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New perspectives in the hormonal treatment of gender dysphoria in adolescence

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Hormonal treatments have been used in adolescents with gender dysphoria in the last decade. The professionals working in gender dysphoria treatment units cannot ignore this new demand. The evolution of care for such adolescents according to the last three versions of the Standards of Care (SC) of the World Professional Association for Transgender Health is described. Starting with the fifth version of the SC, hormonal treatment of adolescents has been contemplated. Recent protocols for hormonal intervention carried out by specialized clinics are analyzed. Finally, the pros and cons of hormonal treatment are debated. These hormonal interventions have major impact on the physical, social, and psychosexual development of patients and have ethical and moral implications for professionals.

Keywords: Gender identity disorder, Gender dysphoria, Transsexualism, Standards of Care, Suppression of puberty, Adolescents

Nuevas perspectivas en el tratamiento hormonal de la disforia de género en la adolescencia

En la última década se están aplicando tratamientos hormonales a adolescentes con disforia de género. Los profesionales de las unidades de tratamiento de la disforia de género no pueden hacer oídos sordos a esta nueva demanda. En este trabajo se expone cómo ha evolucionado la atención a estos adolescentes en las tres últimas versiones de los Estándares Asistenciales (EA) de la Asociación Mundial de Profesionales para la Salud Transgénero, en las que, a partir de la quinta versión de los EA, se empieza a contemplar que los adolescentes pueden ser subsidiarios de recibir tratamientos hormonales. También se analizan los recientes protocolos de intervención hormonal llevados a cabo por clínicas especializadas. Por último, se debate sobre los argumentos a favor y en contra de estos tratamientos hormonales. Estas intervenciones hormonales tienen importantes repercusiones en el desarrollo físico, social y psicosexual de los usuarios y conllevan implicaciones éticas y morales para los profesionales.

Palabras clave: Trastorno de identidad de género, Disforia de género, Transexualismo, Estándares Asistenciales, Supresión de la pubertad, Adolescentes

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INTRODUCTION

Since March 2007, the Asturias Gender Identity Treatment Unit (UTIGPA) has been serving people demanding care for gender dysphoria. Research carried out in the first three years of operation of the unit revealed that the mean age at which transsexuals make an appointment was 33.69 years, the mean being 38.42 years for transsexual women (from man to woman, TMW) and 27.28 years for transsexual men (woman to man, TWM). The minimum age of TMW was 16 years and of TWM, 17 years. The people seeking care included a group of TMWs who had previously resorted to self-medication with hormones or had received discrete treatments by different specialists, in some cases including feminizing surgical or cosmetic treatments.² In the last two years of unit operation, the age variable has changed. Although there has been no empirical research into this topic, there has been a higher incidence of people seeking care at younger ages, the minimum age being 13 years. The request for care is made before they have started any type of medical or cosmetic treatment to adapt their bodies to the gender with which they identify.

Since 2007, interdisciplinary treatment units for gender dysphoria have proliferated in the Spanish public health system.³ The availability of care has made treatment units more accessible for users. In consequence, some sociodemographic and clinical variables are changing. For example, people increasingly seek care at younger ages and fewer people resort to self-medication with hormones.

The professionals in these units should respond to this new care reality by developing effective and safe protocols to address the demands and needs of younger people without imposing a dichotomous view of gender, exploring different expressions of gender identity and considering that hormonal and surgical interventions may be appropriate for some adolescents, but not for others.⁴

DIAGNOSTIC CLASSIFICATIONS OF GENDER IDENTITY DISORDERS

Gender identity disorders first appeared in the official nomenclature of the American Psychiatric Association in 1980 (Diagnostic and Statistical Manual of Mental Disorders, third edition – DSM-III)⁵ and in the International Statistical Classification of Diseases and Related Health Problems in 1978 (ICD-9).⁶ Both classifications add a specific section for this disorder when it occurs in childhood, in addition to the diagnosis of transsexualism per se. In DSM-III it is called "gender identity disorder in childhood" and corresponds to the "psychosexual identity disorder" section of ICD-9. Despite the fact that the entity was included simultaneously in both classifications, and the fact that most studies underline the fact that the condition usually starts in

childhood and adolescence, gender identity disorders have been studied mainly in adults.⁷

