



Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2016 April ; 23(2): 172–179. doi:10.1097/MED.000000000000236.

Research Priorities for Gender Nonconforming/Transgender Youth: Gender Identity Development and Biopsychosocial Outcomes

J Olson-Kennedy¹, P. T. Cohen-Kettenis², B.P.C Kreukels², H.F.L Meyer-Bahlburg³, R Garofalo⁴, W Meyer⁵, and S.M. Rosenthal⁶

1
2
3
4
5
6

Abstract

This review summarizes relevant research focused on prevalence and natural history of gender non-conforming / transgender youth, and outcomes of currently recommended clinical practice guidelines. This review identifies gaps in knowledge, and provides recommendations foci for future research.

Recent findings—Increasing numbers of gender nonconforming youth are presenting for care. Clinically useful information for predicting individual psychosexual development pathways is lacking. Transgender youth are at high risk for poor medical and psychosocial outcomes. Longitudinal data examining the impact of early social transition and medical interventions are sparse. Existing tools to understand gender identity and quantify gender dysphoria need to be reconfigured in order to study a more diverse cohort of transgender individuals. Increasingly, biomedical data are beginning to change the trajectory of scientific investigation.

Summary—Extensive research is needed to improve understanding of gender dysphoria, and transgender experience, particularly among youth. Recommendations include identification of predictors of persistence of gender dysphoria from childhood into adolescence, and a thorough investigation into the impact of interventions for transgender youth. Finally, examining the social environments of transgender youth is critical for the development of appropriate interventions necessary to improve the lives of transgender people.

Corresponding author: Johanna Olson-Kennedy, MD, 5000 Sunset Blvd, 4th floor, Los Angeles, CA 90027, jolson@chla.usc.edu, (323) 361-3128.

Conflicts of Interest

The remaining authors have no conflicts of interest.

Keywords

transgender youth; gender dysphoria; gender nonconforming

Introduction

While significant advances in the last two decades have been made in the understanding of transgender individuals and approach to care, many questions remain unanswered. In June of 2014, a group of Endocrinologists and other medical professionals experienced in the care of transgender individuals convened at the Endocrine Society Annual Meeting to form TransNet. TransNet is an international collaboration aimed at studying the medical and behavioral outcomes of psychological, hormonal, and surgical interventions currently utilized to alleviate gender dysphoria, as well as the epidemiology and etiology of the transgender phenomenon. The focus of this manuscript is to summarize the report of the TransNet working group on **Gender Nonconforming/Transgender Youth** presented at the National Institute of Child Health and Human Development in May of 2015. This working group was charged with summarizing relevant existing research focused on prevalence, natural history, and outcomes of currently recommended clinical practice guidelines, identifying gaps in knowledge, as well as limitations of and barriers to optimal care. In addition, the group focused on current knowledge of biologic factors that influence the development of gender identity. Finally, this summary concludes with recommendations foci for future investigations in this rapidly expanding field.

Background

Individuals with gender behaviors, expression and identities that depart from the cultural norms and expectations implied by their assigned sex at birth have been labeled “gender nonconforming,” “gender expansive,” or most commonly, “transgender.” Many, but not all, gender nonconforming or transgender individuals experience gender dysphoria, the ongoing distress that arises from the incongruity of assigned sex at birth and internal experience of gender. Gender Dysphoria is described in the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5), and replaces the previous clinical entity, “Gender Identity Disorder [1].”

An increasing number of preadolescents and adolescents identifying as “gender nonconforming”, “gender expansive”, or “transgender”, are seeking medical services to diminish gender dysphoria, and enable the development of physical characteristics consistent with their experienced gender. Concomitantly, the number of dedicated transgender youth clinics has been expanding in pediatric hospitals and institutions around the United States [2–5,6], while the average age at referral has dropped over the last decade [2,7].

As transgender stories have become increasingly visible in the mainstream media, as well as an increase in access to the transgender community via the Internet, conversations about gender identity have been changing. While data describing pre-pubertal gender nonconforming youth indicate that most do not persist as transgender adolescents or adults,

some studies have yielded tentative predictors of persistence. What is missing is information that can be used clinically for predicting individual psychosexual development pathways [8–11].

