

## TREATMENT OF MEN WITH PARAPHILIA WITH A LONG-ACTING ANALOGUE OF GONADOTROPIN-RELEASING HORMONE

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### ABSTRACT

**Background** Men with deviant sexual behavior, or paraphilia, are usually treated with psychotherapy, antidepressant drugs, progestins, and antiandrogens, but these treatments are often ineffective. Selective inhibition of pituitary–gonadal function with a long-acting agonist analogue of gonadotropin-releasing hormone may abolish the deviant sexual behavior by reducing testosterone secretion.

**Methods** In an uncontrolled observational study, we treated 30 men (mean age, 32 years) with severe long-standing paraphilia (25 with pedophilia and 5 with other types of abnormal behavior) with monthly injections of 3.75 mg of triptorelin and supportive psychotherapy for 8 to 42 months. The efficacy of therapy was evaluated monthly by the Intensity of Sexual Desire and Symptoms Scale and yearly by the Three Main Complaints questionnaire.

**Results** All the men had a decrease in the number of deviant sexual fantasies and desires, from a mean ( $\pm$ SD) of  $48 \pm 10$  per week before therapy to zero during therapy ( $P < 0.001$ ), and a decrease in the number of incidents of abnormal sexual behavior (from  $5 \pm 2$  per month to zero,  $P < 0.001$ ) while receiving triptorelin. These effects were evident after 3 to 10 months of therapy ( $P < 0.001$ ) and persisted in all 24 men who continued therapy for at least 1 year. The men's mean serum testosterone concentration fell from  $545 \pm 196$  ng per deciliter ( $18.9 \pm 6.8$  nmol per liter) before therapy to  $23 \pm 14$  ng per deciliter ( $0.8 \pm 0.5$  nmol per liter,  $P < 0.001$ ) after 42 months of triptorelin. The main side effects were erectile failure, hot flashes, and decrease in bone mineral density in some men.

**Conclusions** Continuous administration of triptorelin, a long-acting agonist analogue of gonadotropin-releasing hormone, together with supportive psychotherapy, may be an effective treatment for men with severe paraphilia. (N Engl J Med 1998;338:416-22.)

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**E**ACH year in the United States between 100,000 and 500,000 children are sexually molested by men.<sup>1,2</sup> Proportionally high rates have also been reported in Canada,<sup>3</sup> Australia,<sup>4</sup> the United Kingdom,<sup>1,5</sup> the Netherlands,<sup>1</sup> Denmark,<sup>6</sup> Germany,<sup>1,6</sup> and Belgium.<sup>7,8</sup> The numbers of affected children are probably higher, because many do not report the molestation. On the basis of extensive epidemiologic studies, Abel estimated that approximately 10 to 20 percent of chil-

dren had been sexually molested by the age of 18 years.<sup>9</sup> These findings indicate that deviant sexual behavior (paraphilia) in men is a serious problem.

Paraphilias are complex psychiatric disorders whose cause is not known.<sup>9</sup> Whether they represent an addiction, an obsessive–compulsive disorder, or a pattern of hypersexualism is still a matter of controversy.<sup>10,11</sup> Although the psychiatric literature describes a wide variety of paraphilias in men,<sup>10</sup> pedophilia and exhibitionism are probably the most common forms.<sup>9,12</sup> The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines pedophilia (“love of children”) as recurrent and intense sexual urges and sexually arousing fantasies that involve sexual activity with a child.<sup>12</sup> A man with pedophilia may victimize family members or children who are not relatives. The victims may be girls or boys, or in some cases, both girls and boys. Some men are exclusively attracted to children, whereas others are attracted to both children and adults.

