Electronic Supplementary Online Materials I: Adapted abbreviated English version

Beyond NICE:

Updated systematic review on the current evidence for using puberty blockers and cross-sex hormones in minors with gender dysphoria

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ABSTRACT

Background: Suppression of physiological puberty using puberty blockers (PB) and cross-sex hormones (CSH) is discussed as an intervention in minors (<18 yrs.) with gender dysphoria (GD). In clinical practice, PB and CSH are used on this population. In 2020, the National Institute for Clinical Excellence (NICE) conducted 2 systematic reviews on PB and CSH, respectively, in minors with GD. The NICE review on PB didn't find a clear intervention-specific clinical benefit of PB for critical outcome variables or improvements in GD symptoms in minors. The NICE review on CSH described some possible benefits using results from 5 small and uncontrolled observational studies, but the specificity of the observed effects is unclear. It was concluded that any potential benefits of CSH should be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with GD. Due to significant methodological and study related issues the overall quality of the reviewed evidence (PB & CSH studies) was classified with "very low certainty" according to modified GRADE criteria.

Method: This systematic review involved an updated literature search on the use of PB and CSH in minors with GD based on NICE principles and PICO criteria for all relevant original research studies published since the release of those two NICE 2020 reviews (search period July 2020 – August 2023).

Results: This new literature search retrieved no newly published original studies on NICE-defined critical and important outcomes and the related use of PB in minors with GD according to PICO criteria. For CSH treatment, 2 new studies that met PICO criteria were found, but had low sample sizes, added no new significant evidence on specific beneficial effects of CSH in minors with GD and were classified as "*low certainty"* using modified GRADE.

Conclusions: The currently available studies on PB and CSH in minors with GD show significant conceptual and methodological flaws. The current body of evidence is very limited, based on very few studies with small samples and problematic methodology and quality. Adequate and meaningful long-term studies are equally lacking. Current evidence does not clearly suggest that GD symptoms and mental health significantly improve when PB or CSH are given to minors with GD. Children and adolescents with GD should therefore primarily receive psychotherapeutic interventions that address and reduce their experienced burden. Any decision to use PB and/or CSH should be made on a case-by-case basis after judicious risk-benefit evaluation and, if possible, within clinical studies. Beforehand, psychiatric/psychotherapeutic diagnosis and treatment of concomitant mental disorders should be undertaken.

Keywords: Gender dysphoria, gender incongruence, puberty blockers, cross-sex hormone treatment, minors, transgender

BACKGROUND

The significant increase in the number of children and adolescents (defined as minors < 18 years of age) questioning whether their gender identity matches their biological sex and who seek help, counseling and treatment has not only become an important topic in the field of child and adolescent psychiatry, psychosomatics and psychotherapy, but also for society as a whole [1,2,3]. In Germany, there currently is no central register that captures clinical data on the numbers of young people seeking gender identity services. Nonetheless, recent developments there seem to be comparable with other European countries. In Sweden, the diagnostic frequency of gender dysphoria (GD) increased by 1500% between 2008 and 2018 in the group of 13- to 17-year-old girls [4]. In Great Britain, the number of help-seeking natal females increased more than 70-fold between 2009 and 2016, only to double again between 2020 and 2022. The reasons for these dramatic rises are multicausal and currently a subject of debate among professionals [2, 5].

The exact prevalence of GD as a diagnosis and of individual GD symptoms in children and adolescents is currently unknown. One review that identified a total of 21 prevalence studies on transsexualism found that only 12 had data sufficient for meta-analysis [6]. The meta-analytically determined transsexualism prevalence therein was overall 4.6 per 100,000 (6.8 for male-to-female transitions (MtF, trans women) and 2.6 for female-to-male transitions (FtM, trans men). On a societal level there are currently very dynamic developments underway with regards to the overall field of GD, as for example in terms of related policies and regulations. Moreover, on an individual level GD diagnoses and expressed symptoms leading to a demand for clinical services can shift over time. As a result, societal as well as individual factors make adequate and time-distinct assessments of the exact GD prevalence virtually impossible.