The onset of puberty in transgender youths is often accompanied by specific anatomic dysphoria, that is, distress evoked by the incongruence between the experienced gender identity and the developing secondary sex characteristics. In 2009, the Endocrine Society published Guidelines for the Care of Transsexual Individuals that included recommendations for the treatment of gender dysphoric youth. One important recommendation is the use of gonadotropin hormone releasing hormone analogues (GnRHa) to suspend the endogenous puberty of gender dysphoric youth in the early stages of puberty (Tanner 2–3) with the addition of cross sex hormones at about the age of 16 in order to induce masculine or feminine features that more closely align with the young person's internal experience of gender. Surgical intervention to improve gender dysphoria is recommended after the age of majority [12]. These recommendations are based on limited longitudinal studies demonstrating that those individuals identified as gender dysphoric in early or middle childhood who still meet the mental health criteria for being transgender at early puberty are likely to identify as transgender adults.

While recent reports from the Netherlands have shown that gender dysphoria may indeed be ameliorated by a gender-affirming model of care including puberty suppression, cross sex hormones and gender confirming surgery, currently available data are relatively limited, and many questions remain unanswered [13–15].

Well outlined in the extant literature are data that consistently reveal transgender youth are at increased risk for depression, suicide, and other adverse outcomes, including illicit drug use and HIV infection [16–18]. The goal of ongoing and future research is to understand more completely gender nonconformity and transgender experiences from early childhood through early adulthood. For the youngest cohort of gender nonconforming children, the impact of early social transition on physical health and social functioning has not been determined. For older youth, further specific inquiry is necessary to determine if puberty suppression in early pubertal gender dysphoric youth, followed by cross sex hormones, leads to improved quality of life and a decrease in negative mental health outcomes. In addition, for gender dysphoric youth presenting in late puberty or after completion of puberty, it will also be important to determine the impact of phenotypic transition on quality of life and mental health outcomes. Also useful would be studies examining the characteristics of those youth who choose to not pursue cross sex hormones, or discontinue their use after starting.

Biologic underpinnings of gender

Gender identity development is thought to reflect a complex interplay of biologic, environmental, and cultural factors. Studies that shed light on the biologic underpinnings of gender identity may underscore the concept that, much like sexual orientation, gender identity is not a choice, and may thus promote further understanding and acceptance of transgender individuals. With respect to evidence supporting biologic underpinnings of

gender identity, data are derived primarily from three biomedical disciplines: endocrine, genetic, and neuroanatomical, recently reviewed [19, 20].

Androgens and gender identity

While the majority of transgender individuals do not have a disorder of sex development (DSD), studies of persons with DSDs have helped inform our understanding of gender identity. Such studies have primarily explored the role of prenatal and postnatal androgens in gender identity development. While a detailed analysis is beyond the scope of this manuscript, insights about the potential role of androgens have been derived primarily from infants assigned female who had diverse hormonal DSDs (e.g., 46,XX individuals with increased androgen exposure and 46,XY individuals with decreased androgen exposure/activity) and non-hormonal DSDs (e.g., 46,XY individuals with cloacal exstrophy). When raised female, the majority of these individuals reported a female gender identity in adulthood, but the prevalence of transmasculine identity was significantly greater than expected in the general population [21,22]. Thus, studies conducted with people with DSDs suggest a limited, but significant role of prenatal and potentially postnatal androgens in gender identity development.

Genetic contribution to gender dysphoria

Numerous studies have suggested a role of genetics in gender identity development. A review of earlier case reports on twin pairs yielded a 39.1 % concordance rate of transgender identities in monozygotic twin pairs versus 0% in dizygotic twin pairs, which implicates genetic factors in the development of gender identity [23]. Studies aimed at identification of individual candidate genes have been inconsistent.

Neuroanatomical considerations

A review of the magnetic resonance imaging (MRI) structural brain studies using voxel based morphometry, cortical thickness, and diffusion tensor imaging, shows that the brain phenotype of adult transgender individuals might consist of a mixture of feminine, masculine and defeminized traits in transgender men and feminine, masculine and demasculinized traits in transgender women [24–28].

