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Review

Managing Gender Dysphoria in Minors—What Insights Does Evidence-Based Medicine Offer in 2024?

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Abstract: Context: A dramatic increase in young people experiencing gender distress has been observed globally over the past 10–15 years, resulting in a surge in demand for specialized care. This increase is particularly notable among female adolescents. Significant misinformation surrounds the clinical management of minors with gender dysphoria/incongruence. While guidelines from organizations such as the *World Professional Association for Transgender Health* (WPATH) have historically guided treatment of the minors, based on the *Dutch Protocol*, these are increasingly challenged due to their reliance on weak scientific evidence. Recent systematic reviews, including those informing the UK's *Cass Review*, have critically evaluated existing evidence, highlighting inconsistencies and insufficient data on the benefits and risks associated with established treatment protocols. This has prompted a readjustment of the framework use of the protocol in several countries, fueled by concerns over both clinical outcomes and ethical implications. The emergence of the debated notion of "*rapid-onset gender dysphoria*" (ROGD) further complicate the clinical landscape and necessitate a critical review of current approaches. **Method:** The article reviews available evidence-based data on the care of children and adolescents diagnosed with gender dysphoria/incongruence, primarily focusing on systematic reviews, including those used to inform the recent *Cass Review*. The analysis includes international literature and hypotheses regarding the increase in children and adolescents seeking for sex/gender reassignment. **Results:** Systematic reviews reveal a lack of sufficient data regarding the benefits and risks linked to the use of the *Dutch Protocol*. Many guidelines promoting gender-affirming care are based on weak evidence. Studies highlight a high co-occurrence of mental health issues in young people seeking care for gender dysphoria. The systematic reviews also reveal significant methodological inconsistencies across different studies, mainly focusing on the lack of long-term follow-up. **Conclusions:** The evidence suggests the arguments supporting the use of early interventions such as puberty blockers and cross-sex hormones are not sufficiently supported by scientific evidence. Concerns regarding the long-term effects and ethical implications of current treatments are raised. Moreover, the article advocates for a more holistic approach to care, prioritizing evidence-based principles and addressing the mental health needs of these young people. It also highlights the recommandations of the *Cass Review* and the European Society of Children and Adolescent Psychiatry (ESCAP), calling for further research with larger, more representative samples and long-term follow-up to fully evaluate treatment protocols.

Keywords: trans-identification; case review; Dutch Protocol; systematic reviews

1. Introduction

Over the past 10–15 years, international literature has consistently agreed that there has been a drastic increase in the number of young people experiencing gender distress [1–5]. The number of these individuals seeking help from specialized care centers is rising at a similarly rapid pace [1,2,4,6]. Additionally, the sex ratio shows a growing predominance of individuals of female sex registered at birth, particularly among adolescents [1,2,7–10]. The same literature highlights the co-occurrence of both psychosocial and mental health issues in these children and adolescents [2,10–15].

There is widespread misinformation both in the general population and in the medical and psychological communities regarding the care of minors presenting what is currently labeled under the international diagnosis of "gender dysphoria" or "gender incongruence," according to the 5th Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) or the 11th Edition of the *International Classification of Diseases* (ICD-11), respectively; both terms continue to be used in clinical practice [3]. Until recently, most specialized centers relied on the recommendations issued by the *World Professional Association for Transgender Health* (WPATH) to manage these young individuals [3,16–18]. This association, along with the *Endocrine Society* (ES), whose recommendations are mutually supportive [3,16,17], has issued guidelines for the care of minors with gender dysphoria, which were long considered the gold standard to follow. In fact, all regional, national, or international guidelines issued thereafter are based on these recommendations [3,16]. Each of them follows a treatment protocol based on gender affirmation, named the *Dutch Protocol* due its origins in the Netherlands. It advocates psychosocial care during the prepubertal period, and hormonal interventions, first with puberty blockers then cross-sex hormones, for adolescents who meet the eligibility criteria as determined by a multidisciplinary team [3,16,19,20]. However, shortly after the international distribution of this treatment protocol, its eligibility criteria began to loosen. In fact, the original *Dutch Protocol* stipulated that treatment could only be initiated in cases of early onset gender dysphoria aggravated during puberty and required a minimum age for receiving treatment. Very quickly, this strict protocol would be applied outside of the established eligibility criteria, in some situations by the pioneers [21–24], but mainly due to the fact that "over time, guidelines across different countries were progressively shaped by a rights-based approach that removed previous safeguards and increased availability of gender-reassignment medical interventions for children and adolescents" [25].

As early as in the 7th version of the WPATH guidelines (2012), both the minimum age requirement for hormonal intervention [3,16] and the medical provider's role as a gatekeeper were removed [26]. Gender specialists therefore adopted the model of 'gender affirming care,' relying on young people's 'self-determination' [3,16,24,26].

However, few clinicians are aware that the strong recommendations made in the guidelines of these associations are actually based on very weak scientific evidence [26–33]. This lack of evidence was highlighted through several systematic reviews. Levels of evidence (or hierarchy of evidence) is a system used to rank medical studies based on the quality and reliability of their designs. [https://openmd.com/guide/levels-of-evidence (accessed on 17 August 2021)].

