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Epilepsy Management in Transgender and Gender Diverse People

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Abstract

Purpose of review The goal of this review is to outline important topics in epilepsy management for transgender and gender diverse individuals. Specifically, we describe the common gender-affirming hormone treatment regimens, how these changes in estrogens and androgens may affect seizure threshold and anti-seizure medications, and how anti-seizure medications may in turn impact hormone levels.

Recent findings Although data are mixed, most studies point to proconvulsant properties of estrogen and anticonvulsant properties of progesterone and testosterone, raising the possibility of an increased risk of breakthrough seizures when starting on feminizing gender-affirming hormone treatment. Feminizing hormone regimens containing estrogen are likely to significantly decrease serum concentration of lamotrigine. Enzyme-inducing anti-seizure medications decrease circulating levels of estrogens and androgens, which may potentially decrease the efficacy of gender-affirming hormone treatments.

Summary While a general approach to the care of transgender individuals with epilepsy may be extrapolated from existing studies on hormonal interactions in cisgender individuals, there is a clear need for further research more closely examining the complex interactions between epilepsy, anti-seizure medications, and gender-affirming hormone therapy in transgender and gender diverse individuals.

Introduction

Epilepsy is a disease that affects 50 million people worldwide as reported by the World Health Organization [1]. The mainstay of epilepsy treatment is anti-seizure medications, with the goal of reducing seizure burden or obtaining seizure freedom. Many of our current anti-seizure medications either affect or are affected by changes in hormone levels or other medications. These specific interactions have been most studied in the context of physiologic hormone fluctuations, such as in females during menstrual cycles and pregnancy, as well as treatment with oral contraceptives or hormone replacement therapy in menopause. However, we lack studies that are specifically focused on the complex interaction between hormones and anti-seizure medications in transgender and gender diverse (TGD) patients, as well as treatment outcomes [2••]. There are unique considerations to take into account when treating seizures in this patient population, particularly when they are simultaneously receiving or planning to initiate gender-affirming hormone therapy (GAHT). These considerations include not only the typical concerns regarding seizure control—such as how different feminizing or masculinizing hormone regimens can affect both intrinsic seizure threshold in an individual as well as levels of anti-seizure medications—but also the impact of anti-seizure medications on hormone levels, and potentially on the efficacy of gender-affirming care [2••, 3]. Here we will review important topics in epilepsy management for TGD individuals and highlight the need for further research specifically focused on transgender individuals receiving GAHT.

Overview of transgender and gender diverse people

Transgender and gender diverse people, as defined by the World Professional Association for Transgender Health (WPATH), are individuals whose self-expressed or self-identified gender differs from the gender socially attached to their sex assigned at birth [4••]. Survey-based studies estimate those who identify as gender diverse are 0.5–4.5% among adults and 2.5–8.4% among children and adolescents [5]. The prevalence of epilepsy worldwide is 50 million people [1] and although there is no published data specifically on the rates of epilepsy in the TGD population [6•], if these rates hold true, we can estimate that there may be anywhere from 250,000 to 4,200,000 TGD individuals with epilepsy.

When caring for TGD individuals, it is imperative to confirm preferred name and pronouns, and to adhere to these preferences during documentation in the medical chart and communication with patients and other providers of their care team [7]. Reports of negative health experiences even within health care settings that identify as alliance to the TGD population are reported when these practices are not followed [8].

Current treatments in gender-affirming hormonal therapy

Gender affirmation refers to social, medical, legal, and behavioral components of recognizing and affirming an individual's gender [9]. Medical gender-affirming treatment using hormonal medication is one component of

gender affirmation. Feminizing and masculinizing hormone treatments are described in more detail below.

Trans women (male to female transition)

Feminizing gender-affirming hormone therapy aims to decrease testosterone in order to suppress male secondary sex characteristics and to increase estrogen in order to induce female secondary sex characteristics. This results in physical changes including decreased muscle mass, decreased sexual desire, decreased spontaneous erections, decreased sperm production, decreased testicular volume, decreased terminal hair growth, redistribution of body fat, and breast development [4••, 10, 11].

In adolescents entering endogenous male puberty, gonadotropin-releasing hormone agonists (GnRHas) may be used to suppress further pubertal progression until an appropriate time when GAHT can be introduced. In adults, estrogen supplementation is most commonly administered in the form of 17-beta estradiol, which may be administered orally or sublingually (2–6 mg/day), transdermally (0.025–0.2 mg/day), or intramuscularly (IM; 5–30 mg every 2 weeks) [4••, 10, 11].

Adolescents require an alternative dosing regimen depending on whether they are early in puberty or postpubertal. Testosterone levels can be reduced with antiandrogen medications including spironolactone (25–300 mg/day), cyproterone acetate (10–50 mg/day), finasteride (1–5 mg/day), or leuprolide (3.75 mg IM/SQ monthly or 11.25 mg IM/SQ every 3 months) [4••, 10, 11].