During the last couple of years the first study of structural connectivity using graph theory was reported. Connectivity has also been approached using resting-state functional magnetic resonance imaging (fMRI) [29]. Both structural and connectivity studies provide evidence for phenotypes for transgender women and men. Functional MRI studies have been focused on sexually dimorphic traits like visuospatial abilities (mental rotation) [30, 31] and verbal fluency [32]. In addition, positron emission tomography (PET) studies have addressed hypothalamic responses to putative pheromones that act in a sexually dimorphic manner [33].

While fMRI and PET studies show that gender incongruent persons have patterns of activation that differ from their natal sex, more integrative work and future research on the etiology of gender incongruence and gender dysphoria are needed.

One recent neuroimaging study showed that gray matter volumes of adolescents with gender dysphoria are, on a whole brain level, in line with their natal sex, but when analyses are done in regions of interest, there is some indication for sex atypical differentiation [34]. There is only one fMRI study exploring puberty suppression and executive functions [35]. Brain studies are potentially important in the child and adolescent age group (a) to clarify the etiology of gender dysphoria and (b) to examine the effects on the brain of puberty blockers and cross-sex hormone treatment.

Prevalence of gender non-conforming children and adolescents

There is no consensus on the prevalence of gender non-conformity amongst children and adolescents, and conducting studies in this area is fraught with methodological challenges ranging from recruitment and reporting biases to difficulties in measurement given the fluidity and non-binary nature of gender expression and identity. Amongst Dutch children assessed on the Child Behavior Checklist, 2.5 – 5% of parents responded positively to a question related to their child “behaving like the other sex” and 1.4 – 2% responded positively to their child identifying as the other sex. Among Dutch adolescents, 1.1 – 3.1% responded positively to behaving like the other sex, and 0.2 – 0.4% identifying as the other sex [36]. Among children in the United States assessed with the Child Behavior Checklist, between 1.3 and 5.0% of parents responded positively to queries regarding their children “wishing to be of the opposite sex” and between 0.9 and 12.9% responded positively to the query regarding “behaving like the opposite sex [36].” The sex ratio of gender dysphoric youth evaluated in Toronto and Amsterdam prior to 2006 indicated that there were significantly higher numbers of individuals assigned male at birth than those assigned female at birth. However, from 2006–2013, the ratio in both clinics favored individuals assigned female at birth [38]. Clinicians from gender clinics in the United States report a ratio closer to 1:1, with a growing number of assigned females at birth [4, 39].

Developmental Pathways

Two areas of interest and importance to both families and caregivers is the percentage of gender dysphoric children who go on to have gender dysphoria and/or transgender identities in adolescence and adulthood (“persisters”), and what the predictors are of this developmental trajectory. The earliest studies published prior to 1987 identify a very small number of “persisters” ranging from 2–9% [40, 41]. The subjects in these reports were small in number, assigned male at birth, with unclear diagnoses in terms of DSM criteria of gender identity disorder (DSM IV-TR) or gender dysphoria [42]. In more recent studies persistence rates range from 12 to 39%, but also include children who are sub-threshold for DSM diagnoses [8, 43, 44]. All of the existing studies include both gender nonconforming and gender dysphoric youth, drawn from clinics with different approaches to care, and using differing follow-up intervals. Predictors associated with the persistence of gender dysphoria in the Netherlands include intensity of gender dysphoria in childhood, older age of presentation to the clinic, female assignment at birth, and social transition to the asserted gender in childhood [8–11, 43]. Clinicians in the United States and the Netherlands report that increasing numbers of children are choosing to socially transition prior to the onset of puberty [10]. In a qualitative study from the Netherlands, 14 youth with persistent gender

dysphoria, and 11 youth whose gender dysphoria dissipated were interviewed to further understand the differences in their experiences of gender over time. The age that seemed to be crucial for the developmental trajectory of persistent gender dysphoria or transgender identity was between 10 and 13 years. Reported factors that affected persisters and desisters differentially were the changes in their social environment, body changes associated with puberty and the experience of falling in love or experiencing sexual attraction [11].

