

## Suppression of puberty with GnRH analogues in adolescents with Gender Dysphoria

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### Abstract

**Introduction:** Gender Dysphoria (GD) is defined as a mismatch between biological sex characteristics and gender identity. The percentage of teenagers with doubts about their gender identity has dramatically increased over the past decade.

**The aim of the study:** This article presents the positions of supporters and opponents regarding suppression of puberty with GnRH analogues in GD adolescents.

**Material and method:** Standard criteria were used to review the literature data. The search of articles in the PubMed database was carried out using the following keywords: gender dysphoria, transsexualism, suppression of puberty.

**Description:** Due to the extension of the time needed to shape gender identity, suppression of puberty seems to be a beneficial preventive measure for the development of sexual dysphoria. Adolescents avoid suffering associated with the development of unwanted sex. However, there are numerous concerns about the negative effects of puberty inhibition on bone development, neuropsychological development and future fertility.

**Summary:** The safety and effectiveness of therapy that inhibits puberty is not properly grounded in scientific evidence. There is still a lack of research assessing the long-term effects of administering hormones that interfere with adolescent sexual development.

**Keywords:** gender dysphoria, transsexualism, suppression of puberty

## 1. INTRODUCTION

Gender dysphoria (GD) is defined as a mismatch between biological sex characteristics and gender identity [1]. To receive a GD diagnosis, a minor must display six of the eight indicators listed in DSM-5 for at least six months: 1. A strong desire to live as an opposite sex; 2. A strong preference for wearing clothes typical of the opposite gender; 3. A strong preference for cross-gender roles in make-believe play or fantasy play; 4. A strong preference for the toys, games or activities stereotypically used or engaged in by the other gender; 5. A strong preference for playmates of the other gender; 6. A strong rejection of toys, games and activities typical of one's assigned gender; 7. A strong dislike of one's sexual anatomy; 8. A strong desire for the physical sex characteristics that match one's experienced gender [1]. The term „gender dysphoria” was introduced in May 2013 in the Diagnostic and Statistical Manual of Mental Disorders DSM-5, in place of the "gender identity disorder" (GID) in DSM-IV belonging to "mental and behavioral disorders" [2]. The change in the name and classification of this state was the result of the postulates of communities working for LGBT people (Lesbian, Gay, Bisexual, Transgender), according to which the problem of transsexual people is not about the "disturbed" psyche, but only about discomfort between the body and the psyche, therefore the word "disorder" is inadequate to the described phenomenon. The name change is aimed at preventing stigmatization of transgender people and emphasizing distress, which may be accompanied by discrepancies between the experienced and expressed sex and the assigned gender [1].

The Endocrine Society and the World Professional Association for Transgender Health in 2009 introduced guidelines for the treatment of teenagers with gender dysphoria. The guidelines recommend the use of gonadotropin-releasing hormone agonists (GnRH) during puberty to suppress sexual maturation [3].

## 2. MATERIAL AND METHODS

The purpose of this article was to present the positions on suppression of puberty with GnRH analogues in people with GD. The published studies assessing the efficacy and safety of this treatment were also reviewed.

Standard criteria were used to review literature data: 1. We searched articles in English which was published in the PubMed and Google Scholar databases using the following keywords: gender dysphoria, gender identity disorder, puberty suppression; 2. Only full-length scientific articles that were published in the years 2009-2019 were analyzed; 3. All papers found were published in peer-reviewed journals.

### **3. GROWTH OF GENDER DYSPHORIA**

Data from 2017 indicate that the occurrence of transsexualism in Europe is estimated at 1 in 30.000 in somatic male and 1 in 100.000 in female somatic people [4]. In addition, the number of people who have changed legal gender has increased significantly in recent years. It amounted to 1 in 7.000 men and 1 in 13.000 female persons [4].

Epidemiological data indicate that GD is becoming more common, both among adults and adolescents [5]. The reasons for the change in the prevalence of this condition are not fully understood, but it is postulated that genetic factors play a decisive role in determining gender identity. Bejsterveldt et al. indicated that the intensification of behavior incompatible with biological sex in children is a strongly hereditary feature [6]. Similar conclusions are provided by the study by Coolidge et al. [7]. The genetic role is also argued by the fact that the determination of gender identity begins to appear in the very early years [8]. However, despite the assumption that a genetic aspect plays a large role in shaping sexuality, the impact of environmental factors cannot be excluded. These include increased access to knowledge (e.g. via the Internet), the spread of the phenomenon of disapproval of your gender, numerous proposals of modern medicine regarding gender change, increased openness in society regarding issues related to gender identity and gender expression, and a general reduction in the stigmatization of people with different identities sexually. Therefore, it should be recognized that the formation of gender identity is the result of the interaction of genetic and psychosocial factors [9].