Whereas the ICD-10⁸ maintained the term "transsexualism" and retains "gender identity disorder in childhood," DSM-IV⁹ replaced the diagnosis of transsexualism with "gender identity disorder" (F64.x) and contemplated in this single category the criteria for children, adolescents and adults, and required that the current age be specified. It should be noted that DSM-IV-TR,¹⁰ although similar to the previous edition, begins to introduce the term "gender dysphoria."

These classifications define gender identity disorders in childhood as the persistent and intense identification with the opposite sex together with persistent discomfort with one's own sex or feelings of inadequacy about one's gender role, which causes deep psychological distress and significant alterations in the social, occupational, and other important performance areas. It first occurs during the preschool years and must appear before puberty to be diagnosed.

HORMONE TREATMENT IN DIFFERENT VERSIONS OF STANDARDS OF CARE (SOC)

The Standards of Care (SOC) of the World Professional Association for Transgender Health constitute a benchmark used internationally by professionals who treat people with gender dysphoria. This association was previously known as the Harry Benjamin International Gender Dysphoria Association (HBIGDA). Seven versions have been published until now:

- *The first four versions*, published in 1979, 1980, 1981, and 1990, did not include hormonal and surgical sex reassignment in adolescence, stating that these procedures must be requested by the applicant and carried out through informed consent: "*Hormonal and surgical sex reassignment may be carried out or administered only to persons of legal age (defined by state law) or persons legally declared as adults by a court (emancipated minors).*"¹¹
- Starting with the *fifth version*, young people are mentioned in relation to hormone therapy, stating that the administration of hormones is advisable only in exceptional cases under the age of 18 years.¹²
- The *sixth version*¹³ states that adolescents may be eligible for puberty-delaying hormones as soon as hormonal changes start, although they should have reached Tanner stage II. They are also eligible to start hormone treatment at the age of 16 years. Therefore, the medical treatment of adolescents is relatively recent, having been implemented in different clinics in the last decade.^{14,15}

- *The seventh and final version*,⁴ like the draft of DSM-5,¹⁶ replaces the term "gender identity disorder" with "gender dysphoria." As in the sixth version, hormonal interventions are allowed at early ages in people with gender dysphoria.

ADDRESSING GENDER DYSPHORIA IN THE LAST THREE VERSIONS OF THE STANDARDS OF CARE

From the *fifth*¹² to the *seventh version*,⁴ a progressive change is observed in the early initiation of reversible and partially irreversible medical treatments in adolescents.

a) Recommended stages

The last three versions of the SOC establish three stages in the physical interventions.^{12,13,4}

- First stage of hormone therapy: fully reversible interventions designed to postpone puberty.* These interventions involve delaying the physical changes of puberty by using gonadotropin releasing hormone (GnRH) analogues, also known as LHRH or LHRF, to suppress the production of LH and FSH (gonadotropins). This blockade of the gonadotropins in adolescents with male genitalia (TMW) stops testosterone secretion and sperm production; in adolescents with female genitalia (TWM) it stops the production of estrogen and progesterone and the maturation of oocytes. The preferred treatment is thus any GnRH analogue in both groups. In order to administer GnRH analogues, the patient must have reached Tanner stage II¹⁷ of pubertal development. For those who cannot use analogues, the alternative for biological males is an anti-androgen (which neutralizes the effects of testosterone), and for biological women it is an androgen (testosterone, in practice) or progestin (if testosterone cannot be used), which inhibit the production of estradiol, estrone, and progesterone, thus suppressing menstruation. The interventions cited above are the only ones established by the fifth version¹² for all phases. In the sixth and seventh versions, these options are not recommended for use in the first stage of pubertal development, GnRH analogues being preferred due to the reversibility of their effects.
- Second stage of hormone therapy: partially reversible interventions with testosterone or estrogen.* These options include hormonal therapies for feminizing or masculinizing the body, which involve the administration of testosterone to biological females and estrogens plus anti-androgens to biological males.
- Surgery: irreversible interventions.* These are surgical procedures involving either sex reassignment,