Behavioral and Emotional Problems

The behavioral and emotional problems of children with gender dysphoria have been fairly consistent in the extant literature. The data come from sites outside of the United States: Canada, Netherlands, United Kingdom and Germany, again highlighting the need for studies conducted within the United States. Children with gender variance show both increased internalizing and externalizing behavioral and emotional problems compared to non-referred controls [44,45]. Additionally, studies have shown that adolescents with gender dysphoria have even greater emotional and behavioral problems than gender variant children [46, 47]. In 2011, deVries et al. reported on 70 transgender youth eligible (by conservative criteria) for medical intervention at the Amsterdam Gender Identity Clinic of The VU University Medical Center. Forty-four percent of the sample scored in the clinical range on the Child Behavior Checklist (CBCL) total problem scale (compared with 8%-9% Dutch adolescent norm), and 29.6% scored in the clinical range on the Internalizing Scale of the Youth Self-Report (also compared with 8%-9% Dutch adolescent norm) [48]. In another Dutch study on 105 adolescents it was found that, according to DSM-IV criteria, anxiety disorders occurred in 21%, mood disorders in 12.4% and disruptive disorders in 11.4% [49]. A 2012 report of transgender youth presenting to the Gender Management Service at Boston Children's Hospital showed high prevalence of psychiatric morbidities including depression (58.1%), and anxiety (16.3%) [38]. In 2014, a report from Vancouver, BC reported similar psychiatric morbidity among 84 transgender youth, including mood disorders (35%), anxiety disorder (25%), suicide attempt (12%), and psychiatric hospitalizations (12%) [3]. In a study of 101 youth in Los Angeles with gender dysphoria, 35% of participants had depression scores in the clinical range, 51% reported ever thinking about suicide, and 30% had attempted suicide at least once in their lives [4].

Evaluation of the outcome of puberty suppression followed by cross sex hormone administration has only taken place in cohorts of youth undergoing treatment in the Netherlands. Of the first 70 youth presenting to the clinic in childhood, 55 had, at the time of the study, "completed" the Dutch treatment model (beginning puberty suppression at the age of 12 years, initiating cross-sex hormones at 16 years, and performing gender confirmation surgeries after age 18 years) and agreed to participate. After puberty suppression with GnRH analogues, scores on the CBCL were significantly reduced. One year after surgery, gender dysphoria was significantly decreased, body satisfaction with primary sexual characteristics significantly improved, and subjective well-being was similar or better than in age-comparable young adults from the general Dutch population [14].

Standardized quantitative measures and systematic qualitative studies designed to collect information about children's experience of gender and gender dysphoria would help us understand the cognitive and emotional processes involved.

Autism Spectrum Disorders and Gender Variance

The prevalence of autism spectrum disorder (ASD) was found to be 10 times higher in the population of Dutch children with gender dysphoria, who were referred to a gender identity clinic, than in a population of typical children [50]. Prevalence statistics from a referral population may not be generalized to the larger population. Because it may be more difficult to diagnose and counsel children and adolescents who have gender dysphoria and autism, future studies should examine the relationship between these two conditions in more detail.

Existing tools to measure gender

Critical to understanding optimal timing and outcomes of intervention for children and youth is the development of accurate tools to measure gender dysphoria. Currently, there are four scales used to evaluate gender identity/dysphoria. For adolescents there is the Utrecht Gender Dysphoria Scale and the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults [51]. The Utrecht Gender Dysphoria Scale is a 12-item tool that assesses aspects of female and male experience that may be problematic for gender dysphoric youth. Higher scores on this scale indicate higher or more intense levels of gender dysphoria. There are two different sets of questions, one for assigned girls and one for assigned boys. The questions are different, and therefore not comparable. This limits understanding of the differences between transmasculine and transfeminine experiences of gender dysphoria. Additionally, the elements of the scale are such that comparisons of gender dysphoria in pre and post treatment participants necessitate administration of the opposite questions in the post treatment evaluation. Finally, the questions are very gender binary in nature, with no adequate mechanism to capture those youth who have non-binary gender identities. The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults is not appropriate for younger adolescents, and is also gender binary in the nature of the inquiries. To identify gender identity and gender dysphoria in children there is the Gender Identity Questionnaire of Childhood (GIQC) [52–55] and the Gender Identity Interview for Children [49]. The parent-administered GIQC assesses both gender-typical behaviors and gender identity in combination rather than separately. However, the Gender Identity Questionnaire is an instrument that does examine the child's own gender experience. The development of culturally relevant tools that reflect the child/adolescent's experience of gender identity, as well as measures of gender dysphoria that might change over time are absolutely necessary to understand the impact of interventions.

