

The Use of Cross-Sex Steroids in the Treatment of Gender Dysphoria

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Abstract. Current clinical guidelines for the treatment of individuals who experience gender dysphoria include the administration of testosterone to women who desire to appear as men and estrogen to men who desire to appear as women. Despite the rapid and widespread adoption of this practice, strikingly little scientific evidence supports this treatment approach as a safe and effective medical intervention to prevent associated depression and suicide. Although low-quality, short-term studies have demonstrated a reduction of dysphoria, emerging evidence reveals significant bodily harm from this practice and a lack of long-term benefit in preventing depression and suicide. From an ethical perspective, this practice distorts a proper view of human nature and violates bodily integrity by directly inducing sterility. The use of exogenous cross-sex hormones reinforces rather than alleviates underlying psychiatric dysfunction while significantly increasing the risk of other medical morbidities. Despite the valid goal of alleviating suffering, this practice cannot be justified by the use of the principles of totality or double effect. *National Catholic Bioethics Quarterly* 17.4 (Winter 2017): 661–671.

In a culture that increasingly asserts that truth is relative, the world appears to be in the midst of a “gender revolution.”¹ This includes a major ideological shift in attitudes toward what it even means to be a man or a woman. In contrast to long-standing knowledge and acceptance of sexual dimorphism—that is, the presence of only two

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1. Katie Couric, “Gender Revolution: A Journey with Katie Couric,” *National Geographic*, <http://channel.nationalgeographic.com/>.

sexes—defined in relation to the biological process of reproduction, attempts are now being made to present sexuality along a continuum of forms.² In stark contrast to Pope St. John Paul II’s teaching on the theology of the body, which illuminates a teleological complementarity between male and female forms and an inseparable unity of body, mind, and soul, it is now openly argued that the mind alone can and in some circumstances should determine, or at least influence, reality in medical practice.³ The dualistic rejection of an intrinsic connection between mind and body and the attempt to redefine fundamental aspects of human biology have given birth to a host of societal problems of unprecedented complexity. Discussions of gender identity are among the most contentious. These include heated public debates and lawsuits related to government hiring, bathroom access rights, and proper pronoun usage.⁴

In this context, the recognition, acceptance, and encouragement of individuals who experience discordance between their gender identity and biological sex have grown at an astounding rate among physicians and in society in general.⁵ It is unknown whether this increased awareness has contributed to the concomitant increase in the reported prevalence of transgender people, with some recent estimates as high as 0.4 percent of the US population.⁶ The medical profession, in possessing a technical ability to chemically and surgically manipulate the appearance of the human body, has been drawn into the ideological battlefield by offering a variety of interventions aimed at alleviating the significant distress that many transgender patients experience as a result of the incongruity between their minds and bodies. The practice of administering cross-sex hormones—that is, testosterone to women who identify as men and estrogen to men who identify as women—as a treatment for gender dysphoria is widely endorsed by several medical societies, including the American Psychiatric Association, the American Academy of Pediatrics, and the Endocrine Society.⁷

2. Helen Lewis, “The Battle over Gender: What Makes You a Man or a Woman, Anyway?,” *New Statesman*, September 13, 2013, <https://www.newstatesman.com/>; Claire Ainsworth, “Sex Redefined,” *Nature* 518.7539 (February 19, 2015): 288–291; and Amanda Montañez, “Beyond XX and XY,” *Scientific American* 317.3 (September 2017): 50–51, doi: 10.1038/scientificamerican0917-50.

3. Hugh Marshall McHugh and Simon Thomas Walker, “‘Personal Knowledge’ in Medicine and the Epistemic Shortcomings of Scientism,” *Journal of Bioethical Inquiry* 12.4 (December 2015): 577–585, doi: 10.1007/s11673-015-9661-5.

4. “Recent EEOC Litigation regarding Title VII and LGBT-Related Discrimination,” fact sheet, US Equal Employment Opportunity Commission, updated July 8, 2016, <https://www.eeoc.gov/>.