According to a pyramidal classification, systematic reviews and their meta-analyses are at the top and represent the highest level of study quality. A systematic review of evidence is *"the analysis of a clearly formulated question that uses systematic and reproducible methods to identify, select, synthesize and critically appraise all relevant research that meets predefined eligibility criteria to answer a given research question, and to collect and analyze data from the studies that are included in the review. It should not be confused with a general review in which the literature search is generally not exhaustive and which more often represents the opinion of an expert or a group of experts"* [34].

Systematic reviews can include meta-analyses in which statistical methods are applied to evaluate and synthesize quantitative results from multiple studies [https://openmd.com/guide/levels-of-evidence (accessed on 17 August 2021)].

Prior to those published in April 2024 as part of the recent *Cass Review* [33] conducted in the UK, systematic reviews had already revealed a lack of sufficient data, both on the benefits and on the risks, to justify the use of the *Dutch Protocol* in routine clinical practice in gender services for pediatric population [29,30,35–38]. In this context, Sweden, followed by Finland, reversed course, considering the *Dutch Protocol* to be experimental due to inconsistency and insufficiency of evidence supporting either the benefits or risks of such treatments in children and adolescents. As a result, they issued stricter medicalization criteria for minors treated in gender clinics: puberty blockers and cross-sex hormones can now only be administered within the framework of specific experimental research, at the locations where they are carried out [38–41].

More recent systematic reviews [31,32] commissioned by the NHS in the United Kingdom as part of the *Cass Review* [33], as well as the recent German systematic reviews [28] have also highlighted the inconsistency and insufficiency of data on both the benefits and risks associated with the application of the *Dutch Protocol*. On this basis, the UK has aligned with Sweden and Finland to prohibit the routine use of these treatments in pediatric gender clinics [42].

Despite the current inescapable evidence-based data, transgender rights advocacy groups, activists, patients, and lobbies continue to fight for the removal of restrictions governing the prescription of gender-affirming treatments, often claiming to base their arguments on 'science' as represented by the WPATH guidelines. The administration of these treatments is grounded in the young patient's "self-determination" to support gender expression; the freedom to 'be oneself' should face no medical obstacles. Clinical opposition to the medical aspects of these interventions relying on evidence-based frameworks, for example, would be considered transphobic [24].

The aim of this article is to provide an account of the available evidence-based data to date concerning the care of children and adolescents diagnosed with gender dysphoria/incongruence. In order to do this, the article draws primarily on the findings and analyses of all systematic reviews [1–4,16,31,32,43,44] used to develop the Cass Review [33] published in April 2024, commissioned by the NHS in England. Additionally, through the analysis of international literature, it explores hypotheses that may explain the current increase in the number of children, especially adolescents, experiencing distress related to their sex/gender, and for some seeking clinical interventions.

These individuals deserve to receive, like anyone else, high-quality care [27] based on strong evidence. On the one hand, their unique voices, as well as those of their families, must be met with the utmost respect and professionalism. On the other hand, the care pathways proposed by the medical community must be supported by evidence-based principles.

2. From Transsexualism to Transgender… to "Trans-Identification"

In 1954, Harry Benjamin introduced the term 'transsexualism' as a psychosomatic or somatopsychic syndrome [45]. This term became a diagnosis in the DSM-III-R, before evolving to include Gender Identity Disorders in the fourth version of the DSM.

In 1963, Stoller and Greenson introduced the concept of "gender identity", defined as "the sense of knowing to which sex one belongs" [46,47]. Stoller maintained a clear distinction between sex (male or female), and gender ("a person's degree of masculinity or femininity") [47,48]. As philosopher Alex Byrne noted, referring to the work of Archer and Lloyd, it would have been more "appropriate to speak of *sex* identity" [47,49] because "*gender* identity anticipates the tendency in scientific writing to use 'gender' as a synonym for 'sex'" [47,50]. The DSM-III, in 1980 and 1987, drew on Stoller's definition to describe "gender identity disorder" as a psychopathological condition characterized by incongruence between anatomical sex and "gender identity". This incongruence was not required to be transsexual or experience dysphoria.

When John Money introduced the notion of "gender role" in his new definition of "gender identity", confusion arose: "*Gender identity is the private experience of gender role, and gender role is the public expression of gender identity*" [47,51]. In 1999, Bockting's work further complexified the concepts by introducing an additional stage: "G*ender identity refers to a person's intimate conviction of being male, female, or another gender such as transgender[...] Which "includes transsexuals [...]*], *transvestites [...] transgenders (those who live in the gender role associated with another sex without desiring sex reassignment surgery), bigender, [...] drag queens and kings, [...] female and male impersonators [...]*'' [52].