Gaps in Knowledge

Virtually all of the outcome data in gender non-conforming children, peri-pubertal and adolescent transgender youth have been carried out in Europe and Canada [13, 14,15, 56]. There are no long-term outcome data for either pre-pubertal or adolescent transgender youth originating from the United States. Recently, a four-site study in the United States designed

to examine the impact of early treatment in transgender youth was funded by the NIH and is about to begin.

While the work in the Netherlands has been critical to the field of transgender youth care, the results are limited for several reasons. Primarily, gender dysphoric youth in the Netherlands may not reflect the ethnic or cultural diversity of transgender youth in the United States and elsewhere around the world. In addition, the social context of growing up as a gender dysphoric child in the Netherlands including outcomes related to the use of pubertal blockers and cross sex hormones may be quite different than in other parts of the world. Transgender and gender nonconforming youth are seen in one specific gender identity clinic that is the primary resource for the majority of gender dysphoric children and adolescents in the Netherlands. Additionally, due to the constraints of the current health system and resulting lack of access to adequate and timely care in the United States, there is poor consistency to medical practice models around the country.

Conclusion

Significant gaps in knowledge exist in nearly all aspects of gender variance, gender dysphoria and transgender experiences of children, adolescents and young adults. This working group has divided the research priorities and recommendations into three distinct cohorts; pre-pubertal gender nonconforming/variant children, early pubertal youth and late pubertal/post-pubertal youth.

1. Pre-pubertal youth
 - a. Assess the prevalence and predictors of persistence among children with gender dysphoria
 - b. Examine outcomes of a gender-affirming model (the process by which individuals are affirmed in their gender identity through social, peer, familial, medical, and legal interactions) vs. other approaches to the care of pre-pubertal youth
 - c. Examine the impact and implications of social transition in childhood
2. Early pubertal youth
 - a. Understand optimal timing of intervention with puberty blockers
 - b. Assess the effect of puberty blockade on mental and social health/behavior and the potential effect on adolescent risk-taking behaviors including but not limited to suicidality, substance use and sexual activity
 - c. Assess the impact and safety of puberty blockade on bone health, metabolic markers, brain development and fertility
 - d. Assess efficacy of different medications used to suppress puberty; GnRH analogue implants, GnRH analogue injections, and GnRH antagonists
 - e. Determine implications of the use of GnRH analogues in early puberty for future vaginoplasty and other surgical procedures

3. Late Pubertal/post-pubertal youth
 - a. Understand optimal timing of interventions including cross-sex hormones and gender confirming surgeries.
 - b. Assess the impact and safety of cross-sex hormone use initiated in adolescence on metabolic markers, brain development and fertility.
 - c. In adolescents initiating cross-sex hormones, assess the effects on mental and social health, including risk-taking behaviors such as suicidality, substance use, and sexual activity.
 - d. Determine impact of sex steroid exposure during puberty on bone health, cardiovascular health and risk of breast or prostate cancer.
4. Research priorities for all gender non-conforming and transgender youth:
 - a. Develop accurate tools for assessing gender dysphoria; standardize measurements used to evaluate treatment models.
 - b. Explore the impact of societal/ structural interventions – such as legal name change, or broader state and federal policies that impact transgender communities.
 - c. Explore how school environments impact the health and well-being of gender non-conforming and transgender youth.
 - d. Explore biological underpinnings of gender identity and gender dysphoria.
 - e. Explore the role of peer relations in vivo and on the internet for gender identity development.
 - f. Examine sexual development in those youth with incongruence between their physical bodies and their experienced gender.
 - g. Explore desire for, and availability of fertility options for those youth undergoing medical intervention related to gender dysphoria.
 - h. Examine the experience of parenting a gender non-conforming youth.
 - i. Explore experiences and needs of gender non-binary identified youth.
 - j. Identify and explore stigma and other barriers that contribute to health disparities for transgender youth – particularly youth of color.
 - k. Clarify the issue of consent for medical intervention when legal guardianship is uncertain.