The clinical management of children and adolescents with GD by health care professionals, psychiatrists and psychotherapists is often challenging. One main reason is the current paucity of knowledge about future developments and outcomes in young people presenting to clinical services during childhood or puberty due to incongruence between experienced and biological sex. GD in minors can take various clinical courses, and these can include: Renewed changes in one's experienced gender, many non-persistent variations (as for example in terms of "growing out of it"), a decline in experienced GD over time, the development of a homosexual orientation during adolescence, and persistent GD culminating in transsexual development in adulthood. These varying trajectories may be accompanied by mental health problems [3, 7, 8, 9, 10, 11]. Data on the occurrence and frequency of clinical GD courses are also subject to variation, particularly with regard to characteristics of the investigated cohorts. Minors with GD, their families and the attending health care professionals are presently confronted with a dearth of exact prognostic criteria. Therefore, it cannot be predicted with sufficient certainty how GD as a disorder will develop in any individual in terms of its persistence or desistance.

The variability in developmental trajectories poses a diagnostic-therapeutic dilemma when discussing the use of puberty blockers (PB) and cross-sex-hormones (CSH). Physiological, psychological and sexual developments in young people take time. In minors with GD, this period is shortened when puberty begins with its associated physical, emotional and social changes. In this context, a "non-decision" for or against a particular intervention, such as the use of PB and/or CSH or not is still a decision *per se* [12]. From the perspective of child and adolescent psychiatry and psychotherapy, the level of evidence for such decisions or "non-decisions" consequently holds a crucial position in individualized counselling, diagnostic assessments and treatments. As in other medical subspecialties, no general recommendations can be made in the absence of clear evidence, whereas critical evaluations informed from multifaceted perspectives and expert opinions are necessary in each individual case.

On the one hand, the early use of PB and/or CSH is assumed to allow minors with GD to develop and live in their preferred gender identity. However, it is argued on the other hand that starting treatments too early may suppress homo-, bi- or heterosexual developments. Moreover, physiological changes may cause regret if improvements in well-being are insufficient and infertility is permanent [3, 7, 10, 11]. Given the bioethical considerations and the potential for suppression of homosexuality or for a desire to have children in later adulthood, the significant consequences of potentially irreversible treatments initiated too early deserve critical appraisal.

When making a decision or "non-decision" for medical interventions, clinicians need to be informed by the current evidence on PB/CSH and their effects on critical outcome measures. A compassionate, professional and evidence-based management of minors with GD can be a considerable challenge for practitioners. GD sufferers and their families should therefore be provided with evidence-based information, especially before any partially or fully irreversible medical interventions are performed on minors with primarily biologically healthy bodies. Here, it is important to ask if the expected biological and psychological effects of PB (in terms of identity experience, mental health) are measurable and potentially reversible and if so, in what constellation (treatment duration, dosage) can this be achieved. The term "reversible" also needs to be defined precisely in this particular context. Finally, the question about the actual clinical benefit of using CSH in children and adolescents with GD remains to be answered for the above-mentioned individuals.

Clinical rationale, mechanism of action, risks and side effects of PB

The rationale behind medically delaying physiological puberty in minors with GD is to allow them more time to find their own gender identity. By blocking puberty affected individuals are supposed to not to be fixed towards the non-preferred biological sex by the time secondary sexual characteristics begin to develop but gender-related identity development is not yet

147 complete. In doing so the aim is to reduce the subjective burden and risk for mental health
148 disorders in affected individuals. Because hormone exposure can impact properties like target
149 tissue strength, PB may affect prerequisites for other interventions like CSH treatment or
150 surgeries. After PB, a decision needs to be made if CSH treatment should follow.
151
152 The most frequently used puberty blockers are gonadotropin-releasing hormone analogues
153 (GnRHa). These medications are also used for treating prostate and breast cancer,
154 endometriosis, and precocious puberty in adolescents. During puberty, GnRH is secreted by
155 neuroendocrine cells in the hypothalamus and binds to specific receptors on the cell-plasma
156 membrane of the adenohypophysis. In both females and males, GnRH stimulates the release of
157 LH and FSH – the hormones that make the gonads synthesize and secrete testosterone in males
158 and estrogen and progesterone in females. Most current data on the desired and adverse effects
159 of PB in children and adolescents were obtained from studies on precocious puberty in
160 biological females [13, 14, 15, 16, 17, 18, 19, 20, 21, 22].
161
162 GnRHa have a chemical structure similar to GnRH that enables them to bind with GnRH
163 receptors in the pituitary gland and achieve similar effects. The resulting release of
164 gonadotropins leads to desensitization of gonadotropin receptors. When GnRHa are taken for
165 several weeks, hormone production declines and puberty is paused. If puberty blockers are
166 given very early, the body can sometimes be returned to an earlier pubertal stage. Once
167 treatment with GnRHa is stopped, pubertal development continues. In females, “normal”
168 physiological (but not necessarily psychosocial) puberty along with menstruation and later
169 pregnancy is basically possible, albeit now at a different point in time. CSH given after PB
170 therapy runs a high risk for infertility [23].
171