This broadening of diagnostic criteria and the introduction of the notion of gender role also influenced revisions of the concept of Gender Identity Disorder in the DSM. In fact, during the preparatory work for DSM-V, Zucker had already pointed out that the expanded criteria in DSM-IV might have led to diagnostic errors [53]. He points out that the excessive focus on gender roles obscures the fact that the desire to be of another sex should remain a key element of the diagnosis. He therefore proposed several revisions to the DSM-V criteria, including "tightening" the criteria, and clarifying ambiguous terminology [53]; proposals that were not followed, given that "gender" has almost replaced sex. Alex Byrne notes that "*the original clear definition of 'gender identity' as* "*the sense of knowing to which sex one belongs has been lost [...]. WPATH's glossary entry for 'gender' provides three options, none of which is sex [...]. The term 'gender' can refer to gender identity, gender expression and/or the social role of gender, including conceptions and expectations culturally related to people who have been assigned to male or female at birth*" [47,54].

Starting out with questions about certain young people who already displayed all the traits of future authentic transsexuals [55–57], the concept of the transgender child was introduced, thereby challenging research paradigms. Indeed, "*Research now supports that prepubescent children who identify as transgender understand their gender as clearly and consistently as their developmentally equivalent peers who identify as cisgender*" [58]. Because of this notion, a direct causal relationship has therefore been established in the general population: on the one hand, gender dysphoria is *caused* by a discrepancy between a person's gender identity and their birth sex [57]; On the other hand, gender dysphoria indicates that the child is transgender. This causality—which to our point of view, could be considered as a sophism—has thus introduced the idea that, to alleviate the suffering caused by gender dysphoria, the divergence between "gender identity" and birth sex must be addressed through medicalization prior to adulthood [57]. This oversimplification overlooked the fact that "*not all children with GID [Gender Identity Disorder] will turn out to be transsexuals after puberty [...]. Prospective studies of GID boys show that this phenomenon is more closely related to later homosexuality than to later transsexualism*" indicates Michael Biggs [24], in reference to the 1999 publication of Cohen-Kettenis and Gooren [55].

As a result of this evolution, combined with a widespread depsychiatrization campaign, the distress caused by the mismatch between one's birth sex and the gender/sex with which one identifies was labeled Gender Dysphoria in the DSM-V, and later as Gender Incongruence in the ICD-11.

The near-exponential increase in young people identifying themselves as "trans" and seeking medical gender/sex transition in most industrialized countries is a phenomenon that continues to rise [1,2,4,31]. Previously, gender dysphoria was rare, affecting around 2 to 14 per 100,000 adults [59]. According to data reported by the Tavistock Gender Clinic in the UK, referrals to the service increased from 77 in 2009 to 2700 in 2019–2020 [60]. Furthermore, while historically Gender Identity Disorders were observed in children (GIDC in the DSM-III-R) [53], today, dysphoria primarily begins during adolescence [2,61].

Large-scale data provided by the recent systematic review from the *Cass Review*, which analyzed both the number and characteristics of children and adolescents referred to specialized gender or endocrinology services, confirm these findings [2]. Indeed, the analysis of data from 1972 to 2021 in this review shows a 2 to 3-fold increase in the number of young adolescents referred to gender services over the last 5–6 years (except in the Netherlands, where this increase began in 2011, coinciding with the more routine implementation of the *Dutch Protocol*). Systematic reviews also highlight a gradual inversion of the sex ratio over time: patients referred are now predominantly female [1,2,7–10]. Additionally, international literature agrees that the recent population tends to "self-diagnose as 'trans'", with 60% having already taken steps to refer themselves at specialized centers in their "preferred" gender, and having therefore undergone social transition [2]. This population also shows a higher prevalence of psychiatric co-occurrences that most often precede the onset of dysphoria during adolescence [14,15].

This is when American researcher Lisa Littman introduced the concept of "*Rapid Onset Gender Dysphoria*" [5,6,62] (as distinct from the previously described concepts of "*Early-Onset Gender Dysphoria*") to describe this new clinical phenomenon arising in that population. With this concept, she identifies the sudden emergence of gender dysphoria during or after adolescence in young people who would have never previously exhibited diagnostic criteria suggestive of gender identity disorder [62]. Girls are the first to be affected, in a context of peer contagion. Among these adolescents, 63% had received one or more neurodevelopmental or psychiatric disorder diagnosis prior to the onset of gender dysphoria (46.6% Anxiety, 39.4% Depression, 12% Attention Deficit and Hyperactivity Disorder (ADHD), 8% Obsessive Compulsive Disorder (OCD), 8% Autistic spectrum disorder (ASD), 7% Eating disorder) [62]. Traumatic events preceding dysphoria (such as parental inadequacy, physical, sexual or psychological abuse, and relational breakdowns) were present in nearly 50% of cases [62]. These findings were also noted in an Australian study driven by Kozlowska, raising the issue of insecure attachment patterns in youth identifying as transgender [15]. Recent systematic reviews of the literature strongly confirm these observations [2,63]. They indicate that mental health issues are more frequent among young people seeking care for gender dysphoria compared to the general population of children and adolescents [2,63].