Acknowledgments

Special thanks to Antonio Guillamon, MD

Financial support and sponsorship

This work was supported in part by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health (R13HD084267), the Endocrine Society, the Tawani Foundation, the World Professional Association for Transgender Health (WPATH), and the Program in Human Sexuality at the

University of Minnesota Medical School. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, the Endocrine Society, or WPATH

Robert Garofalo MD, MPH is on the Speaker's Bureau for Bristol Myers Squibb.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, D.C: American Psychiatric Association; 2013.
2. deVries A, Cohen-Kettenis P. Management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex.* 2012; 59(3):301–320. [PubMed: 22455322]
3. Khatchadourian KAS, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. *J Peds.* 2014; 164(4):906–911. **This demographic analysis of a Canadian cohort of gender dysphoric youth, helps set the stage for defining important questions.
4. Olson J, Schrager S, Belzer M, et al. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *J Adolesc Health.* 2015; 57(4):374–380. [PubMed: 26208863] **This demographic analysis of a Canadian cohort of gender dysphoric youth, helps set the stage for defining important questions.
5. Sherer I, Rosenthal SM, Ehrensaft D, et al. Child and Adolescent Gender Center: a multidisciplinary collaboration to improve the lives of gender nonconforming children and teens. *Pediatr Rev.* 2012; 33(6):273–275. [PubMed: 22659258]
6. Hsieh S, Leininger J. Resource list: clinical care programs for gender-nonconforming children and adolescents. *Pediatr Ann.* 2014; 43(6):238–244. [PubMed: 24972419]
7. Olson J, Garofalo R. The peripubertal gender-dysphoric child: puberty suppression and treatment paradigms. *Pediatr Ann.* 2014; 43(6):e132–e137. [PubMed: 24972421]
8. Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry.* 2008; 47(12):1413–1423. [PubMed: 18981931]
9. Drummond KD, Bradley SJ, Peterson-Badali M, et al. A follow-up study of girls with gender identity disorder. *Dev Psychol.* 2008; 44(1):34–45. [PubMed: 18194003]
10. Steensma TD, McGuire JK, Kreukels BP, et al. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2013; 52(6):582–590. [PubMed: 23702447]
11. Steensma TD, Biemond R, de Boer F, et al. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry.* 2011; 16(4):499–516. [PubMed: 21216800]
12. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009; 94(9):3132–3154. [PubMed: 19509099]
13. de Vries AL, Steensma TD, Doreleijers TA, et al. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med.* 2011; 8(8):2276–2283. [PubMed: 20646177]
14. de Vries AL, McGuire JK, Steensma TD, et al. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics.* 2014; 134(4):696–704. [PubMed: 25201798] **This was the first manuscript describing longitudinal outcomes of youth undergoing puberty suppression, cross sex hormone treatment and gender confirmation surgeries.
15. Klink D, Caris M, Heijboer A, et al. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria.

J Clin Endocrinol Metab. 2015; 100:E270–E275. [PubMed: 25427144] *First longitudinal series to assess the potential impact of GnRH analogue and cross sex hormone treatment on bone mass in adolescents.