The treatment of men with paraphilia is difficult. Surgical castration,<sup>13</sup> psychotherapy,<sup>14</sup> and pharmacotherapy<sup>15</sup> have all been used but are often unsuccessful. Some men have benefited from serotonergic drugs.<sup>16</sup> Treatment with the antiandrogens medroxyprogesterone,<sup>17,18</sup> which inhibits the secretion of gonadotropin and therefore of testosterone, and cyproterone acetate,<sup>19,20</sup> which antagonizes the action of testosterone, is not always successful, mostly because the inhibition of the secretion or action of testosterone is incomplete.

Selective suppression of pituitary–gonadal function with a long-acting agonist analogue of gonadotropin-releasing hormone may abolish the deviant sexual fantasies, urges, and behavior of men with paraphilia by reducing serum testosterone to very low concentrations.<sup>21,22</sup> In an uncontrolled observational trial we tested the efficacy of monthly injections of triptorelin, a long-acting agonist analogue of gonadotropin-releasing hormone, together with supportive psychotherapy in men with paraphilia.

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## METHODS

## Selection of Study Subjects

Over a period of two years 49 men with paraphilia were referred to us by psychiatrists, courts, or lawyers in Israel in response to an advertisement circulated among psychiatrists and community centers, published in a medical journal, and mentioned in an interview on the television news. The initiation (or continuation) of therapy was not a condition for leaving jail or avoiding prosecution. Nineteen men were excluded from the study because of mental retardation (two men), denial of having a problem (one), inactive paraphilia (four), the presence of other active psychiatric disorders (four), refusal to undergo therapy (four), and imprisonment (four). The clinical features of the 30 men who did enter the study are summarized in Table 1. All had severe paraphilia, as defined by DSM-IV criteria,<sup>12</sup> that was resistant to other therapies. Sixteen had previously been convicted of sex crimes (three to eight times each) and sentenced to prison for a total of 2 to 29 years. Although 22 men had other psychiatric disorders, they were in remission and were receiving, if necessary, maintenance doses of various psychoactive drugs. Nine men had previously been treated with cyproterone acetate (150 to 300 mg per day) for 4 to 10 years. All the men had received psychotherapy for various periods of time. These therapies had not been effective, resulting in recurrent abnormal sexual behavior and, in some cases, repeated convictions.

## Study Design, Treatment, and Evaluation of Patients

For legal and ethical reasons (because the men might have continued to offend while receiving a placebo), the study was open and none of the men received placebo. The protocol was approved by an institutional ethics committee, and all the men consented to the treatment. The men's behavior during treatment was compared with that before triptorelin administration or with periods during which they had received serotonergic drugs (Table 1). In the men who had been taking cyproterone acetate, that treatment was discontinued at least 12 months before triptorelin therapy was begun, and in those who were taking serotonergic drugs, treatment was stopped 2 months before triptorelin was begun.

For each man who entered the study, a complete medical and psychiatric history was obtained, followed by a physical examination. Testicular volume was measured with an orchidometer.<sup>23</sup> Serum luteinizing hormone, follicle-stimulating hormone, and testosterone and bone mineral density of the femoral neck and lumbar spine were measured. The results of these measurements were normal, except in 14 men, who had low values for femoral-neck bone mineral density (mean  $\pm$ SD, 78  $\pm$ 8 percent of the value for age-matched men) or lumbar-spine bone mineral density (85  $\pm$ 8 percent of the value for age-matched men); 7 had previously received cyproterone acetate. The men were then treated with monthly intramuscular injections of 3.75 mg of triptorelin (Decapeptyl-CR, Ferring, Malmö, Sweden) for an indefinite period. During treatment, serum luteinizing hormone, follicle-stimulating hormone, and testosterone were measured monthly, testicular volume every three months, and bone mineral density every six months.

The effects of triptorelin on the men's paraphilia were evaluated with the Three Main Complaints questionnaire<sup>24</sup> and the Intensity of Sexual Desire and Symptoms Scale.<sup>25</sup> The first was administered at the beginning and the end of the first year of therapy, and the second at least twice before therapy and then monthly during therapy. The questionnaires were always administered by the same physician. Additional information was obtained from the partners and relatives of the men.

