Medicina (Kaunas) 2012;48(11):605–11

Pharmacovigilance and Principle of Nonmaleficence in Sex Reassignment

Kristina Zamarytė, Donatas Stakišaitis, Agnė Širinskienė, Andrius Narbekovas, Jonas Juškevičius
Department of Biolaw, Faculty of Law, Mykolas Romeris University, Lithuania

Key Words: *gender dysphoria; replacement hormonal therapy; pharmacovigilance; ethics; sex reassignment.*

Summary. *Physicians are obliged to provide treatment that is consistent with their commitment to avoid or minimize harm (nonmaleficence) and their commitment to do good (beneficence). Therefore, if patient's desires were contradictory to the primary aim of medicine, the doctor's calling would require him/her to thoroughly analyze the cause of the disease and provide an adequate as well as ethical treatment rather than obediently follow patient's requests. Yet, chemical and surgical sex reassignment is one of the areas where some physicians surrender to the desire of their patients instead of finding out what their real condition is and trying to manage it in a way the essence of medicine would require.*

The objective of this article was to provide specific pharmacovigilance search details for the evaluation of the current situation and the scientific background of the treatment of gender dysphoria and to analyze its conformity with one of the two main ethical principles of medicine – nonmaleficence. Literature retrieval was accessed through Medline (1979–2011) using the terms "gender dysphoria," "replacement hormonal therapy," and "pharmacovigilance." The article concludes that hormonal and surgical interventions have not proven to be medically justified and could be harmful, not treating the cause, but resulting in irreversible disability. Thus, these interventions contradict the principle of nonmaleficence and goals of basic therapeutics and pharmacovigilance. They are not based on clinical trials and are lacking a thorough follow-up assessment.

Introduction

The nature of medicine is embedded in the Hippocratic Oath as a promise to use medical knowledge for the good of the patient and to refrain from harm. The Hippocratic Oath obligates a physician the end of his art to be healing – relief of pain and suffering. As professionals dedicated to healing, in the first place, they are obliged to provide treatment that is consistent with their commitment to avoid or minimize harm (nonmaleficence) and their commitment to do good (beneficence) (1). These commitments constitute the basis and serve as justification of the practice of medicine, and without them, the whole therapeutic gesture falls apart (2). Nonmaleficence refers to a health professional's duty to prevent or do no harm to patients. Nonmaleficence corresponds with the aim to avoid adverse drug reactions. Physicians and other health care professionals are called to practice in ways that are consistent with the intentions and goals of medicine and to avoid taking up the role of mere technicians who are expected to do whatever the patient desires. Therefore, if patient's desires were contradictory to the primary aim of medicine, the doctor's calling would require him/her to thoroughly analyze the cause of the disease and provide adequate as well as ethical treatment, rather than obediently follow patient's requests. Yet, chemical and surgical sex reassignment is one of the areas where some physicians surrender to the symptoms of their patients instead of finding out what their real condition is and trying to manage it in a way the essence of medicine would require.

Transsexualism has been defined as an extreme gender dysphoria for the imitation of the gender of the opposite sex, contrary to one's genetic-biological sex at birth. Transsexualism is not a common choice, and its nature is largely unknown. Psychologically, the desire to be accepted as a member of the opposite sex cannot be regarded as the main criterion to determine human sex identity, but is rather a symptom of an underlying psychiatric problem. The majority of transsexuals progress to taking opposite-sex hormones in the long term, and many proceed to irreversible mutilative genital surgery and destruction of biological fertility for the imitation of external genitalia of the opposite sex. The current scientific data on the balance of risks and benefits of the long-term hormonal replacement therapy (HRT) have been deemed unfavorable

Correspondence to K. Zamarytė, Department of Biolaw, Faculty of Law, Mykolas Romeris University, Ateities 20, 08303 Vilnius, Lithuania. E-mail: biok@mruni.lt

in healthy women (3–5). For safety reasons, the replacement and supplementation of testosterone for healthy men have also been discredited. The use of opposite-sex hormones with the intention to change personal identity is not only biologically, but also medically experimental.