16. Corliss HL, Belzer M, Forbes C, et al. An evaluation of service utilization among male to female transgender youth: qualitative study of a clinic-based sample. *J LGBT Health Res.* 2007; 3(2):49–61. [PubMed: 19835041]
17. Wilson EC, Garofalo R, Harris RD, et al. Transgender female youth and sex work: HIV risk and a comparison of life factors related to engagement in sex work. *AIDS Behav.* 2009; 13(5):902–913. [PubMed: 19199022]
18. Reisner SL, Vettes R, Leclerc M, et al. Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. *J Adolesc Health.* 2015; 56(3):274–279. [PubMed: 25577670] **This is a large study that demonstrates the disparity in negative mental health outcomes of transgender adolescents and young adults compared with cisgender counterparts.
19. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab.* 2014; 99(12):4379–4389. [PubMed: 25140398] **This article presents current clinical practice protocols for transgender youth and an analysis of evidence supporting biologic underpinnings of gender identity.
20. Saraswat A, Weinand JD, Safer JD. Evidence supporting the biologic nature of gender identity. *Endocr Pract.* 2015; 21(2):199–204. [PubMed: 25667367] **This recent review demonstrates evidence supporting the biologic nature of gender identity.
21. de Vries ALC, Doreleijers TAH, Cohen-Kettenis PT. Disorders of sex development and gender identity outcome in adolescence and adulthood: understanding gender identity development and its clinical implications. *Pediatr Endocrinol Rev.* 2007; 4(4):343–351. [PubMed: 17643082]
22. Berenbaum SA, Meyer-Bahlburg HF. Gender development and sexuality in disorders of sex development. *Horm Metab Res.* 2015; 47:361–366. [PubMed: 25853895]
23. Heylens G, De Cuypere G, Zucker KJ, et al. Gender identity disorder in twins: a review of the case report literature. *J Sex Med.* 2012; 9(3):751–757. [PubMed: 22146048]
24. Luders E, Sanchez FJ, Gaser C, et al. Regional gray matter variation in male-to-female transsexualism. *Neuroimage.* 2009; 46(4):904–907. [PubMed: 19341803]
25. Luders E, Sanchez FJ, Tosun D, et al. Increased Cortical Thickness in Male-to-Female Transsexualism. *J Behav Brain Sci.* 2012; 2(3):357–362. [PubMed: 23724358]
26. Savic I, Arver S. Sex dimorphism of the brain in male-to-female transsexuals. *Cereb Cortex.* 2011; 21(11):2525–2533. [PubMed: 21467211]
27. Rametti G, Carrillo B, Gomez-Gil E, et al. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res.* 2011; 45(2):199–204. [PubMed: 20562024]
28. Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiaurre-Elorza L, et al. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res.* 2011; 45(7):949–954. [PubMed: 21195418]
29. Hahn A, Kranz GS, Kublbock M, et al. Structural Connectivity Networks of Transgender People. *Cereb Cortex.* 2014; 25(10):3527–3534. [PubMed: 25217469]
30. Sommer IE, Aleman A, Somers M, et al. Sex differences in handedness, asymmetry of the planum temporale and functional language lateralization. *Brain Res.* 2008; 1206:76–88. [PubMed: 18359009]