The psychological and behavioral changes during treatment were evaluated by the Three Main Complaints questionnaire. This questionnaire focuses on the three problems that most affect the subject, as ascertained by psychiatric evaluation, and for which the man particularly expected help and relief. A 13-point scale was used to rate the severity of each of these problems (from least to most severe).<sup>24</sup>

TABLE 1. CLINICAL FEATURES OF 30 MEN WITH SEVERE PARAPHILIA.\*

CHARACTERISTIC	VALUE
Age (yr)	32 $\pm$ 8
Marital status (no.)	
Single	16
Married	9
Divorced	5
Victim of sexual abuse in childhood (no.)	
Yes	9
No	21
Years of sexually deviant behavior	16 $\pm$ 9
Pedophilia (no.)	25
Sexually attracted to boys	6
Sexually attracted to girls	12
Sexually attracted to boys and girls	7
Incestuous	2
Sexually attracted only to children	8
Sexually attracted to children and adults	17
Exhibitionism (no.)	7
Voyeurism (no.)	2
Frotteurism (no.)	2
Uncontrollable sexual drive (no.)	30
Masturbation (times/wk)†	32 $\pm$ 6
Deviant sexual fantasies (no./wk)†	48 $\pm$ 10
Abnormal sexual behavior (incidents/mo)†	5 $\pm$ 2
Other psychiatric disorders (no. of men)	
Paranoid schizophrenia	5
Personality disorder	9
Affective disorder	3
Schizoaffective disorder	1
Borderline intellectual functioning	2
Obsessive-compulsive disorder	2
Previous convictions for sex crimes (no. of men)	16
Previous or current medication (no. of men)	
Cyproterone acetate‡	9
Fluvoxamine§	4
Fluoxetine§	3
Thioridazine	3
Perphenazine	4
Penfluridol	2
Lithium	2

\*Plus-minus values are means  $\pm$ SD. The disorders were classified according to DSM-IV criteria.<sup>12</sup>

†Values are the average of the values for the four months preceding triptorelin therapy.

‡Treatment was discontinued at least 12 months before triptorelin therapy was begun.

§Treatment was discontinued two months before triptorelin therapy was begun.

The Intensity of Sexual Desire and Symptoms Scale was used to assess three types of behavior. To assess sexual interest and desire, the men were asked to indicate the nature, intensity, and frequency of their sexual thoughts and desires in the preceding month (ranging from no sexual thoughts to very frequent sexual thoughts with intense sexual urges). To assess sexual activity, the men were asked about the number of times per week they masturbated, the number of times they engaged in any overt acts that resulted in orgasm, and the nature and number of incidents of abnormal sexual behavior in the previous month. To assess sexual fantasies, the men were asked to imagine their erotic fantasies as vividly (and for as long) as possible and to describe the object of the fantasy (child or adult; female, male, or both), the intensity (ranging from no arousal at all to maximal arousal), and the frequency (per week) during the preceding month. All three types of behavior were rated on an eight-point scale, and the average of the three scores was used. A score of 1 indicates minimal or no

sexual arousal and no deviant sexual fantasies or abnormal sexual behavior, whereas a score of 8 indicates maximal and uncontrollable arousal and abnormal sexual behavior, with all symptoms present.

Supportive psychotherapy was provided on a regular basis (one to four sessions a month) by a psychiatrist experienced in treating men with paraphilia or by one of us. Seven men continued to receive maintenance doses of one psychoactive drug, and two men continued to receive two drugs, during triptorelin therapy.

**Laboratory Methods**

Serum luteinizing hormone, follicle-stimulating hormone, and testosterone were measured by sensitive and specific radioimmunoassays.<sup>26</sup> The bone mineral density of the femoral neck and the lumbar spine (L2 to L4) was determined by dual-energy x-ray absorptiometry (XR26, Norland Scientific Instruments, Fort Atkinson, Wis.). The respective coefficients of variation of the measurements of bone mineral density were 2 percent and 1 percent.