Trans men (female to male transition)

Masculinizing GAHT aims to increase testosterone to induce male secondary sex characteristics. This results in physical changes including cessation of menses, redistribution of body fat, increased muscle mass, growth of facial and body hair, scalp hair loss, deepening of voice, clitoral enlargement, and vaginal atrophy [4••, 10].

In adolescents entering endogenous female puberty, gonadotropin-releasing hormone agonists (GnRHas) may be used to suppress further pubertal progression until an appropriate time when GAHT can be introduced. In adults, male secondary sex characteristics are induced with testosterone, which may be administered in the form of testosterone enanthate/cypionate (20–100 mg IM/SQ weekly), testosterone undecanoate (750 mg IM every 10 weeks), in a gel (12.5–100 mg/day), or in a transdermal patch (2.5–7.5 mg/day) [4••, 10, 11]. Adolescents may require an alternative dosing regimen. If menstruation does not stop with testosterone alone, progestin may be added.

Gender nonbinary

Gender nonbinary individuals may be treated with a range of hormonal therapies depending on their particular gender identity and goals of treatment.

This may include the regimens outlined above, or variations including androgen blockers alone, lower doses of estrogen or lower doses of testosterone. Given the wide variety of possible doses and combinations, we are unable to address each specific treatment regimen; however, similar considerations should be taken into account.

Current treatments in epilepsy care

Medication, surgical, and dietary treatment options are available to treat epilepsy. Sixty percent of people with epilepsy can achieve seizure freedom with medication treatment [12]. There are currently 25 FDA-approved anti-seizure medications available for the treatment of epilepsy [13] (Table 1). The choice of which anti-seizure medication to use is individualized based on patients' seizure and epilepsy type, comorbidities, medication interactions, and side effect profile. In those patients who have drug-resistant epilepsy that is not controlled by anti-seizure medications alone, referral to comprehensive epilepsy center is recommended for evaluation of surgical treatments for epilepsy, including resection, laser ablation, neuromodulatory treatments, or ketogenic diet [14].

Table 1. Anti-seizure medications

Enzyme-inducing anti-seizure medications	Non-enzyme-inducing anti-seizure medications
Carbamazepine	Brivaracetam
Cenobamate	Clonazepam
Clobazam	Ethosuximide
Eslicarbazepine	Gabapentin
Felbamate	Lacosamide
Oxcarbazepine	Lamotrigine
Perampanel (>8 mg/day)	Levetiracetam
Phenobarbital	Pregabalin
Primidone	Perampanel (<8 mg/day)
Phenytoin	Topiramate (<200 mg/day)
Rufinamide	Valproic acid
Topiramate (>200 mg/day)	Zonisamide

Interactions between gender-affirming treatments and epilepsy treatments

Hormone effects on seizure threshold

The data on the effects of sex hormones on seizures are complex and, at times, conflicting. Some evidence suggests that estrogens are mainly proconvulsant whereas progesterone and its metabolites are mainly anticonvulsant; however, results are mixed [15, 16, 17•, 18, 19]. Androgens are mainly thought to be anticonvulsant; however, data are also mixed, perhaps due to the metabolism to both the anticonvulsant androstanediol derivatives as well as the largely proconvulsant estradiol [15, 16, 17•, 20]. Overall, this suggests the possibility of breakthrough seizures when initiating feminizing hormone treatments, whereas masculinizing hormone treatments may be less likely to increase seizure frequency. However, it should be noted that there are no studies that have specifically examined the effect of GAHT on seizure control. Based on what is known about potential interactions, it may be necessary to increase a patient's seizure medication dose or add a new seizure medication if seizure frequency increases with initiation of or changes to GAHT. Risk of seizures, including sudden unexplained death in epilepsy (SUDEP), and injury must be balanced with the necessity of GAHT.

Hormone effects on epilepsy medications

Estrogen induces the glucuronidizing enzyme involved in the metabolism of lamotrigine, and to a lesser extent valproic acid. This can lead to a substantial decrease in lamotrigine levels, and a less pronounced decline in valproic acid levels, which may in turn worsen seizure control [21–23]. Thus, circumstances involving an increase in estrogen levels—including gender-affirming medication regimens including estradiol, initiation of systemic estrogen-containing birth control (such as combined oral contraceptives), hormone therapy for assisted reproduction, pregnancy, or peri/post-menopausal hormone replacement therapy—do warrant close monitoring of lamotrigine and valproic acid serum levels. When following serum levels of lamotrigine or valproic acid with estrogen therapy, dose up-titration may be required to remain within therapeutic range and maintain seizure control. It should be noted that the doses of estradiol used for gender affirmation are orders of magnitude higher than those used in combined oral contraceptives (often 20–35 mcg/day for combined oral contraceptive pills, as opposed to 2000–6000 mcg/day orally for gender affirmation) and may be anticipated to have a more significant impact on lamotrigine and valproic acid levels.