5. Jack L. Turban and Diane Ehrensaft, “Gender Identity in Youth: Treatment Paradigms and Controversies,” *Journal of Child Psychology and Psychiatry*, e-pub October 26, 2017, doi: 10.1111/jcpp.12833.

6. Esther L. Meerwijk and Jae M. Sevelius, “Transgender Population Size in the United States: A Meta-Regression of Population-Based Probability Samples,” *American Journal of Public Health* 107.2 (February 2017): 216, doi: 10.2105/AJPH.2016.303578a.

7. William Byne et al., “Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder,” *Archives of Sexual Behavior* 41.4 (August 2012): 759–796, doi: 10.1007/s10508-012-9975-x; American Academy of Pediatrics, “Office-Based

Regardless of one's religious, political, or ideological beliefs, it is easy to see that many transgender individuals experience real suffering, as evidenced by high rates of depression, anxiety, and substance abuse among them.⁸ By some estimates, half of all patients with gender dysphoria have considered suicide, and nearly a third have attempted to act on these thoughts.⁹ Transgender individuals have long endured various forms of prejudice, misunderstanding, mistreatment, and marginalization.¹⁰ Without question, these people need help. Catholic physicians and health care systems thus have a duty to serve this extremely vulnerable population.¹¹ The central questions are whether the currently offered intervention is truly beneficial and whether the potential and known harms of cross-sex hormone administration are justified. Careful consideration and proper application of the principles of totality and double effect clearly demonstrate that, despite the rapid and widespread expansion of cross-sex steroid use in patients with gender dysphoria, this practice violates fundamental principles of biomedical ethics and cannot be endorsed as a means to alleviate suffering in affected patients.

Gender ideology

Although knowledge of people who believe they were “born into the wrong body” has existed for decades,¹² until recently, this condition was generally recognized as a psychological disorder. This is reflected in the listing of “gender identity disorder” in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* used by psychiatrists to classify psychological disease.¹³ Accordingly, understanding and correcting underlying psychosocial disturbances were the primary

Care for Lesbian, Gay, Bisexual, Transgender, and Questioning Youth,” *Pediatrics* 132.1 (July 2013): 198–203, doi: 10.1542/peds.2013-1282; and Wylie C. Hembree et al., “Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline,” *Journal of Clinical Endocrinology and Metabolism* 102.11 (November 2017): 3869–3903, doi: 10.1210/jc.2017-01658.

8. Sari L. Reisner et al., “Mental Health of Transgender Youth in Care at an Adolescent Urban Community Health Center: A Matched Retrospective Cohort Study,” *Journal of Adolescent Health* 56.3 (March 2015): 274–279, doi: 10.1016/j.jadohealth.2014.10.264.

9. Noah Adams, Maaya Hitomi, and Cherie Moody, “Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature,” *Transgender Health* 2.1 (April 2017): 60–75, doi: 10.1089/trgh.2016.0036.

10. Jaclyn M. White Hughto, Sari L. Reisner, and John E. Pachankis, “Transgender Stigma and Health: A Critical Review of Stigma Determinants, Mechanisms, and Interventions,” *Social Science and Medicine* 147 (December 2015): 222–231, doi: 10.1016/j.socscimed.2015.11.010.

11. US Conference of Catholic Bishops, *Ethical and Religious Directives for Catholic Health Care Services*, 5th ed. (Washington, DC: USCCB, 2009), dir. 3.

12. Jordan D. Frey et al., “A Historical Review of Gender-Affirming Medicine: Focus on Genital Reconstructive Surgery,” *Journal of Sexual Medicine* 14.8 (August 2017): 991–1002, doi: 10.1016/j.jsxm.2017.06.007.

13. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. text revision (Washington, DC: American Psychiatric Publishing, 2000).

goals of treatment. With the publication of the fifth edition of this manual (*DSM-5*) in 2013, the diagnosis of “gender identity disorder” transitioned to “gender dysphoria,” with the assertion that gender–sex discordance is a normal manifestation of human diversity.¹⁴ Treatment aims accordingly shifted to the patient’s level of “dis-ease,” or negative feelings, about the appearance of his or her body. Turning the understanding of the relationship between wellness and disease on its head, the mind is now considered healthy and the body diseased. In this light, the simplest solution to the problem is to alter the body to conform to mental belief.