**Statistical Analysis**

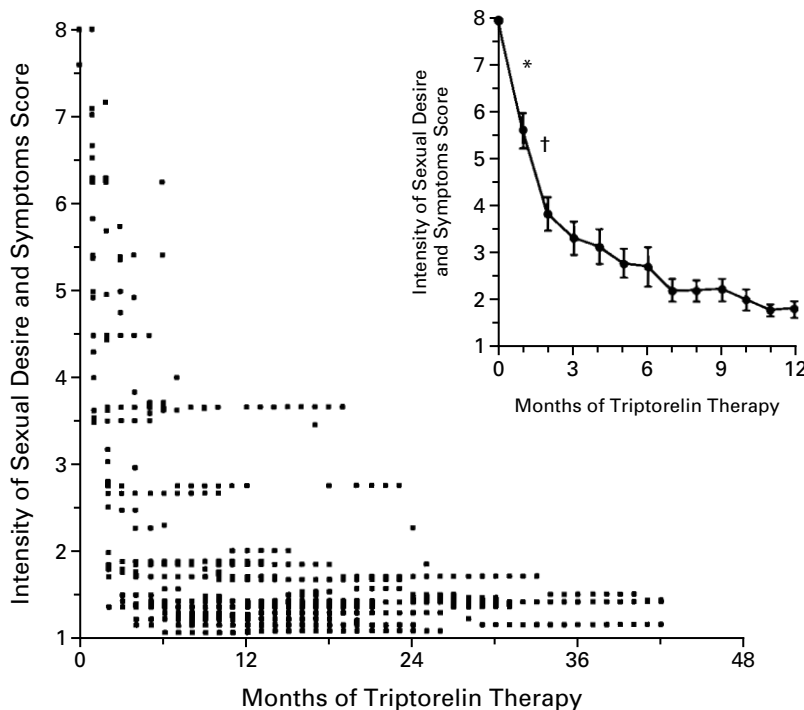
Only the results for the 24 men who were treated for at least 12 months were analyzed statistically. For each variable, Fisher's test for a protected experiment-wise level of significance<sup>27</sup> was adapted to the repeated nature of the data and to the nonparametric setting. First, two-way analysis of variance was used to test the overall homogeneity of the values at all time points. If the results of this test were significant, we proceeded with sequential pairwise comparisons using the Wilcoxon matched-pairs signed-rank test. The base-line values (time 0) for the Intensity of Sexual

Desire and Symptoms Scale were arbitrarily set at 8, as detailed above. Therefore, the values entered in the analysis were the differences from this base-line value. Statistical analysis of the results of the Three Main Complaints questionnaire was performed with Student's t-test. All P values are two-sided.

**RESULTS**

**Effect of Triptorelin on Paraphilia**

All 30 men had a prompt reduction in all paraphilic activities during therapy. The maximal reductions in the Intensity of Sexual Desire and Symptoms scores occurred after 3 to 10 months (Fig. 1 and Table 2) in all but one man, in whom it was achieved after 2 years. All 30 men stated that their sexual desire had decreased considerably and that their sexual behavior had become easily controllable. Deviant sexual fantasies and urges disappeared completely, and the frequency of masturbation was markedly reduced (to none at all or once or twice in a fortnight). The mean ( $\pm$ SD) number of self-reported incidents of abnormal sexual behavior decreased from  $5 \pm 2$  per month (range, 2 to 8) before triptorelin therapy to zero during therapy ( $P < 0.001$ ). Not a single sexual offense against a child or any acts of exhibitionism, voyeurism, or frotteurism were committed during



**Figure 1.** Intensity of Sexual Desire and Symptoms Scores in 30 Men with Severe Paraphilia during Triptorelin Therapy.

