

PUBERTY SUPPRESSION: *Medicine or Malpractice?*



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ABSTRACT

Statement of Purpose

In recent years, it has become standard practice for doctors in the United States and other countries to prescribe puberty-blocking drugs to adolescents who express dissatisfaction with their bodies or social roles. These drugs are often referred to as a “pause button,” a reversible intervention that gives adolescents time to explore, allows families to consider options for future medical intervention, and prevents the worsening of mental illness. However, a substantial body of research suggests that puberty-blocking drugs carry a significant risk of harmful and potentially irreversible effects.

The purpose of this document is to collect the highest-quality studies on puberty-blocking drugs and present their findings. This document’s primary research questions are:

1. What are the effects of puberty-blocking drugs on the developing body?
2. What are the effects of puberty-blocking drugs on mental health?
3. To what degree, if any, are these effects reversible?

Methods

This document considers over 300 relevant sources, the majority of which are peer-reviewed scientific studies. It brings in evidence not only from recent studies of adolescents, but also from older and better-designed studies of adults and children treated with the same drugs for different conditions (e.g. prostate cancer, endometriosis, and central precocious puberty). Studies were evaluated for sample size, presence or absence of a control group, retention rate, relevance of evidence to conclusion, and other factors.

Summary of Findings

Substantial evidence from peer-reviewed scientific studies, case studies, and clinical trials suggests that puberty-blocking drugs can negatively affect the skeleton, cardiovascular system, thyroid, brain, genitals, reproductive system, digestive system, urinary tract, muscles, eyes, and immune system. Particularly urgent concerns for adolescents treated with puberty-blocking drugs are loss of bone mineral density and increased risk of osteoporosis; potential for decreased IQ and other cognitive deficits; increased risk of depression and suicidal thoughts; and stunted sexual and reproductive development.

Evidence suggests that many of these effects are wholly or partially irreversible.

INTRODUCTION

Since the 1990s, a growing number of researchers have produced scientific studies on the administration of puberty-blocking drugs to children as an experimental treatment for a condition the psychiatric community calls *gender dysphoria*.¹ Youth diagnoses of gender dysphoria are on the rise worldwide, especially in female and autistic populations, and among children who show early signs of homosexuality.² The pharmaceutical suppression of puberty has become the standard medical response for adolescents diagnosed with gender dysphoria. The growing body of research into puberty suppression therefore has important implications for the health and safety of minors worldwide, especially for girls and children of minority status.

The Gender Dysphoria Diagnosis

In the United States, clinicians use the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* to diagnose children with gender dysphoria. The *DSM* defines “gender dysphoria” as “the distress that may accompany the incongruence between one’s experienced or expressed gender and one’s assigned gender.”³ Diagnosis of the condition in children is based on “clinically significant distress” and several other symptoms, which can include non-stereotypical dress, choice of non-stereotypical toys, and a preference for playmates of the opposite sex.⁴

Suppressing Puberty

The term *puberty* refers to the period of physical, cognitive, and sexual maturation between childhood and adulthood, beginning between the ages of 8-13 in healthy girls, and 9-14 in healthy boys. During this time and into adulthood, the hypothalamus produces a hormone known as GnRH (gonadotropin-releasing hormone), which binds to GnRH receptors on the pituitary gland and signals the gonads to produce sex hormones (estrogen and testosterone).⁵ During puberty, sex hormones cause sexual maturation, brain development,⁶ and the adolescent growth spurt.⁷ They are also responsible for bone density accrual during puberty, and the maintenance of bone density throughout a person’s life.⁸

Because GnRH is naturally produced in pulses, the body’s GnRH receptors have developed to process it in pulses. Puberty-blocking drugs, which are more accurately known as *GnRH agonists*,⁹ bombard the GnRH receptors with a continuous stream of GnRH, overloading them and forcing them to become desensitized as the body defends itself against the overload.¹⁰ The desensitization of GnRH receptors shuts down sex hormone production in both adolescents and adults; in adolescents, it prevents or arrests the process of maturation.

¹ Or *gender identity disorder*, in studies published before 2013.

² Data published by healthcare systems in several countries suggests a worldwide boom in childhood gender dysphoria diagnoses. The U.K.’s National Health Service reported a 2,500% increase in children referred for gender dysphoria over the last decade, with a 4,400% increase in female referrals (97 total referrals in 2009-2010, of which 40 were girls, vs. 2,519 total and 1,806 female referrals in 2017-2018). A clinic in Israel reported an 11-fold increase in gender dysphoria referrals between 2013 and 2020 (see Segev-Becker et al. 2020). Sweden’s Board of Health and Welfare reported a 1,500% increase in gender dysphoria diagnoses among girls aged 13-17 from 2008 to 2018. Additional evidence from Canada and the Netherlands demonstrates that girls are disproportionately likely to be diagnosed with gender dysphoria (see Aitken et al. 2015; Steensma, Cohen-Kettenis, and Zucker 2018).

Of the girls in the Swedish cohort, 15.2% were reported to have autism; for comparison, the United States Centers for Disease Control and Prevention reported in 2020 that 0.69% of the general population has autism. Scientific studies have confirmed a correlation between autism and a gender dysphoria diagnosis (see Zucker et al. 2017; van der Miesen, de Vries, Steensma, and Hartman 2018).

Substantial evidence suggests that a majority of children diagnosed with gender dysphoria grow up homosexual (see Drummond, Bradley, Peterson-Badali, and Zucker 2008; Wallien and Cohen-Kettenis 2008; Singh 2012; Cerwenka et al. 2014; Singh, Bradley, and Zucker 2021). Homophobic bullying has also been identified as a risk factor for gender dysphoria diagnosis (DeLay, Martin, Cook, and Hanish 2018). A strong correlation between

homosexuality and childhood non-conformity to sex-based stereotypes has been observed (e.g. by Li, Kung, and Hines 2017), suggesting that several of the listed symptoms of gender dysphoria are also early signs of homosexuality.

³ American Psychiatric Association 2013, 451.

⁴ American Psychiatric Association 2013, 452-53.

⁵ Cohn and Crowley 1991.

⁶ Blakemore, Burnett, and Dahl 2010.

⁷ Caufriez 1997.

⁸ Khosla, Oursler, and Monroe 2012.

⁹ Gonadotropin-releasing hormone agonists. This document uses the term *GnRH agonists* to refer to these drugs; studies cited here also refer to these drugs as *GnRH α* , *GnRH- α* , *GnRH analogues*, *LHRH agonists* (luteinizing hormone-releasing hormone agonists), *hormone blockers*, or *puberty blockers*.

The class of GnRH agonists includes leuprolide or leuprorelin (brand name Lupron, Lupron Depot, Lupron Depot-Ped, Eligard, Viadur, Fensolvi, Camcevi), buserelin (Suprefact, Suprecor), goserelin (Zoladex), nafarelin (Synarel), triptorelin (Decapeptyl, Gona-peptyl, Trelstar, Trelstar LA, Trelstar Depot, Triptodur), histrelin (Supprelin LA, Vantas), and gonadorelin (Factrel).

¹⁰ Kumar and Sharma 2014: “Pituitary gonadotropin secretions are blocked upon desensitization when a continuous GnRH stimulus is provided by means of an agonist or when the pituitary receptors are occupied with a competitive antagonist.” See also Conn and Crowley 1991; Mahfouda et al. 2017; Ghelani et al. 2020.

Because sex hormones are systemic—meaning that they act on multiple areas in the body, including the nervous system, cardiovascular system, and skeleton—interfering with sex hormone production can be expected to have multiple and cascading effects on the body.

History and Uses of Puberty-Suppressing Drugs

The United States Food and Drug Administration first approved the GnRH agonist leuprorelin as a treatment for advanced prostate cancer in 1985.¹¹ GnRH agonists have since been approved as a treatment for central precocious puberty (1993), endometriosis (2001), and uterine fibroids (2001).¹² As of June 2022, GnRH agonists are not FDA-approved as a treatment for any mental illness. Their prescription to adolescents diagnosed with gender dysphoria is off-label.

GnRH agonists have been prescribed to adolescents diagnosed with gender dysphoria since at least 1998, when Dutch doctors Peggy Cohen-Kettenis and Stephanie van Goozen published a case study of a teenage girl.¹³ In the United States, GnRH agonists have also been prescribed off-label as a treatment for autism.¹⁴ Their prescription to autistic children resulted in a national scandal and the revocation of Dr. Mark Geier’s medical license.¹⁵

A third off-label use of GnRH agonists is to chemically castrate sex offenders.¹⁶ This use of the drugs has proved controversial. When Alabama Governor Kay Ivey signed a 2019 law requiring sex offenders to take GnRH agonists to reduce their rate of recidivism, medical experts argued that the law was “impermissibly cruel” due to the drugs’ side effects.¹⁷

As of June 2022, the FDA has received over 60,400 reports of adverse reactions to common GnRH agonists, including over 7,900 deaths.¹⁸ For reference, studies suggest that 82-98% of adverse drug reactions go unreported.¹⁹

Table 1. Adverse drug reaction (ADR) reports for common GnRH agonists.

Brand Name	Total ADR	Deaths
Eligard	18,860	3,966
Lupron	9,117	252
Lupron Depot	20,067	2,244
Lupron Depot-Ped	1,308	10
Supprelin LA	684	26
Synarel	2,009	6
Trelstar	780	48
Triptodur	1,095	26
Zoladex	6,484	1,344
Total	60,404	7,922

¹¹ Schaffenburg 1985.

¹² Food and Drug Administration 2017; Orleans 2012.

¹³ Cohen-Kettenis and van Goozen 1998.

¹⁴ From 2006-11, Dr. Mark Geier and David Geier (no medical qualification) filed three patents for an autism treatment protocol using the GnRH agonist Lupron and ran clinical trials. See Geier and Geier 2006; Geier and Geier 2007; Geier and Geier 2011.