The recent systematic review titled "*Characteristics of Children and Adolescents Referred to Specialist Gender Services: A Systematic Review"* [2] highlights an overrepresentation of the following conditions in the population of young people referred to gender services:

- Autism spectrum disorders (ASD) (combined estimate across studies: 9%)
- Attention deficit hyperactivity disorder (ADHD) (combined estimate across studies: 10%)
- Anxiety and Depression, self-mutilation, suicidal tendencies, and eating disorders, with very high rates, particularly among girls and at older ages (the wide disparities between studies and measurement methods make it impossible to estimate combined figures).
- Adverse childhood experiences:

- Combined abuse and neglect (combined estimate: 11.1% to 67.4%)
- Neglect alone (combined estimate: 10.5% to 11.4%)
- Physical abuse (combined estimate: 15.2–20%)
- Sexual abuse (combined estimate: 5.2–19%)
- Domestic violence (combined estimate: 22.8% and 24.6%), abandonment/adoption (combined estimate: 0.9–8.2%), parental mental illness or addiction (combined estimates: 49.4% to 52.6% for mothers and 38% for fathers).

In light of the conceptual evolution of “gender identity” discussed above, and the changing profile of individuals experiencing gender-related distress, several researchers have come to question the relevance of the “gender dysphoria” diagnosis and its causal connection to “trans-identification” [63–65]. Could the recent increase in reports of ‘trans-identity’ be better understood as a cultural idiom of distress [65], perhaps reflecting a collective way of expressing the challenges associated with puberty and adolescence?

The identification of these young adolescents with the signifier “trans” has led Ledrait and Masson to propose the French concept of “*trans-identification*” [66] to account for the fact that identification with the signifier “trans” appears to be more a process than a fixed identity in response to the distress these young people experience in the face of pubertal challenges. This concept raises questions about the appropriateness of a gender dysphoria diagnosis for these individuals. In this context, clinicians at the *Observatoire La Petite Sirène* have introduced a new clinical proposal called “Angoisse de Sexuation Pubertaire” (Pubertal Sexuation Anxiety) (ASP) [64].

Various findings point to a positive answer to these clinical questions. For example, the *Dutch Protocol* was initially framed by exclusion criteria that now apply to most of this new clinical population of trans-identified adolescents, i.e., those with *Rapid Onset Gender Dysphoria (ROGD).* Yet, the Dutch Protocol has been widely applied to this population, outside its own eligibility criteria [25]. The *Cass Review* highlights the use of such a treatment protocol on an “other” population, drawing attention primarily to the mental health problems of Generation Z [33,42].

These findings underpin one of the main sources of concern for clinicians, who are calling for a need to rethink care in a holistic way [26].

3. Foundations of the Clinical Management of Gender Dysphoria in Minors: The Case of the *Dutch Protocol*

The Dutch Protocol originated from a collaboration between Utrecht psychology professor Peggy T. Cohen-Kettenis and endocrinologist Henriette A. Delamarre-van de Waal from the adult transsexual care center at the Vrije Universiteit Amsterdam Center [19,20, 22,55,56,67,68]. The ability to block pubertal development at Tanner stage II would have the benefit of facilitating future bodily transformation to resemble the desired sex, while also preventing discrimination responsible for psychiatric disorders, according to the minority stress theory [69]. It was also argued that this pubertal blockade would allow the dysphoric young person a “break” allowing them on the one hand a time for reflection on a potential transition later on, and on the other hand allowing time to deepen the diagnosis, while alleviating the worsening of dysphoric symptoms linked to puberty [19,20,55,68].

Puberty suppression entered the sixth version of the Harry Benjamin International Gender Dysphoria Association’s Standards of Care for Gender Identity Disorders (HBIGDA’s Standards of care) in 2002 [70]—which became later the WPATH guidelines—although the number of cases treated since then had remained exceptional [67,68]. The widening of the strict eligibility criteria were already drawn in these guidelines in which the Dutch pioneers were co-writers, as it was “recommended that the adolescent experience the onset of puberty in his or her biologic sex, at least to Tanner stage Two, while also allowing earlier intervention on the recommendation of more than one psychiatrist” [24,70]·

The *Dutch protocol* was published in 2006 [20]. Even though its worldwide adoption relies on only two publications of one cohort study, the first one on a 70-patient cohort [22], and the second one on another sub-study of the same population [71], the *Dutch Protocol* started to be integrated even prior to their publication in 2011 and 2014 in international guidelines [25,57].

In fact, in 2006 “it was incorporated into guidelines developed for the Canadian province of British Columbia” [25] and started to be implemented in the USA in 2007, by the pediatric endocrinologist Norman Spack who co-founded the first Gender Management Service for children in the USA at Boston Children’s Hospital [24].

The Dutch protocol was therefore transcribed in the guidelines of the Endocrine Society in 2009 [57], in which Spack and the Dutch, including Cohen-Kettenis and Delamarre-van de Waal, were part of the comitee [24], driving therefore an increase in puberty blockers prescription in the USA.

Concerning the cohort studies published in 2011 and 2014, the first publication is a prospective study, which involved a cohort of 70 patients who received puberty blockers followed by cross-sex hormones [22]. The second one refers to a subgroup of the same cohort who underwent reassignment surgery [71]. The results of these two studies showed an improvement in gender dysphoria after treatment, using measurement scales which researchers had inverted between the beginning and the end of the study. The first scale of the protocol measured dysphoric feelings toward the patients' biological sex while by the end, the second scale focused on the dysphoric state, in relation, not to the biological sex, but to the resulting sex phenotype after reassignment [22,71]. Such switching of assessment tools in pre- and post- intervention measurements is unprecedented in credible clinical research.