Epilepsy medication effects on hormones

The main mechanism of interaction between anti-seizure medications and sex hormones is through medication induction of cytochrome P450 hepatic enzymes. Anti-seizure medications that are considered enzyme inducers (Table 1) include carbamazepine, phenobarbital, phenytoin, and primidone, and to a lesser degree, cenobamate, clobazam, eslicarbazepine, felbamate, oxcarbazepine, perampanel (>8 mg/day), rufinamide, and topiramate (>200 mg/day) [24–28]. There are two studies that have investigated the effect of lamotrigine on oral combined oral contraception with documented decreases in progestin [29] and levonorgestrel [30] levels; however, the clinical impact of these decreases on the efficacy of contraception are unclear, and there are currently no restrictions around use of lamotrigine and oral contraception as recommended by the CDC [31] and therefore should not be considered in the enzyme-inducing category. P450 enzyme induction leads to increased estrogen metabolism, which lowers circulating estrogen levels; it also increases the production of sex hormone binding globulin (SHBG), which binds both estrogens and androgens to decrease their levels in the blood [24, 32]. Thus, the ultimate outcome of taking an enzyme-inducing anti-seizure medication is to decrease circulating levels of estrogens and androgens, which may decrease the efficacy of gender-affirming hormone treatments for both trans men and trans women. Non-enzyme-inducing anti-seizure medications (Table 1) should be considered for transgender individuals with epilepsy in order to avoid interfering with hormonal treatment goals; these include brivaracetam, clonazepam, ethosuximide, gabapentin, lacosamide, levetiracetam, pregabalin, low-dose topiramate (<200 mg/day), valproic acid, and zonisamide [24]. If an enzyme-inducing anti-seizure medication is used, free (unbound) hormone levels should be monitored and adjusted accordingly in order to achieve therapeutic targets.

An additional consideration when using non-enzyme-inducing anti-seizure medications is the effect of valproic acid, and possibly levetiracetam, on testosterone levels. Valproic acid is well known to increase serum testosterone levels in both men and women [33, 34]. There is also mixed evidence about whether levetiracetam may increase testosterone levels in men [35, 36]. From a hormonal perspective, the possibility of increased testosterone levels may make these medications more favorable for trans men than trans women. However, the teratogenicity of valproic acid must still be considered for all individuals with childbearing potential.

Effects of non-medication epilepsy treatments on hormones

There is no evidence to suggest that non-medication epilepsy treatments, such as a ketogenic diet, neuromodulatory devices, and resective or ablative epilepsy surgery, have any significant interaction with the hormones involved in gender-affirming treatments. No changes need to be made to gender-affirming hormone regimens in patients undergoing epilepsy surgery. When taking care of TGD individuals with medically refractory epilepsy, if their epilepsy is drug resistant, it is recommended that they be evaluated at a comprehensive epilepsy center to incorporate appropriate surgical or dietary treatments into their epilepsy care.

Conclusion

Epilepsy treatment involves an individualized approach of medical decisions around seizure medication choice and non-medication approaches with the goal of seizure freedom or reduced seizure frequency. When a patient identifies as transgender or gender diverse, this adds another level of complexity to medical care, which must be taken into account in the treatment of their epilepsy. The first step in care of epilepsy in the TGD population is confirmation of preferred name and pronouns and incorporation of these preferences into a healthcare provider's communication and medical documentation. Detailed discussion of a patient's gender-affirming care goals should be discussed in the context of their epilepsy treatment. To the best of our knowledge, there are currently no peer-reviewed medical studies on GAHT in TGD people with epilepsy to directly guide our care practices. Thus, extrapolation from cis-gender populations, including epilepsy management in the setting of contraception use, infertility treatments, and physiologic hormone fluctuations, currently guides our discussion of the interactions between GAHT, seizure control, and epilepsy treatments. Existing research does provide a framework around key issues such as potential interactions between estrogen and lamotrigine levels, enzyme-inducing medication effects on GAHT, and GAHT effects on seizure threshold [2••, 3]. However, there is a need for research in this specific patient population to enable us to more comprehensively understand epilepsy care and treatment outcomes in the setting of transgender and gender diverse care.

Author Contribution

C.K. and G.W. wrote main manuscript text and reviewed manuscript. G.W. prepared Table 1.

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Conflict of Interest
Catherine V. Kulick-Soper declares that she has no conflict of interest. Genna Waldman declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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