such as breast surgery (breast augmentation in TMWs or mastectomy and chest masculinization in TWMs) or genital surgery (orchietomy, penectomy and vaginoplasty in TMWs, and hysterectomy, vaginectomy, oophorectomy, phalloplasty and metoidioplasty in TWMs), or cosmetic interventions, such as liposuction (TWM) or liposculpture (TMW), reduction of facial bones (TMW), thyroid cartilage plasty to reduce the Adam's apple (TMW), and laryngeal surgery to change the tone of the voice (TMW).

b) Age at which starting analogue therapy is recommended

The fifth version states that hormonal or surgical therapy should never be used in children. Treatment should be conservative in adolescents because the development of gender identity can evolve rapidly and unexpectedly. According to this version, the minimum age at which hormonal interventions generally should be carried out is 18 years, preferably with parental consent. Hormone treatment for adolescents should be implemented in two phases only after puberty is fully established. It is established that: "*There are few cases in which the administration of hormones to adolescents younger than 18 years is recommended.*"¹² Therefore, hormones are only used in exceptional cases and only in patients who satisfy the criteria listed in Table 1.

In the *sixth version*, the cutoff age for starting hormone treatment is no longer the age of majority. It is stated that adolescents may be eligible for hormone therapy (inhibitors) to delay puberty as soon as pubertal changes start, recommending that they reach Tanner stage II (1962)¹³ and satisfy the criteria required (Table 1). This version, while eliminating criteria 3 and 4 of the fifth version, conserves the general principle that extensive research of social, familial, and psychological areas be conducted before initiating physical interventions.

*The seventh version*⁴ continues to recommend experiencing Tanner stage II before starting hormone treatment with inhibitors to delay puberty. The minimum criteria for the administration of puberty suppressing hormones are shown in Table 1. Therefore, compared with the sixth version, a criterion is added that establishes, not as a general principle but as an eligibility criterion, identifying and taking into account any medical, psychological or social problems that may interfere with treatment so that the adolescent's situation and functioning is sufficiently stable to carry out treatment. This criterion of the seventh version, which was already in the fifth version, more strictly established that the presence of severe psychopathology is an exclusion criterion and the individual's development had to be limited by the gender identity disorder. (Table 1)

c) Recommended age of onset of treatment with feminizing or masculinizing hormones

Table 1		
Criteria for the first phase of hormonal treatment (HBIGDA, 1998; HBIGDA, 2001 and WPATH, 2011)		
Fifth version (Criteria for exceptional cases)	Sixth version	Seventh version
1. Exhibit throughout childhood a clear pattern of gender identity with the opposite sex and aversion toward expected gender role behavior.	1. During childhood, the adolescent has shown an intense model of sexual and gender identity with the opposite sex, and an aversion to the behavior expected because of the assigned gender role.	1. The adolescent has demonstrated a pattern of disconformity or intense and lasting gender dysphoria (whether or not expressed and accepted).
2. Significant increase in the sense of sexual mismatch with the start of puberty.	2. Discomfort with one's sex and gender increased significantly at the beginning of puberty.	2. Gender dysphoria has emerged or worsened with the onset of puberty.
3. Social, intellectual, psychological, and interpersonal development are limited as a result of the gender identity disorder.		3. Any medical, psychological, or social problems that may interfere with treatment have been noted and taken into account, so the adolescent's situation and functioning are stable enough to carry out the treatment.
4. Absence of severe psychopathology, independently of the alterations caused by the gender identity disorder.		
5. Family consent and participation in the therapeutic triad.	3. The family consents to and participates in therapy.	4. The adolescent has given informed consent and, especially when the adolescent has not reached the age for giving such consent, the parents or other guardians have consented to treatment and are involved in supporting the adolescent during treatment.