Considering the purported merits of reordering health and disease with respect to human sexuality, there is a notable paucity of objective scientific evidence to support the diagnosis change that occurred in *DSM-5*.¹⁵ Ideology reflecting cultural shifts in sexual mores, not science, was the primary influence on this major diagnostic revision.¹⁶ Even the most vocal advocates of the current treatment paradigm readily acknowledge that the etiology of gender discordance remains largely unknown.¹⁷ According to the incomplete and largely methodologically flawed gender-science literature, the development of gender dysphoria appears to be multifactorial, with genetic, hormonal, and environmental mediators.¹⁸ Consequently, it is difficult to assert from a purely empirical perspective that a single approach centered on cross-sex steroid administration is the best means to alleviate human suffering from gender dysphoria.

Sex Steroids in Normal Human Physiology

Assessment of the ethics of cross-sex steroid administration to individuals with gender dysphoria requires an understanding of the nature and biological function of these hormones. Steroid hormones comprise a family of structurally related compounds with a common cholesterol backbone. These hormones are produced in male and female gonads and in the adrenal glands. Upon synthesis and secretion, these compounds circulate in the bloodstream and enter cells, where they bind to specific receptors that carry the hormones to the cell nucleus. There, the hormone–receptor complex binds to DNA at multiple targeted locations to turn on and off specific genes

14. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Arlington, VA: American Psychiatric Association, 2013).

15. Jack Drescher, Peggy T. Cohen-Kettenis, and Geoffrey M. Reed, “Gender Incongruence of Childhood in the ICD-11: Controversies, Proposal, and Rationale,” *Lancet* 3.3 (March 2016): 297–304, doi: 10.1016/S2215-0366(15)00586-6.

16. Titia F. Beek, Peggy T. Cohen-Kettenis, and Baudewijntje P. C. Kreukels, “Gender Incongruence–Gender Dysphoria and Its Classification History,” *International Review of Psychiatry* 28.1 (2016): 5–12, doi: 10.3109/09540261.2015.1091293.

17. Daniel Trotta, “Born This Way? Researchers Explore the Science of Gender Identity,” *Reuters*, August 3, 2017, <https://www.reuters.com/>.

18. Gunter Heylens et al., “Gender Identity Disorder in Twins: A Review of the Case Report Literature,” *Journal of Sexual Medicine* 9.3 (March 2013): 751–757, doi: 10.1111/j.1743-6109.2011.02567.x; and D. F. Swaab, “Sexual Differentiation of the Human Brain: Relevance for Gender Identity, Transsexualism and Sexual Orientation,” *Gynecological Endocrinology* 19.6 (2004): 301–312, doi: 10.1080/09513590400018231.

that influence cell function.¹⁹ Thus, the effect of altering sex-hormone levels, through either disease or artificial manipulation, can have pleiotropic effects throughout the body.

The steroids that are primarily responsible for sexual differentiation and function are testosterone, estrogen, and progesterone. However, several additional steroids, such as androstenedione and dehydroepiandrosterone (DHEA), also activate the androgen receptor. Men and women make both estrogen and testosterone, but at markedly different levels, which vary throughout the life span of an individual.²⁰ The control of sex-hormone levels occurs primarily in the brain via the highly regulated production of luteinizing hormone and follicle stimulating hormone in the pituitary gland. A notable effect of exogenous steroid administration is the disruption of LH and FSH secretion. This is the mechanism of contraceptive agents that are composed of synthetic sex steroids.²¹ Thus, it is not possible to separate the effects of sex-hormone administration on secondary sex characteristics, such as facial hair and breast development, from the function of the gonads and other tissues that respond to these steroids.