This protocol for minors was quickly adopted internationally and became part of the WPATH best practice recommendations [3,16,54]. However, the eligibility criteria [19,20,56] gradually fell into disuse, as the protocol was prescribed outside these criteria, even by the Dutch [21–24]. In his article entitled "*The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence*" [24], the sociologist Michael Biggs, indicates that *"the protocol as published was not always strictly followed by the clinicians. The minimum age of 12 for puberty suppression was not observed in every case [21] [...] cross-sex hormones sometimes started before the age of 16, as young as 13.9 years [22]. Family support was not essential, as the clinic administered GnRHa to a 14-year-old—who was institutionalized due to a physical handicap—against the parents' objections*" [23].

Despite these critical observations, the Dutch did maintain some safeguards. In fact, the pioneers re-evaluated the Dutch approach [72,73], in the light of the sharp increase of birth-registered female seeking for gender-affirming care in their clinic since 2012. The results of their findings showed that "*the percentage of referrals diagnosed with gender dysphoria remained the same, such as the percentage of diagnosed adolescents that started with affirmative medical treatment, in between 2000 and 2016*" [72,73]. However, they point out the limits of their findings, indicating that "*the adolescents in this study are part of a clinic-referred sample. Therefore, the drawn conclusions cannot be generalized to transgender identifying youth from the general population. It could be that outside of our gender identity clinic, changes over time have taken place that we did not observe*" [72,73].

In fact, in the 7th revision of the WPATH guidelines in 2012 [74], the minimum age requirement for hormonal interventions was removed and the role of medical guarantor weakened [3,16,26,74].

The erosion of safeguards around the prescription process worldwide has to do with rights-based approach claimed by parents and patients themselves [25]. In fact, soon after the first puberty suppression trials, the media coverage of the topic, publicising the possibility of endocrine interventions to suppress puberty in children identifying as transgender, led parents and patients forming groups that became later activists, putting on pressure on medical authorities to authorize the use of puberty blockers in this indication [24]. Without any sufficiently consistent evidence-based data supporting the routine use of the protocol, its application became a question of social justice [24,25].

This confusion between social justice, rights and evidence-based medicine in the application of treatments led to the worldwide adoption of gender-affirming care, often with a lack of rigor and significant heterogeneity in how young people referred to specialized centers were assessed [1,25].

Furthermore, the validity of the Dutch Protocol has been widely questioned [75]. First, the results of the Dutch pioneers proved to be non-reproducible when compared with those of the *Gender Identity Service* (GIDS) at the Tavistock Clinic in the UK [24,75–77]. Second, systematic reviews to date have shown that the data are insufficient and inconsistent both in relation to the benefits on gender dysphoria and mental health and in relation to the risks with this treatment protocol [28–32,37]. Moreover, the systematic reviews analyzing current guidelines have also pointed to a lack of rigor and clarity in the methodological development of the recommendations promoted by WPATH, the Endocrine Society (ES), and the American Academy of Pediatrics (AAP), as well as a lack of transparency in their editorial connections [3,16,33].

4. The Return of the Dutch Protocol to a Strictly Experimental Status? What do We Learn from Recent Systematic Reviews Integrated in the *Cass Review*?

4.1. About the Current Guidelines

The systematic reviews commissioned by the NHS, titled "Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: a systematic review of guideline quality" [3,16] consist of two parts. These reviews are in line with recently published evaluations that have already raised concern about the validity of internationally accepted guidelines [17,18].

These two reviews focus on all globally available guidelines on this issue: twenty-three were identified (including four international guidelines: the 8th version of the WPATH, the Endocrine Society (ES), three regional and the rest national). The evaluation of these 23 guidelines using the AGREE II methodology (AGREE II: Appraisal of Guidelines Research & Evaluation. The AGREE grid is a generic tool primarily intended to help develop recommendations for clinical practice and assess their methodological quality. For more information, please refer to https://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_Instrument_French.pdf (accessed on 17 August 2021)) revealed poor validity scores, particularly in terms of developmental rigor, editorial independence and applicability. On the one hand, the reviews highlighted a lack of clarity regarding the composition of the expert groups drafting the guidelines and the people consulted. On the other hand, they point out that very few guidelines based their recommendations on systematic reviews that had already assessed the benefit/risk balance of hormonal treatments in minors, particularly with regard to their long-term effects [29,30,36–38]. Although some of the guidelines acknowledged the lack of robust evidence to support medicalization in minors, they still concluded that the existing data was sufficient to issue strong recommendations in favor of prescribing puberty blockers and cross-sex hormones [3,16,27].

To explain this phenomenon, the part 1 of the *Cass* systematic reviews on clinical guidelines [3] have dissected the editorial independence mechanisms of these guidelines. They highlighted the fact that they sponsored each other using a circular reference model. The 2009 guidelines from the Endocrine Society [57] and the 2012 guideline versions from the WPATH [74] make few references to other guidelines. This phenomenon could be understood firstly by the fact that the Dutch protocol was quite recent [19,20] and that there were at that time few publications available [55,56,67,68], and secondly, they almost entirely depended on the Dutch who were those sitting in the editorial committees [24].