There is a lack of studies evaluating the effects and consequences of using sex hormones in persons with transient or long-term psychiatric conditions, disorders, and disturbances from the viewpoint of pharmacovigilance.

The objective of this article was to provide specific pharmacovigilance search details for the evaluation of the current situation and the scientific background of the gender dysphoria treatment and to analyze its conformity with one of the two main ethical principle of medicine – nonmaleficence. Considering the fact that pharmacovigilance is concerned with the detection, assessment, understanding, and prevention of adverse effects of medicinal products, the psychological effects of sex reassignment and their significance for the ethical evaluation of sex change are not the objects of the present article.

Methods and Current Data

Methods. Literature retrieval was accessed through Medline (1979–2011) using the terms *gender dysphoria*, *replacement hormonal therapy*, and *pharmacovigilance*, including appropriate Boolean operators "AND" and "OR."

Current Data. The prevalence of transsexualism in the Netherlands is estimated to be 1:11 900 for men and 1:19 400 for women (6) and in Germany (between 1981 to 1990) between 2.1 and 2.4 per 100 000 of the adult population (7).

According to the International Statistical Classification of Diseases and Related Health Problems, transsexuality is classified among psychiatric gender identity disorders: "F.64.0 Transsexualism. A desire to live and to be accepted as a member of the opposite sex, usually accompanied by a sense of discomfort with, or inappropriateness of, one's anatomic sex, and a wish to have surgery and hormonal treatment to make one's body as congruent as possible with one's preferred sex" (8). This definition could be criticized as fallacious leading to confounded individuals demanding methods from medical caregivers and the community, which are known as harmful for healthy individuals and have unknown effects for those with psychiatric conditions. It is the underlying psychiatric disturbance (transient or long-term), which needs to be adequately addressed and treated. According to present day's scientific understanding, the use of opposite-sex hormones for the purpose of attempting to change one's sex is not only misleading in its goal, but seriously fails to meet the main criteria of the definition of the rational use of medicines. The WHO defines the rational use of medicines as when "patients receive medications appropriate to their clinical needs in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community" (9). The desire of a genetically and physiologically healthy man or woman to change gender cannot be accepted as a clinical need in any pathophysiological sense.

The treatment presented below is an example of a scientifically ill-grounded treatment of transsexuals (off-label use of medicines). The doses of typical estrogens for the feminization of male-to-female (M→F) transsexuals were 2 to 3 times as high as the recommended doses for the HRT in postmenopausal women (10, 11); several articles have reported the lowering of testosterone with cyproterone acetate in M→F (12), which is not approved for use; GH-releasing hormone agonists have been considered by some to increase estrogen effects in persons with the risk factors of estrogens in transsexuals (13); addition of progesterone for M→F transsexual people is advocated (14); testosterone has often been used alone, both before and after oophorectomy, for masculinizing female-to-male (F M) transsexuals. The addition of progestin with the aim of menses cessation in case testosterone does not adequately suppress menstruations within several months of opposite sex hormone treatment has been recommended (10). GH-releasing hormone agonists have been used in adolescent transsexual people to delay puberty and to allow cross-sex hormones to be postponed until adulthood (15).

Allowing such an inappropriate use of medicines may not only be unsafe, but also encourage misleading promotion, expectations, and use (16, 17). The use of opposite-sex hormones by individuals who have been legally allowed to change their personal identity and sex-identifying code is not only biologically, but also medically artificial.

Transsexualism cannot and does not bring about any change in this biogenetic attribute of a particular individual. One cannot change a human karyotype. Genetic scientists acknowledge and insist that one's sex is biologically determined and genetically imprinted by a karyotype in all nucleated cells of an individual. Science disproves a historical dogma of transsexualism theory that male and female embryos develop in an identical fashion: there are gender-related differences at the very early stages of the development of human embryos (18).