¹⁵ Maryland State Board of Physicians 2011. The Maryland State Board of Physicians found that Lupron posed a danger to children, citing “risk of bone and heart damage,” “fertility suppression,”

and “a known substantial risk of serious harm.” Geier is quoted in the Board’s findings as saying: “If you want to call it a nasty name, call it chemical castration. If you want to call it something nice, say you are lowering testosterone.”

¹⁶ Turner and Briken 2018.

¹⁷ Iati 2019.

¹⁸ Data on adverse drug reactions drawn from the FDA Adverse Events Reporting System (FAERS) Public Dashboard (<https://rb.gy/vurabq>).

¹⁹ Hazell and Shakir 2006.

Several countries have begun to urge caution in the use of GnRH agonists on minors. In 2020, Finland’s Council for Choices in Health Care recommended psychotherapy as an alternative to GnRH agonists for minors diagnosed with gender dysphoria.²⁰ A year later, Sweden’s Karolinska Hospital released new guidelines forbidding the use of GnRH agonists on minors except in a clinical trial setting with strict oversight.²¹ In 2022, France’s National Academy of Medicine urged “great medical caution” in the prescription of GnRH agonists to minors.²²

Evaluation of Sources

Sources for the effects of GnRH agonists on children and adolescents are relatively few and far between. This document makes use of the best available studies, as determined by sample size, presence of a control group, and retention of the original study cohort in longitudinal studies.²³ Voluntary-response surveys are considered to be of lower quality, as are studies whose authors have obvious financial conflicts of interest or have demonstrated political bias. Each study’s exclusion criteria were also considered, particularly in the case of studies that rely on a gender dysphoria diagnosis but exclude subjects who are showing symptoms of mental illness.²⁴

This document also reviews case studies, which are considered anecdotal and do not necessarily predict the prevalence or likelihood of a particular outcome. They can, however, point toward potential issues in under-studied areas, or areas that need further research.

EVIDENCE

Global Effects

The primary effect of GnRH agonists is to artificially induce central hypogonadotropic hypogonadism (CHH), an otherwise rare illness characterized in adolescents by absence of growth spurt, failure to develop secondary sex characteristics, and lack of sexual maturation. CHH is associated with negative health outcomes, including low bone density and osteoporosis, infertility, depression, fatigue, and low libido.²⁵

In particular, girls with CHH have an increased risk of fracture, loss of bone mineral density (BMD), and osteoporosis: “Congenital hypogonadism may be particularly detrimental to the skeleton because it may lead to failure to achieve peak bone mass, in addition to loss of established bone mass.”²⁶ Studies also suggest that CHH may be associated with premature aging, and that girls with CHH often experience psychological, neurological, urinary, and genital complications usually associated with the postmenopausal phase of life.²⁷

In adolescent girls, GnRH agonists artificially induce menopause, a condition that occurs naturally in middle-aged women when menstruation ceases and estrogen levels lower. Premature menopause, or premature ovarian insufficiency (POI), has been linked to numerous negative effects on health, including shortened lifespan;²⁸ increased risk of cardiovascular disease²⁹ and stroke;³⁰ low bone mineral density, fractures, and increased risk of osteoporosis;³¹ and increased risk of dementia and cognitive decline.³² For an overview of the effects of premature menopause, see Faubion, Kuhle, Shuster, and Rocca 2015.

²⁰ Palveluvalikoima 2020.

²¹ Karolinska Universitetssjukhuset 2021.

²² National Academy of Medicine 2022.

²³ In a *longitudinal study*, researchers observe the study cohort over time and collect data periodically. Low-quality longitudinal studies often lose track of a large percentage of study participants over time (*loss to follow-up*).

²⁴ *Exclusion criteria* are criteria that disqualify certain subjects from participating in a study. We find studies that exclude mentally ill subjects but require their subjects to be diagnosed with a mental illness (gender dysphoria) to be inherently self-contradictory, and their data is likely skewed as a result.

²⁵ Marino et al. 2014; Sultan et al. 2018; Raivio and Miettinen 2019.

²⁶ Silveira and Latronico 2013.

²⁷ Ilovayskaya, Zektser, and Lazebnik 2017.

²⁸ Shuster et al. 2010.

²⁹ Kalantaridou et al. 2004; Atsma, Bartelink, Grobbee, and van der Schouw 2006; Kannel, Hjortland, McNamara, and Gordon 2006; Shuster et al. 2010; Ebong et al. 2014; Rahman, Åkesson, and Wolk 2015.

³⁰ De Leciñana et al. 2007; Lisabeth et al. 2009; Baba et al. 2010; Rocca et al. 2012.

³¹ Vega, Egea, and Mautalen 1994; Gallagher 2007; Shuster et al. 2010.

³² In subjects who developed POI after oophorectomy (removal of the ovaries), Rocca et al. 2007 observed that “The risk [of cognitive decline] increased with younger age at oophorectomy.” Bove et al. 2014 found increased risk of cognitive decline and increased risk of Alzheimer’s disease. See also Phung et al. 2010; Scott, Zhang, Valamudi, and Brann 2014; Soni and Hogervorst 2014.

Skeleton

A major function of sex hormones is to develop bones during adolescence and maintain skeletal integrity throughout adulthood. Studies suggest that most of the human body's bone mass is accrued by the end of puberty,³³ and that peak bone mineral density (peak BMD), or the measure of a person's bone density at the end of adolescence, is a major determinant of a person's risk for osteoporosis later in life.³⁴

Substantial evidence exists to suggest that deprivation of sex hormones in adulthood causes a rapid decline in bone mineral density (BMD) and can lead to osteoporosis,³⁵ a condition characterized by weak and brittle bones. The suppression of sex hormones with GnRH agonists can thus be expected to result in lowered BMD and increased risk of osteoporosis and fractures.

This hypothesis is confirmed by the findings of Spry et al. 2009, which studied adult men treated with leuprolide for prostate cancer. The study found that BMD decreased after 9 months of treatment, and rates of osteoporosis increased within 3 years. Another study of prostate cancer patients treated with leuprorelin found that the drug "caused significant reductions in hip BMD," and that "Incident non-spinal fractures ... were significantly related to AS [leuprorelin] duration."³⁶ These findings are backed up by numerous studies of adult men treated with GnRH agonists.³⁷ One large study examined the records of over 50,000 men diagnosed with prostate cancer, 31% of whom had received androgen deprivation therapy (ADT; in this case either a GnRH agonist or surgical castration). The study concluded that "Androgen-deprivation therapy for prostate cancer increases the risk of fracture."³⁸ Another study with a sample size of over 94,000 found a 39% increased risk of fracture, and the risk "increased steadily as the number of ADT doses increased."³⁹ Taylor, Canfield, and Du 2009's review of the evidence concluded that studies "reported both significant and nonsignificant increases in BMD loss and osteoporosis."

Studies of children and adolescents taking GnRH agonists have found detrimental effects on bone growth. Carmichael et al. 2021 found that "pubertal suppression reduced growth that was dependent on puberty hormones, i.e. height and BMD ... BMD and BMC [bone mineral content] increased ... more slowly than in peers so BMD z-score fell."⁴⁰ Vlot et al. 2017 found decreased bone turnover among adolescents taking triptorelin,⁴¹ and subjects' BMD fell below the normal range while taking the drug. Other studies concur.⁴²

Inman et al. 2013, a case study of three girls who experienced slipped capital femoral epiphysis (a disorder of the hip joint) during treatment with GnRH agonists, raised additional concerns about the effects of GnRH agonists on skeletal development: "We suggest that a lack of adequate sex hormone exposure at a 'critical period' of bone formation may result in a weakened epiphysis [bone end] that becomes susceptible to slipping."

The best available longitudinal study of adolescents treated with GnRH agonists, Klink et al. 2015, found BMD significantly lower than the normal range in subjects who had taken triptorelin. The study concluded that "BMD was below [subjects'] pretreatment potential" even after several years of added artificial estrogen or testosterone, and "either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated." Vlot et al. 2017, however, found that BMD returned "towards normal" after 2 years on artificial hormones. No study has yet demonstrated complete reversibility of GnRH agonist-induced BMD loss in humans of any age.

³³ Matkovic et al. 1994.

³⁴ Hernandez, Beaupré, and Carter 2003; Bonjour, Chevalley, Ferrari, and Rizzoli 2009.

³⁵ Stépán et al. 1989; Riggs, Khosla, and Melton 2002; Khosla, Oursler, and Monroe 2012; Cauley 2015; Khosla and Monroe 2018.

³⁶ Denham et al. 2013.

³⁷ See e.g. Kiratli, Srinivas, Perakash, and Terris 2001; Stoch et al. 2001; Basaria et al. 2002; Berruti et al. 2002; Preston et al. 2002; Morote et al. 2003; Greenspan et al. 2005; Smith et al. 2005; Smith et al. 2006; Morote et al. 2007; Wadwha, Weston, Mistry, and Parr 2009; Hamilton et al. 2010; Wang et al. 2015; Wang et al. 2017.

³⁸ Shahinian, Kuo, Freeman, and Goodwin 2005.

³⁹ Nguyen, Lairson, Swartz, and Du 2018.

⁴⁰ *Z-score* refers to a data point's relationship to the average value. A low z-score in this case means that the subjects' BMD was far below the normal BMD range for their age. This may be partially explained by the BMD of peers increasing during normal puberty, while subjects taking GnRH agonists were left behind.

⁴¹ *Bone turnover* refers to the natural renewal of bone tissue, which takes place constantly but gradually in healthy humans. Bone turnover is naturally increased in healthy adolescents; see van Coeverden et al. 2002. In adults, both high and low bone turnover can lead to bone weakness, osteoporosis, and fractures.