The guidelines from the Endocrine Society and the one from the WPATH maintained close mutual ties (in 2012 [74], the WPATH integrated the Endocrine Society (ES) recommendations [57] into its own guidelines and in 2017 sponsored and influenced the Endocrine Society). Moreover, systematic reviews show that the 2012 WPATH [74] and 2009 ES guidelines [57] had a strong influence on all subsequent guidelines (whether international, regional or national) [3,16]. As previously said, this phenomenon could in part be explained by a political reclaim of the guidelines, due to a right-based “shift” [25], under the pressure of transgender rights advocacy groups, activists, patients, etc. The right to ‘be oneself’ should not face any boundaries.

Finally, WPATH boasts that its new guidelines issued in 2022, are based on numerous national and international guidelines. However, these new guidelines are, in reality, based on those of the 2012 WPATH. This is how strong recommendations were issued based on insufficient and inconsistent evidence [27].

The reviews also raise the point that the guidelines subsequently drawn up based on the 2012 version of the WPATH guidelines, lack precision on the clinical assessment methodology as well as on clinical intervention. They do not clearly specify when psychosocial and hormonal interventions should be suggested, nor on which criteria they should be based [3,16]. They also lack precision as to the necessary psychological care and the way associated psychiatric comorbidities should be managed.

Moreover, the WPATH guidelines, in addition to blurring the principles that determine eligibility criteria for hormonal intervention, lack clarity on certain subgroups (particularly regarding youth who experience later onset gender dysphoria, during mid-puberty or adolescence) [3,16].

Lastly, a systematic analysis of the twenty-three guidelines identified in the two reviews [3,16] reveals that only the national guidelines from Finland and Sweden stood out from the others. The assessment was carried out using the AGREE II methodology. It highlighted the rigor of their development and the transparency of their evidence-based approach. In fact, they were already based on previous systematic reviews that predated the *Cass Review* which pointed out the lack of sufficient evidence to routinely justify the use of the *Dutch Protocol* [29,30,35–38]. They recommend a cautious approach and emphasize that these experimental treatments should be administered within a very strict research framework. However, although of high quality, these guidelines lack practical directions on how to operationalize, regarding how they could be systematically implemented on national and international level [3,16].

4.2. Regarding the Care Trajectories of Children and Adolescents Referred to Specialized Centers

The recent systematic review titled “*Care Pathways of Children and Adolescents Referred to Specialist Gender Services: A Systematic Review”* [1] analyzed the care trajectories of young people referred to gender services or dedicated endocrinology services. Its findings, now incorporated into the *Cass Review*, provide a quantified view of how young people have been directed through different care pathways–specifically, how many individuals received an assessment, a diagnosis of gender dysphoria/incongruence, medication, how many of them discontinued care, and what psychological support they were offered. Twenty-three studies from nine countries (Australia n = 2, Canada n = 3, Netherlands n = 4, Spain n = 2, USA n = 8, Finland n = 1, Israel n = 1, Scotland n = 1, the UK n = 1) met the eligibility criteria for this systematic review of care pathways.

“*Eighteen studies reported the total number of adolescents who started either puberty suppression and/or masculinising or feminising hormone interventions [...]. Of the 4797 assessed in these 18 studies, 68% (95% CI*

57% to 77%) received either puberty suppression and/or hormones; however, the proportions varied considerably between services (from 21% to 100%) and there were differences between gender (60%; 95%CI 50% to 69%) and endocrine (83%; 95% CI 68% to 94%) services" [1].

Focusing on service type, 83% (95% CI, 68–94%) of young people assessed in dedicated endocrinology services received treatment, while only 60% (95% CI, 50–69%) of those assessed in gender services received treatment. This discrepancy between service facilities is concerning.

The systematic review highlights a significant lack of information in existing studies, both on patient assessment methods and eligibility criteria for treatments. Additionally, there is a notable gap in both qualitative and quantitative data regarding psychological follow-up for young people referred to dedicated services–details such as the type, frequency, duration, and eligibility criteria for such follow-up.

Given the prescription rates, it is worth questioning the argument made by proponents of "the 'pause' concept" [68] to refine the diagnosis before administering puberty blockers, as treatment appears to already represent a first step toward transition.

The systematic review reveals that some of the referred young people drop out at various stages of the process–whether immediately after referral, during assessment, at the beginning of treatment, or when treatment is more advanced. Furthermore, a significant percentage of young people do not pursue treatment after being assessed and/or deemed eligible. Information is lacking on the reasons for these discontinuations or withdrawals, what becomes of these young people, and long-term comparisons with patients who continue with treatment.

Based on these findings, this systematic review recommends that prospective studies follow children into adulthood and gather information on all possible care trajectories (discontinuation, follow-up, transition, etc.) and the long-term effects of each [1].

4.3. Regarding Puberty Blocker Treatments

The recent systematic review titled "*Interventions to Suppress Puberty in Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review*" [31], conducted under the mandate from the NHS, included 50 studies meeting the inclusion criteria for the systematic review. As with the systematic reviews mentioned above, any studies of poor methodological quality, not peer-reviewed, and/or unpublished in English (the international research language), were excluded.