Scientific Evidence on Hormonal Replacement Therapy in Women and Men

The low rate of cardiovascular diseases before and the increased rate after menopause have led to

the conviction that the female hormone estrogen is the source of cardioprotection enjoyed by premenopausal women. This has resulted in the first meaningful study of estrogen and heart disease, the Coronary Drug Project, known ironically as a study in men. It was designed to find out whether men with coronary heart disease could avoid new attacks by taking estrogen. In 1972, the high rate of coronary events was determined in the treated groups, and this caused the termination of the study and rejection of the idea to treat men with estrogens (19).

HRT containing either estrogen alone or in combination with progestin is not longer widely recommended for women. This advice takes into consideration the latest findings from the Women's Health Initiative (WHI) Trial and the Million Women Study (3, 4) and has been adopted by the European Medicines Agency (EMA) (20). The WHI, the Million Women Study, and previous studies provide good evidence that the use of estrogen-only HRT increases the risk of breast cancer, endometrial cancer, and possibly ovarian cancer in a duration-dependent manner (3, 4). For combined HRT, the Million Women Study has shown that there is an increase in the risk of breast cancer, which is substantially higher than that for estrogen-only products (4). HRT has been shown to increase the risk of myocardial infarction and venous thrombosis, especially in the first year of use, and of ischemic stroke (3, 21). HRT may also increase the risk of dementia and has no beneficial effect on the cognitive function (5, 22); it has been linked to an increase in the risk of venous thromboembolism, biliary tract surgery (23), and lung cancer (24). Women who take estrogen plus progestin may have a significant rate of urinary incontinence than women who do not take the hormones (25).

As a result, a group of experts on HRT from a number of European countries have now reassessed all the risks and benefits of HRT and concluded the following: 1) HRT for a short-term treatment of menopausal symptoms that adversely affect the quality of life remains a suitable treatment option, but the minimum effective dose should be used for the shortest period; 2) for a long-term use, i.e., for the prevention of osteoporosis or osteoporotic fractures in women with risk factors or established osteoporosis, the balance of risks and benefits is unfavorable as the first-line treatment for this indication; and 3) in healthy women without menopausal symptoms, the balance of risks and benefits is generally unfavorable and HRT is not recommended (20).

Researchers have observed a dramatic fall in breast cancer incidences that perfectly mirrors the decline in the use of HRT in women (26, 27).

Recent information on increased risks associated with HRT in women has aroused a concern that men receiving hormone replacement may also be vulnerable to increased health risks (28). High doses of exogenous testosterone are associated with substantial hepatotoxicity, including the development of benign and malignant neoplasms (29, 30). However, few data support a causal relation between higher testosterone levels, as a risk factor for cardiovascular disease, and sudden cardiac death (30, 31). The testosterone replacement therapy has been associated with the exacerbation of sleep apnea or with the development of sleep apnea suggesting that androgen replacement contributes to sleep-disordered breathing by central mechanisms (32).

A major report from the congressionally chartered Institute of Medicine concluded that if there is no proven benefit, testosterone should not be taken no matter what the risk. The American National Institute on Aging and the National Cancer Institute asked to review the issue and called for a series of small studies to determine whether testosterone could help men cope with some of the predictable effects of aging, but these studies were recommended not to include young men because they were expected to receive less benefit for the same risks (33).

Aspects of Pharmacovigilance in Attempting Sex Reassigment

There is no proven scientific background at present about the benefit of the use of opposite-sex hormones in transsexuals. No sex hormones have approved indications in their Summary of Product Characteristics for use in attempting sex reassignment, and manufacturers cannot publish such recommendations in the absence of scientific data to support such claims because of medicolegal consequences. Legal changes allowing attempts to change sex undoubtedly also increase interest in the number of interested patients (34). It should be noted that corresponding laws in the world were passed when pharmacovigilance as a concept and a medical discipline was in its infancy worldwide. Pharmacovigilance centers were only established in the majority of countries in the aftermath of the thalidomide disaster (35). Pharmacovigilance is defined as "[t]he science and activities relating to the detection, assessment, understanding and prevention of adverse effects, or of any other drug-related problems." One of the tasks of pharmacovigilance is to assess the safety implications of the use of medicinal products outside their approved indications (36).

