Neurological Health in Sexual and Gender Minority Individuals

Rubinee Simmasalam, MD, MPH[1] Mary C. Zuniga, MD[1] H.E. Hinson, MD, MCR, FAAN, FNCS[1]

[1] Department of Neurology, University of California, San Francisco, California

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Address for correspondence H.E. Hinson, MD, MCR, FAAN, FNCS, Department of Neurology, University of California, San Francisco, Zuckerberg San Francisco General Hospital, Box 0896, 2540, 23rd Street, Floor 5, San Francisco, CA 94110 (e-mail: h.e.hinson@ucsf.edu).

Abstract

Despite representing a significant proportion of the U.S. population, there is a paucity of population-based research on the health status and health needs of sexual and gender minority (SGM) individuals in neurology. Compared with heterosexual peers, some SGM populations have a higher burden of chronic health conditions. In parallel, SGM individuals are more likely to experience stigma and discrimination producing psychological distress, which may contribute to and be compounded by reduced health care access and utilization. In this narrative review, we summarize the existing literature on common neurological health conditions such as stroke, headache, epilepsy, movement disorders, and traumatic brain injury through the lens of intersection of SGM identity. Special focus is attuned to social determinants of health and gender-affirming hormonal therapy. Given the limitations in the available literature, there is an urgent unmet need for datasets that include sexual orientation and gender identity information, as well as funding for research that will characterize the prevalence of neurological conditions, unique risk factors, and health outcomes in SGM populations. In the health care community, providers should address deficiencies in their professional training and integrate inclusive language into their clinical skillset to build trust with SGM patients. There is an opportunity in neurology to proactively engage SGM communities, collaborate to remove barriers to care, promote resilience, and develop targeted interventions to ensure high-quality, culturally competent care for SGM populations to improve neurological health for all.

Keywords

- sexual and gender minority
- sexual orientation
- gender identity
- neurology
- gender affirming hormone therapy
- stroke

According to the 2020 Gallup Survey, lesbian, gay, bisexual, transgender, queer, and intersex (LGBTQI) individuals represent 7% of the U.S. population.[1] The term sexual and gender minorities (SGM) is an inclusive term to signify individuals whose sex, gender identity, and/or sexual orientation are something other than heterosexual and cisgender.[2] Despite representing a significant proportion of the U.S. population, there is a paucity of population-based research on the health status and health needs of SGM individuals. Within the neurology literature, studies including SGM individuals are often limited by small sample sizes. Investigators may report sex assigned at birth or focus on sexual behaviors (e.g., men having sex with men) without nuanced consideration of gender identity, limiting generalizability. Throughout this article, we utilize the term SGM when addressing issues that potentially affect multiple subpopulations. However, it is important to recognize that each subpopulation and individuals within a subpopulation may have a unique set of health and psychosocial risk factors that requires special focus. Here, we present a narrative review of the most current literature characterizing the intersection between SGM status and neurological disease and identify the gaps in need of further study. We begin by reviewing terminology and overarching themes then discuss specific neurological diseases.

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Terminology Acknowledgment

As we discuss the neurological health of SGM individuals, we want to acknowledge that some of the vocabulary may be unfamiliar to some readers. Hence, we provide a glossary with important definitions for inclusive language adapted from prior literature[3,4] and incorporating additional terminology used in this article, with the understanding that terminology will continue to evolve over time. We also recognize that although SGM is an inclusive term, it groups multiple identities together despite differences in lived experiences, risk factors, and social circumstances. Lastly, we acknowledge that some individuals within these groups may define terminology differently than presented here in ►**Tables 1** and **2**.

Overarching Themes Relevant to Neurological Health in Sexual and Gender Minority Populations

Below we discuss overarching themes that are integral in understanding the drivers of neurological health in SGM populations. ►**Table 3** summarizes key points of each of these themes relative to neurological health.