The studies selected for this review were conducted between 2006 and 2022, with 29 completed between 2020 and 2022. They were conducted in the Netherlands (n = 17), the USA (n = 15), the UK (n = 6), Canada (n = 4), Belgium (n = 3), Israel (n = 1), Brazil (n = 1), and Germany (n = 3). Among these studies, 11 are cohort studies comparing adolescents treated with puberty blockers to a comparator cohort; eight are cross-sectional studies with a control group; and 31 studies are pre-post studies within a single treated group, without a comparator cohort. Only four of the studies with comparator cohorts used matched control subjects. Nearly all studies refer to groups of children or adolescents with gender dysphoria from specialized gender or endocrinology services; the vast majority of these studies relied on samples from a single regional or national specialized center per study.

The systematic review highlights the following:

- There are major methodological concerns regarding the studies carried out on this subject and selected for the systematic review. This raises the question of how representative the population samples really are, since most of the studies involve samples selected from a single site of a specialized center per study [31]. Notably, conclusions that internationally supported the *Dutch Protocol* were based on a single-site sample in the Netherlands. The lack of broad representativeness of a single sample was confirmed when results from the cohort treated by the *Gender Identity Development Service* (GIDS) at the *Tavistock Clinic* in London failed to replicate those of the pioneering Dutch cohort studies [24,75,76].
- Significant disparities exist between studies and the outcomes assessed in each, due to considerable heterogeneity in protocols and a lack of accounting for confounding factors, making it challenging to draw general conclusions. Indeed, the systematic review notes insufficient data, in the studies, on eligibility and selection criteria, as well as medium- and long-term follow-up of treated group [31]. It also raises concerns about the comparability of control and treated groups, given insufficient consideration of confounding factors, such as other therapeutic interventions.
- Extensive reproducible evidence indicates the physiological effects of puberty blockers. Studies consistently show that puberty-suppressing treatments reduce sex hormone levels, delay puberty progression, and decrease bone mass, as previously observed in children treated for early puberty. However, as the systematic review points out, unlike the indication of precocious puberty, puberty suppression in the context of gender dysphoria is initiated later [19,20,24,56,68]. Physiological effects may therefore vary depending on whether

treatment is initiated in early or mid-puberty, with different repercussions for those born male or female. In this specific population, the systematic review highlights that the effects are reproducible on bone density, which is compromised, and peak growth, which is delayed compared to control subjects.

- It finally highlights that evidence is insufficient and/or inconsistent regarding the effects of puberty blockers on gender dysphoria, body satisfaction, psychological health, cognitive development, cardiovascular and metabolic risks, and fertility. These results are in line with the systematic reviews already carried out for this population on this issue [28–30,35–38].

4.4. Regarding Cross-Sex Hormone Treatments

The recent systematic review titled "Masculinizing and Feminizing Hormone Interventions for Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review" [32], commissioned by the NHS, included fifty-three studies that met the inclusion criteria. Any studies of poor methodological quality, not peer-reviewed, and/or unpublished in English (the international research language), were excluded.

The studies selected for this systematic review were conducted between 2006 and 2022, with 60% completed between 2020 and 2022. They were conducted in the Netherlands (n = 17), the USA (n = 24), the UK (n = 1), Canada (n = 2), Belgium (n = 2), Israel (n = 3), Brazil (n = 1), Germany (n = 1) Finland (n = 1), and Spain (n = 1). Of the fifty-three studies that met the inclusion criteria for the systematic review, 12 are cohort studies, 9 are cross-sectional studies, and 32 are pre-post studies.

As with puberty blockers, almost all studies referred to groups of gender-dysphoric adolescents from specialized gender services or endocrinology departments, and almost all studies originated from a single regional or national specialized center. In total, all studies included in the systematic review involved 40,906 participants, 22,192 of whom were adolescents with gender dysphoria (including 8164 undergoing hormonal treatment), compared with 18,714 control subjects.

The results of this review point to the same methodological flaws as those cited above for puberty blockers (representativeness of samples and heterogeneity of protocols). In addition, they are in line with other systematic reviews carried out previously, which have also highlighted lack of evidence, insufficiency and inconsistency to date with regard to the benefits and risks attributed to cross-sex hormone therapy in gender-dysphoric minors [28,30,36,37,78–80]·

The findings are also corroborated by the German systematic review published in early 2024 [28], stressing that "*there is currently no evidence of a potential cost-effectiveness ratio for the use of puberty blockers and cross-sex hormones in minors with gender dysphoria compared to one or more psychosocial interventions, social transition to the preferred gender, or no intervention*" [28].

The only systematic review to have given some weight to the beneficial effects of cross-sex hormone treatment in minor [35] included studies of low to very low methodology quality, unlike the one from the *Cass Review* and the German review, which may explain the discrepancy in results [28,32].