The score, determined monthly, reflects the intensity and frequency of deviant sexual fantasies, sexual desire, and abnormal sexual behavior. The main graph shows the individual data for all the men for as long as they continued therapy or through the most recent follow-up assessment. The inset shows the mean ( $\pm$ SE) scores for 24 men treated continuously for at least 12 months. The asterisk indicates a significant difference ( $P < 0.001$ ) from base line, and the dagger indicates a significant difference from month 1.

TABLE 2. EFFECT OF CONTINUOUS ADMINISTRATION OF TRIPTORELIN IN MEN WITH SEVERE PARAPHILIA.\*

VARIABLE	MONTHS OF TRIPTORELIN THERAPY								P VALUE†	NORMAL RANGE
	0	6	12	18	24	30	36	42		
No. of men‡	30	30	24	18	15	11	8	6		
Intensity of Sexual Desire and Symptoms score	8.0±0.2	2.7±2.3§	1.7±0.85	1.6±0.7	1.5±0.5	1.4±0.2	1.3±0.15	1.4±0.15	<0.001	
Serum luteinizing hormone (mIU/ml)	10.6±5.3	4.0±2.4§	2.7±2.7	3.1±2.5	0.8±0.3	0.8±0.5	0.9±0.4	0.8±0.4	<0.001	3–15
Serum follicle-stimulating hormone (mIU/ml)	7.1±6.8	4.6±2.6	3.5±1.9	3.8±1.8	2.2±0.7	2.1±0.4	2.0±0.7	1.9±0.9	0.29	2–10
Serum testosterone (ng/dl)¶	545±196	26±14§	32±14	23±12	26±21	23±12	23±14	23±14	<0.001	280–870
Testicular volume (ml)	26.2±4.6	19.6±4.0§	17.3±4.1§	17.4±5.5	15.6±6.0	14.9±6.2	13.5±9.1	13.8±9.3	<0.001	18–30
Bone mineral density (% of value in age-matched normal men)										
Vertebral	92.8±13.0	88.1±12.2§	86.5±10.7§						0.005	
Femoral	84.5±15.7	83.1±14.5	80.4±8.8						0.43	

\*Plus-minus values are means ±SD.

†Two-way analysis of variance was used to test the overall homogeneity of the values at all time points. Only the 24 men who completed at least 12 months of therapy were included in the statistical analysis.

‡Values are the number of men who completed the specified number of months of triptorelin therapy.

§P<0.05 for the comparison with the previous months (Wilcoxon matched-pairs signed-rank test).

¶To convert values for serum testosterone to nanomoles per liter, multiply by 0.03467.

||The analysis included 14 men.

therapy (as reported by the men, their relatives, or a probation officer) once the maximal effects were achieved. These beneficial effects persisted in all 24 men who were treated for at least one year.

Six men stopped treatment after 8 to 10 months: two emigrated, three had intolerable side effects, and one wanted to father a child. In addition, two married men interrupted treatment for 12 and 6 months to achieve fertility. During this interim the symptoms returned in all five men in whom follow-up was possible (Fig. 2). Two men (Patients 3 and 6) resumed triptorelin therapy, with good results. On the other hand, three men (Patients 8, 10, and 12) who stopped triptorelin therapy because of side effects were subsequently given cyproterone acetate at a dose of 200 mg per day. This treatment did not control their paraphilia, and two of them were subsequently prosecuted for sex crimes and sentenced to prison.

The results of the Three Main Complaints questionnaire also showed that triptorelin therapy was effective. In all the men the first problem cited was the paraphilia. The severity of the problem decreased from a mean score of 10±3 to 3±3 after one year (P<0.001). The second and third problems related to a variety of interpersonal issues. These problems were, in decreasing order of importance, marital and familial, work related, and related to social functioning. The one-year scores for the second and third main problems also decreased, from 10±3 to 4±3

(P<0.003) and from 10±4 to 6±6 (P<0.02), respectively.