⁴² Hirsch et al. 2005; Tung, Lee, Tsai, and Hsiao 2007; Kaya, Cayir, Turan, and Ozkan 2015; Joseph, Ting, and Butler 2019; Navabi, Tang, Khatchadourian, and Lawson 2021.

To date, there has been no long-term study on the reversibility of GnRH agonist-induced BMD loss in children or adolescents.⁴³ There is some scientific consensus that adult men treated with GnRH agonists partially recover BMD after discontinuing treatment, contingent on recovery of testosterone levels. Spry et al. 2009 found that “BMD change in those remaining ‘off’ therapy for 2 years ... was strongly associated with the level of testosterone recovery ... Failure of testosterone recovery was associated with worse final BMD.” Other similar studies concur.⁴⁴ However, a study of adult women treated long-term with GnRH agonists for endometriosis found that lost BMD “is not fully recovered by up to 6 years after treatment. Use of HRT [hormone replacement therapy] does not affect this process.”⁴⁵ It should also be noted that data from studies of adults recovering lost BMD long after normal puberty cannot responsibly be extrapolated to children developing new BMD during artificially-delayed puberty.

The suppression of sex hormones may also impact dental health, which is related to bone health. One study of 68 men with prostate cancer found an 80.5% prevalence of periodontal disease in those receiving unspecified androgen deprivation therapy, and only a 3.7% prevalence in the control group.⁴⁶ Another found an increase in salivary MMP-8 (an indicator for periodontal disease) among men receiving unspecified androgen deprivation therapy.⁴⁷

Cardiovascular System and Diabetes Risk

There is some evidence to show that sex hormones play a role in maintaining heart health, though the exact relationship between hormones and the heart is not fully understood.⁴⁸ The consequences of GnRH agonists for the heart are therefore not fully understood. However, significant evidence demonstrates that GnRH agonists can have various and serious effects on the cardiovascular system.

Studies of adult men receiving GnRH agonists as a treatment for prostate cancer are the most plentiful and highest-quality source for these drugs’ effects on the cardiovascular system. The largest available study on this topic included data from over 108,000 men, and found that men who received GnRH agonists had a 9% increase in myocardial infarction (heart attack) risk.⁴⁹ Another large study, which examined the records of over 31,000 prostate cancer patients, found a 31% increase in risk for myocardial infarction and stroke among patients taking GnRH agonists.⁵⁰ A similar study, which examined the records of over 73,000 prostate cancer patients, concluded that “GnRH agonist treatment ... may be associated with an increased risk of incident diabetes [44%] and cardiovascular disease [16%].”⁵¹ Kintzel, Chase, Schultz, and O’Rourke 2008’s review of the evidence observed that “the increased risk for serious cardiovascular disease becomes evident within months of beginning ADT [including GnRH agonists].”

Nguyen, Lairson, Swartz, and Du 2018, with a sample size of over 94,000, found increased risks for diabetes (a 21% increase), coronary heart disease (12%), and acute myocardial infarction (11%) among adult men treated with GnRH agonists. Other large studies have found similar results.⁵²

These findings may be mitigated by the presence of other factors: “the use of ADT [including GnRH agonists] is skewed towards those who are not deemed fit for treatment with intention to cure.”⁵³ It must also be noted that an increased risk of cardiovascular symptoms may not be as severe a consequence in children and adolescents as in adults, as children naturally have a lower baseline risk of heart attack and stroke.

⁴³ Klink et al. 2018 did not collect data on subjects older than 22 years. Gallagher et al. 2018, a survey of young women who had been treated with Lupron Depot for endometriosis up to 7 years previously, found that 10% of respondents who had discontinued the medication reported bone loss they considered to be “irreversible.” Since the survey was based on self-reporting and therefore subjective experience of symptoms, it is impossible to determine whether additional respondents had experienced bone loss without noticeable symptoms.

⁴⁴ Yu et al. 2012; Wang et al. 2017.

⁴⁵ Pierce, Gazvani, and Farquharson 2000.

⁴⁶ Famili, Cauley, and Greenspan 2007; see also Trost et al. 2013.

⁴⁷ Memon, Aleem, Memon, and Lee 2022.

⁴⁸ Ayaz and Howlett 2015: “receptors for all major sex steroid hormones, including testosterone, are present on individual cardiomyocytes [cells that control the heartbeat] ... these hormones may influence the heart at the cellular level.” See also Aryan et al. 2020: “There is considerable evidence suggesting that estrogen modulates cardiovascular physiology and function in both health and disease, and that it could potentially serve as a cardioprotective agent.”

⁴⁹ Keating, O’Malley, Freedland, and Smith 2013.

⁵⁰ Jespersen, Nørgaard, and Borre 2014.

⁵¹ Keating, O’Malley, and Smith 2006.

⁵² Lage, Barber, and Markus 2007; Saigal et al. 2007.

⁵³ Rhee et al. 2014.

Nevertheless, case studies of adult men and women who experienced cardiovascular events while taking GnRH agonists abound and should not be glossed over. Reported symptoms include ischemic stroke,⁵⁴ myocardial infarction,⁵⁵ angina (severe chest pain),⁵⁶ supraventricular tachycardia,⁵⁷ central retinal vein occlusion,⁵⁸ and “histologic features of vasculitis [vein inflammation] and atherosclerosis [plaque-lined arteries].”⁵⁹

Evidence for cardiovascular symptoms in children and adolescents receiving GnRH agonists is sparse. Wojniusz et al. 2016 found that girls treated with Decapeptyl for central precocious puberty “showed significantly lower resting heart rates than the controls,” while Gallagher et al. 2018’s survey of young women treated with Lupron Depot for endometriosis found that one respondent (out of 20) considered high blood pressure to be an “irreversible” side effect of the treatment.

In both adults and adolescents, GnRH agonists have been shown to adversely impact other risk factors for cardiovascular events and type 2 diabetes.⁶⁰ Studies suggest that GnRH agonists increase body weight⁶¹ and percentage body fat,⁶² increase glycemic markers,⁶³ decrease insulin sensitivity,⁶⁴ and increase arterial stiffness.⁶⁵ Smith et al. 2002 also found that GnRH agonists raise total and LDL (“bad”) cholesterol, though a number of smaller studies previously found no change in LDL.⁶⁶ The impact of GnRH agonists on cholesterol levels is thus uncertain.

In 2010, the FDA issued a memo requiring all GnRH agonists to be labeled with a warning of “increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer.”⁶⁷ The FDA’s 2017 report on Lupron found that each of the following adverse reactions had a greater than 5% incidence in clinical trials: ECG changes or ischemia (obstructed blood flow), high blood pressure, and peripheral edema (swelling of the extremities).⁶⁸

Thyroid

GnRH agonists may negatively impact the thyroid, a gland in the throat that maintains many bodily functions, including metabolism,⁶⁹ bone development and maintenance,⁷⁰ and brain development.⁷¹ One study of 50 children treated with GnRH agonists for central precocious puberty found that “more than 70% ... had impaired thyroid function,”⁷² and a recent study of adult women found that “GnRH-a can significantly increase serum TSH [thyroid-stimulating hormone] levels with possible development of subclinical thyroid dysfunction.”⁷³ Massart, Harrell, Federico, and Saggese 2007 found “no evidence of thyroid dysfunction ... though changes in [thyroid-related hormones] TSH, FT3, and FT3/FT4 ratios were noted”; one other study found no change in thyroid function on GnRH agonists.⁷⁴

⁵⁴ Fujiki, Tsuboi, and Yamada 2007. *Ischemic stroke* is the most common kind of stroke, occurring when a blood clot blocks blood flow to the brain.

⁵⁵ McCoy 1994; Coli et al. 2007; Sasaki et al. 2010; Perez, Menegus, and Taub 2015.

⁵⁶ McCoy 1994. Angina is caused by inadequate blood flow to the heart.

⁵⁷ Sharma and Muggia 2013. *Supraventricular tachycardia* is a rapid heartbeat caused by the disruption of the heart’s normal electrical impulses.

⁵⁸ Federici 2007. Blockage of the central retinal vein is a common cause of vision loss in older populations.

⁵⁹ Mesia et al. 1997. *Histologic features* ... refers to the observation of symptoms in biopsied tissue under a microscope.

⁶⁰ Levine et al. 2012; see also Kintzel, Chase, Schultz, and O’Rourke 2008.

⁶¹ Tayek et al. 1990; Smith et al. 2002; Smith 2004; Gallagher et al. 2018.

⁶² Smith et al. 2001; Berruti et al. 2002; Smith et al. 2002; Smith 2004; Smith, Lee, and Nathan 2006; Schagen, Cohen-Kettenis, Delemarre-van de Waal, and Hannema 2016; Nokoff et al. 2021.

⁶³ Nokoff et al. 2021.

⁶⁴ Tropeano et al. 1997; Smith et al. 2001; Dockery et al. 2003; Smith, Lee, and Nathan 2006.; Nokoff et al. 2021. Matsui et al. 2012 found that GnRH agonists caused changes in insulin sensitivity that varied “depending on baseline insulin sensitivity before treatment.”

⁶⁵ Smith et al. 2001; Dockery et al. 2003.

⁶⁶ Bagatell et al. 1992; Eri, Urdal, and Bechensteen 1995; Arrer et al. 1996; von Eckardstein et al. 1997.

⁶⁷ U.S. Food & Drug Administration 2010.

⁶⁸ Center for Drug Evaluation and Research 2017. These adverse reactions “were reported to have a possible or probable relationship to drug as ascribed by the treating physician.”

⁶⁹ Brent 2012.

⁷⁰ Gogakos, Bassett, and Williams 2010; Waung, Bassett, and Williams 2012.