4.5. Conclusions and General Observations Concerning the Analyses of These Evidence Systematic Reviews

In short, these systematic reviews highlight the urgent need to standardize studies and conduct them on a much larger scale. They should follow a rigorous, high-quality protocol, with appropriate comparators, to adequately assess the long-term effects of puberty blockers and cross-sex hormones. To achieve this, the short-, medium-, and long-term objectives of these treatments must be defined, as well as what specifically should be evaluated, using valid measurement tools. Also, the future trajectories of these young people previously treated with puberty blockers–toward treatment with cross-sex hormones or toward discontinuation of the process–should be quantified in much larger population samples. Furthermore, the underlying reasons for the various care trajectories (such as withdrawal, continuation, etc.) should be recorded and clarified [1,2,4,31,32,44].

5. Conclusions

The arguments that originally justified using a drug treatment protocol before adulthood in "young transsexuals" [19,20,56] seem to have been invalidated. While the Dutch justified this protocol on the grounds of improved psychosocial functioning later in life, the systematic reviews have failed to demonstrate this. Furthermore, the assertion that a "pause" [68] would help refine the diagnosis has been refuted: systematic reviews have shown that social transition is already an intervention [28,43], and the use of puberty blockers is an additional transition stage rather than a time of "pause" as previously suggested [28,29,31,37]. Lastly, the claim that earlier interventions would yield better outcomes in adulthood requires longer-term studies, which to date have not been published.

Additionally, numerous ethical concerns have been raised regarding the use of the *Dutch Protocol*. Smeehuijzen et al. argue that this protocol inadequately addresses long-term risks and potential regret among patients and does not sufficiently consider the possibility of spontaneous remission of gender dysphoria in adolescents. They suggest the fundamental ethical principle of "non-maleficence" is not upheld, as a follow-up on treated patients has not accounted for their adult sexual functioning, fertility, or brain development outcomes [81]. Clinically and ethically, administering puberty blockers halt not only puberty but also the psychological and physical experiences of puberty. Can a patient who has not experienced the emotions of sexual life in adolescence and adulthood make fully informed decisions about permanently altering reproductive and sexual capacities [24,81]?

An increasing number of clinical studies indicate that borderline personality disorders or other psychiatric difficulties are often co-occurrent with the diagnosis of gender dysphoria, with the risk—if we only focus on the gender issue—to misdiagnose the concurrent personality/psychiatric diagnosis [10,12,15]. It could be of note to question whether it is possible to consider a patient capable of providing informed consent for gender reassignment when they have significant psychiatric comorbidity [14,63]. There could be concerns regarding the genuinely respected ethical principle of "autonomy" when proposing treatments with unknown long-term effects [81,82].

In this context, and without any ideological stance, our clinical approach—guided by differential and functional diagnosis as an evaluative method—compels us toward utmost caution. This caution is further justified by the lack of consensus and uncertainties surrounding the permanence of gender identity in children or adolescents [83–87] as well as by the prominent presence of traumatic symptoms that contribute to the urgency to transition.

Thus, the European Society of Child and Adolescent Psychiatry (ESCAP) (We hereby refer to the ESCAP website: https://www.escap.eu/members (accessed on 17 August 2021)), representing 36 European psychiatry societies, quickly issued recommendations following the publication of the *Cass Review* and associated systematic reviews, relegating the *Dutch Protocol* to an exclusively experimental status [82].

According to the ethical principle of "non-maleficence," the *Society for Evidence-Based Gender Medicine* (SEGM) reports the ESCAP recommendations to "avoid using experimental interventions with potentially irreversible effects or interventions with unknown long-term consequences outside a research setting; to avoid prematurely adopting new practices without sufficient evidence; and to avoid continuing outdated practices that may not be in the best interest of the patient." [82,88].

It is nowadays hard to implement this systematic evidence across regions, in order to perform the revision of their guidelines [3,16]. As exposed in this article, this can certainly be explained by the fact that a right-based approach has slowly driven the erosion of the safeguarding boundaries of treatment protocol application. There could be a conflation between personal narratives and identity formation, on the one hand, and scientific rationality, on the other.

The fact that scientists who are criticizing the low quality of current data, and are trying to improve it are accused of not being well-meaning, illustrates well the confusion between evidence-based practice and rights-based practice in that specific field of gender dyphoria in minors.

It is unprecedented in the history of medicine that referring to systematic evidence to justify whether a drug treatment protocol is relevant "should be interpreted as "phobic" or as "hatred" or "discrimination".

ESCAP calls on "the EU to set up a framework or registry of studies that should include patients currently being treated, patients not receiving treatment and those who have discontinued treatment, in order to better understand the outcomes of different treatment pathways, including cognitive, psychological and physiological effects" [84,88].

As the *Cass Review* states, returning to a holistic approach, without "exceptionalizing" the diagnosis of gender dysphoria, by taking a holistic and comprehensive account of the patient and his or her family, is essential, in order, as ESCAP states, to derive "active learning from any potential past failings in the management of children and adolescents with gender dysphoria, in order to prevent violations of existing clinical, scientific and ethical standards." [82,88].

Author Contributions

B.K.: Conceptualization, Investigation, Methodology, Project administration, Resources, Visualization, Writing—Original draft, Writing—review & editing; A.L. Conceptualization, Investigation, Resources, Writing—Original draft; C.M. Supervision, Resources, Writing—review & editing. All authors have read and agreed to the published version of the manuscript.

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