Biological Sex and Anthropology

Before exploring the medical aspects of cross-sex hormone administration, consideration of the basic biology of human sexuality exposes a violent distortion of fundamental anthropological principles in the new gender mentality. Reproduction is the primary purpose of sex, not just in humans but also across the entire animal kingdom.²² It is objectively irrational to accommodate contrary thinking by rejecting a male or female body that is fully competent with respect to its innate reproductive purpose. Cross-sex hormones, by their very nature, render an individual incapable of fulfilling the intrinsic biological role of the human body as male or female.²³ Although potentially reversible after short-term administration, the effects of cross-sex steroids on fertility are expected to be permanent when treatment is started in children.²⁴ The readily accepted view that reproductive capacity can be dissociated

19. Mitchell A. Lazar, "Mechanism of Action of Hormones That Act as Nuclear Receptors," in *Williams Textbook of Endocrinology*, 10th ed., ed. P. Reed Larsen et al. (Philadelphia: Saunders, 2002), 35–44.

20. Melvin M. Grumbach and Dennis M. Styne, "Puberty: Ontogeny, Neuroendocrinology, Physiology, and Disorders," in Larsen et al., *Williams Textbook of Endocrinology*, 1115–1286.

21. Roberto Rivera, Irene Yacobson, and David Grimes, "The Mechanism of Action of Hormonal Contraceptives and Intrauterine Contraceptive Devices," *American Journal of Obstetrics and Gynecology* 181.5 (November 1999): 1263–1269, doi: 10.1016/S0002-9378(99)70120-1.

22. Holger Breithaupt, "The Science of Sex," *EMBO Reports* 13.5 (May 2012): 394, doi: 10.1038/embor.2012.45.

23. Hembree et al., "Endocrine Treatment," 3893. Advocates of the new medical treatment paradigm readily recognize this direct effect of cross-sex hormones and specifically counsel patients on the expected "complication" of induced sterility.

24. T.D. Pache et al., "Ovarian Morphology in Long-Term Androgen-Treated Female to Male Transsexuals: A Human Model for the Study of Polycystic Ovarian Syndrome?,"

from what it means to be male and female, which has grown from the seeds of “biological mutiny” that began with the acceptance of contraception as a solution to difficult social circumstances,²⁵ must be held to close scrutiny in assessing the morality of cross-sex steroid use.

Medical Risks Associated with Cross-Sex Steroid Use

With respect to the physiological effects of altering sex-steroid levels, it is important to recognize the numerous genetic and epigenetic differences between men and women, not just in the gonads or other reproductive organs but also in every cell in the body.²⁶ These differences direct unique cellular programs of gene expression, often leading to markedly different phenotypes between the sexes.²⁷ Recognition of these differences underlies the requirement by the National Institutes of Health that any federally sponsored research must include both male and female subjects unless otherwise justified, so that valid conclusions may be drawn from preclinical studies.²⁸ Thus, giving testosterone to a woman is not the same as giving the same hormone to a man. Similarly, giving estrogen to a man is not the same as giving the same hormone to a woman. There is ample evidence of the adverse effects of having elevated levels of sex steroids that normally predominate in members of the opposite sex. For example, women with elevated androgens—testosterone and androstenedione—due to congenital adrenal hyperplasia or polycystic ovarian disease have a significantly higher incidence of insulin resistance, dyslipidemia, and cardiovascular disease.²⁹ As the practice of giving cross-sex hormones is relatively new, there

Histopathology 19.5 (November 1991): 451, doi: 10.1111/j.1365-2559.1991.tb00235.x; Cornelia Schulze, “Response of the Human Testis to Long-Term Estrogen Treatment: Morphology of Sertoli Cells, Leydig Cells and Spermatogonial Stem Cells,” *Cell and Tissue Research* 251.1 (January 1988): 37, doi: 10.1007/BF00215444; and Renata Walczak-Jędrzejowska et al., “Estradiol and Testosterone Inhibit Rat Seminiferous Tubule Development in a Hormone-Specific Way,” *Reproductive Biology* 13.3 (September 2013): 243–250, doi: 10.1016/j.repbio.2013.07.005.

25. Lambeth Conference, 1930 Resolutions, para. 15, August 17, 1930, Lambeth Conference Resolution Archive, <http://www.anglican communion.org/>.