31. Schoning S, Engelen A, Bauer C, et al. Neuroimaging differences in spatial cognition between men and male-to-female transsexuals before and during hormone therapy. *J Sex Med.* 2010; 7(5): 1858–1867. [PubMed: 19751389]
32. Soleman RS, Schagen SE, Veltman DJ, et al. Sex differences in verbal fluency during adolescence: a functional magnetic resonance imaging study in gender dysphoric and control boys and girls. *J Sex Med.* 2013; 10(8):1969–1977. [PubMed: 23433223]
33. Berglund H, Lindstrom P, Dhejne-Helmy C, et al. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. *Cerebral Cortex.* 2008; 18(8):1900–1908. [PubMed: 18056697]
34. Burke SM, Cohen-Kettenis PT, Veltman DJ, et al. Hypothalamic response to the chemo-signal androstadienone in gender dysphoric children and adolescents. *Front Endocrinol (Lausanne).* 2014; 5:60. [PubMed: 24904525] *This is the first study demonstrating gender dysphoric adolescents have sex atypical functional brain characteristics.
35. Staphorsius AS, Kreukels BP, Cohen-Kettenis PT, et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology.* 2015; 56:190–199. [PubMed: 25837854] *This is the only manuscript describing neurologic function in gender dysphoric youth treated with puberty blockers, and showed no negative impact of GnRH analogue treatment on executive functioning.
36. Cohen-Kettenis, PT.; Pfafflin, F. *Transgenderism and intersexuality in childhood and adolescence: Making choices.* Thousand Oaks, CA: Sage Publications; 2003.
37. Achenbach TM, Edelbrock CS. *Behavioral Problems and Competencies Reported by Parents of Normal and Disturbed Children Aged Four Through Sixteen.* Monographs of the Society for Research in Child Development. 1981; 46(1):1–82. [PubMed: 7242540]
38. Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med.* 2015; 12(3):756–763. [PubMed: 25612159]
39. Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics.* 2012; 129(3):418–425. [PubMed: 22351896]
40. Zuger B. Early effeminate behavior in boys. Outcome and significance for homosexuality. *J Nerv Ment Dis.* 1984; 172(2):90–97. [PubMed: 6693867]
41. Green, R. *The "sissy boy syndrome" and the development of homosexuality.* New Haven: Yale University Press; 1987.
42. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders : DSM-IV-TR.* 4th. Washington, DC: American Psychiatric Association; 2000. American Psychiatric Association. Task Force on DSM-IV.
43. Singh, D. *A follow-up study of boys with gender dysphoria.* Toronto: University of Toronto; 2012.
44. Zucker, KJ.; Bradley, SJ. *Gender identity disorders and psychosexual problems in children and adolescents.* New York, London: Guilford Press; 1995.
45. Wallien MS, Swaab H, Cohen-Kettenis PT. Psychiatric comorbidity among children with gender identity disorder. *J Am Acad Child Adolesc Psychiatry.* 2007; 46(10):1307–1314. [PubMed: 17885572]
46. Di Ceglie D, Freedman D, McPherson S, et al. Children and adolescents referred to a specialist gender identity development service: Clinical features and demographic characteristics. *Int J Transgend.* 2002; 6(1)
47. Steensma TD, Zucker KJ, Kreukels BP, et al. Behavioral and emotional problems on the Teacher's Report Form: a cross-national, cross-clinic comparative analysis of gender dysphoric children and adolescents. *J Abnorm Child Psychol.* 2014; 42(4):635–647. [PubMed: 24114528]
48. de Vries AL, Kreukels BP, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res.* 2011; 186(2–3): 414–418. [PubMed: 20801524]

49. de Vries AL, Doreleijers TA, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry*. 2011; 52(11):1195–1202. [PubMed: 21671938]
50. de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord*. 2010; 40(8):930–936. [PubMed: 20094764]
51. Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997; 36(2):263–271. [PubMed: 9031580]
52. de Vries AL, Cohen-Kettenis PT, Delemarre-van de Waal H. Clinical management of gender dysphoria in adolescents. *Int J Transgend*. 2006; 9(3/4):83–94.
53. Cohen-Kettenis PT, Wallien M, Johnson LL, et al. A parent-report Gender Identity Questionnaire for Children: A cross-national, cross-clinic comparative analysis. *Clin Child Psychol Psychiatry*. 2006; 11(3):397–405. [PubMed: 17080776]
54. Zucker KJ, Bradley SJ, Sullivan CB, Kuksis M, Birkenfeld-Adams A, Mitchell JN. A gender identity interview for children. *J Pers Assess*. 1993; 61(3):443–456. [PubMed: 8295110]
55. Deogracias JJ, Johnson LL, Meyer-Bahlburg HF, et al. The gender identity/gender dysphoria questionnaire for adolescents and adults. *J Sex Res*. 2007; 44(4):370–379. [PubMed: 18321016]
56. Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011; 40(4): 843–847. [PubMed: 21503817]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Bullet Points

- Increasing numbers of gender nonconforming youth are presenting for care.
- Transgender youth are at high risk for poor medical and psychosocial outcomes.
- Longitudinal data examining the impact of early social transition and medical interventions are sparse.
- Biomedical data are beginning to change the trajectory of scientific investigation.
- Extensive research is needed to improve understanding of gender dysphoria, and transgender experience, particularly among youth.