Over the past dozen years, in addition to the increased incidence of GD, the prevalence of other psychiatric diagnoses, such as the autism spectrum, mood disorders or anxiety disorders has also increased [10]. Adults have seen a twofold increase in the frequency of psychiatric diagnoses over the past 15 years. In the case of children and adolescents, this severity is even greater - now three times more often psychiatric diagnoses are given to children and adolescents than 15 years ago [11]. Mental problems such as mood disorders, anxiety behaviors or the use of psychoactive substances may also apply to young people who have doubts in determining their gender identity - in this situation, the combination of symptoms of various ailments can generate a complex clinical picture that becomes a challenge for clinicians to diagnose disorders related to gender and choosing appropriate therapeutic recommendations [12, 13].

### **4. DISABILITY OF OWN GENDER IN CHILDREN AND YOUNG ADULTS**

Dutch research suggests that as many as 7% of boys aged 7 are perceived as extremely girlish, and slightly lower percentage of girls considered extremely boyish [14]. It is not uncommon for children to express a desire to belong to the opposite sex. However, studies show that no more than 20% of children who in the pre-pubertal period meet the diagnostic criteria for gender dysphoria will constantly desire to belong to the opposite sex [15, 16]. For the majority, it is more likely that instead of disapproval of their own sex it is about sexual orientation (homosexuality). This encourages treatment with some caution of visible differences in the perception of your sex in children [16].

Children and adolescents with GD are highly exposed to violent behavior, which can lead to deep mental suffering. Therefore, they develop large development of drug disorders, depression, self-harm and even suicide [17]. The most difficult period for adolescents with GD traits is the time when a child begins to physically mature and hated biological traits appear [18].

## **5. PROPOSALS FOR CONTEMPORARY MEDICINE**

For about 10 years, medicine has been offering young teenagers suffering from transsexualism a specific pharmacological procedure aimed at stopping unwanted development of puberty.

In 2009, modern guidelines for endocrine treatment of transsexual persons were introduced. They were created by the Endocrine Society and the World Professional Association for Transgender [3]. Therapy using gonadotropin-releasing hormone analogs involves reversible inhibition of the development of tertiary sexual characteristics (breast development and pelvic dilatation in women, lowering of voice and increase in penis in men) [3]. Hembree et al. Recommend starting therapy when the first physical changes related to puberty occur, confirmed by the measurement of sex hormones (estradiol in girls and testosterone in boys), but not earlier than before reaching stage 2 on the Tanner scale (corresponding to the initial stage of breast development in girls and testicular volume > 4 ml in boys) [19]. Dutch researchers who were the first to use sexual maturation blockers as part of gender dysphoria therapy argue that this gives the child more time to examine his gender identity without the anxiety caused by emerging features of biological sexuality and to make a balanced decision about the next stages of treatment [9].

Suppression of puberty with GnRH analogues can be used up to 16 years of age [20]. If, after reaching this age, sexual dysphoria persists, you can begin treatment with sex-appropriate steroids for the desired sex (cross-sex hormone therapy, CSHT), and then after the age of 18 carry out sex reassignment surgery [20].

## **6. THE RESULTS OF EARLY BREAKING MATURE**

In addition to the hopes of significantly improving the quality of life of GD teenagers and the possibility of avoiding traumatization associated with the development of unwanted sex, there are concerns about possible negative results of inhibiting puberty. Due to the fairly short period since the introduction of puberty suppression therapy, only a few studies appeared that assessed the efficacy and safety of the treatment (Table 1).

Research conducted by S.E. Schagen et al. in 2016 on a group of 126 adolescents aged 12 to 16 years (49 male and 67 female adolescents) with GD treated with GnRH evaluated the effectiveness and safety of this therapy [21]. Regular physical and laboratory tests were performed every 3 months, in which levels of gonadotropins, sex steroids, AlAt, Aspat, creatinine and ALT were determined. GnRH analogues were found to effectively inhibit puberty (reduction in testicular volume in 43 boys and reduction in breast development in 65 girls). In addition, there were no deviations from the norm in the values of sex steroids, creatinine, liver enzymes and alkaline phosphatase [21].

Data published by A.L. de Vries et al. regarding the result of suppression of puberty, indicate that young people with gender dysphoria can benefit significantly in psychosocial functioning as a result of GnRH treatment [22]. A study of 70 transsexual people assessing their psychosocial functioning before and after suppressing puberty in behavioral and emotional problems, depressive symptoms, anxiety and anger, and overall functioning showed that all children who received this treatment significantly improved well-being, self-aggression and suicidal behavior have disappeared. There was also an improvement in social functioning. What's more, during the entire period of treatment, no teenagers withdrew from the therapy. Everyone started treatment with sex hormone appropriate to the desired sex, which was the first step towards a real change of sex [22].