⁷¹ Oppenheimer and Schwartz 1997; Bernal 2007.

⁷² Naderi, Soheilrad, and Haghshenas 2019.

⁷³ Du et al. 2019.

⁷⁴ Chantilis, Barnett-Hamm, Byrd, and Carr 1995.

Case studies provide additional, if anecdotal, evidence for the impact of GnRH agonists on the thyroid. Han et al. 2013 reported three cases of thyroid dysfunction in Korean women who received a long-acting GnRH agonist, and concluded that “GnRH agonist-induced alteration in serum levels of gonadotropin and sex hormones may trigger thyroid autoimmunity.” Case studies of patients receiving leuprolide have also reported thyroiditis, both hypo- and hyperthyroidism, and fluctuating thyroid levels.⁷⁵

Brain

By design, GnRH agonists act on the brain; their primary function is to disrupt the relationship between the hypothalamus and the pituitary gland.⁷⁶ These drugs may also affect other parts of the brain where GnRH receptors are present, as per Wilson, Meethal, Bowen, and Atwood 2007’s evaluation of leuprolide:

the presence of GnRHR [GnRH receptors] in a multitude of non-reproductive tissues including the recent discovery of GnRHR expression in the hippocampi and cortex of the human brain indicates that GnRH analogs such as leuprolide acetate may also act directly via tissue GnRHRs to modulate (brain) function. Thus, the molecular mechanisms underlying the therapeutic effect of GnRH analogs ... may be more complex than originally thought.

Hough et al. 2019 adds: “administration [of GnRH agonists] during the peripubertal period could influence normal brain development and function because GnRH receptors are expressed in brain regions that regulate emotions, cognition, motivation and memory.”

Indeed, evidence suggests that GnRH agonists may have long-term consequences for intelligence and memory in children and adolescents. Mul et al. 2001 found that “Intelligence quotient levels decreased significantly during treatment” with triptorelin. Among the 30 children studied, the average IQ dropped from 100.2 to 93.1, an overall loss of 7.1 points. Another study, Wojniusz et al. 2016, found that girls treated with GnRH agonists tested 8 IQ points lower than controls, yet concluded that “the difference was not significant.”⁷⁷ The 8-point difference reported by Wojniusz et al. 2016 may be too small; the study notes that it excluded several subjects in the treatment group because their IQ scores were below 70. Had Wojniusz et al. included all subjects in their analysis, the average IQ of the treatment group would have dropped to 77—25 points below the average IQ of the control group, and certainly statistically significant.

The findings of Staphorsius et al. 2015 were similarly self-contradictory. The study administered the common “Tower of London” test for executive function⁷⁸ to children taking GnRH agonists and to control groups, and found that boys receiving GnRH agonists “had significantly lower accuracy scores [in the ToL test] than the control groups”—yet concluded that “GnRH treatment had no effect on ToL performance” and “there are no detrimental effects of GnRH on EF [executive function].”⁷⁹

An additional neurological concern was raised by Gallagher et al. 2018’s survey of young women who had taken GnRH agonists for endometriosis. 12% of respondents reported memory loss during treatment; 20% reported memory loss persisting more than 6 months after treatment; and 10% reported irreversible memory loss. While Gallagher et al. 2018 is a relatively small survey, it provides anecdotal evidence for memory loss after treatment with GnRH agonists during adolescence. Schneider et al. 2017 also provides anecdotal evidence for loss of working memory in a boy taking GnRH agonists.

⁷⁵ Kasayama, Miyake, and Samejima 2000; Amino et al. 2003; Krstevska-Konstantinova, Jancevska, and Gucev 2010; Miao, Yan, Wang, and Wang 2018.

⁷⁶ The pituitary gland sits directly beneath the hypothalamus, a part of the brain. Under normal circumstances, the hypothalamus produces GnRH, which is picked up by GnRH receptors on the pituitary gland. GnRH agonists overload GnRH receptors on the pituitary gland with artificial GnRH, forcing them to become desensitized. See Mejia-Otero, White, and Lopez 2021; and “Suppressing Puberty” above.

⁷⁷ Wojniusz et al. 2016. As Hayes 2017 observed, the paper “minimize[s] the fairly substantial difference found in IQ scores ... These IQ estimations are presented as standardized IQ scores,

which places a girl scoring 102 at the 55th percentile, and a girl scoring of 94 at the 34th percentile. It is questionable whether scores that indicate a percentile gap of this size can be described as “very similar.”

⁷⁸ *Executive function* refers to a group of cognitive skills that are essential for learning, productivity, and problem-solving (attention, working memory, flexible thinking, and self-control).

⁷⁹ Staphorsius et al. 2015 also provides evidence for the overrepresentation of homosexuals among adolescents diagnosed with gender dysphoria: “All controls had a heterosexual orientation. The adolescents with GD were all sexually attracted to partners of their natal sex.”

Studies of adults treated with GnRH agonists for prostate cancer or endometriosis have also demonstrated impaired brain function and a possible risk of other serious neurological side effects. Green et al. 2002 found that men treated with GnRH agonists showed “impaired memory, attention, and executive functions” compared to controls. Nearly half of subjects who were treated with a GnRH agonist showed a decline in attention and memory, while no subjects in the control group showed any decline. Nelson, Lee, Gamboa, and Roth 2008, a review of the cognitive effects of GnRH agonists in adult men, observed that “depletion of testosterone may impact the areas of working memory, verbal memory, and visual spatial ability.” Additional studies have found evidence of cognitive decline in men taking GnRH agonists,⁸⁰ though several studies found improved scores specifically in verbal tests⁸¹ or object recall.⁸²

GnRH agonists may increase dementia risk in adults. Two large studies of over 20,000 prostate cancer patients found that those taking GnRH agonists had a 15% or 13% increased risk of dementia.⁸³ Smith et al. 2018, however, suggested that GnRH agonists may protect against Alzheimer’s disease in elderly men. This may be explained by potential links between luteinizing hormone levels and Alzheimer’s; GnRH causes the pituitary gland to produce LH, and GnRH agonists therefore lower LH levels.⁸⁴

Additional effects of GnRH agonists on the brain include slowed reaction times,⁸⁵ seizures,⁸⁶ and intracranial hypertension (increased pressure around the brain).⁸⁷ Case studies have reported intracranial hypertension caused by a GnRH agonist-induced pituitary tumor,⁸⁸ and pituitary apoplexy (bleeding of a pituitary tumor).⁸⁹ Pseudotumor cerebri, a form of intracranial hypertension whose symptoms mimic a brain tumor and include vision loss, has been reported several times in both children and adults treated with GnRH agonists.⁹⁰

Studies of pubertal male sheep have demonstrated that GnRH agonists impair long-term spatial memory,⁹¹ increase risk-taking behavior,⁹² and temporarily increase emotional reactivity⁹³ but may decrease emotional reactivity by early adulthood.⁹⁴ An additional study of pubertal sheep of both sexes demonstrated that GnRH agonists increased the size of the amygdalae, and suggested that “increasing GnRH concentration during puberty may have an important impact on normal brain development in mammals.”⁹⁵ Anacker et al. 2021, which studied the effects of leuprolide on male and female mice, found increased hyperlocomotion and neuroendocrine stress responses among males, and “hyponeophagia and despair-like behavior” in females.⁹⁶

⁸⁰ Bussiere, Beer, Neiss, and Janowsky 2005; Jenkins, Bloomfield, Shilling, and Edginton 2005; Salminen et al. 2005.

⁸¹ Cherrier, Rose, and Higano 2003; Salminen et al. 2005. Almeida et al. 2004 found improvements in both verbal and visual memory after 9 months on GnRH agonists, and further improvement one year after discontinuing treatment; however, the cognitive test portion of this study is poorly designed. As Nelson, Lee, Gamboa, and Roth 2008 observe, “the extremely frequent administration of neuropsychological tests leads to practice effects (ie, patients improve over time with practice), and no comparison group was included in the study. It is quite possible that the results of this study were artifacts because of practice effects.”

⁸² Salminen et al. 2004.

⁸³ Respectively, Robinson et al. 2019; Huang et al. 2020. See also Nead et al. 2017; Nguyen, Lairson, Swartz, and Du 2018. Shim et al. 2020 concluded that GnRH agonists have no effect on dementia risk, but this conclusion is highly suspect due to unusual exclusion criteria and extreme adjustments made to raw data—which seem instead to suggest an association between higher doses of GnRH agonist and higher risk of dementia.

⁸⁴ See Burnham and Thornton 2015.

⁸⁵ Salminen et al. 2004; Stenbæk et al. 2016.

⁸⁶ Gatti, Brinker, and Avigan 2013. Seizures have also been reported in children. See Feuillan et al. 1999; Akaboshi and Takeshita 2000. Minagawa and Sueoka 1999 found worsening of seizures in a girl with epilepsy who was treated with leuprolide for precocious puberty.

⁸⁷ Alexander and Levi 2013; Tan et al. 2020.

⁸⁸ Massoud et al. 2006(a); Massoud et al. 2006(b).

⁸⁹ See Huang et al. 2013, which cites ten additional case studies of GnRH agonist-induced pituitary apoplexy in adult men and women, and Guarda et al. 2021, which cites seven cases.

⁹⁰ Boot 1996; Gül et al. 2016; Omar, Nyaga, and Mungai 2020.

⁹¹ Hough et al. 2017a. Hough et al. 2017b demonstrates that the spatial memory of rams treated with GnRH agonists does not improve after treatment ends.

⁹² Wojniusz et al. 2011.

⁹³ Hough et al. 2017a.

⁹⁴ Evans et al. 2012; Hough et al. 2019. The latter concluded: “There appears to be a window during late puberty or early adulthood where suppression of testosterone is associated with lower emotional reactivity, which will be of relevance for patients receiving GnRH-treatment during this time.”