The fifth version allowed in exceptional cases the administration of hormones that induce characteristics of the opposite sex (second phase) before reaching the age of majority, although never before the age of 16. A minimum of six months of intervention of the mental health professional with the adolescent and family is required to start hormone therapy.

In the sixth version, the exception has become the rule and establishes that adolescents may be eligible to begin hormonal treatment (second phase) when they are 16 years old, preferably with parental consent.

In the seventh version, it also states that adolescents can start these treatments, preferably with parental consent, although consent is not essential in countries where young people are considered legally adults to make medical decisions at age 16 years. No minimum duration of the mental health professional's intervention is indicated, but the following general principle for physical interventions is established: "Before any intervention in adolescents is considered, the social, psychological, and familial consequences should be explored thoroughly. The duration of this study can vary considerably depending on the complexity of the situation."⁴

d) Sex reassignment surgery

The fifth version does not contemplate irreversible interventions, i.e. surgery, in minors.

The sixth edition dedicates a section to this population. It states that irreversible interventions should be delayed as

much as possible and that "no surgical intervention should be performed before adulthood, or prior to real-life experience of at least two years in the gender role of the sex with which the adolescent identifies."³

The seventh version requires two criteria for genital surgery: the age of majority in the country where they are and have lived continuously for at least 12 months in the gender role that is consistent with their gender identity. This latest version specifies that age should be viewed as the mandatory minimum criterion and not as an indication for intervention. It also states that for TWMs, chest surgery should be performed, preferably but not necessarily, after a prolonged period of living in the desired gender role and one year of treatment with testosterone. These flexible criteria are set in accordance with each adolescent's specific clinical situation and goals of expressing gender identity. It emphasizes the risks of delaying or restricting medical interventions in adolescents because it "may prolong gender dysphoria and contribute to the development of an appearance that favors abuse and stigmatization."⁴

e) Information about the risks of hormone therapy

The seventh version also includes a new section detailing the risks of inhibiting puberty. It indicates that early administration of hormones is more likely to have negative social and emotional consequences for gender dysphoria than later use. This version also incorporates the physical impact it may have on bone development and growth or insufficient genital tissue.

f) The dichotomous model versus the extended model

The Harry Benjamin model⁸ is essentially dichotomous. Since inception, the first four versions of the SOC are titled "hormonal and surgical sex reassignment of persons with gender dysphoria."¹¹ For the fifth and sixth versions,^{12,13} biological men and women continue to be the object of attention, thus perpetuating gender and sexual dimorphism. The seventh version to some extent breaks with the traditional dichotomous model, becoming more flexible and opening up a wider range of possibilities. It offers different opportunities for people who may not request hormone therapy or surgery, or who are unwilling to undergo the real-life experience. However, after overcoming the model based on the therapeutic triad,^{12,13} it continues in the same vein as the sixth version with regard to early hormonal therapy in adolescents, maintaining the established order (masculine men and feminine women).

CURRENT RESEARCH AND CLINICAL EXPERIENCE WITH NEW APPROACHES TO HORMONAL TREATMENT FOR GENDER DYSPHORIA IN ADOLESCENCE IN THE AMSTERDAM UNIT

Before the seventh version of the SOC became effective, specialized centers like the Gender Identity Clinic of Amsterdam¹⁵ in recent years have applied hormonal therapy before age 16 years in carefully selected adolescents.¹⁴ Cohen-Kettenis and colleagues have pioneered the early use of puberty-inhibiting hormones and feminizing/masculinizing hormones in children and adolescents.¹⁴ Recently, other treatment centers in Europe (Ghent, Oslo) and North America (Toronto, Boston) have followed this protocol.¹⁹ Professionals experienced in the treatment of gender dysphoria in these centers offer these medical interventions before the age of 16 years in cases where puberty has begun and progressed to at least Tanner stage II.¹⁷

The team of the Gender Identity Unit in the VU University Medical Center in Amsterdam developed the first protocol for applying hormonal treatment by stages from age 16 years on.¹⁵ They adapted the method for diagnosing adults in the sixth version of SOC to adolescents. Hormone treatment in stages begins once they are at least 16 years old. Transsexual women initially are given anti-androgens and, if they respond positively to this first phase, at 3 to 6 months they are prescribed estrogens. Transsexual men initially are given progesterone, followed by androgens after 3 to 6 months. This first protocol established the eligibility criteria shown in Table 2.