When GnRHa are used in GD, puberty does not occur at the same time as puberty of one's peers. However, this is an important aspect of adolescence [24], particularly regarding satisfaction with one's own body image [25]. Research has shown an interaction between the timing of puberty (for example, very early) and a risk for depressive symptoms later. Social acceptance is a potential moderating factor when puberty occurs early [26]. Current research suggests that complex interactions take place between the actual timing of puberty, biological sex and the quality of peer relationships [27]. However, these studies did not include minors with GD and thus make ongoing research on this subject necessary. The question of a potential "psychosocial reversibility" of the medical and psychosocial consequences after stopping PB remains unanswered. Aspects of fertility counselling in minors with GD are the subject of current research [28].

Progestins are another type of PB, but less efficacious than GnRHa. A differentiation is made between antiandrogenic (for MtF transition) and proandrogenic progestins. Antiandrogenic progestins like spironolactone and cyproterone acetate can induce natural breast development and reduce masculinization. Spironolactone blocks androgen-receptors and suppresses androgen-dependent hair growth. Proandrogenic progestins are used for FtM transitions and can induce amenorrhea.

The assumption that the use of PB is completely reversible as often communicated in the media currently lacks evidence, and potential long-term effects are unclear [29, 30], see also [2]. Potentially persisting psychological and somatic effects such as changes in cognitive [22, 31m 32, 33, 34] and socio-emotional development [35], sexual experience ability [36] and a possibly iatrogenic induced persistence of GD with suppression of non-transsexual developments (see [37, 38, 39]) as well as a reduction in bone density are of concern (see for example [29, 30] and [40, 41] for an overview). By the same token, a potentially elevated risk for osteoporosis,

hypertension, changes in insulin and lipid metabolism (for example hypercholesterolemia), changes in liver function, and cardiovascular as well as also potentially malignant diseases after CSH treatment need to be discussed (see for example [29, 30, 42]; see also [40, 41]). Overall, the currently available data regarding this particular topic in children and adolescents with GD is very limited, and further studies are necessary.

Clinical rationale, mechanism of action, risks and side-effects of cross-sex-hormones

PB and CSH are given to adapt the GD sufferer's body to the appearance of the preferred sex. For example, testosterone is administered for FtM transitions to induce a male appearance (beard growth, muscle mass, deeper voice, etc.). Conversely, the administration of estrogen for MtF transitions is intended to produce a female appearance (higher pitched voice, breast development, etc.). Transitioning minors risk infertility if CSH are administered after puberty blockage. Despite the medical possibility of prior cryopreservation, i.e., obtaining and freezing eggs or sperm pre-CSH use, there are currently no established standards for fertility counseling for minors with GD in Germany.

METHODS

This systematic review involves an updated literature search on the use of PB and CSH in minors with GD based on principles of the British National Institute for Clinical Excellence (NICE) and PICO criteria for all relevant original research studies published since the release of the two 2020 NICE reviews [40, 41] (search period July 2020 – August 2023)[1]. The latest

[1] *Reviews conducted by the* National Institute for Health and Care *Excellence (NICE) aim to examine the evidence for clinical effectiveness, safety and cost effectiveness of new medical (including pharmacological) interventions. NICE also prepares evidence-based guidelines for the treatment of specific disorders, and publishes recommendations that Public Health and social institutions can use to support affected individuals. Moreover, NICE emphasizes that research studies use the so-called PICO*

evidence as indexed by the most recent systematic NICE reviews on the use of PB [40] and [41] and studies published after this period will be presented and discussed in the following.

In 2020 NICE conducted 2 systematic reviews on PB [40] and CSH [41], respectively, in minors with GD. Neither review found clear intervention-specific clinical benefit of PB and CSH for critical outcomes or improvements in GD symptoms. Moreover, the overall quality of the reviewed evidence was classified according to modified GRADE criteria with *"very low certainty"*.

The NICE review on PB [40] defined "critical outcomes" as impact on gender dysphoria, mental health and quality of life and "important outcomes" as impact on body image, psychosocial impact, engagement with health care services, impact on extent of and satisfaction with surgery and stopping treatment. As regards CSH NICE defined "critical outcomes" as impacts on gender dysphoria, mental health and/or quality of life; "important outcomes" as impact on body image, psychosocial impact, engagement with healthcare services, impact on extent of and satisfaction with surgery and de-transition as well as short- and long-term safety outcomes and adverse effects [41]. These reviews used PICO criteria, briefly for example:

format, and which is common practice in evidence-based clinical research. The use of PICO criteria aims to describe a specific research question in the most accurate manner whilst taking four key characteristics into account:(1) Patient problem or Population, (2) Intervention, (3) Comparison, (4) Outcome(s).