**Table 1.** Characteristics of studies assessing selected aspects of suppression of puberty by GnRH analogues in adolescents with GD

Reaserch	Study group	Age (years)	Aim of the study	Methods of measuring variables
A.L. de Vries et al., 2011	70	12-16	Comparison of psychological functioning and sexual dysphoria before and after suppression of puberty in adolescents with GD	Child Behavior Checklist (CBCL); Youth Self-Report (YSR); Beck Depression Inventory (BDI); State-Trait Anxiety Inventory (STAI); Clinical Anger Scale (CAS); Children's Global Assessment Scale (CGAS); Utrecht Gender Dysphoria Scale (UGDS); Body Image Scale (BIS)
R. Costa et al., 2015	200	10-16	Comparison of general functioning of adolescents with GD after psychological supervision and after suppression of puberty.	Utrecht Gender Dysphoria Scale (UGDS); Children's Global Assessment Scale (CGAS)
S.E. Schagen et al., 2016	126	12-16	Assessment of efficacy and safety of GnRH inhibition of puberty in adolescents with GD	Gonadotropins; sex steroids; Alat; Aspat; creatinine; alkaline phosphatase
D. Klink et al., 2015	34	22	Assessment of the effect of puberty suppression on bone mass development after treatment with GnRH analogues in adolescents with GD	peak bone mass (PBM)

With the introduction of GnRH treatment of dysphoria, there have been postulates that psychotherapeutic treatment is more appropriate for children who declare gender uncertainty. However, R. Costa et al. assessing both forms of treatment showed the advantage of drug therapy over psychotherapy [23]. 200 teenagers with GD participated in the study. In the group that used GnRH analogues, the final result on the Children's Global Assessment Scale (CGAS) was higher ( $67.4 \pm 13.9$ ) than in the group in which psychotherapeutic treatment was performed ( $60.7 \pm 12.5$ ) [23]

Proponents of adolescence suppression also emphasize that early suppression of puberty also allows for better results in physical appearance in people who decide to continue sex change [24].

Despite the hopeful first results of GD treatment with GnRH analogues, still not all specialist circles recommend this therapy. It is emphasized that between 80 and 90% of children who experience gener dysphoria identify themselves according to their biological gender when they reach adulthood. And because GnRH therapies begin before the age of 16, when teenagers have poorly developed emotional and cognitive competences necessary to

make an informed decision about starting or rejecting therapy, there is a risk that some children may be unnecessarily exposed to hormonal interference [25]. Researchers emphasize that gender identification in children is flexible (that is, it can change over time) and plastic (that is, it can be formed by the influence of forces such as parental approval and social conditions). Due to the high percentage of people whose dysphoria disappears when they enter adolescence or adulthood, the British Psychiatric Association recommends individual case consideration and careful assessment of the appropriateness of initiating therapy with GnRH analogues in the early stages of adolescence [26].

Suppression of puberty may also have a lasting effect on psychosexual development [27]. Restrained sex drive and the lack of sexual experiences typical of adolescence negatively affect the process of forming sexual identity, orientation and preferences, and assessing one's own functioning in relations with others [27].

The effect of GnRH analogues on bone development is also of concern. In 2015, the first study on the impact of early medical intervention on GnRH analogs on bone mineral density (BMD) was published, which was evaluated in each person undergoing treatment at age 22. [28]. The study showed a decrease in BMD, which may reflect a delay in reaching peak bone mass (PBM) or loss of PBM potential, and may be due to the hypogonadal state induced by GnRH<sub>a</sub>. Continuous monitoring of bone mass development in this population is justified, preferably by a specialist endocrinologist with experience in transgender healthcare [29].

There were also fears in the literature about the change in neuropsychological development during the cessation of puberty and the resumption of sexual maturation with sex steroids characteristic of the opposite sex [30]. However, currently no studies have been published assessing the neurological aspects when using GnRH analogues to suppress puberty. Issues related to achieving final growth in adults, future fertility options and other long-term consequences of puberty suppression also remain worrying.

## **7. SUMMARY**

The percentage of teenagers with doubts about their gender identity has dramatically increased over the past decade. This prompted the Endocrinological Society and the World Association of Transsexual Health Specialists to publish guidelines for the treatment of transsexual adolescents. The use of gonadotropin-releasing hormone analogs (GnRH) to suppress puberty in people with sexual dysphoria has been in operation since 2009. Since then, there has been an ongoing debate on the appropriateness of this therapeutic form.

Proponents point out that suppression of puberty prevents the harmful effects of persistent gender dysphoria. Adolescents are given more time to finally determine their gender identity, and therefore adolescence may be better with mental health and social performance. Inhibiting puberty in its early stages not only prevents severe suffering, but also allows the development of healthy youth living in the right sex.

On the other hand, however, it is emphasized that the safety and effectiveness of hormones that inhibit puberty are not well-grounded in scientific research. Regardless of whether the inhibition of the development of sexual maturity is safe and effective, the legitimacy of choosing this form of therapy for sexual dysphoria remains unclear, which is why more systematic, interdisciplinary multi-center studies, even with global coverage, are required.

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