26. Sonja Grath and John Parsch, “Sex-Biased Gene Expression,” *Annual Review of Genetics* 50 (November 2016): 29–44, doi: 10.1146/annurev-genet-120215-035429. The term “epigenetic” refers to heritable changes in gene function, such as histone acetylation and DNA methylation, that do not involve changes in DNA sequence. See Cathérine Dupont, D. Randall Armant, and Carol A. Brenner, “Epigenetics: Definition, Mechanisms and Perspective,” *Seminars in Reproductive Medicine* 27.5 (September 2009): 351–357, doi: 10.1055/s-0029-1237423.

27. Nichole Rigby and Rob J. Kulathinal, “Genetic Architecture of Sexual Dimorphism in Humans,” *Journal of Cellular Physiology* 230.10 (October 2015): 2304–2310, doi: 10.1002/jcp.24979.

28. Janine A. Clayton and Francis S. Collins, “NIH to Balance Sex in Cell and Animal Studies,” *Nature* 509.7500 (May 14, 2014): 282–283.

29. Christiaan F. Mooij et al., “Cardiovascular and Metabolic Risk in Pediatric Patients with Congenital Adrenal Hyperplasia Due to 21 Hydroxylase Deficiency,” *Journal of Pediatric*

are few long-term, controlled safety studies in the transgender population.³⁰ The available data, however, do reveal several dangerous effects of cross-sex hormones in these individuals. In addition to sterility, known risks include stroke, diabetes, osteoporosis, hyperprolactinemia, disfiguring acne, and hypertension.³¹ There are also potential risks of breast, ovarian, and prostate cancer.³² Consequently, existing treatment guidelines for patients with gender dysphoria include recommendations to counsel all patients on these risks prior to initiating hormonal interventions and to conduct regular screening during treatment.³³

Principle of Totality

Many medical practitioners, recognizing the harm done to the body by destroying reproductive capacity, still maintain that cross-sex hormone treatment is justified

Endocrinology and Metabolism 30.9 (August 28, 2017): 957–966, doi: 10.1515/jpem-2017-0068; and Panagiotis Anagnostis, Basil C. Tarlatzis, and Robert P. Kauffman, “Polycystic Ovarian Syndrome (PCOS): Long-Term Metabolic Consequences,” *Metabolism*, e-pub October 10, 2017, doi: 10.1016/j.metabol.2017.09.016.

30. M.J.H.J. Dekker et al., “A European Network for the Investigation of Gender Incongruence: Endocrine Part,” *Journal of Sexual Development* 13.6 (June 2016): 994–999, doi: 10.1016/j.jsxm.2016.03.371.

31. Anne Laure Bourgeois et al., “Risk of Hormonotherapy in Transgender People: Literature Review and Data from the French Database of Pharmacovigilance,” *Annals of Endocrinology (Paris)* 77.1 (February 2016): 14–21, doi: 10.1016/j.ando.2015.12.001; Katrien Wierckx et al., “Long-Term Evaluation of Cross-Sex Hormone Treatment in Transsexual Persons,” *Journal of Sexual Medicine* 9.10 (October 2012): 2641–2651, doi: 10.1111/j.1743-6109.2012.02876.x; Katrien Wierckx et al., “Prevalence of Cardiovascular Disease and Cancer during Cross-Sex Hormone Therapy in a Large Cohort of Trans Persons: A Case–Control Study,” *European Journal of Endocrinology* 169.4 (October 2013): 471–478, doi: 10.1530/EJE-13-0493; Lucia Turrion-Merino et al., “Severe Acne in Female-to-Male Transgender Patients,” *JAMA Dermatology* 151.11 (November 2015): 1260–1261, doi: 10.1001/jamadermatol.2015.0761; Mohamed B. Elamin et al., “Effect of Sex Steroid Use on Cardiovascular Risk in Transsexual Individuals: A Systematic Review and Meta-analyses,” *Clinical Endocrinology* 72.1 (January 2010): 1–10, doi: 10.1111/j.1365-2265.2009.03632.x; Carl G. Streed Jr. et al., “Cardiovascular Disease among Transgender Adults Receiving Hormone Therapy: A Narrative Review,” *Annals of Internal Medicine* 167.4 (August 15, 2017): 256–267, doi: 10.7326/M17-0577; and Spyridoula Maraka et al., “Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis,” *Journal of Clinical Endocrinology and Metabolism* 102.11 (November 1, 2017): 3914–3923, doi: 10.1210/jc.2017-01643.