(1) **P**atient or population = Minors (children and adolescents) with GD

(2) **I**ntervention = Suppression of physiological puberty using puberty blockers (PB) or using cross-sex hormones (CSH)

(3) **C**omparison = One or a combination of: Psychological support, social transitioning to the gender with which the individual identifies, no intervention.

(4) **O**utcome(s) = see critical/important above.

CURRENT EVIDENCE ON PUBERTY BLOCKAGE USING GNRH ANALOGUES ACCORDING TO NICE [40]:

PICO characteristics of the studies covered by the NICE review on PB are given in original publication [40]. Relevant information on studies published since the two NICE reviews on PB and CSH (identical literature search methodology) are presented in the Electronic Supplementary Online Materials (ESM II & III) along with the literature research protocol of this paper.

The NICE review on PB [40] comprised publications up to July 23rd 2020 (= date of literature research; according to the original authors the content of this particular NICE review was up-to-date on October 14th 2020). The literature search for the present publication comprised papers published from July 23rd, 2020 to September 7th, 2023 (Embase, Cochrane Library, APA PsycInfo, Ovid MEDLINE®, see Electronic Supplementary Online Materials (ESM) II & III for more details) and used an identical search methodology as NICE.

For reasons of completeness and to not simply reword the previously published PB-related NICE review [40], we here only provide its short but yet very clear concluding statement:

"The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up. Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. The study by de Vries et al. 2011 reported statistically significant reductions in the Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) scores from baseline to follow up, which include measures of distress. As the aim of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics, this may be an important finding. However, as the studies all lack appropriate controls who were not receiving GnRH analogues, any positive changes could be a regression to mean. The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the expected increase in bone density (which is expected during puberty). However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after they are stopped. All the studies that reported safety outcomes provided very low certainty evidence. No cost-

effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria. The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales)."

FINDINGS ON PB POST-NICE REVIEW [40]

Electronic Supplementary Online Materials (ESM) II & III present the detailed results of our new post-NICE [40, 41] literature search from July 23rd, 2020 to September 7th, 2023 (Embase, Cochrane Library, APA PsycInfo, Ovid MEDLINE®). None of the studies on NICE-defined critical or important outcomes identified post-NICE [40] met the PICO criteria and therefore provide no new knowledge on this topic area. The exact reasons for study exclusions are given in Electronic Supplementary Online Materials (ESM) II & III.

CURRENT EVIDENCE ON THE USE OF CSH ACCORDING TO NICE [41]

For reasons of completeness and to not simply reword the previously published CSH-related NICE review, we here only provide its short but yet also very clear concluding statement:

"Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria. Results from 5 uncontrolled, observational studies suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty using modified GRADE. Safety outcomes were reported in 5 observational studies. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass

index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are required. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes. This review did not identify sub-groups of patients who may benefit more from gender affirming hormones. No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria."

FINDINGS ON CSH POST-NICE [41]

The following presents the new post-NICE [41] results of this literature search for CSH studies published between July 23rd, 2020 and September 7th, 2023 (Embase, Cochrane Library, APA PsycInfo, Ovid MEDLINE®). The detailed methodology is provided in Electronic Supplementary Online Materials (ESM) II & III (search protocol). There were only two new CSH studies with original data that met PICO criteria [48, 49]. Twenty-nine other (mostly observational or retrospective) studies that did not meet PICO criteria were excluded mostly for lack of adequate comparisons of treatment effects, i.e., no treated/untreated groups (see Electronic Supplementary Online Materials II & III, reasons for exclusion). The following will focus on the 2 remaining studies that met PICO criteria [48, 49].