⁹⁵ Nuruddin et al. 2013. The amygdalae are two gray matter regions in the brain. They are involved with processing emotions, especially fear response; see Calder, Lawrence, and Young 2001.

⁹⁶ *Hyperlocomotion* refers to excessive movement due to overstimulation of the nervous system. *Hyponeophagia*, or “bait shyness,” refers to low consumption of new foods or of familiar foods in new situations, and is often used as a measure of anxiety in mice and rats.

Mental Health

Currently, there are two main clinical models for responding to a childhood or adolescent gender dysphoria diagnosis. In the first, known as the watchful waiting method, clinicians observe the patient over the course of puberty to determine whether the gender dysphoria diagnosis applies long-term. The second model, the affirmative model, requires that clinicians affirm the patient as a member of the opposite sex, and begin a regimen of GnRH agonists in early puberty.⁹⁷ The “affirmative model” assumes that children and adolescents diagnosed with gender dysphoria will be unable to live happy or healthy lives without intervention. It is widely believed that those who receive a gender dysphoria diagnosis are likely to attempt or commit suicide when not affirmed as the opposite sex, though it is not clear what evidence, if any, supports this belief.⁹⁸

The available evidence shows that the vast majority of children and adolescents diagnosed with gender dysphoria are likely to achieve positive mental health outcomes (*desistance*) if treated with the watchful waiting method. Steensma et al. 2013’s review of the available studies found desistance rates of 61-98% in children treated with watchful waiting. The World Professional Association for Transgender Health (WPATH), which frequently argues for the use of GnRH agonists, agrees that children are much more likely to desist than persist without intervention.⁹⁹ Indeed, studies generally show high desistance rates.¹⁰⁰ Singh, Bradley, and Zucker 2021, which had the largest study cohort to date, studied 139 boys and found an 87.8% desistance rate.

A smaller body of evidence suggests that treatment with the affirmative model may prevent desistance. Several studies have shown that the vast majority of children who receive GnRH agonists after a gender dysphoria diagnosis persist in seeking artificial estrogen or testosterone, and the majority later undergo breast and/or genital surgeries.¹⁰¹ It is unknown whether GnRH agonists are the root cause of persistence, or whether other related factors contribute; for instance, Steensma et al. 2013 found that factors including “a social role transition” “were associated with the persistence of childhood gender dysphoria.”

Numerous studies have shown that GnRH agonists negatively impact mental health. Most relevant and most concerning are the findings of the Tavistock and Portman Trust, a mental health trust in London attached to a gender clinic for minors (the Gender Identity Development Service). In 2015, the Trust reported a statistically significant increase in suicidal thoughts and self-harm behaviors among adolescents taking GnRH agonists.¹⁰² Subjects were asked to mark the statements “I deliberately try to hurt or kill myself” and “I think about killing myself” as *not true*, *sometimes*, or *often true*. After one year of puberty suppression, the percentage of *sometimes* and *often true* responses increased (from 28.9% to 32.10% for the first question; from 34.1% to 41.3% for the second question). The same document reports that “girls showed a significant increase in behavioural and emotional problems.”¹⁰³

⁹⁷ Levine, Abbruzzese, and Mason 2022.

⁹⁸ This claim is repeated in the introductions of numerous peer-reviewed scientific studies, including Olson-Kennedy et al. 2019 and Olson-Kennedy et al. 2021. Olson-Kennedy et al. 2021 cites Hembree et al. 2017, which provides no information on suicide. Olson-Kennedy et al. 2019 cites Corliss, Belzer, Forbes, and Wilson 2007; Olson et al. 2015; and Reisner et al. 2015, all of which suggest that there may be a correlation between a gender dysphoria diagnosis and suicidality, but do not indicate whether treatment with the affirmative model has any effect on suicidality. Turban, Beckwith, Reisner, and Keuroghlian 2020 and Turban, King, Carswell, and Keuroghlian 2020 attempt to demonstrate a correlation between treatment with the watchful waiting method and suicidality, but their methodology is critically flawed (see the section “State of Research,” below).

⁹⁹ World Professional Association for Transgender Health 2012: “in follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6-23% of children [= 77-94% desistance rate] ... Boys in these studies were more likely to

identify as gay in adulthood than as transgender ... Newer studies, also including girls, showed a 12-27% persistence rate [= 73-88% desistance rate] of gender dysphoria into adulthood.”

WPATH goes on to argue that persistence is more likely in adolescents, citing de Vries, Steensma, Doreleijers, and Cohen-Kettenis 2011. This conclusion is too strong given that all subjects in that study received GnRH agonists, and GnRH agonists are a possible cause of persistence (see next paragraph above).

¹⁰⁰ See e.g. Drummond, Bradley, Peterson-Badali, and Zucker 2008; Singh 2012; Wallein and Cohen-Kettenis 2008.

¹⁰¹ De Vries, Steensma, Doreleijers, and Cohen-Kettenis 2011; de Vries et al. 2014; Brik et al. 2020; Carmichael et al. 2021. These procedures are treated as the logical next steps in a process known as *transition*: artificial estrogen, breast augmentation, and vaginoplasty for boys/men; artificial testosterone, mastectomy, hysterectomy, and phalloplasty or metoidioplasty for girls/women.

¹⁰² Tavistock and Portman NHS Foundation Trust 2015, p. 53.

¹⁰³ Tavistock and Portman NHS Foundation Trust 2015, p. 51.

Other studies have reported that girls taking GnRH agonists experience anxiety¹⁰⁴ and higher emotional reactivity.¹⁰⁵ Studies of adults have found an increased risk of depression¹⁰⁶ or “sub-clinical depressive symptoms”¹⁰⁷ and anxiety,¹⁰⁸ and provide anecdotal evidence of mania and psychosis,¹⁰⁹ transient psychosis,¹¹⁰ or psychotic symptoms¹¹¹ in previously mentally healthy patients. Insomnia and trouble sleeping have also been reported,¹¹² and the FDA’s 2017 report on Lupron found a 7% incidence of insomnia and other sleep disorders in clinical trials.¹¹³ All of the above psychiatric disorders have been linked to a heightened risk of suicidality in adolescents specifically.¹¹⁴

Sexuality and Reproductive System

The intended effect of GnRH agonists is to desensitize GnRH receptors on the pituitary gland and therefore stop the pituitary gland from signaling the gonads to produce sex hormones (estrogen and testosterone). Ample evidence demonstrates that sex hormone deprivation causes the reproductive system and sex organs to stop functioning (in adults) or developing (in adolescents).

GnRH agonists are known to cause chemical castration in adult men,¹¹⁵ and have been used intentionally to chemically castrate sex offenders.¹¹⁶ There is some evidence to suggest that they also decrease libido in women¹¹⁷ and adolescent girls.¹¹⁸

Adolescents who receive GnRH agonists do not mature sexually while taking the drugs, and may be stunted sexually even after stopping treatment. Studies have found regression of breast development in adolescent girls taking GnRH agonists, and a decrease in testicular size in adolescent boys.¹¹⁹ Anecdotal evidence also exists for the underdevelopment of male genitals.¹²⁰ Several studies have suggested that stunted sexual maturation may be reversible specifically in girls treated with GnRH agonists for central precocious puberty,¹²¹ but it is unknown whether the same applies to adolescents taking GnRH agonists during the normal window for puberty.

Korte et al. 2008 raised additional concerns about the effects of GnRH agonists on sexual development:

early hormone therapy may interfere with the patient’s development as a homosexual. This may not be in the interest of patients who, as a result of hormone therapy, can no longer have the decisive experiences that enable them to establish a homosexual identity.

GnRH agonists are known to affect genital and reproductive function in women and girls. Several studies have found that women treated GnRH agonists often experience vaginal dryness,¹²² and at least one case of vaginal stenosis (narrowing) related to GnRH agonist-induced vaginal dryness has been reported.¹²³ Yeshaya et al. 1998, which studied girls with central precocious puberty, found that 28.5% of the study cohort developed vaginal bleeding after treatment with GnRH agonists. In 14.3% of subjects, the bleeding lasted for 11-13 days.

¹⁰⁴ Gallagher et al. 2018.

¹⁰⁵ Wojniusz et al. 2016; Feuillan et al. 1999 may provide anecdotal evidence for depression in girls taking GnRH agonists.

¹⁰⁶ Toren et al. 1996; Warnock, Bundren, and Morris 1998; Almeida et al. 2004; Frokjaer et al. 2015; Macoveanu et al. 2016; Stenbæk et al. 2016; Fisher et al. 2017; Frokjaer 2020. Van Tol-Geerdink et al. 2011, which studied prostate cancer patients treated with both a GnRH agonist and an anti-androgen, found a more modest increase in depression rates. Case studies of depression in patients treated with GnRH agonists include Warnock and Bundren 1997 and Ahmadi-Davis, Velasco, and Stewart 2014.

¹⁰⁷ Henningsson et al. 2015.

¹⁰⁸ Warnock and Bundren 1997; Almeida et al. 2004.

¹⁰⁹ Chavez and Reilly 2010.

¹¹⁰ Seeman 2015.

¹¹¹ Warnock and Bundren 1997.

¹¹² Joffe et al. 2013; Gallagher et al. 2018. The former concluded that sleep difficulties were a result of GnRH agonist-induced hot flashes.

¹¹³ Center for Drug Evaluation and Research 2017; Gallagher et al. 2018. In the former, these adverse reactions “were reported to have a possible or probable relationship to the drug as ascribed by the treating physician.”

¹¹⁴ For depression and anxiety as risk factors for suicide in adolescents, see Carballo et al. 2020; insomnia, see de Zambotti, Goldstone, Colrain, and Baker 2018; mania, see Conus and McGorry 2002; psychosis, see Martin et al. 2015 and Hielscher et al. 2019.