Table 1 Gender terminology

Gender terminology	Definition
Binary	Refers to the idea held by some that there are only two gender identities (woman/man) and often erroneously used to discuss issues of sex and gender in dominant society
Cisgender	Individuals whose sex assigned at birth is aligned with their gender identity
Cisnormativity	The concept/assumption that cisgender is the normative gender identity and thus leads to marginalization of those who do not identify as such
Endosex	Having natal sex characteristics (chromosomes, gonads, sex hormones, and/or genitals) that fit a male/female binary
Gender	A socially created construct referring to the characteristics and qualities associated with a particular self-presentation in a certain culture
Gender-affirming hormone therapy	Hormones used to align secondary sex characteristics to one's gender identity. Also known as cross-sex hormone therapy
Gender-affirming surgery	Surgical procedures to align one's physical body to one's gender identity. Examples include vaginoplasty, phalloplasty, and metoidioplasty. Outdated terms include "sex change," "gender reassignment," and "sex reassignment," among others
Gender dysphoria	Clinically significant discomfort and/or psychological distress pertaining to the incongruence between one's sex assigned at birth and one's gender identity due to dominant societal expectations of gender performance. This concept is listed in the DSM-5, but there is considerable controversy as to the appropriateness of this experience as a formal diagnosis
Gender expression	One's external communication of gender, e.g., speech, mannerisms, clothing, etc.
Gender fluid	Refers to the concept that someone's gender identity can change over the course of one's life, can also be used as a gender identity term by individuals whose gender identity changes or is fluid
Gender identity	A person's internal sense of gender
Gender neutral	The absence of gender, which may be used in contexts like pronouns (they/them), spaces (e.g., bathrooms), or identities
Gender nonconforming	Expressing gender in a way that does not align with the socially prescribed roles and behaviors of one's gender identity. People of any gender can be gender nonconforming
Nonbinary	An individual who does not identify strictly as man or woman
Transfeminine	Term sometimes used in the literature to describe individuals undergoing male-to-female gender-affirming therapy or procedures. It may also be used to describe a person who was assigned male sex at birth, but whose gender expression is aligned with society's feminine standards
Transgender	An umbrella term to describe a person whose gender identity differs from assigned sex at birth. Terms within the transgender umbrella include transgender woman or transwoman, transgender man or transman, gender expansive, and genderqueer, among others
Transmasculine	Term sometimes used in the literature to describe individuals undergoing female-to-masculine gender-affirming therapy or procedures. It may also be used to describe a person who was assigned female sex at birth but whose gender expression is aligned with society's masculine standards
Transsexual	Term sometimes used in medical literature to describe someone who has undergone medical interventions to align one's physical appearance more closely with one's gender identity. Not a synonym for transgender and currently its use should be restricted to those who self-identify as such. Generally, this is an outdated term that is not preferred

Table 2 Sexual orientation terminology

Sexual orientation terminology	Definition
Asexual	Refers to someone who has little or no interest in sexual contact with another person. Some asexual individuals experience romantic attraction to others while some do not
Bisexual	Someone who is attracted to those of the same gender and different gender
Gay	Someone who is attracted to those of the same gender and/or sex. Most commonly referring to a man who is attracted to other men
Heteronormativity	The concept that heterosexuality is the normative sexual orientation and thus leads to marginalization of those who do not identify with this orientation
Intersex	An umbrella term used by those with differences of sex development, in which there are variations in reproductive or sex anatomy, which can appear in a person's chromosomes, genitals, or internal organs. Some intersex traits are identified at birth, while others may not be identified until later
Lesbian	Refers to a woman who is attracted to other women. Someone who identifies as lesbian may also identify as gay
LGBTQIA+	Lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual, and other related identities
Pansexual	Refers to a person who is attracted to people of all genders and sexes
Queer	A previously derogatory term used to describe an LGBTQ person which has now been reclaimed by some people within the community. This term may still be seen as derogatory to some in the LGBTQ community and should not be used unless someone self-identifies as queer
Sex	A term used to describe someone's biology as male, female, or intersex. This determination is usually based on a combination of physiological, genetic, anatomical, and hormonal attributes and is typically assigned at birth
Sexual orientation	A term referring to attraction toward other people (can be emotional, sexual, romantic, etc.)
Sexual and gender minority	People whose sexual orientation, gender identity or expression, or reproductive development is characterized by nonbinary constructs of sexual orientation, gender, and/or sex (as defined by the National Institutes of Health Sexual & Gender Minority Research Office)