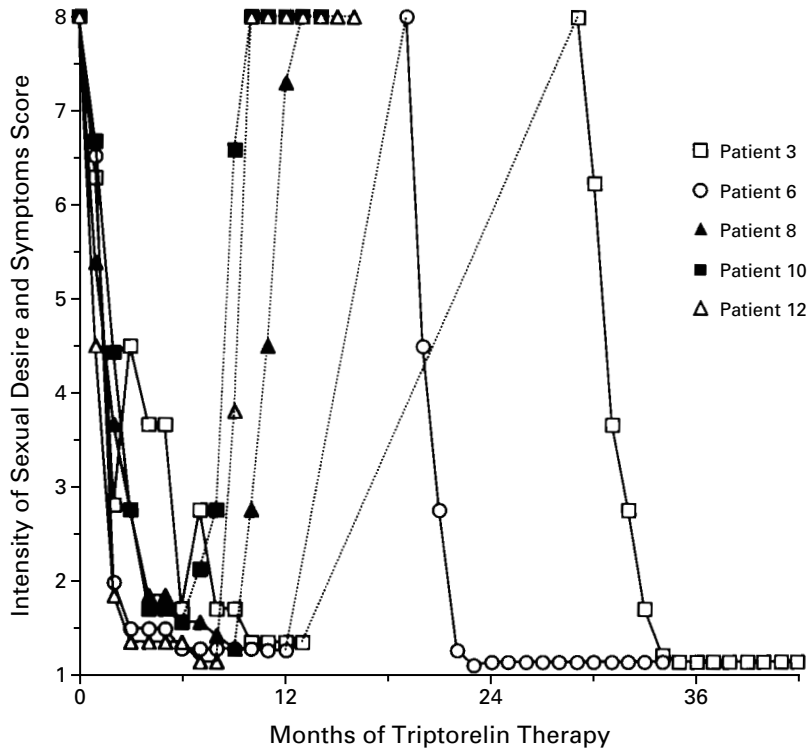
#### Effects of Triptorelin on Pituitary–Gonadal Function and Testicular Volume

The mean base-line serum luteinizing hormone, follicle-stimulating hormone, and testosterone concentrations were normal (Table 2). During treatment serum luteinizing hormone and testosterone concentrations fell significantly and remained low as long as triptorelin was administered regularly. In men who interrupted or discontinued treatment, the serum testosterone concentration returned to base line within two months.

Testicular volume was within the normal range in all the men before therapy. It decreased progressively during treatment, reaching a nadir of approximately 50 percent of the base-line volume after 36 months of treatment.

#### Effect of Triptorelin on Bone Mineral Density

Among the 18 men in whom all planned measurements were made, the bone mineral density of the femoral neck or lumbar spine decreased after 6 to 12 months of therapy in 11 men and did not change in 7 men (Fig. 3). In the group as a whole, the mean value for bone mineral density decreased significantly during treatment only in the lumbar spine (Table 2). Two men who had progressive demineralization were given oral calcium (2 g per day)



**Figure 2.** Intensity of Sexual Desire and Symptoms Scores in Five Men with Severe Paraphilia Treated with Triptorelin Who Discontinued Therapy Temporarily or Permanently.

Patients 3 and 6 interrupted triptorelin therapy for 12 and 6 months, respectively, to achieve fertility. Both resumed therapy thereafter, with good results. Patients 8, 10, and 12 stopped triptorelin therapy permanently because of side effects. They were subsequently treated with 200 mg of cyproterone acetate per day, with little benefit. The dotted lines indicate the periods during which triptorelin was discontinued.

and  $1\alpha$ -hydroxyvitamin D<sub>3</sub> (0.5  $\mu$ g per day) supplements after completing 24 months of triptorelin therapy.

#### Other Side Effects

Most of the men had transient pain at the sites of injection of triptorelin. Six men reported persistent hot flashes, three decreased growth of facial and body hair, and two asthenia and diffuse muscular tenderness.