Transsexuals tend to experience common serious adverse effects of taking opposite-sex hormones, and these adverse effects are a frequent cause for discontinuing their use (37, 38). Short-term 1-year investigations of the sex reassignment outcomes of young individuals revealed that a significant portion

of them had to interrupt the treatment because of unfavorable adverse effects (39). Serious adverse effects of sex steroid therapy in M→F transsexuals are real and apparent. A reported 20-fold increase in venous thrombosis is one of the greatest concerns (40, 41). The adverse effects of taking opposite-sex hormones in the M→F group enhanced tendencies to anger and aggression and decreased sexual arousability and cognitive spatial ability (42). Other common phenomenon is an increase in prolactin levels. The combined use of estrogen and cyproterone acetate is associated with hyperprolactinemia (77.4%) and elevation of liver enzymes (12.9%) (41, 43). Hyperprolactinemia is possibly associated with an accelerated growth of prolactinomas with the feminizing therapy (15, 44). Chemical castration is associated with a significant rise in the plasma levels of beta-amyloid, which is likely to be involved in the pathogenesis of Alzheimer's disease and, clinically, with increased depression and anxiety scores (45). The use of ethinylestradiol by men has been reported to induce insulin resistance (46). Breast cancer related to apocrine metaplasia in M→F transsexuals may also occur (47). Histological and DNA histogram studies of testes after the use of opposite-sex hormones, obtained at castration, revealed a pattern of maturation arrest in the absolute majority of cases, in which the diploid cell compartment occupied most of the spermatogenetic element, followed by tetraploid and monoploid cells (48).

The adverse effects of masculinizing treatments in female-to-male transsexuals are of great concern. Thorough evaluation of the risks of androgen administration to F→M transsexual people has been limited because a small population has presented at treatment centers (41); therefore, serious adverse risks may be underestimated (39).

The administration of androgens to women has been clearly associated with an increase in the tendency to aggression and has had a deteriorating effect on verbal fluency tasks (42). Testosterone may also promote atherogenicity in women (49, 50) and induce insulin resistance (46). A combination of increased weight, decreased insulin sensitivity, poor lipid profile, an increase in the amount of visceral fat (51), and an increase in hematocrit has raised the concern for cardiac and thromboembolitic events. In fact, cerebral vascular accidents have been reported for individuals with supraphysiological levels of testosterone (52). Androgen use in F→M caused hyperprolactinemia in 38.5% and elevation of liver enzymes in 19.2% of cases (37). Other common findings in F→M transsexuals seem to be hyperandrogenism with polycystic ovary syndrome and adrenocortical hyperresponsiveness to adrenocorticotrophic hormones (53). Polycystic ovarian disease is a risk factor for endometrial cancer, and polycystic ovarian morphology of the ovary has been seen in greater numbers in transsexual people (52, 54). After the treatment with testosterone, mild endometrial hyperplasia has been documented on the removal of the uterus (55). A case report detailed 2 transsexual patients with ovarian cancer in F→M transsexual people: long-term exposure to the increased levels of endogenous and exogenous androgens is further hypothesized to constitute an additional risk for F→M transsexuals for associated ovarian epithelial cancer (56).

The use of opposite-sex hormones, therefore, deserves first and foremost serious, responsible, and critical assessment and evaluation (57). Finally, "one must remember that chemical surgery, namely exposing the body to chemical products, is more intrusive than physical surgery" (58).

Iatrogenic Effects After Hormonal and Surgical Intervention

Transsexuality, classified and considered predominantly as a psychiatric disorder and condition, is not an indication for, nor has it been proven to benefit from, surgical intervention. The fact that psychiatric patients have actually become the object of surgical treatment was partially predetermined also by one of the darkest episodes in the history of that field of treatment, i.e., John/Joan case story, which had been misleading medical professionals for about 3 decades and eventually became an open secret in the science and literature (59). The news about the tragic outcome of this case flew round the world in May 2004 (60).