32. L. Gooren et al., “Five New Cases of Breast Cancer in Transsexual Persons,” *Andrologia* 47.10 (December 2015): 1202–1205, doi: 10.1111/and.12399; D.S. Dizon et al., “Ovarian Cancer Associated with Testosterone Supplementation in a Female-to-Male Transsexual Patient,” *Gynecologic and Obstetric Investigation* 62.4 (November 2006): 226–228, doi: 10.1159/000094097; and Asma Sharif et al., “The Development of Prostate Adenocarcinoma in a Transgender Male to Female Patient: Could Estrogen Therapy Have Played a Role?,” *Prostate* 77.8 (June 2017): 824–828, doi: 10.1002/pros.23322.

33. Hembree et al., “Endocrine Treatment,” 3871, 3886.

by the good that it achieves in preventing suicide.³⁴ In other words, the removal or alteration of normally formed and functioning primary and secondary sex organs is a necessary means to prevent loss of life. This moral argument appeals to the ethical principle of totality, which asserts that the individual parts of the body exist and function for the good of the whole body. Being subservient to the whole, parts of the body can be justifiably removed if their existence threatens the whole of the body.³⁵ For the principle of totality to be valid, however, alternative, less invasive interventions cannot be possible, and the action performed must have a reasonable hope of achieving the intended good effect, which in this case is suicide prevention. Yet the existing scientific evidence fails to establish that the administration of cross-sex hormones satisfies either of these conditions.

The standards of care published by the World Professional Association for Transgender Health summarily dismisses efforts to help individuals with gender dysphoria explore the psychological basis for gender discordance with the intent of facilitating the reintegration of gender identity with biological sex. The WPATH directives specifically assert that “treatment aimed at trying to change a person’s gender identity and expression to become more congruent with sex assigned at birth has been attempted in the past without success, particularly in the long term. Such treatment is no longer considered ethical.”³⁶ Reflecting either an ideological bias or lack of scientific rigor, studies cited as supporting evidence contain numerous methodologic limitations—for example, case studies and lack of experimental controls³⁷—and include data showing that many patients did successfully realign gender identity with sex following psychological intervention.³⁸ Furthermore, the work of Kenneth Zucker and others demonstrates that many children who underwent psychotherapy

34. Brendan S. Abel, “Hormone Treatment of Children and Adolescents with Gender Dysphoria: An Ethical Analysis,” *Hastings Center Report* 44.s4 (September–October 2014): S23–S27, doi: 10.1002/hast.366.

35. Pius XII, “The Moral Limits of Medical Research and Treatment,” Address to the First International Congress of Histopathology of the Nervous System (September 14, 1952).

36. E. Coleman et al., “Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7,” *International Journal of Transgenderism* 13.4 (2012): 175, doi: 10.1080/15532739.2011.700873.

37. “The nature of sex reassignment precludes double blind randomized controlled studies of the result. . . . Transsexualism is rare, and many follow-ups are hampered by small numbers of subjects. . . . Many sex reassigned persons decline to participate in follow-up studies or relocate after surgery, resulting in high drop-out rates and consequent selection bias. . . . Several follow-up studies are hampered by limited follow-up periods. Taken together, these limitations preclude solid and generalisable conclusions. A long-term population-based controlled study is one way to address these methodological shortcomings.” Cecilia Dhejne et al., “Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden,” *PLoS One* 6.2 (February 22, 2011), e16885, doi: 10.1371/journal.pone.0016885.