The study by Grannis et al. [48] comprised only FtM-transitioned minors with (N = 19; mean age 17.03 yrs. +/- 1.24; mean treatment duration with testosterone 13.13 months +/- 10.28; mean testosterone dose 242.11 mg +/- 82.97) and without testosterone treatment (N = 23; mean age 15.75 yrs. +/- 1.47) as part of an fMRI study examining the processing of facial expressions. The untreated group (N = 8) consisted of treatment-naïve minors awaiting testosterone treatment. A further N = 6 participants had been referred to endocrinological counseling but had not yet received testosterone, and for N = 5 participants, there was no parental consent

available regarding testosterone treatment. A total of N = 3 participants had multiple or other unspecific reasons for not receiving testosterone treatment, and N = 1 participant refused testosterone ([48] in Electronic Supplementary Online Materials). There were no group differences regarding screening for symptoms of autism spectrum disorders (SRS raw values [50]). Generalized and social anxiety, suicidality and body satisfaction were also assessed, but the study did not focus on the treatment effects on these variables. Available data on these outcomes do not allow a pre-post comparison. There was no randomization by group allocation (not a PICO criterion). Anxiety and depression were significantly lower in the testosterone group at the time of assessment, with a tendency for lower suicidality, although direct antidepressant effects of testosterone cannot be excluded. Body dissatisfaction was lower in the testosterone group, and there also was stronger connectivity within a neurocircuitry between the prefrontal cortex and the amygdala in comparison to the untreated group. Group differences in depression and suicidality showed a correlation with body satisfaction/dissatisfaction. The degree of anxiety symptoms was moderated by between-group connectivity differences between the amygdala and the prefrontal cortex.

The study by Morningstar et al. [49] examined the effects of testosterone on neural processing of vocal emotional stimuli compared to similar parental stimuli in minors with FtM-transition with and without testosterone treatment. All participants were PB naïve. Mean treatment duration with testosterone was approx. 1.1 years (range: 1 month to 2.8 years) in the GAH^+ group. There was a significant age difference between the two groups (GAH^+/ GAH^-), and therefore, the results were controlled for age. Regarding potential symptoms for autism spectrum disorders, there were no group differences found using the SRS-2 screening tool [51].

Morningstar et al. (2023) did not look at NICE-defined *critical* or *important outcomes*, but speculated about a potentially more advanced social reorientation in the GAH^+ group because

the reduced neural response toward parental angry voices in the GAH+ group was associated with a stronger relative connectedness to friends in comparison to parents. These authors argued that this was consistent with adolescent development since testosterone influences evaluation of emotional stimuli.

The evidence found in these two new CSH studies [48, 49] can be classified as "low certainty" using modified GRADE criteria (Electronic Supplementary Online Materials IV & V).

Characteristics of excluded studies

The NICE methodology [40] has been criticized on social media in that other relevant studies were not accounted for. For example, Deckert [52] argues that this was the case for studies by Achille et al. [53], van der Miesen et al. [54], De Vries et al. [55], Turban et al. [56], Kuper et al. [57], Schagen et al. [58], Swendiman et al. [59], Jensen et al. [60], Ghelani et al. [61], Klaver et al. [62, 63], and the publication by Vrouenraets et al. [64]. Therefore, a detailed evaluation of these studies seemed reasonable and showed that they

- were without a clear comparative research question with predefined endpoints and PICO format (Ghelani et. al. [61]; Klaver et al. [62, 63]; Jensen et al. [60]; Schagen et al. [58]; Vrouenraets et al. [64]),
- had inadequate quality (Turban et al. [56]; here, the data related to GnRH analogues were not reported separately from other interventions; in the study by Swendiman et al. [59], less than 10% of participants had GD and data were not reported separately; Achille et al. [53] also did not report data separated by intervention).
- had identical participants (de Vries et al. [55] reported in 2014 on a sample already used by de Vries et al in 2011 [65]), which explicitly impacts data interpretation.

The study by Kuper et al. [57] was only discussed in the NICE review on CSH [41] because the majority of participants received CSH; it had similar methodological problems as other excluded research, such as no control group. There were other interventions besides CSH and the findings cannot be linked to specific interventions. The study by van der Miesen et al. [54] was not discussed by NICE [41] as the reported effects could not be specifically linked to PB due to concomitant psychosocial support, it had no control group either.

DISCUSSION

This systematic review presented the currently available evidence on the use of PB and CSH in minors with GD based on PICO criteria by providing short summary and evaluation of the 2020 systematic NICE reviews [40,41[2]] and performing a similar literature search on studies published post-NICE 2020 [40, 41]. The evidence found was evaluated for methodological quality using modified GRADE criteria based on NICE-defined outcomes. The certainty of reported effects was evaluated based on study design, bias, precision, inconsistencies and magnitude of effects. This PICO methodology led to studies on PB and CSH being excluded from the NICE reviews [40, 41] – a fact that, although criticized, was methodologically correct.