Preclinical and clinical data show that castration could be related with anxiety or "depressive-like" symptomatology due to chronic estrogen deficiency in females (61, 62). In a study aimed to show differences between two groups of hysterectomized and nonhysterectomized women with a fairly long follow-up period (7.9 years), hysterectomized women showed significantly higher levels of body complaints, depression, and decreased psychological well-being (63). Loss of estrogenic and androgenic underpinnings may destabilize women with unstable psychiatric axes (62). Surgical menopause may precipitate psychiatric disorders in women with previous psychiatric disorders and may increase the risk of depression in them (64). An oophorectomy and a hormone-deficient state were associated with a definite loss of bone mass (38). Articles addressing the outcomes of such surgical intervention have provided conflicting evidence and have, in fact, shown a more negative effect in the long-term (65–68). A long-term follow-up study of female transsexuals, for instance, revealed that only 59% were willing to go through the operation again (69).

The pioneers of such genitalia surgery at John Hopkins University in Baltimore terminated such an intervention program, concluding that this type of surgery offered no advantage over psychotherapy (70, 71). Other study of Medicaid funding of such surgery has also supported this conclusion (72). Surgery removing both gonads and other sex organs destroys the individual's natural fertility (73), itself causing harm and loss and conferring a degree of severe disability, and would in any other case lead to medicolegal consequences.

Castration not only renders infertility and incapacity conferring the invalidity status, but also increases the risk of atherosclerosis, myocardial infarction, and stroke (74). The premature decrease in sex hormone levels is thought to be linked to a comparatively higher risk of atherosclerosis and related morbidity and a shorter lifespan (64, 75). Technical advances in such surgical methods do not address or solve these fundamental problems (69). According to the US Medicare Coverage Issues Manual, transsexual surgery for sex reassignment of transsexuals is controversial. Because of the lack of well-controlled, long-term studies of safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental. Moreover, there is a high rate of serious complications for these surgical procedures. For these reasons, transsexual surgery is not covered (76).

Sex reassignment is related to high psychiatric morbidity, suicide, and suicide attempt rates (77–79), high rates of depression, and low quality of life (77, 79); sex-reassigned persons are at a higher rate of psychiatric hospitalizations. The most striking result was the high mortality rate in both M→F and F→M as compared with the general population (77). A prolonged hormonal treatment might increase the risk of malignancies (80), e.g., the cause-specific risk of death from neoplasms was increased about twice (77). Besides, both M→F and F→M individuals were at a higher risk of criminal convictions as compared with female controls (77). The data indicate the need of a continued psychiatric and somatic follow-up for persons after sex reassignment, because the evidence of sex reassignment is of a very low quality due to the serious methodological limitations of the published studies; most of them had been poorly designed, and the results were unsound because researchers lost track of more than half of the participants (77, 78, 81–85). A recent meta-analysis has concluded that the data on cardiovascular outcome after cross-sex steroid use are sparse, inconclusive, and of a very low quality (83).

Concluding Remarks

Hormonal and surgical interventions have been developed on the premise that transsexualism (gender dysphoria) has been impervious to treatment by psychotherapy and has not proved to be medically justified (as recently HRT in postmenopausal women), but it could be harmful, not treating the cause, resulting in an irreversible disability. Such medical interventions only attempt to satisfy in some way the individual's wish, but do not medically address the underlying psychiatric condition. These interventions are also contrary to the principles and goals of basic therapeutics and pharmacovigilance. They are not based on clinical trials, and there is no long-term assessment. It is obvious that transsexualism pharmacotherapy does not comply with the good clinical practice requirements that are the background of pharmacovigilance. Hormone replacement therapy with opposite-sex hormones should be regarded as a "chemical surgery," a fatal factor that impels the next phase, i.e., surgical treatment. Therefore, using opposite-sex hormones in an attempt to change one's gender should be considered inconsistent with the principle of nonmaleficence because it exposes the patient to a risk of serious side effects. The demand for such services stems from the customer's perception of the goals of medicine, entrenched in the oath of medical practitioners. Thus, the treatment of gender dysphoria not only evokes a series of problems in theoretical medicine, pharmacotherapy in psychiatry and psychosociological spheres, each of them demanding a comprehensive assessment, but also raises the ethical debate.