Table 3 Key points of overarching themes

Theme	Key points	Relationship to SGM neurological health
Minority stress and intersectional framework	Minority stress refers to chronic excess stress experienced by marginalized individuals from internalized homophobia, stress-related to self-concealment, harassment, violence, victimization, bullying, and discrimination, which leads to increased risks of developing mental and physical health conditions Intersectional framework refers to the intersection of multiple marginalized identities and risk factors that may impact health and outcomes such as comorbid marginalized health conditions, environmental stressors, religion, race, and socioeconomic status	In pooled cohort studies, minority populations such as SGM populations, were found to have a higher burden of chronic health conditions compared with heterosexual peers due to cumulative burden of minority stress. Many of these chronic health conditions impact the development and severity of neurological health conditions. We must consider how minority stress and the intersection of multiple marginalized identities impact the development of neurological diseases when creating solutions to improve disparate health outcomes
Barriers to care	SGM populations experiences many barriers to care including being refused needed care, being blamed for their health status, having health care professionals refuse to touch them, use abusive language, and experience physically rough or abusive acts The is significant mistrust in the health care system leading to underutilization of primary and specialized care services contributing to delays in diagnosis	Longitudinal care is needed to diagnose, prevent progression, and reduce disability associated with many neurological conditions. Many SGM populations experience disjointed care leading to inequitable care and potentially disparate health outcomes compared with non-SGM populations
GAHT	A lifesaving therapy that is associated with higher quality of life and reduced rates of anxiety, depression, and suicidality in select SGM populations Providers should embrace their discomfort with GAHT, be proactive about learning about GAHT regimens and engage experts when possible	Extrapolating data about GAHT from cisgendered populations using hormone therapy such as stroke risk are inadequate Dedicated research about GAHT and how it interacts with various disease processes such as seizure and headache pathways or risk of developing neuromuscular or movement disorders are needed to provide higher-quality neurological care

Abbreviations: GAHT, gender-affirming hormonal therapy; SGM, sexual and gender minority.

Minority Stress and Intersectional Framework

In the last few decades, pooled statistics showed that compared with heterosexual peers, some SGM populations have a higher burden of chronic health conditions.[5,6] SGM individuals are more likely to experience stigma and discrimination producing psychological distress, which may contribute to and be compounded by reduced health care access and utilization.[5] The causes for these disparities are manifold. Throughout this article, we utilize two frameworks to understand these disparities: minority stress and intersectionality. Minority stress refers to chronic excess stress experienced by marginalized individuals, which leads to increased risks of developing mental and physical health conditions.[5] For SGM populations, this includes internalized homophobia, stress-related to self-concealment, harassment, violence, victimization, bullying, and discrimination. The intersectional framework considers the intersection of multiple marginalized identities and risk factors that may impact health and outcomes such as comorbid marginalized health conditions, environmental stressors, religion, race, and socioeconomic status.[6] We must consider how minority stress and the intersection of multiple marginalized identities impact the developing of neurological diseases when developing solutions to improve disparate health outcomes.

Barriers to Care for Sexual and Gender Minority Populations

Experiences of invalidation, stigma, and discrimination significantly impact access to and quality of medical care for SGM populations. In a 2009 survey, 56% of lesbian, gay, and bisexual respondents and 70% of transgender respondents reported at least one instance where they experienced discrimination in a health setting, including being refused needed care, being blamed for their health status, having health care professionals refuse to touch them, use excessive precautions, use abusive or harsh language, or act physically rough or abusive.[7] These experiences engender mistrust in the health care system leading to underutilization of primary and specialized care services contributing to delays in diagnosis. A limited number of LGBTQI affirmative and competent health care providers and disparate insurance coverage may also contribute.[5] This is especially relevant to neurology, as consistent longitudinal care is often needed to diagnose, prevent progression, and reduce disability associated with many neurological conditions. As we explore the limited data and negative impact of disjointed care throughout this article, we also highlight the importance of striving to promote communication, trust, and equitable care for SGM populations.