New studies post-NICE [40, 41]

The new CSH study by Grannis et al. [48] did not correct for multiple testing on the same dataset and thus risks false-positive findings. It is also unclear whether its findings are actually related to testosterone treatment, particularly regarding *critical outcomes*. This is because no pre-testosterone data were available on the treatment group, and there was no randomized group

[2] *Results of these two already published NICE reviews (NICE 2020a/b) are not presented in great detail in the present paper as they have already been published in English. The original German version of the present paper aimed to present the German readership a summary of available evidence on these particular topics including the already published NICE reviews (2020a/b). Because these two NICE reviews are already available in English and can be freely accessed online, we do not present the findings of these already published reviews in great detail.*

allocation or details on other potentially concomitant psychotherapeutic or other psychosocial interventions. The publication only indicated that *"All participants were receiving gender affirming behavioral health support for gender dysphoria and had not been prescribed pubertal blockers prior"*. No further information on potential psychotherapeutic or other psychosocial interventions was to be found.

In the study by Grannis et al. [48] a total of 52,63% in the treatment group received antidepressive or anxiolytic pharmacological treatments, in the untreated group (= no testosterone) this proportion was 78,26%. The difference in proportion of study participants receiving pharmacological treatments between the testosterone treatment group and the group without testosterone was not statistically significant (significance level of $p < 0{,}01$). Because of the considerable proportion of participants receiving psychopharmacological treatments a significant and relevant mental health burden in the majority of participants of both groups needs to be assumed, and effects of received psychopharmacological treatments on the assessed variables cannot be excluded. Because of the outlined limitations the specificity of the findings by Grannis et al. [48] remains unclear, and the overall sample size of this study is limited. In addition, potential direct (or possibly additive) antidepressive effects of testosterone treatment cannot be excluded. In the light of the aforementioned aspects no further statements can currently be made regarding the effects of testosterone treatment on NICE defined outcome variables in adolescents with GD whilst taking PICO criteria into account.

Overall, the two new post-NICE 2020 [40, 41], PICO-compliant CSH studies [48, 49] do not provide any new robust findings on NICE-defined critical and important outcomes. Reasons for this include study design: neither study explicitly aimed to evaluate the clinical effectiveness of PB and CSH interventions on NICE-defined outcomes, no randomization, no treatment-related baseline or longitudinal data; a very small sample size; the unclear specificity of findings

and a high bias risk. Although the lack of randomization is not a PICO criterion for exclusion, it does increase the risk of systematic bias because potentially detected effects can occur not because of non-intended experimental manipulation, but rather because of unwanted differences between the respective groups. Furthermore, the 2 new studies only looked at people with FtM-transition, while a direct effect on the critical outcome GD was not assessed; no conclusions can be drawn about the cost effectiveness of PB/CSH from them either.

Currently available studies

The currently available evidence on the use of PB and CSH in minors with GD is very limited and based on only a few studies with often insufficient methodology, which were only conducted at a few centers. The results of this review summarizing the effects on the reduction or cessation of GD as well as on critical outcomes and important outcomes are therefore of low quality, and the clinical-scientific certainty of the reported (and often unspecific) effects is low.

All studies discussed in the two previously published NICE reviews [40, 41] are observational and at risk for bias as well as for the impact of other factors that were not assessed. Documentation and control of the impact of psychological and somatic comorbidities as well as other accompanying treatments was insufficient in all studies. These particular studies were conducted in a limited number of centers and often involved small samples, which in turn do not allow for any generalization. As outlined by NICE [40, 41], some earlier studies did not report confidence intervals, and the few detected statistically significant differences in pre-post assessments of variables and bone density were mostly small in magnitude (see NICE 2020 [40, 41] for a summary of previous studies). Therefore, the clinical meaning of these findings currently remains unclear. Some studies have other severe methodological weaknesses, such as

deficient data analysis, a lack of randomization [48, 49], and no predetermined endpoints of treatment-related data.

The results presented here do not suggest that PB or CSH actually improve GD specifically or mental health in a broader sense. Indeed, an alternative interpretation could be that an unchanged experience of GD and body dissatisfaction after PB use constitutes successful treatment in that PB use prevented any further exacerbation of GD by stopping the development of secondary sexual characteristics. Nonetheless, a control group would have been necessary to prove such an interpretation.

The rise in the administrative GD prevalence in the last few years has been accompanied by changed characteristics in populations demanding services and being enrolled in studies [5]. Recently, an increase in the number of biological girls with GD onset in early or mid-adolescence has been observed [5]. Moreover, minors with GD present with more covarying mental disorders compared to the total population [66, 67].

The strength of this review lies in its broad literature search based on identical criteria and methodology as the last two NICE reviews on this topic area [40, 41]; the evidence found was additionally evaluated using modified GRADE.