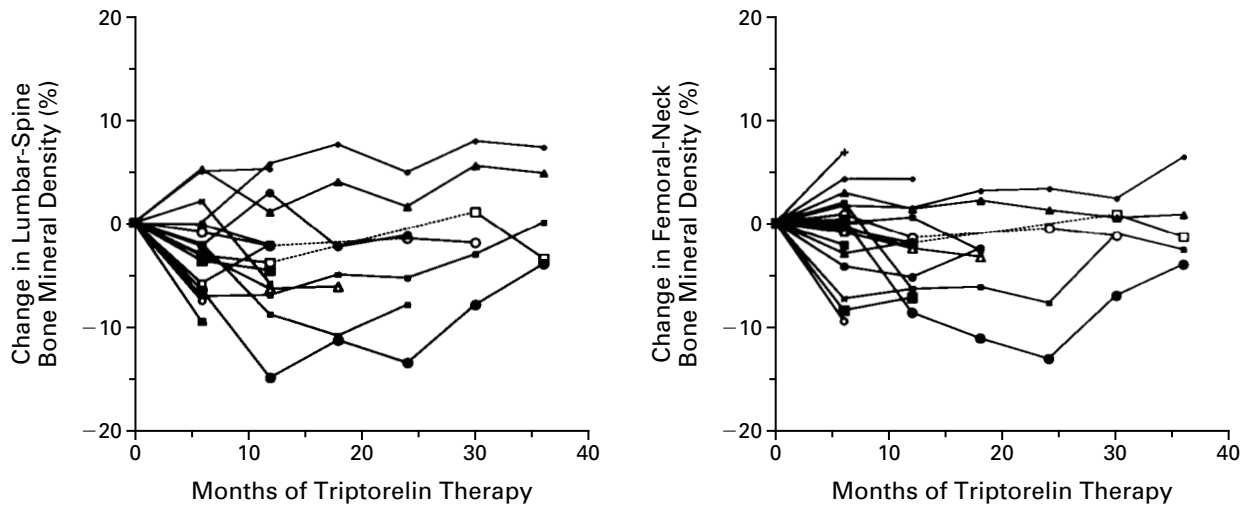
Although all the men were very satisfied with the results of therapy, 21 reported progressive erectile failure after 6 to 12 months of triptorelin therapy. The lack of sexual interest toward women, with an inability to achieve or maintain an erection or perform sexual intercourse, was proportional to age, occurring in some younger men but in all men older than 35 years.

#### DISCUSSION

In humans testosterone has a crucial role not only in the development and maintenance of male sexual characteristics but also in the control of sexuality,

aggression, cognition, emotion, and personality.<sup>28</sup> Testosterone is a major determinant of sexual desire, fantasies, and behavior, and it increases the frequency, duration, and magnitude of spontaneous and nocturnal erections.<sup>29</sup> All these functions are impaired in men with hypogonadism but can be restored with testosterone replacement.<sup>30</sup> The deviant sexual fantasies, urges, and behavior of men with paraphilia also appear to be triggered by testosterone. Therefore, reducing testosterone secretion or inhibiting its action may control these symptoms.

In the past, surgical castration was advocated as a therapy for men with paraphilia, but it was abandoned because it is a cruel punishment. It is now illegal in most countries.<sup>13</sup> Antiandrogenic drugs such as medroxyprogesterone and cyproterone acetate have been widely used as therapy in these men,<sup>17-20</sup> but their efficacy is limited and they have many side effects. The side effects of medroxyprogesterone include weight gain, lethargy, nightmares, hyperglycemia, and leg cramps, and the side effects of cyproterone acetate include gynecomastia, thromboembolic phenomena, depression, and hepatocellular damage.<sup>31</sup> Both



**Figure 3.** Percentage Change from Base-Line Values in the Bone Mineral Density of the Lumbar Spine and Femoral Neck during Triptorelin Therapy in 18 Men with Severe Paraphilia.