Gender-Affirming Hormonal Therapy

Gender-affirming care encompasses a range of services that aim to support an individual's gender expression and gender identity when their gender presentation doesn't match the sex they were assigned at birth. Gender-affirming care does not always include medical or surgical therapies, and approaches must be uniquely tailored to each individual. Medical therapies range from puberty blockade to supplementation with feminizing or masculinizing hormones. It is important to recognize that gender-affirming hormonal therapy (GAHT) is a lifesaving therapy and is associated with higher quality of life and self-esteem and reduces rates of anxiety, depression, and suicidality in SGM individuals of all ages with gender dysphoria.[8] There are limited clinical studies examining the interactions of GAHT with neurological conditions in SGM populations. Recommendations extrapolated from population studies of cisgendered women taking contraceptives or postmenopausal women taking hormonal replacement therapy are inadequate for understanding hormonal impacts in gender minority individuals. Transgender people must frequently advocate for their own hormone regimen, up to 70% of transgender adults[9] and 71% of transgender youth,[10] due to difficulty in accessing care, provider discomfort, and/or lack of knowledge regarding GAHT. We encourage providers to embrace their discomfort with GAHT, be proactive in learning about how GAHT as it relates to the diseases they manage, and engage experts when possible. This will allow for patient-centered discussions about gender identity and expression and encourage shared decision-making about how GAHT regimens can be adjusted to maximize benefits and minimize side effects. Throughout this article, we offer treatment considerations regarding GAHT but recommend to providers to be creative and thoughtful in their own practice.

Stroke

We herein describe the traditional and nontraditional risk factors associated with stroke in SGM, and literature on the epidemiology of ischemic and hemorrhagic stroke and the role of GAHT in SGM. Finally, we end this section highlighting treatment considerations. ►**Table 4** summarizes key points from each section as it relates to stroke care for SGM populations.

Risk Factors

Stroke is the main cause of disability and fifth leading cause of death in the United States.[11] Although scientific literature on stroke in SGM populations is limited, several studies have identified unique risk factors in SGM groups. An important stroke risk factor is minority stress associated with discrimination and unique social circumstances and barriers to care that SGM individuals face. This has been described in the past as allostatic load, which is the physiological dysregulation due to disease-mediated and psychosocial stress and has been associated with chronic inflammation, increased risk for cardiovascular disease, and increased risk of mortality.[12–14] Overall, the contributions of traditional stroke risk factors in SGM populations remain incompletely understood, but some observations are described below.

Hypertension

Several studies have reported elevated rates of hypertension in sexual minority (SM) men,[15,16] whereas survey-based studies have suggested that SM women are more likely to report hypertension.[17–20] In contrast, a recent retrospective study by Diaz et al identified no statistical differences in

Table 4 Summary of stroke-related topics for sexual and gender minority populations

Stroke care	Key points
Risk factors	An important stroke risk factor in SGM individuals is minority stress, compounded by discrimination, unique social circumstances, and barrier to health care The overall impact of sex hormones on blood pressure remains unclear due to purely observational literature Literature shows no significant differences in lipid/cholesterol levels or rates of diabetes when comparing SGM to heterosexual individuals Some studies suggest that transfeminine individuals taking estrogen may have an elevated risk for venous thromboembolism. A large cohort study at Kaiser focusing on GAHT revealed a higher risk of stroke in transfeminine individuals taking estrogen when compared with cisgender individuals. There are no studies on the impact of GAHT in hemorrhagic stroke in transgender individuals
Epidemiology	Literature on stroke epidemiology and SGM people is limited and often with conflicting results Tobacco smoking, stimulant use, syphilis, and HIV rates have been reported to be higher among certain SGM groups. Special focus should be given to screen and treat patients with these unique risk factors
Treatment considerations	The risk for vascular events associated with estrogen therapy should not be a reason to deny SGM populations GAHT. Providers should have patient-centered risks–benefits discussions and work with patients to optimize benefits and minimize risks and side effects. Transdermal estrogen confers a lower risk of venous thromboembolism as compared with oral estrogen, which could represent an alternative replacement option for many patients

Abbreviations: GAHT, gender-affirming hormonal therapy; SGM, sexual and gender minority.

hypertension, diabetes, and hyperlipidemia in SGM people compared with non-SGM who had strokes (multiple sexual orientation/gender identities combined).[21] Similarly, studies evaluating hypertension in transgender individuals have shown inconsistent findings. A recent review by Connelly et al reported that GAHT did not impact blood pressure in transgender men, whereas both increases and decreases in systolic blood pressure were observed in transgender women receiving GAHT.[22] However, most of these studies are observational, and the overall impact of sex hormones on blood pressure trends remains to be elucidated.

