts, it is necessary to provide potentially effective risk management options (i.e., study-specific psychotherapy) to all patients. With view to the potential risk of recidivism and thus to the public's safety, it is necessary to recruit the patients out of closed institutions for psychiatric criminals. Otherwise, it would be difficult to justify a controlled trial where only half of high-risk patients receive a verum medication. In Europe, no Ethics Committee, no (inter) national authority, no insurance, no sponsor and no court of law will allow or take responsibility for a clinical trial treating convicted high risk sexual offenders who will have the potential chance to abuse children or offend. However, treatment of incarcerated sexual offenders does not reflect a real-life situation in which patients in society have more difficulty in adherence as sexual stimuli are readily available. The present study will endeavor to assess sexual fantasy and urges and to imitate "sexual stimuli" present in the real world as far as possible using different approaches (i.e., presenting pictures of children and measuring attention processes with eye-tracking techniques; see under Methods). All researchers involved in the planning of this study realize the limitations of the trial. These comprise investigating a relatively small sample of sexual offenders without a "real" risk to reoffend due to the fact that they are in a forensic psychiatric hospital. Only indirect measure-

ments on one of the major risk factors for reoffending ("paraphilia") will serve to assess efficacy. However, there is no other legal way to evaluate initial data, which can ethically be justified.

Beyond that, the use of a rigid approach to study procedures, implicit in a RCT design, should produce groups with similar patterns of offending and similar risk levels. Both groups will be compared statistically to validate their comparability.

Special care must be taken during the informed consent process in vulnerable populations such as prisoners. Offenders must freely provide their informed consent, without external pressure or coercion or any suggestion that participation will affect the length of time or quality of the mandatory forensic psychiatric hospital treatment (30-32). Therefore, an external psychiatrist unaffiliated with the study will fully inform each eligible individual regarding all aspects of the study and assess whether or not he truly understands what he is consenting to, including all possible risks, including failure of therapy, and side effects (30-32). When considering potential side effects, it should be stressed that antiandrogens must be given continuously, perhaps for years or even a lifetime in order to prevent relapse.

As seen with other LHRH-agonists or after surgical castration, the most commonly observed adverse effects related to triptorelin treatment are due to testosterone suppression and, apart from hypogonadism with decreased libido and erectile dysfunction, include hot flashes, an increased risk of developing a metabolic syndrome, manifested by changes in glucose and lipid metabolism, as well as diabetes mellitus; and a small increased risk of cardiovascular mortality and depression (11, 12, 37, 38). The long-term use of synthetic LHRH-agonists may also be associated with increased bone loss and may lead to osteoporosis (WHO criteria: T-score <-2.5 SD) and elevated risk of bone fracture (13, 14, 38-40). Effective and safe management of patients undergoing ADT must therefore include careful monitoring for AEs and their prevention (if possible) and treatment (37). Information on AEs will be collected regularly throughout the proposed study. A limitation of the study is that blinding could be broken by the observation of AEs (e.g., hot flashes). However, there is no solution for this problem since for legal reasons the investigating physician has to be the one who also monitors the AEs.

In order to prevent treatment-related bone loss, lifestyle modification including smoking cessation, moderation of alcohol consumption and regular weight bearing exercise will be recommended and are of additional benefit for the patients. Adequate dietary calcium and vitamin D supplementation will also be provided. According to the recommendations of Briken et al. (3), physical examinations of each participant and laboratory as well as BMD screening tests at baseline and regularly throughout the study are included in the study protocol.

The rigorous validation of all possible legal and methodological aspects in this pilot study is essential to minimize the risk of failure and biased results, and, thus, provide the first controlled data on the efficacy and tolerability of psychotherapy combined with antiandrogen treatment, in terms of reduction in paraphilic urges and interests as well as in risk assessment measures, in patients with severe pedophilia. The planned pilot study will be an initial, but important step in ADT treatment research of sex offenders.

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