Follow-up studies showed that early intervention yielded better psychological outcomes. The physical appearance of the adolescents was better accepted as a full member of the new gender compared with those who

started treatment as adults. In addition, after surgery they stopped suffering gender dysphoria and their social and psychological functioning was very similar to that of their new peer group.¹⁵

After these results, the same team prepared a second protocol advancing the age of onset of hormonal treatment by stages to 12 years.¹⁵ Transsexual women were administered GnRH analogues and then estrogens, and transsexual men were given GnRH analogues and then androgens (testosterone). The eligibility criteria were maintained for the first protocol, except for the minimum age, which changed from 16 to 12 years. The adolescent had to have achieved minimal pubertal development, Tanner stage II or III. The Amsterdam team claims that the initial results are promising but recognizes that more research and replication in other care settings are required before these treatments can be recommended on a global scale.

Further research supports the approach of the seventh version and there are arguments for and against early intervention.¹⁹

ARGUMENTS FOR AND AGAINST EARLY TREATMENT

Several arguments favor early initiation of hormonal treatment. The arguments in favor are postulated based on the assumption that gender identity disorder in adolescence will continue into adulthood. These arguments are:

- a) Intervention prevents the development of psychological problems (depression, suicide attempts, anorexia, etc.) as a result of the suffering entailed in the development of the physical characteristics of puberty, which have a negative impact on social and intellectual development.¹⁹
- b) By avoiding full pubertal development, it can make some surgery less invasive or even unnecessary. There are unfavorable outcomes in adults that are related to late initiation.
- c) This type of intervention favors the diagnostic process. On the one hand, it gives professionals more time to explore their gender identity and desire for sex reassignment without interference from the development of secondary sexual characteristics and, on the other hand, it gives adolescents more room to make future decisions about their treatment.¹⁹ According to this research, the argument is that the implementation of the first stage of hormonal treatment at the age of 12 is not in itself a sex change.¹⁹

There are also arguments against early intervention:

- a) The first argument refers to diagnosis. It is difficult to establish a definite diagnosis of gender dysphoria in

Table 2 | **Criteria for eligibility of the first protocol for hormonal treatment (Kreukels and Cohen-Kettenis, 2011)**

Eligibility criteria for hormonal treatment	
Age: 16 to 18 years	
Clear early onset of disorder (before puberty)	
Persistent (or even growing) gender dysphoria during early puberty	
No psychological comorbidity or other circumstances that might interfere with diagnosis or treatment	
Adequate support from parents or guardians	
Adequate understanding of the effects of treatment	

adolescence. The epidemiological studies that can provide estimates of the incidence and prevalence of gender dysphoria in each age group are few and disparate. The existing research shows that the proportion of gender dysphoria that persists into adulthood is different for children and adolescents. The figures show that only a minority of these children exhibit transsexuality in adulthood.²⁰⁻²⁷ Whereas some research indicates that symptoms of prepubertal gender dysphoria disappear before or in the early stages of puberty in 80% to 95% of cases,¹⁹ other studies show that 20% to 25% of children will maintain gender dysphoria after the first episodes of puberty.¹⁵ In some children, these feelings intensify and their aversion to their own bodies grows during adolescence, together with the secondary sexual characteristics.^{25,28,29} While gender dysphoria remits in most prepubertal children,^{25,27} it persists in most adolescents with gender dysphoria.²⁹ Several authors argue that the prevalence of gender dysphoria in adults is higher when the disorder has started in adolescence.⁴