Quality of current evidence

The current evidence on the efficacy of PB/CSH treatment for children and adolescents with GD is poor. The results of the 2 NICE reviews [40, 41] and our systematic literature published since then do not reveal a clear intervention-specific clinical benefit for affected minors regarding the studied outcomes with sufficient certainty. Controlled long-term studies on the effects of PB and CSH in children and adolescents with GD are missing. This prompts the question of the content and evidence-based value of the clinical conclusions of such studies on PB and CSH. In this context, careful evaluation between *"harming through active actions"* versus *"harming through waiting"* as part of both a dialogical process and a multi-professional concept for assessment and treatment needs to occur. Developments in other European countries can provide some orientation in this particular context.

The European perspective

Given the insufficient evidence on the efficacy and safety of PB/CSH for treating GD in children and adolescents, England, Sweden, Finland and Norway have enacted health policy consequences.

In England, PB may only be used in clinical studies as far as the NHS is concerned [68], stressing that most children and adolescents with GD also have psychological problems or neurological developmental issues in addition to personal, family-related or social conflicts. According to the NHS, this might encourage the desire for treatments. The relationship between such factors and perceived GD may not be entirely visible and potentially uncovered after careful examination.

Primary interventions for minors should therefore be psychosocially based, including psychoeducation and psychotherapy, with the main aim of reducing the burden associated with

519 the perceived incongruence and improving the overall global functioning and well-being of
520 affected individuals. It is argued that clinical practice should be open to evaluating all
521 developmental psychological and psychosocially appropriate options for children and
522 adolescents with perceived gender-specific incongruence. It should be considered that GD can
523 be a temporary phase, particularly in prepubertal children. In this context it is stressed that an
524 early social transition has risks, such as children and adolescents having difficulties later
525 following their own wish to return to their initial gender role.
526
527 In 2022, the *Swedish* NBHW updated its health guidelines on and restricted the use of PB/CSH
528 in minors with GD [4]. The need for a thorough assessment was emphasized, and hints for
529 autism spectrum disorders require further diagnostic steps. Psychological and
530 psychotherapeutic interventions were recommended as first-line treatments for children and
531 adolescents with GD. It was stressed that the therapeutic emphasis should comprise aspects of
532 gender identity, and that therapy should be open toward various outcomes. Treatment with PB
533 and/or CSH should only occur in rare cases and at highly specialized centers as part of research.
534 Prepubertal onset of GD as well as a minimum 5-year duration of GD are prerequisites for using
535 PB in adolescents. Only rare isolated cases of post-pubertal onset of GD, particularly
536 biologically male patients, should be offered PB treatment. Suitability for PB/CSH as well as
537 the minor's capacity to consent to the magnitude and meaning of the planned interventions
538 should be assessed by an interdisciplinary clinical team. In Sweden, a minimum age of 12 years
539 and Tanner stage 3 are mandatory for receiving PB treatment, and CSH can only be given from
540 at a minimum of 16 years of age.
541
542 In 2020, *Finland* had already strictly limited the use of PB as recommended by the Council for
543 Choices in Health Care. In *Norway,* recommendations are currently subject to revision.
544

The authors of this paper believe that England and the Scandinavian countries mentioned have drawn adequate conclusions from the current evidence on diagnostic assessments and treatments for minors with GD. In particular, these countries consider the developmental variability and significant heterogeneity of GD [3] and that the underlying causes of GD and gender incongruent self-identification can be myriad and multicausal. Regulations in England and Scandinavia are in line with recommendations made in the review by Thompson et al. [69]. Following the principle "*primum non nocere – first do no harm",* Germany should also focus on psychological and psychotherapeutic interventions for minors with GD. Inaction, of course, also carries risks and consequences, and only high-quality evidence can reliably guide clinicians to make the right decisions for vulnerable young people [70].

Based on the grounds of the currently available evidence treatments using PB and / or CSH should therefore only be done on an individual case-by-case basis after a through child and adolescent psychiatric assessment and treatment of potentially co-occurring mental health problems or disorders. In this context indication for treatment should be made after thorough clarification of the above-mentioned aspects as part of a multidisciplinary team and involvement of the patients and relevant carers, and while considering co-occurring symptoms as well as adolescent identity development.

CONCLUSIONS

Based on the currently available evidence, treatments using PB/CSH should only be given on a case-by-case basis after comprehensive child and adolescent psychiatric assessment. Any potential co-occurring mental health problems or disorders should be treated. The indication for treatment should be rendered after thorough diagnostics within a multidisciplinary team,

involving the patients and relevant caregivers with consideration of co-occurring symptoms and adolescent identity development.