¹¹⁵ Marumo and Murai 1999. This can be considered common knowledge; many of the studies of adult men cited throughout this document refer to treatment with GnRH agonists as chemical or medical castration.

¹¹⁶ Briken, Hill, and Berner 2003; Houts, Taller, Tucker, and Berlin 2011; Turner and Briken 2018; Iati 2019.

¹¹⁷ Lemay et al. 1988; Letassy, Thompson, Britton, and Suda 1990.

¹¹⁸ Gallagher et al. 2018.

¹¹⁹ Hirsch et al. 2005; Schagen, Cohen-Kettenis, Delemarre-van de Waal, and Hannema 2016.

¹²⁰ Negenborn et al. 2016: “penoscrotal hypoplasia [underdevelopment] ... resulted from previous treatment with puberty suppressing hormones.” Compare Nied 2020’s reporting on Jazz Jennings, who “hadn’t developed enough tissue to construct a vagina ... doctors used tissue from” Jazz’ “stomach lining.”

¹²¹ Jay et al. 1992; Thornton et al. 2014.

¹²² Lemay et al. 1988; Letassy, Thompson, Britton, and Suda 1990; Warnock, Bundren, and Morris 1998.

¹²³ Sato et al. 2016.

Additional evidence for the effects of GnRH agonists on genital function and development comes from studies of adult men treated with GnRH agonists for prostate cancer. Haliloglu, Baltaci, and Yaman 2007 found that “Penile shortening was statistically significant at a mean followup of 18 months (mean 14.2 to 8.6 cm.”¹²⁴ Subjects in this study were treated with both a GnRH agonist (either leuprolide or goserelin) and radiation therapy—but other studies confirm that GnRH agonists alone cause penile shortening as well. Parekh et al. 2013 found that penile shortening was more prevalent in men treated with both GnRH agonists and radiation therapy than in men treated with radiation therapy alone; Park, Lee, and Chung 2011 found penile shortening in men treated with GnRH agonists alone, with an average reduction of 10.76 cm to 8.05 cm.

Studies of adult men also demonstrate loss of fertility after treatment with GnRH agonists, including no or extremely reduced spermatogenesis (sperm production),¹²⁵ a reduced number of Leydig cells,¹²⁶ Leydig cell inactivity,¹²⁷ fibrosis (scarring) of the testes,¹²⁸ reduced response to GnRH,¹²⁹ and reduced levels of natural GnRH after stopping treatment.¹³⁰ Smith and Urry 1985 concluded that “spermatogenic suppression seen after prolonged gonadotropin-releasing hormone analogue administration may not be as reversible as previously suggested,” and Decensi et al. 1989 found “gonadal impairment that may not be as reversible as generally suggested.”

Reviews of the implications of GnRH agonists for adolescents’ future fertility agree that “Suppression of puberty ... can pause the maturation of germ cells, and thus, affect fertility potential”;¹³¹ “GnRH_a [prevents] maturation of germ cells, which could be used for biological fertility potential”;¹³² and “GnRH-a ... suspends germ cell maturation.”¹³³

Additional fertility concerns for girls have been suggested but not fully investigated. One study of 80 girls treated with GnRH agonists for central precocious puberty found an increased rate of polycystic ovary syndrome (PCOS), which increases risk for infertility, in girls treated with GnRH agonists.¹³⁴

Digestive System and Urinary Tract

As explained above, the hypothalamus region of the brain produces GnRH, and GnRH receptors are present on the pituitary gland and in other areas of the brain. GnRH is also produced in the *enteric nervous system*, colloquially known as the “second brain” in the gut.¹³⁵ The role of GnRH in the enteric nervous system is less studied, and GnRH agonists may thus have unexpected implications for the digestive system and urinary tract. For a review of the evidence on GnRH and the enteric nervous system, see Ohlsson 2017.

Evidence for the effects of GnRH agonists on the gut is split. Some studies have found that women treated with GnRH agonists experienced worsened gastrointestinal symptoms¹³⁶ or new abdominal pain,¹³⁷ while others have suggested that leuprolide treatment may relieve symptoms including nausea, vomiting, bloating, diarrhea, constipation, and abdominal pain in women with existing bowel diseases.¹³⁸ One case study found that a woman treated with buserelin developed a chronic intestinal pseudo-obstruction “due to buserelin-induced formation of anti-GnRH antibodies destroying GnRH-producing neurons of the myenteric plexus,”¹³⁹ and another study linked poor gut motility to low GnRH levels in the enteric nervous system.¹⁴⁰

¹²⁴ Haliloglu, Baltaci, and Yaman 2007.

¹²⁵ Rafjer, Swerdloff, and Heber 1984; Smith and Urry 1985; Giberti et al. 1988.

¹²⁶ Rafjer, Swerdloff, and Heber 1984; Smith and Urry 1985; Giberti et al. 1988. *Leydig cells* are cells in the testes that produce testosterone.

¹²⁷ Rafjer, Swerdloff, and Heber 1984.

¹²⁸ Smith and Urry 1985.

¹²⁹ Decensi et al. 1989.

¹³⁰ Rolandi et al. 1988.

¹³¹ Cheng et al. 2019.

¹³² Finlayson et al. 2016.

¹³³ Johnson and Finlayson 2016, con’t: “Puberty appears to progress normally after discontinuation.” For this claim, the review cites only Hagen, Sørensen, Anderson, and Juul 2012, a study of girls with early or central precocious puberty who took GnRH agonists for one year and discontinued treatment by age 11, still well within the

normal window of puberty for healthy girls. It is unclear whether this study’s findings could be reproduced in girls or boys whose puberty is delayed further into or beyond the normal window.

¹³⁴ Chiavaroli et al. 2010. For the claim that PCOS increases risk for infertility, see Hart 2008; Hanson et al. 2017.

¹³⁵ See Gershon 1999; Schneider, Wright, and Heuckeroth 2019.

¹³⁶ Ek et al. 2015.

¹³⁷ Hammar et al. 2013: “Patients experience gastrointestinal symptoms during buserelin treatment, and abdominal pain is still increased after five years.”

¹³⁸ Mathias et al. 1994; Mathias, Clench, Roberts, and Reeves-Darby 1994; Mathias et al. 1998; Palomba et al. 2005.

¹³⁹ Ohlsson et al. 2007. In other words, the woman developed an autoimmune gastrointestinal disease as a result of treatment with a GnRH agonist. This reaction destroyed neurons in her enteric nervous system and prevented food from passing through her gut.

¹⁴⁰ Hammar et al. 2012.

The FDA's 2017 report on Lupron found that each of the following adverse reactions had a greater than 5% incidence in clinical trials: frequent urination, hematuria (bloody urine), constipation, and nausea and vomiting.¹⁴¹

Pain and Discomfort

The use of GnRH agonists has frequently been linked to pain and discomfort, including serious and chronic pain disorders and disorders of the muscles. Case studies have attributed myopathy (muscle pain and weakness),¹⁴² fibromyalgia (a chronic pain disorder),¹⁴³ and myositis (muscle inflammation)¹⁴⁴ to the use of GnRH agonists in adults. Rhabdomyolysis, a potentially life-threatening disease caused by inflammation of the muscles, has also been reported.¹⁴⁵

Studies also demonstrate the prevalence of hot flashes among patients treated with GnRH agonists. Joffe et al. 2013 tested GnRH agonists on healthy adult women and found that 69% of subjects reported hot flashes or night sweats; Shore et al. 2019 found that 77.3% of adult men treated with hormone blockers reported hot flashes.

The FDA's 2017 report on Lupron found that each of the following pain- or discomfort-related adverse reactions had a greater than 5% incidence in clinical trials: hot flashes (in 56% of subjects), bone pain, dizziness, general pain, headache, asthenia (abnormal weakness), sinus congestion, and dermatitis (skin irritation).¹⁴⁶ Gallagher et al. 2018, which surveyed young women who had taken GnRH agonists as adolescents, received reports of headaches and migraines, hot flashes, muscle spasms, injection site pain, "general body pain," and nerve, joint, and bone pain. Many of these symptoms persisted more than 6 months after discontinuing treatment, and several respondents considered their hot flashes, joint pain, or injection site pain to be "irreversible."

Injection site pain is among the most commonly reported side effects of leuprolide and other GnRH agonists.¹⁴⁷ This pain can be severe. A case study of a girl treated with Lupron for precocious puberty found "swelling and muscle pain at the injection site on her right thigh. She also reported an impaired ability to walk."¹⁴⁸

Evidence suggests that GnRH agonists can cause the formation of injection site granulomas, small, often painful clusters of immune cells and other tissue that form in areas of chronic inflammation. A study of 180 adult men taking either leuprorelin or goserelin for prostate cancer found that granulomas formed at the injection site in 11.7% of subjects, after 4 to 62 months of treatment with the drug.¹⁴⁹ Case studies have also found injection site granulomas in adults taking GnRH agonists.¹⁵⁰ Such studies often attribute the formation of granulomas to a foreign body reaction to the polymers present in leuprorelin and similar drugs, meaning that the body's tissues encapsulate and isolate a foreign object the body recognizes as potentially harmful.¹⁵¹

¹⁴¹ Center for Drug Evaluation and Research 2017. These adverse reactions "were reported to have a possible or probable relationship to the drug as ascribed by the treating physician."

¹⁴² Van Gerpen and McKinley 2002; Bergner, Rohacek, and Erne 2011.

¹⁴³ Toussirof and Wendling 2001.

¹⁴⁴ Crayton, Bohlmann, Sufit, and Graziano 1991.

¹⁴⁵ Bergner, Roacek, and Erne 2011.