These men completed 6 to 36 months of triptorelin therapy. The dotted lines indicate the periods during which triptorelin was temporarily discontinued in two men.

drugs probably cause bone mineral loss.<sup>19,32</sup> Even if compliance is good, only 60 to 80 percent of men benefit from either drug.<sup>18,19</sup>

Long-acting analogues of gonadotropin-releasing hormone, such as triptorelin, induce severe but reversible hypogonadism with no side effects other than those related to hypoandrogenism.<sup>21,22</sup> They act by inhibiting the secretion of luteinizing hormone (and to a lesser extent follicle-stimulating hormone), and consequently, testosterone secretion decreases markedly. Previous studies of the effects of these analogues in men with paraphilia have consisted of case reports<sup>33-36</sup>; the exception is a study in which five of six men with severe paraphilia who were treated with triptorelin for up to seven years stopped all abnormal sexual behavior.<sup>22,37</sup> In these studies, and in ours, triptorelin therapy markedly reduced deviant sexual desires and behaviors, especially the intensity and frequency of sexual fantasies. These fantasies appear to be influenced by and responsive to both internal stimuli (abnormal imagery) and external stimuli (visual, tactile, olfactory, and auditory) and, as in normal men, are basically androgen-dependent.<sup>9-11,38</sup>

In spite of the methodologic limitations of an uncontrolled study, continuous therapy with triptorelin was very effective in controlling paraphilia in the men who continued therapy, whereas previous therapy with cyproterone acetate or serotonergic drugs failed to do so. Either triptorelin is more potent than cyproterone acetate in reducing the effects of testosterone in tissues, or it also has a direct effect on the central nervous system in suppressing deviant sexual behavior. The intracerebroventricular administration of agonist analogues of gonadotropin-releas-

ing hormone suppresses aggression in male rats.<sup>39</sup> Furthermore, gonadotropin-releasing hormone neurons project to extrapituitary sites, such as the olfactory bulb and amygdala, where the hormone may act as a neuromodulator.<sup>40</sup>

Continuous triptorelin therapy has side effects. It causes hypogonadism, which can lead to osteoporosis.<sup>41</sup> Eleven of 18 men in our study had a decrease in bone mineral density during the therapy. In addition, many had reductions in normal sexuality as well as in their abnormal sexual behavior, and a few had other symptoms of testosterone deficiency.

Nevertheless, triptorelin appears to have several advantages over other drugs for men with severe paraphilia.<sup>22,37</sup> It is potent, and it is effective in men resistant to other treatments. It has fewer side effects, and although continuous therapy may cause loss of bone mineral mass, this could probably be prevented by the concomitant administration of calcium and vitamin D or a bisphosphonate drug.<sup>42</sup> It is given parenterally once monthly, which reduces the likelihood of an interruption in therapy due to noncompliance and allows therapy to be directly observed. Once the maximal effects are achieved, the men have few symptoms of abnormal sexual behavior, and pose a much lower threat to society. Therapy with triptorelin or another long-acting agonist analogue of gonadotropin-releasing hormone is therefore probably more cost effective than imprisonment or inpatient rehabilitation programs.<sup>43</sup>

The abnormal sexual behavior of men with paraphilia persists for many years and may be lifelong, even when it can be treated effectively. Clearly, abnormal sexual behavior recurred in the men in our

study who discontinued therapy. Therefore, triptorelin therapy must be continuous. However, it is possible that the dose of triptorelin could be lowered with time, thereby ameliorating the erectile failure and bone mineral loss and yet maintaining the benefit in terms of reducing abnormal sexual behavior.

Finally, we would like to stress two points. First, compliance was excellent in all men who continued therapy regularly, even though they were not legally bound to continue treatment. Second, it seems unlikely that the beneficial effects occurred because the men expected them, although the study was not placebo-controlled and the men knew they were receiving potentially beneficial therapy.

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