Statement of Conflict of Interest

The authors state no conflict of interest.

References

1. Rubin SB. If we think it's futile, can't we just say no? HEC Forum 2007;19:45-65.
2. Pellegrino ED. Profesional code. In: Sugaram J, Sulmasy DP, editors. Methods in medical ethics. Washington: Georgetown University Press; 2001. p. 70-87.
3. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women – the women's health initiative randomized trial. JAMA 2003;289:3243-53.
4. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-27.
5. Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the women's health initiative memory study: a randomized controlled trial. JAMA 2003;289:2663-72.
6. van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Nether-

lands. Arch Sex Behav 1996;25:589-600.
7. Weitze C, Osburg S. Transsexualism in Germany: empirical data on epidemiology and application of the German Transsexuals' Act during its first ten years. Arch Sex Behav 1996;25:409-25.
8. International statistical classification of diseases and related health problems. 10th revision. WHO; 1992.
9. Promoting rational use of medicines: core components. WHO policy perspectives on medicines. September 2002, WHO, Geneva.
10. Schlatterer K, von Werder K, Stalla G. Multistep treatment concept of transsexual patients. Exp Clin Endocrinol Diabetes 1996;104:413-9.
11. Climera, estradiol transdermal system. In: Walsh P, editor. Physicians desk reference. 56th ed. Montvale, NJ: Medical Economics Company; 2002. p. 958-62.
12. Jequier A, Bullimore N, Bishop M. Cyproterone acetate and a small dose of oestrogen in the pre-operative management of male transsexual people. A report of three cases. Andrologia 1989;21:456-61.
13. van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexual people treated with cross-sex hormones. Clin Endocrinol (Oxf) 1998;48:347-54.
14. Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. Arch Sex Behav 1998;27:209-26.
15. Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. Eur Child Adolesc Psychiatry 1998;7:246-8.
16. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, et al. Survey of unlicensed and off-label drug use in pediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 2000;320:79-82.
17. Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983-1993. Lancet 1997; 351:643-4.
18. Mittwoch U. Genetics of sex determination: exceptions that prove the rule. Mol Genet Metab 2000;71:405-10.
19. The Coronary Drug Project. Findings leading to discontinuation of the 2.5-mg/day estrogen group. The Coronary Drug Project Research Group. JAMA 1973;266:652-7.
20. EMEA public statement on recent publications regarding hormone replacement therapy. London, 3 December 2003 EMEA/330065/03. Available from: URL: http://www.ema.europa.eu/ema/
21. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523-34.
22. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the women health initiative memory study: a randomized controlled trial. JAMA 2003;289:2651-62.
23. Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). JAMA 2002;288:58-64.
24. Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A. Hormone replacement therapy is associated with decreased survival in women with lung cancer. J Clin Oncol 2006;24:59-63.