- b) Psychosexual development refers to gender role behavior, gender identity and sexual orientation,³⁰ and biological factors, especially hormonal and genetic factors, and psychological, social, and cultural factors are involved in this complex process. Along these lines, another argument against delaying puberty is that preventing the development of secondary sexual characteristics inhibits the "spontaneous formation of a consistent gender identity"¹⁹ and the adolescent misses the natural puberty resulting from their own hormones.¹⁵ Early hormone treatment can lead to a hasty change in gender identity with a great impact on sexuality. It interferes with the proper sexual experience associated with age in the adolescent's biological body, eliminating erotic impulses and possibly inhibiting the process of clarifying the object of desire.¹⁴
- c) Recent research also refers to the negative consequences that hormone treatment can have on bone development and individual growth.¹⁹ The possible effects of hormone therapy on brain development are still being studied

and are not known.^{14,19} Clinically, there do not seem to be effects on social, emotional, and educational functioning, although the effects may be too subtle to be observed in clinical monitoring sessions.¹⁹

Children and adolescents are in a process of physical, psychological, and social development. Considering how the body is developing and evolving at this age, it is necessary to assess the benefit/risk ratio of these interventions. This is an age that is crucial for learning, bonding, and everything related to integral development in general.

CONSIDERATIONS AND SUMMARY

Care for children and adolescents with gender identity disorders or, more recently, gender dysphoria^{4,16} is a controversial and highly complex question due to its ethical and moral implications.^{14,15}

The seventh and latest version of the SOC⁴ expands the section referring to the care and treatment of children and adolescents with gender dysphoria. It maintains the interventions at early ages, as in the sixth version,¹³ and incorporates arguments for and against starting hormonal treatment early. It states that adolescents may be eligible for puberty-delaying hormones as soon as pubertal changes start, recommending reaching Tanner stage II. They may also be eligible for starting hormone treatment at 16 years.

Although follow-up studies are positioned in favor of hormonal interventions at an early age,¹⁵ they also support the need to select the proper candidates to benefit from early treatment to delay puberty.¹⁴ The Netherlands are pioneers in the defense of early treatment of adolescents with gender dysphoria. They have developed and implemented intervention protocols for years with promising results.¹⁹ Some professionals do not favor these early interventions because they fear that the disadvantages of this approach may outweigh the benefits.¹⁵ The diagnosis of gender dysphoria as a starting point for hormonal treatment is made transversely, which carries the risk of making wrong decisions. These young people are at a moment in their life cycle

of change and evolution, which implies the need for precise clinical evaluation and cautious decision-making. Professionals must verify the persistence of symptoms over time and across situations; a variation in symptoms should be considered negative, or unfavorable to intervention and to the prognosis after intervention. This means that the traditional meaning of a favorable prognosis as a reduction in symptoms becomes meaningless here because good prognosis is determined by the persistence of symptoms over time.

Professionals with extensive experience in the treatment of gender dysphoria in Spain have developed clinical practice guidelines for the comprehensive health care of people with gender dysphoria. These guidelines are consistent with international consensus. The protocol for children and adolescents states that the current trend is to maintain prolonged use of GnRH analogues, starting in Tanner stage II and continuing to 18 years, associated with 16 progressive doses of estrogen or androgens.³¹

Diagnostic classifications and SOC are two necessary, but not sufficient, tools. Caring for the population of young people with gender dysphoria requires training and the application of specific intervention protocols, rather than simple extrapolation or adaptation of the protocols used for the adult population. With all the instruments available, professionals must take into account the individuality of each subject.

It has been found that gender dysphoria improves with proper psychological and hormonal treatment, however, more empirical evidence is needed to better justify early interventions.^{15,19} There has been little research or long-term monitoring of either people treated early or those in which no interventions are performed to assess the biopsychosocial impact on adolescent development.

If a child behaves according to the traditional dichotomous model (masculine man/feminine woman), society reinforces this, thus increasing self-esteem and self-concept. According to this point of view, medical treatment favors psychosocial adaptation. However, professionals should also propose alternative therapies that address the different expressions of gender in accordance with each particular case.⁴ Defending a break with a binary view of sexual and gender roles³²⁻³⁴ would bring important and revolutionary social changes.

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