Hyperlipidemia and Diabetes

A systematic review of cardiovascular risk factors in sexual minorities found no significant differences in cholesterol levels between SM individuals compared with heterosexual individuals.[23] Only one study reported higher cholesterol levels in SM men, and only one study reported lower cholesterol levels in SM women. The same review highlighted that diabetes rates were similar among sexual minorities and heterosexual individuals. Regarding transgender patients, a retrospective study in a gender clinic in Catalonia reported no changes in lipid levels in transwomen, but transmen had a general worsening in lipid profiles.[24]

Tobacco and Nontraditional Risk Factors

Tobacco use is higher among SM men and SM women compared with their heterosexual counterparts, although this varies among certain ages, race, ethnicity, and area of residence.[25] Particularly, significantly higher rates of tobacco smoking were observed among individuals identifying as Latinx SGM women[23] and among nonheterosexual individuals living in nonrural areas.[26] In addition, SGM individuals have higher rates of stimulant use[24] syphilis, HIV, and hepatitis C.[21,24] These nontraditional stroke risk factors have also been consistently reported at higher rates among transgender individuals.[27–30] Another focus of the literature to date is on hormone therapy use by transgender individuals. Although the literature is limited, studies have shown that transfeminine gender minorities taking estrogen have an elevated risk of venous thromboembolism.[30] Estrogen, particularly the ethinyl estradiol formulation, has been associated with a threefold increase in risk of cardiovascular death.[31]

Epidemiology

Literature on stroke epidemiology and SGM people is limited and conflicting results have been reported. A cross-sectional study using the Behavioral Risk Factor Surveillance System data found no difference in the odds of stroke between gay/lesbian and heterosexual respondents from 2014 to 2016, but higher odds of stroke in bisexual women compared with heterosexual women.[32] A different cross-sectional study of SM individuals using the National Health Interview Survey (NHIS) data found that SM women were more likely to report stroke compared with heterosexual women. In contrast, there were no statistically significant differences in rates of stroke in SM men.[33] A study exploring racial and ethnic differences using NHIS data found that Black SM women were more likely to report stroke compared with White heterosexual women and Black heterosexual women. Similarly, White SM women were more likely to report stroke compared with White heterosexual women, but Latinx SM women and men had no difference in stroke compared with Latinx or White heterosexual groups.[34]

The literature on gender minority communities has largely focused on the role of GAHT on ischemic and hemorrhagic stroke. One of the largest cohort studies is the Kaiser Permanente electronic medical record–based cohort study. This investigation included 2,842 transfeminine and 2,118 transmasculine patients with a mean follow-up of 4.0 and 3.6 years, and they were matched with cisgender men and women, respectively, by age and year of enrollment into the Kaiser health system. The study found an overall similar initial

incidence of ischemic stroke across groups. However, subgroup analysis revealed a higher risk of stroke in transfeminine individuals who initiated gender-affirming hormones after enrollment, compared with cisgender women. Transmasculine individuals had no difference in stroke risk.[30] The role of Hormone therapy (HT) in hemorrhagic stroke has largely focused postmenopausal women rather than transgender individuals, with some studies suggesting that current oral contraceptive use may increase the risk of subarachnoid hemorrhage[34,35] and others finding no such association.[35,36] Overall, it is unclear how these studies may extrapolate to transgender individuals using GAHT, given the differences in indication, HT formulations, and routes. Lastly, there have been case reports of transwomen presenting with cerebral venous thrombosis in the setting of estrogen GAHT and with no other known risk factors for hypercoagulability.[37,38]

Treatment Considerations

The risks for vascular events associated with estrogen therapy should not be reason to deny SGM populations GAHT. Patient-centered risk–benefits discussions are warranted based on an individual's cardiovascular risk factors. Tailored regimens should be developed to minimize the risks and side effects. For example, transdermal estrogen confers a lower risk of venous thromboembolism as compared with oral estrogen,[39,40] which could represent an alternative replacement option for patients. In addition, special focus should be given to reducing modifiable risk factors, including tobacco use, stimulant use, and ensuring patients are treated for infections that may increase the risk of ischemic stroke.