38. P.T. Cohen-Kettenis and A.J. Kuiper, “Transseksualiteit en psychotherapie,” *Tijdschrift Voor Psychotherapie* 10 (1984): 153–166.

alone or with their families successfully integrated their identity with their biology.³⁹ Although permanent desistance rates are lower in postpubertal patients, a growing number of adult patients, some of whom had received cross-sex steroids for several years, either alone or in addition to surgery, have also experienced resolution of their gender discordance.⁴⁰

The basis for the heterogeneity of outcomes observed in response to psychotherapy remains unknown. Given the emerging evidence for a multifactorial etiology of gender dysphoria, the likelihood of resolution may depend on the contributing factors that are present in each individual. The strength and duration of social reinforcement may also influence outcomes. Another hypothesis is that this heterogeneity is due to variations in the skill and content of the psychotherapy offered by different practitioners. Among the most striking deficiencies of the available scientific evidence regarding treatment is the lack of properly controlled trials investigating the relative effect of alternative approaches to alleviating gender dysphoria. Therefore, there is insufficient evidence to conclude that the mutilation of normally formed and functioning sex organs is the only way to prevent suicide in transgender people. Given the existence of limited but encouraging data on the potential benefits of psychotherapy and the drastic and often irreversible effects of cross-sex hormone exposure, failure to investigate potential means of refining and optimizing psychological support represents a failure of the medical profession to satisfy the long-standing principle of evidence-based practice. It represents both bad science and bad medicine.

Regarding the requirement to preserve the whole person, the totality argument primarily rests on achieving the goal of suicide prevention. Although a few small, uncontrolled, and relatively short-term studies of cross-sex hormone administration coupled with social affirmation report decreased levels of depression and suicidal ideation in youth with gender dysphoria,⁴¹ one of the largest studies to date examining the long-term mental health of people with gender dysphoria who were treated with cross-sex hormones followed by surgery reports a suicide rate nineteen times greater than in the background population.⁴² Among the subjects of this study, rates of substance abuse, conviction for violent crime, psychiatric hospitalization, and

39. Kenneth J. Zucker et al., "A Developmental, Biopsychosocial Model for the Treatment of Children with Gender Identity Disorder," *Journal of Homosexuality* 59.3 (2012): 369–397, doi: 10.1080/00918369.2012.653309; Kenneth J. Zucker, "On the 'Natural History' of Gender Identity Disorder in Children," *Child and Adolescent Psychiatry* 47.12 (December 2008): 1361–1363, doi: 10.1097/CHI.0b013e31818960cf; and Devita Singh, "A Follow-Up Study of Boys with Gender Identity Disorder" (PhD diss., University of Toronto, 2012).

40. I. M. Marks and D. Mataix-Cols, "Four-Year Remission of Transsexualism after Comorbid Obsessive-Compulsive Disorder Improved with Self-Exposure Therapy: Case Report," *British Journal of Psychiatry* 171.4 (October 1997): 389–390; and Walt Heyer, *Paper Genders* (NP: Make Waves Publishing, 2011).

41. See, for example, Annelou L. C. de Vries, "Young Adult Psychological Outcomes after Puberty Suppression and Gender Reassignment," *Pediatrics* 134.4 (October 2014): 1–9, doi: 10.1542/peds.2013-2958.

42. Cecilia Dhejne et al., "Long-Term Follow-Up of Transsexual Persons."

all-cause mortality were far above those in the background population.⁴³ A recent meta-analysis of forty-two studies reports a similar suicidality.⁴⁴ Claims that these disturbing outcomes are the result of social stigma are dubious, given that many of these studies were performed in countries, such as the Netherlands, where sexual diversity is generally praised rather than shunned. Although there is a dire need for further research, the existing data are insufficient to justify the claim that long-term suicide prevention is achieved through cross-sex hormone administration.