25. Peck P. Latest HERS report links HRT to increase risk for urinary incontinence. Available from: URL: http://www.medscape.com/viewarticle/453229
26. Gandey A. Sharp decline in breast cancer linked to HRT, study shows. Available from: URL: http://www.medscape.com/viewarticle/5555404
27. Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ. Recent decline in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol 2006;24:49-50.
28. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482-92.
29. Carrasco D, Prieto M, Pallardó L, Moll JL, Cruz JM, Muñoz C, et al. Multiple hepatic adenomas after long-term therapy with testosterone enanthate: review of the literature. J Hepatol 1985;1:573-8.
30. Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men. European Prospective Investigation into Cancer in Norfolk (Epic-Norfolk) prospective population study. Circulation 2007;116(23);2694-701.
31. Kabakci G, Yildirir A, Can I, Unsal I, Erbas B. Relationship between endogenous sex hormone levels, lipoproteins and coronary atherosclerosis in men undergoing coronary angiography. Cardiol 1999;92:221-5.
32. Schneider BK, Pickett CK, Zwillich CW, Weil JV, McDermott MT, Santen RJ, et al. Influence of testosterone on breathing during sleep. J Appl Physiol 1986;61:618-23.
33. NIA statement on IOM testosterone report. NIH News November 12, 2003. Available from: URL: http://www.nih.gov/news/pr/nov2003/nia-12.htm
34. Pfäfflin F. Psychiatric and legal implications of the new law for transsexualism the Federal Republic of Germany. Int J Law Psychiatry 2004;4:191-8.
35. Meyboom RH, Egberts AC, Gribnau FW, Hekster YA. Pharmacovigilance in perspective. Drug Saf 1999;21:429-47.
36. Meyboom RH, Lindquist M, Egberts AC. An ABC of drug-related problems. Drug Saf 2000;22:415-23.
37. Becerra Fernández A, de Luis Román DA, Piédrola Moroto PG. Morbidity in transsexuals patients with cross-gender hormone self-treatment. Med Clin (Barc) 1999;113:484-7.
38. Goh HH, Ratnam SS. Effects of hormone deficiency, androgen therapy and calcium supplements on bone mineral density in female transsexuals. Maturitas 1997;26:45-52.
39. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adults transsexuals. Psychol Med 2005;35:89-99.
40. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexuals people. J Cin Endocrinol Metab 2003;88:5723-9.
41. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997;47: 337-42.
42. van Goozen SH, Cohen-Kettenis PT, Gooren LJ, Frijda NH, van de Poll NE. Gender differences in behaviour: activating effects of cross-sex hormones. Psychoneuroendocrinology 1995;20:343-63.
43. Asscheman H, Gooren LJ, Assies J, Smits JP, de Slegte R. Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexual people. Clin Endocrinol (Oxf) 1988;28:583-8.
44. Gooren LJ, Assies J, Asscheman H, de Slegte R, van Kessel H. Estrogen-induced prolactinoma in a man. J Clin Endocrinol Metab 1988;66:444-6.
45. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology 2004;29: 1071-81.
46. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 1994;79:265-71.
47. Kanhai RC, Hage JJ, van Diest PJ, Bloemena E, Mulder JW. Short-term and long-term histologic effects of castration and estrogen treatment on breast tissue of 14 male-