¹⁴⁶ Center for Drug Evaluation and Research 2017. These adverse reactions "were reported to have a possible or probable relationship to drug as ascribed by the treating physician."

¹⁴⁷ Hirsch et al. 2005; Lee et al. 2014; Shore et al. 2019.

¹⁴⁸ Everest et al. 2015.

¹⁴⁹ Fukui et al. 2015.

¹⁵⁰ Tachibana et al. 2004; Oida et al. 2005; Sakamoto et al. 2006; Dangle, Palit, Sundaram, and Weston 2007; Segawa et al. 2007; Shiota, Tokuda, Kanou, and Yamasaki 2007; Thway, Strauss, Smith, and Fisher 2015. Dangle, Palit, Sundaram, and Weston 2007 studied 7 men who presented with granulomas after taking GnRH agonists, and concluded that "The reaction appears to be more common with leuprorelin acetate than with other forms" of GnRH agonist.

¹⁵¹ Yasukawa, Sawamura, Sugawara, and Kato 2005; Ouchi, Koyama, Miyata, and Sugiura 2006; Vieu et al. 2007. Ouchi, Koyama, Miyata, and Sugiura 2006 found "granulomatous inflammation with a necrotic centre."

Other Effects

Elderly men treated with GnRH agonists for prostate cancer have been shown to be at increased risk for cataracts.¹⁵² Case studies of adult men have suggested that GnRH agonists may be linked to lipodystrophy¹⁵³ and fatty liver disease.¹⁵⁴

Two separate case studies demonstrated adverse reactions involving sterile abscesses in girls resulting from leuprorelin and other GnRH agonists.¹⁵⁵

One study demonstrated an increase in natural killer cells in adult women treated with GnRH agonists for endometriosis.¹⁵⁶

Reversibility

In recent years, numerous political and medical associations have asserted that GnRH agonists' effects on adolescents are reversible. This includes WPATH, whose *Standards of Care* refer to GnRH agonists as "fully reversible ... their use gives adolescents more time to explore."¹⁵⁷ However, the best available evidence suggests that GnRH agonists have a number of irreversible or possibly irreversible effects on the human body, as outlined in **Table 2**.

¹⁵² Beebe-Dimmer et al. 2011 speculates that the increase in cataracts among the study group may be explained by weight gain, dyslipidemia (high total cholesterol or LDL cholesterol, or low HDL cholesterol), and insulin resistance, which are all known or suspected effects of GnRH agonists, and have all been linked to a heightened risk for cataracts. See also Al-Enezi, Kehinde, Behbehani, and Sheikh 2007.

¹⁵³ Chang and Bucci 2016. *Lipodystrophy* is characterized by irregular fat distribution, and is associated with fatty liver disease and insulin resistance; see Knebel, Müller-Wieland, and Kotzka 2020.

¹⁵⁴ Gabbi et al. 2008. The authors concluded that their findings "support a causal role of leuprorelin in inducing metabolic derangement that, most likely secondary to androgen-deprivation, were, in turn, responsible for the development of NAFLD [non-alcoholic fatty liver disease]."

¹⁵⁵ Miller and Shukla 2010; Johnson et al. 2012.

¹⁵⁶ Hsu, Lin, Wang, and Huang 1997. Natural killer cells are immune cells that fight cancer, but an abnormal increase in natural killer cells can increase the risk of some autoimmune diseases.

¹⁵⁷ World Professional Association for Transgender Health 2012.

Table 2. Probable effects of GnRH agonists and their degree of reversibility

Effect	Evidence for/against reversibility
BMD Loss	Studies disagree. See Spry et al. 2009 (at least partially reversible in adult men whose testosterone levels recover); Pierce, Gazvani, and Farquharson 2000 (still present in adult women 6 years after discontinuing treatment, not helped by artificial estrogen); Vlot et al. 2017 (partially reversible in adolescents); Klink et al. 2015 (BMD deficit still present several years after discontinuing treatment).
Risk of Fracture	If BMD loss is irreversible or only partially reversible, fracture risk remains high.
Risk of Osteoporosis	Osteoporosis is considered irreversible if it develops. If BMD loss is irreversible or only partially reversible, osteoporosis risk remains high.
Risk of Heart Attack, Stroke, and Type 2 Diabetes	Heart attack and stroke are serious medical events that may have long-term consequences for lifespan and quality of life if they occur. Type 2 diabetes is considered irreversible if it develops. GnRH agonists have been shown to increase other risk factors, including atherosclerosis (partially reversible with long-term medications), weight gain (likely reversible), insulin resistance (likely reversible with lifestyle changes), and arterial stiffness (likely reversible with lifestyle changes).
Thyroid Dysfunction	Unknown. Some forms of naturally-occurring thyroid dysfunction are considered reversible; some are not.
IQ Deficiency	Unknown
Risk of Dementia	Dementia is likely irreversible if it develops. It is unknown whether increased dementia risk persists after discontinuing treatment.
Memory Loss	Considered “irreversible” by respondents to Gallagher et al. 2018; otherwise unknown.
Intracranial Hypertension	Reversible, but may require medication (see e.g. Omar, Nyaga, and Mungai 2020). If left untreated, intracranial hypertension can cause permanent vision loss.
Pituitary Tumors	Reversible with radiation, medications, or surgery. If left untreated, pituitary tumors can cause blindness and hypopituitarism.
Depression and Anxiety	Unknown
Sleep Disorders	Likely reversible if related to hot flashes (see below); otherwise unknown.
Risk of Suicide	Suicide is irreversible if carried out. Increased risk may be reversible if GnRH agonist-induced risk factors (depression, anxiety, sleep disorders) are also reversible.
Lack of Sexual Development	Likely reversible in girls treated for precocious puberty who discontinue treatment before the normal window for puberty (Jay et al. 1992; Thornton et al. 2014). Unknown in boys and adolescent girls. The implications of GnRH agonists for adolescents’ future sexual function have not been studied.
Risk of Infertility	May be wholly or partially reversible in adult men, though both Smith and Urry 1985 and Decensi et al. 1989 provide evidence to the contrary. Likely reversible in girls treated for precocious puberty who discontinue treatment before the normal window for puberty (Jay et al. 1992; Thornton et al. 2014). The implications of GnRH agonists for adolescents’ future fertility have not been studied. However, Chiavaroli et al. 2010 found an increased risk for PCOS, which is known to cause infertility.
Chronic Pain	Unknown, but chronic pain conditions are not generally considered easily reversible.
Abdominal Pain	Hammar et al. 2013 found that in some patients, abdominal pain persisted at least 5 years after discontinuing treatment.
Hot Flashes	Considered “irreversible” by respondents to Gallagher et al. 2018. Likely reversible in most cases after sex hormones are reintroduced (for this, see studies of menopausal women treated with artificial estrogen, e.g. Santoro, Epperson, and Mathews 2015).
Injection Site Pain	Likely reversible.
injection Site Granulomas	Reversible, but may require surgical intervention.

CONCLUSIONS

State of Research

The bulk of the research into GnRH agonists concerns adult men treated for prostate cancer. Smaller bodies of evidence exist concerning women treated for endometriosis and children treated for central precocious puberty or early puberty. Several studies concern women treated for uterine fibroids or undergoing fertility treatments.

Among the studies of adults, many are well designed, including several randomized double-blind placebo control studies,¹⁵⁸ often considered the gold standard of clinical research. Prostate cancer patients have received the most attention from researchers, likely because GnRH agonists were originally approved to treat prostate cancer and until recently prostate cancer patients were the most common recipients of these drugs. Indeed, there have been a number of retrospective observational studies examining the records of 20,000-100,000 prostate cancer patients. Based on sample size, exclusion criteria, and comparison of ADT/GnRH agonist recipients to prostate cancer patients not receiving ADT/GnRH agonists, we rate these studies as excellent overall. The fact that several of these studies lump GnRH agonists and surgical castration together under the umbrella of ADT, in our view, only slightly affects their usefulness. Both GnRH agonists (chemical castration) and surgical castration have the effect of suppressing sex hormones, and have been shown to have similar effects, though surgical castration is clearly more permanent.

Fewer studies of children treated with GnRH agonists for central precocious puberty exist, and these are generally of poorer quality, with small sample sizes. Several studies in this category also appear to disregard or contradict their own evidence in the conclusion,¹⁵⁹ inviting speculation as to whether there is greater potential for researcher bias in this area. Additionally, few follow-up studies of children treated with GnRH agonists exist, and these studies examine their subjects only into young adulthood¹⁶⁰ or rely on subjective survey response data.¹⁶¹ More and better follow-up studies are required to gauge the long-term effects of puberty suppression in both children and adolescents.

Results from studies of adults who have already had the chance to go through natural puberty cannot necessarily be extrapolated to adolescents whose puberty is artificially delayed. For instance, the tendency of adults to recover lost BMD in favorable conditions does not necessarily indicate that adolescents whose puberty is delayed will be able to develop new BMD after stopping treatment; and the increased risk of heart attack observed in adults may be negligible in adolescents. Likewise, results from studies of children treated for precocious puberty before the normal window for puberty cannot necessarily be extrapolated to adolescents receiving GnRH agonists during the normal window.

¹⁵⁸ In a *double-blind placebo control study*, some subjects receive the experimental drug and some receive a placebo (e.g. a sugar pill); neither the subjects nor the researchers know which subjects have received the drug until all data has been collected.

¹⁵⁹ See our comments on Staphorsius et al. 2015 and Wojniusz et al. 2016 above, and Hayes 2017's commentary on the latter.

¹⁶⁰ As with Klink et al. 2015; Gallagher et al. 2018.

¹⁶¹ Gallagher et al. 2018.