Headache

Headache is the second most common cause of disability globally.[41] Migraine headaches are the most common, followed by tension-type headaches and cluster headaches.[42] A few cohort studies have found that headache syndromes may be more common among SGM populations compared with their heterosexual/cisgender counterparts. In the 2013 to 2018 National Health Survey, in which sexual orientation and gender identity (SOGI) was collected, the prevalence of severe migraine was higher in SGM individuals with the highest among bisexual women (36.8%), followed by lesbians (24.7%), bisexual men (22.8%), heterosexual women (19.7%), gay men (14.8%), and heterosexual men (9.8%). This study did not include gender minorities.[43] Headaches in SGM populations are also reported as more intense and associated with higher odds of moderate to severe disability.[43,44] The causes for these disparities are not well understood, but potential factors include comorbid mental health conditions, psychosocial risk factors, hormonal fluctuations, and barriers to care leading to insufficient access and treatment.

Mental Health

There is a dose–response relationship between progression from an episodic to chronic migraine syndrome in the setting of traumatic experiences and mental health conditions (e.g., depression, anxiety, and posttraumatic stress disorder [PTSD]).[45,46] In a study of 3,325 SGM individuals, a history of trauma and discrimination was associated with moderate–severe migraine disability even after controlling for sociodemographic and clinical factors. This relationship lost significance when adjusting for history of depression, anxiety, or PTSD, suggesting possible modifiable risk factors.[44] The relationship between mental health and migraines is complex and likely bidirectional. Possible explanations include shared environmental and genetic risk factors that predispose to both conditions,[47] cosensitization of the sensory and affective components of pain that lead to neurological and psychiatric symptom[48] and alteration of mood pathways due to estrogen loss and altered serotonergic activity.[49] Stress and poor sleep are also significant triggers for migraines in SGM populations.[50] Stress regarding food insecurity, financial worry, and caring for family members with unmet health needs are examples of psychosocial stressors that are disproportionally higher in marginalized populations.[43]

Hormones

Hormonal effects on headache syndromes were first noted in the context of cisgendered women. Cisgendered women experience higher rates of migraine, often two to three times that of cisgendered men,[51] whereas cisgendered men experience cluster headaches up to five times that of cisgendered women.[52] The effects of sex hormones are complex, with both direct effects on higher-order functional neural networks and vascular structures, as well as indirect effects through genomic alterations and neurotransmitter signaling.[53] Animal and laboratory models[54] have shown that estrogen increases central opioid tone, decreases serotonin, activates the trigeminovascular system, modulates levels of inflammatory mediators including calcitonin gene-related peptide, and increases susceptibility to cortical spreading depolarization, the mechanism thought to cause auras. Clinical studies with cisgendered women demonstrated that high estrogen levels as seen during pregnancy or with hormonal therapy are associated with higher rates of migraine with auras, whereas the rate of withdrawal of estrogen in the luteal phase of the menstrual cycle[55] and level fluctuations during perimenopause[56] is thought to be associated with migraine without auras. Higher levels of estradiol was also found in nonobese cisgender men with migraine.[57] Testosterone, on the other hand, increases serotonin, stabilizes cortical blood flow, has anti-inflammatory effects, and suppresses cortical spreading depolarization.[54] Low testosterone levels were found in both cisgendered men and women with cluster headaches[58,59] and cisgendered men with chronic migraines.[60] Lastly, progesterone is thought to enhance gamma-aminobutyric acid (GABA) function and reduce nociception in the trigeminovascular pathway. A cross-sectional study found that cisgender women with migraines have lower serum allopregnanolone levels with an inverse relationship to years and frequency of migraines.[61]

There is scant research on the epidemiology of headache syndromes and the effects of GAHT in SGM populations. Close monitoring may be required for transfeminine individuals initiating estrogen supplementation and/or