to-female transsexuals in comparison with two chemically castrated men. Am J Surg Pathol 2000;24:74-80.
48. Chiu AW, Chen MT, Chiang H, Wu LH, Fang RH, Chang LS. Deoxyribonucleic acid histogram of testes in primary transsexualism. Br J Urol 1993;72:495-7.
49. Goh HH, Loke DF, Ratnam SS. The impact of long-term testosterone replacement therapy on lipid and lipoprotein profiles in women. Maturitas 1995;21:65-70.
50. Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, et al. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf) 2003;58:562-71.
51. Elbers JM, Asscheman H, Seidell JC, Megens JA, Gooren LJ. Long-term testosterone administration increases visceral fat in female to male transsexuals. J Clin Endocrinol Metab 1997;82:2004-7.
52. Futterweit W, Weiss R, Fagerstrom R. Endocrine evaluation of forty female-to-male transsexual people: increased frequency of polycystic ovarian disease in female transsexualism. Arch Sex Behav 1986;15:69-78.
53. Bosinski HA, Peter M, Bonatz G, Arndt R, Heidenreich M, Sippell WG, et al. A higher rate of hyperandrogenic disorders in female-to-male transsexuals. Psychneuroendocrinology 1997;22:361-80.
54. Balen AH, Schachter ME, Montgomery D, Reid RW, Jacobs HS. Polycystic ovaries are a common finding in untreated female to male transsexual people. Clin Endocrinol (Oxf) 1993;38:325-9.
55. Futterweit W, Deligdisch L. Histopathological effects of exogenously administered testosterone in 19 female to male transsexual people. J Clin Endocrinol Metab 1986;62:16-21.
56. Hage JJ, Dekker JJ, Karim RB, Verheijen RH, Bloemena E. Ovarian cancer in female-to-male transsexual people: report of two cases. Gynecol Oncol 2000;76:413-5.
57. Edwards R, Wiholm BE, Martinez C. Concepts in risk-benefit assessment. A simple merit analysis of a medicine? Drug Saf 1996;15:1-7.
58. Napke E. A commitment to pharmacovigilance: 40 years on. Uppsala Reports; 25 April, 2004. p. 12-3.
59. Colapinto J. As nature made him: the boy who was raised as a girl. As nature made him. New York: HarperCollins Publishers; 2000.
60. David Reimer, 38, subject of the John/Joan case, dies. New York Times, 12 May, 2004.
61. Dalla C, Antoniou K, Papadopoulou-Dafoiti Z, Baltazart J, Bakker J. Oestrogen-deficient female aromatase knockout (ArKO) mice exhibit depressive-like symptomatology. Eur J Neurosci 2004;20:217-28.
62. Taylor M. Psychological consequences of surgical menopause. J Reprod Med 2001:46(3 Suppl):317-24.
63. Mackinger HF, Graf AH, Keck E, Tempfer C, Kainz C. Differences in the psychological status of hysterectomy and non-hysterectomy women. Wien Klin Wochenschr 2001; 113:954-9.
64. Shoenfeld H. When are menopausal symptoms psychiatric? Harefuah 1999;137:194-6.
65. Landén M, Bodlund O, Ekselius L, Hambert G, Lundström B. Done is done – and gone is gone. Sex reassignment is presently the best cure for transsexuals. Lakartidningen 2001;98:3322-6.
66. Zielinski T. Evaluation of surgical flaps used for creation of an artificial penis in female-male type transsexuals. Pol Merku Lekarski 2001;10:27-30.
67. Fajkowska-Stanik M. Sex reassignment and other kinds of treatment in case of transsexualism. Psychiatr Pol 1999; 33:959-67.
68. Michel A, Ansseau M, Legros JJ, Pitchot W, Mormont C. The transsexual: what about the future? Eur Psychiatry 2002;7:353-62.
69. Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. Ann Acad Med Singapore 1995;24: 664-7.
70. Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry 1979;36:1010-5.
71. Ashley BM, Rourke KD. Health care ethics. 4th ed. Washington DC: Georgetown University Press; 1997.
72. Jacobs SA. The determination of medical necessity. Medicaid funding for sex-reassignment surgery. Case West Reserve Law Rev 1980 Fall;31:179-209.
73. Eicher W. Transsexuality – standards of care. Zentralbl Gynekol 1995;117:61-6.
74. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000;21:890-4.
75. Xu T, Wang X, Hou S, Zhu J, Zhang X, Huang X. Effect of surgical castration on risk factors for arteriosclerosis of patients with prostate cancer. Chin Med J 2002;115:1336-40.
76. Medicare Coverage Issues Manual. 35-61. Transsexual Surgery. Transmittal 142, July 17, 2001.
77. Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011;6(2):e16885.
78. Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 2008;93:19-25.
79. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 2010; 72:214-31.
80. Mueller A, Gooren L. Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2008;159:197-202.
81. Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril 2009;92:1685-89. e3.
82. Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav 2010;39:1429-37.
83. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf) 2010;72:1-10.
84. Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. J Sex Med 2009;6:1018-23.
85. Banks W. Sexing up the dossier. Gender reassignment under attack. National Review of Medicine. Essential news for Canadian physicians. 2004. Vol. 1, No. 17.

Received 25 May 2011, accepted 29 November 2012