Principle of Double Effect

Some supporters have attempted to use the principle of double effect to justify the use of cross-sex hormones as a treatment for gender dysphoria. This argument, similar to the invocation of the principle of totality, acknowledges the harmful effects of the intervention in destroying normal reproductive function. The bad effect, sterility, is justified in relation to the good effect of suicide prevention. For one to apply this principle, it is necessary to satisfy each of its four criteria. First, the action performed must be morally good or, at least, morally neutral. In this regard, the moral agent is the one who gives regular oral or transdermal administration of sex steroids. When performed to correct a disorder of normal hormone secretion, this intervention is morally good. For example, giving estrogen to a woman with premature ovarian failure restores normal levels of this hormone, improving bone health.⁴⁵ Similarly, giving testosterone to a man with hypopituitarism enables the normal development of strength and lean body mass.⁴⁶

The second requirement is that there is proportionality between the good and bad effects. Here again, it can be legitimately argued that the good effect of preserving life through suicide prevention is equal or superior to the bad effect of inducing sterility.

The third requirement is that the bad effect (loss of normal gonadal function), while foreseen, is not directly intended. In examining this criterion in relation to the administration of cross-sex hormones, serious ethical problems become apparent. In attempting to treat gender dysphoria, the administered sex steroids—testosterone for women and estrogen for men—are intended to induce the development of secondary sex characteristics of the desired sexual phenotype. One could potentially argue that the loss of gonadal function is a foreseen but undesired consequence of the desired feminization of men and virilization of women. However, for women who wish to appear as men, normal menstruation also contributes to dysphoria. In this respect, the loss of normal ovarian function to induce amenorrhea is directly intended. Similar,

43. Ibid. Rates of conviction for violent crime were higher specifically among subjects who underwent sex reassignment surgery before 1989.

44. Adams et al., “Varied Reports of Adult Transgender Suicidality.”

45. Shannon D. Sullivan, Philip M. Sarrel, and Lawrence M. Nelson, “Hormone Replacement Therapy in Young Women with Primary Ovarian Insufficiency and Early Menopause,” *Fertility and Sterility* 106.7 (December 2016): 1588–1599, doi: 10.1016/j.fertnstert.2016.09.046.

46. Karen K. Miller, “Androgen Deficiency: Effects on Body Composition,” *Pituitary* 12.2 (June 2009): 116–124, doi: 10.1007/s11102-008-0121-7.

but perhaps less evident, is the desire to suppress normal testicular function to prevent the virilizing effect of testosterone in biological men.

The fourth requirement, which states that the bad effect must not serve as the direct means to achieve the good effect, is similarly problematic. As demonstrated in the consideration of intentionality, loss of normal gonadal function is a direct means to alter the outward appearance of an individual attempting to conform his or her body to the sexual appearance of the discordant gender identity. From this analysis, it is clear that cross-sex hormone administration cannot be ethically justified through the principle of double effect.

Future Directions

With a proper understanding of the anthropology of sex and with the precise application of the ethical principles of totality and double effect, it is clear that the use of cross-sex hormones for the treatment of gender dysphoria is immoral. Nevertheless, there remains a need for ethically permissible alternative interventions. In attempting to address this pressing knowledge deficit, the limits of bodily manipulation must be recognized and upheld.⁴⁷ Advocates and opponents of the current treatment paradigm share a desire to provide real and sustained help for individuals who experience a gender identity that differs from their biological sex. Medical practitioners, however, must not surrender the universally accepted standard of evidence-based medicine. An adequate solution to this urgent problem must await the results of properly designed and controlled clinical trials, which, to date, do not generally exist in the transgender population. Established principles of medical practice can guide efforts to respond in a compassionate manner. These should include uncompromised respect for human dignity and ongoing efforts to combat prejudice, bullying, and unjust discrimination. At the same time, any response must recognize biological reality. Treatment should include patient and family counseling to address primary and secondary psychological dysfunction. The provision of psychiatric care does not necessitate a definitive understanding of whether a patient will experience persistence or desistance of transgendered identity. Rather, reasonable goals can enable an individual to cope with any discomfort or stress related to the presence of incongruity between his or her mind and body. While awaiting the identification of effective, morally licit solutions to this difficult problem, physicians should remember that their first duty is to do no harm.

47. Willem Jacobus Cardinal Eijk, "Is Medicine Losing Its Way? A Firm Foundation for Medicine as a Real *Therapeia*," *Linacre Quarterly* 84.3 (2017): 208–219, doi: 0.1080/00243639.2017.1301112.