- Currently available evidence on the use of PB/CSH in minors with GD is very limited and based on only a few studies with insufficient methodology and quality. There is a lack of controlled long-term studies.

- According to PICO and Modified GRADE criteria current studies do not suggest that GD and mental health show relevant improvements as a result of PB/CSH treatment with sufficient certainty.

- Children and adolescents with GD should therefore primarily receive concomitant psychotherapeutic interventions aimed at reducing the burden associated with experienced gender incongruence and improving overall global functioning and well-being.

- Treatments with PB/CSH in minors with GD should only be performed on an individual case-by-case basis after a thorough risk-benefit analysis, a through child and adolescent psychiatric assessment and treatment of potentially co-occurring mental health problems or disorders, and if possible as part of research studies.

- There is currently no evidence of a potential cost effectiveness for the use of PB/CSH in minors with GD when compared to one or more psychosocial interventions, social transition to the preferred gender or no intervention.

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LIST OF ABBREVIATIONS

ACC = Anterior cingulate cortex

CBCL = Child Behaviour Checklist

CSH = Cross-sex hormones

fMRI = Functional magnetic resonance imaging

FSH = Follicle-stimulating hormone

FtM = Female-to-male transitions (trans men)

GAH = Gender affirming hormones

GD = Gender dysphoria

GnRH = Gonadotropin-releasing hormones

GnRHa = Gonadotropin-releasing hormone analogues

GRADE = Grading of Recommendations, Assessment, Development, and Evaluations[3]

LH = Luteinizing hormone

MtF = male-to-female transitions (trans women)

NBHW = Swedish National Board of Health and Welfare

NHS = National Health Service, England

NICE = National Institute for Clinical Excellence

PB = Puberty blockers

PICO = Patient/Problem/Population, Intervention, Comparison/Control/Comparator, Outcome(s)[4]

SRS = Social Responsiveness Scale

SRS-2 = Social Responsiveness Scale – Second Edition

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[3] *Framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations*

[4] *Process / framework in evidence-based medicine*

YSR = Youth Self-Report

DECLARATIONS

Ethics approval and consent to participate:

Not applicable (systematic review)

Consent for publication:

All authors have consented to publishing this systematic review.

Availability of data and materials:

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Authors' contributions:

FDZ wrote the manuscript together with MH (introduction), ML, CL, TB and VR (discussion) and further input by AK and LK. LK and AK conducted and coordinated the literature search with additional support by see acknowledgements.

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Competing interests / disclosures:

Participation in guidelines:

FDZ: From mid 2020 until November 29th 2022 FDZ was a member of the steering group of the German AWMF-S3-Guidelines "*Sex-incongruence and gender dysphoria in children and adolescents: Diagnosis and treatment"* (adapted author-translated German title of the S3 guidelines, Register No. 028–014). Because of his professional and ethical doubts and concerns regarding these particular S3 guidelines as well as his concerns about the protection of health in children and adolescents in the light of these new S3 guidelines FDZ left the above-mentioned steering group and discontinued working on these particular guidelines.

Consultancy & Speaker-Honoraria (last 3 years):

FDZ: Consultancy and speaker-honoraria by Takeda / Shire. Consultancy was in the context of ADHD and co-morbid disorders. As regards speaker activities two presentations with an extended thematic reference to the topics of the current paper were supported by Takeda. In particular, one of these presentations was an overview on trans-identity and the evidence of blocking puberty including GnRH analogues and the use of hormones in minors with gender dysphoria. The other presentation was on the clinical implications on ADHD with co-varying trans-identity and included aspects of the evidence of using GnRH analogies and CSH. There was no consultancy or other speaker activity supported by Takeda in relationship to GnRH analogies. Speaker honoraria also by Medice (context was only about ADHD and comorbidities). No ownership interests regarding pharmaceutical agents or medical products.

TB: Consultancy for Eye Level, Infectopharm, Medice, Neurim Pharmaceuticals, Oberberg-GmbH and Takeda (no consultancy or speaker activity for Takeda in relationship to GnRH

analogues), and speaker-honoraria by Janssen-Cilag, Medice and Takeda. Author honoraria by Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press.

MH: Honoraria by Hogrefe, Medice and Takeda (no consultancy or speaker activity for Takeda in relationship to GnRH analogues). No ownership interests regarding pharmaceutical agents or medical products.

VR: None. LK: None. AK: None. CL: None. ML: None.

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