Studies of adolescents receiving GnRH agonists after a gender dysphoria diagnosis are beginning to be published, though these studies are few and generally of very poor quality. As with the studies of children, studies of adolescents tend to have small sample sizes. There is also a tendency toward uncontrolled observational studies,¹⁶² poor exclusion criteria,¹⁶³ and voluntary response surveys.¹⁶⁴ Longitudinal studies often show significant loss to follow-up, yet this is largely ignored or glossed over in the studies' conclusions.¹⁶⁵ Finally, some studies have conclusions that contradict or misrepresent their evidence.¹⁶⁶

These problems raise the possibility of researcher bias, which several studies explicitly confirm through the use of politicized language. Tordoff et al. 2022 ends with the mention of "antitransgender legislation" and a plea "for medical systems and insurance providers to decrease barriers and expand access to gender-affirming care." This is not the only study to end with such a plea.¹⁶⁷ It is highly unusual for clinical studies or articles published in medical journals to address legislation or politics directly. For comparison, studies of prostate cancer patients generally end with suggestions for the direction of future research; this is a standard way of closing a scientific paper.

Pang et al. 2020, in which researchers share their opinions on puberty suppression, suggests that several researchers who have conducted studies on adolescents with gender dysphoria diagnoses are biased. The section of this article written by B.A. Clark and J. Olson-Kennedy uses particularly politically-charged language ("Care planning that validates nonbinary experiences ... is essential for promoting justice") and calls into question both authors' ability to conduct objective research on this subject.¹⁶⁸

Very little research has been done into psychotherapy as an alternative to puberty suppression, and recent research into this subject has been of poor quality.¹⁶⁹ A small body of anecdotal evidence suggests that therapy may benefit both adolescents and adults with gender dysphoria diagnoses,¹⁷⁰ and calls for further research are mounting.¹⁷¹ A sizable body of research also suggests that the watchful waiting method leads to positive mental health outcomes, as outlined in the section "Mental Health" above; this evidence has gone unacknowledged by published clinical studies of adolescents and GnRH agonists.

¹⁶² Olson-Kennedy et al. 2019.

¹⁶³ Olson-Kennedy et al. 2019: "The exclusion criteria were ... presence of serious psychiatric symptoms ... or appearing visibly distraught." See also Carmichael et al. 2021. If gender dysphoria is a serious enough psychiatric condition to warrant the suppression of important hormones, and subjects with serious psychiatric conditions are excluded from a study, it follows that all subjects diagnosed with gender dysphoria should be excluded from that study.

¹⁶⁴ Voluntary response surveys often skew data, as the population who *wants* to answer questions about a particular topic does not always represent the entire population who *could* answer those questions. See, e.g., Turban, Beckwith, Reisner, and Keuroghlian 2020 and Turban, King, Carswell, and Keuroghlian 2020, which gathered data from the U.S. Transgender Survey (<https://www.ustranssurvey.org/>), a voluntary response survey that relies on responses from adults who currently believe themselves to have gender dysphoria (thereby excluding desisters), have Internet access, and have a vested personal interest in helping to promote procedures labeled as "transition." The survey was conducted by the National Center for Transgender Equality, which describes itself as a "social justice policy advocacy organization" (see James et al. 2016), and the survey's website includes overtly political language (e.g. "ensure that trans voices will shape the future"). These factors all but ensure a politically biased response, which the authors do not acknowledge.

¹⁶⁵ Olson-Kennedy et al. 2019 (19% lost to follow-up at 18 months); Tordoff et al. 2022 (37.5% lost to follow-up at 1 year). The latter especially fails to account for the possibility that some subjects who did not take GnRH agonists left the study because their mental health improved and they no longer required treatment.

Achille et al. 2020 lost 45% of subjects to follow-up, but attempted to cover this up by only reporting initial data from subjects who were not lost to follow-up later. See also Carmichael et al. 2021, which stopped recording data for subjects who reached 16 years of age and thus followed up on only 54.5% of subjects after 24 months, and 31.8% of subjects after 36 months.

¹⁶⁶ Tavistock and Portman NHS Foundation Trust 2015.

¹⁶⁷ The stated purpose of Olson-Kennedy et al. 2019 is to "substantially expand treatment across the country." Salas-Humara, Sequeria, Rossi, and Dhar 2021 opines that "Primary care pediatricians are in a powerful position to affect change."

¹⁶⁸ All studies in which Clark or Olson-Kennedy participated should therefore be carefully reviewed for signs of bias. This includes Olson-Kennedy et al. 2019; Lee et al. 2020, which purports to show that low BMD occurs in children with a gender dysphoria diagnosis before the administration of GnRH agonists rather than because of the drugs; Olson-Kennedy et al. 2021; and a number of additional studies concerning the diagnosis of gender dysphoria, comorbidities, artificial hormones, breast surgeries, and breast binding.

¹⁶⁹ Again, Turban, Beckwith, Reisner, and Keuroghlian 2020 uses data from the voluntary-response U.S. Transgender Survey, an inherently biased sample.

¹⁷⁰ See, e.g., Shtasel 1979; Marks, Green, and Mataix-Cols 2000.

¹⁷¹ Several recent papers have suggested a social or psychological explanation for the distress associated with a gender dysphoria diagnosis, and therefore a social or psychological approach to treatment. See, e.g., Patterson 2017; Littman 2018; Rustin 2018; Bell 2020; Evans 2022. After Littman 2018 was published, the author was prompted to write an addendum (Littman 2019) reiterating that the original paper relied on parent reports, that "rapid-onset gender dysphoria" is "not a diagnostic guideline," and suggesting that further research be carried out.

Overview of Evidence

Substantial evidence from peer-reviewed scientific studies, case studies, and clinical trials suggests that puberty-blocking drugs can negatively affect the skeleton, cardiovascular system, thyroid, brain, genitals, reproductive system, digestive system, urinary tract, muscles, eyes, and immune system. The evidence is summarized in **Table 3**.

Table 3. Probable effects of GnRH agonists by category.

Skeleton	loss of bone mineral density (BMD) and lowered peak BMD; increased risk of fractures and osteoporosis; periodontal disease	Klink et al. 2015; Vlot et al. 2017; Nguyen, Lairson, Swartz, and Du 2018
Cardiovascular and Diabetes Risk	increased risk of heart attack, heart disease, and stroke; increased risk of type 2 diabetes; lowered resting heart rate; increased risk factors including weight gain, percentage body fat, insulin resistance, glycemic markers, and arterial stiffness; anecdotal evidence for vasculitis, atherosclerosis, and angina	Jespersen, Nørgaard, and Borre 2014; Wojniusz et al. 2016; Nguyen, Lairson, Swartz, and Du 2018; Nokoff et al. 2021
Thyroid	impaired thyroid function; changes in levels of thyroid-related hormones; anecdotal evidence for hypothyroidism, hyperthyroidism, and thyroiditis	Du et al. 2019; Naderi, Soheilrad, and Haghshenas 2019
Brain	lowered intelligence and IQ; memory loss; impaired working memory, attention, executive function, and visual spatial ability; increased risk of dementia; intracranial hypertension and pseudotumor cerebri; anecdotal evidence of pituitary tumors	Mul et al. 2001; Green et al. 2002; Wojniusz et al. 2016; Robinson et al. 2019; Huang et al. 2020; Tan et al. 2020
Mental Health	depression and other mood disorders; anxiety; insomnia and sleep disorders; increased emotional reactivity; increased risk of suicide; anecdotal evidence of psychosis and mania	Joffe et al. 2013; Tavistock and Portman NHS Foundation Trust 2015; Stenbæk et al. 2016; Wojniusz et al. 2016
Sexuality and Fertility	chemical castration; lack of sexual development and regression of sexual development; potentially irreversible infertility; vaginal dryness and vaginal bleeding; polycystic ovary syndrome (PCOS); penile shortening	Smith and Urry 1985; Decensi et al. 1989; Yeshaya et al. 1998; Chiavaroli et al. 2010; Finlayson et al. 2016; Johnson and Finlayson 2016; Cheng et al. 2019
Digestive and Urinary	frequent urination or bloody urine; constipation; nausea and vomiting; abdominal pain; anecdotal evidence of intestinal pseudo-obstruction and poor gut motility	Hammar et al. 2013; Ek et al. 2015; Center for Drug Evaluation and Research 2017
Pain and Discomfort	hot flashes; headaches and migraines; injection site pain; injection site granulomas; anecdotal evidence of fibromyalgia and other chronic pain disorders	Joffe et al. 2013; Fukui et al. 2015; Shore et al. 2019
Eyes	cataracts	Al-Enezi, Kehinde, Behbehani, and Sheikh 2007; Beebe-Dimmer et al. 2011
Immune System	increase in natural killer cells and increased risk of autoimmune disease; anecdotal evidence of autoimmune disease in the thyroid and gut	Hsu, Lin, Wang, and Huang 1997

Closing Remarks

Currently, the research on GnRH agonists as a treatment for adolescents diagnosed with gender dysphoria is of extremely low quality. High-quality research on the effects of GnRH agonists in adults indicates that these drugs have a number of detrimental side effects. Several side effects have been shown to be at least partially reversible, and it is theoretically possible that adolescents taking GnRH agonists will not experience the same side effects as adults. Nevertheless, the use of GnRH agonists carries a well-documented risk of serious and lasting medical harm. Given that the risks of GnRH agonists include depression, suicidal thoughts, and other mental health conditions that could negatively impact quality of life and increase suicidality, we find claims that these drugs alleviate mental health symptoms and decrease suicidality to be highly suspect.

When a child or adolescent is diagnosed with gender dysphoria, there are two possible alternatives to puberty suppression. These are the watchful waiting method, whose positive outcomes are already supported by a substantial body of evidence, and psychotherapy, which has not yet been extensively studied. Neither of these options is likely to carry the same level of risk as GnRH agonists. Further research into both alternatives is therefore warranted.

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