testosterone suppression. Small uncontrolled population studies in the Netherlands and Ontario found that migraine prevalence of transgender women (26%) was similar to cisgendered women (25%) and higher than cisgendered men (7.5%).[62,63] Of those who experienced migraines, 31% had migraine with auras in the first study compared with 54% in the latter study. The increased prevalence of migraines is thought to be due to estrogen supplementation and testosterone suppression with high doses of estrogen leading to auras. Switching to transdermal estrogen formulations can mitigate this risk by maintaining steady plasma concentrations and avoiding fluctuations seen with oral and injection formulations.[64] Testosterone may offer positive effects, but safety and high-quality studies are needed. A study of 16 transmasculine individuals found decreased headache frequency while taking GAHT[65] and a prospective pilot study of subcutaneous testosterone implants in 27 cisgendered women with migraine resulted in improvement of headache intensity.[66] Lastly, providers should be aware of possible secondary causes of headaches.[53] Masculinizing hormones are associated with increased risk of erythrocytosis and secondary polycythemia vera,[67] which can cause hyperviscosity and lead to headaches, blurry vision, paresthesias, and potentially strokes. Feminizing hormones may increase risk for venous thrombosis,[30] stroke, prolactinoma,[68] and meningioma,[69] which can also present as headaches. Population studies are needed to characterize the true prevalence of these conditions in SGM populations taking GAHT.

Treatment Considerations

SGM individuals are more likely to take over the counter medications, less likely to be on a preventative treatment, and have higher rates of emergency room visits for headache treatment.[44,50,70] Possible causes include provider knowledge gaps, difficulty accessing specialty care, lower rates of health insurance, and distrust of the medical system. Providers should use inclusive language to ask patients about their SOGI and screen for headache syndromes in all SGM populations. For those who screen positive for headache, screening for mental health comorbidities and psychosocial factors such as insurance coverage and food and housing insecurity is essential as comprehensive treatment plans may be more effective. For those taking GAHT, providers should consider secondary causes of headaches, potential side effects, and assess medication list for potential drug interactions. Hormones are metabolized by liver enzymes, which also metabolize migraine therapies such as topiramate and valproic acid and antiretroviral (ARVs) therapies for individuals with HIV, leading to changes in serum levels of all therapies. New studies in cisgendered women found that the risk of stroke with migraines with aura is related to the aura frequency and estrogen dose.[71,72] Providers should be proactive about monitoring headaches, optimizing migraine regimens, measuring serum hormone levels regularly and adjusting formulations and doses of GAHT to optimize gender affirmation while treating headaches and minimizing other side effects.

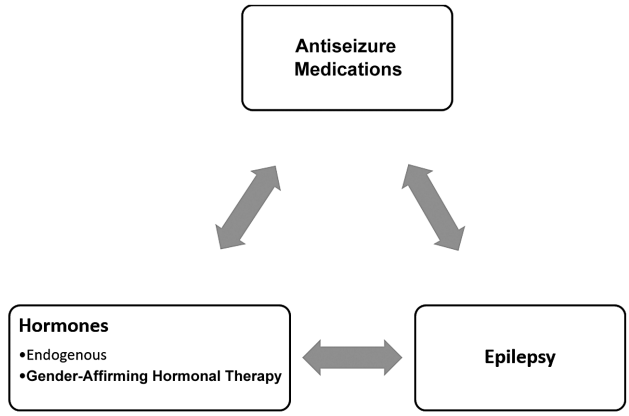

Fig. 1 Dynamic relationships exist between hormones, ASMs, and epilepsy. Sex hormones potentiate central nervous system neuronal activity, thereby affecting seizure control. Both sex hormones and ASMs can directly or indirectly affect liver enzymatic activity leading to varying levels of both agents in the body impacting seizure control and potential side effects. Epilepsy has been linked to hormonal disturbances through temporolimbic connections to hypothalamus and pituitary glands. Exogenous hormones, ASMs, and epilepsy syndromes can all potentially lead to alterations in endogenous hormone levels, which may impact bone health and other health-related issues. There are no studies of GAHT in epilepsy patients. GAHT similarly interacts with liver enzymes and ASMs, which may affect seizure control and minimize intended effects of gender affirmation. Understanding these dynamic relationships is important for dose optimization and providing adequate counseling. ASM, antiseizure medication; GAHT, gender-affirming hormonal therapy.

Epilepsy

There are an estimated 1.2% of people living with epilepsy in the United States.[73] There are no available studies regarding prevalence, unique risk factors and seizure control in SGM individuals with epilepsy. A multidirectional relationship exists between sex hormones, epilepsy syndromes, and antiseizure medications (ASMs), which is depicted in ►**Fig. 1**.

Sex Steroid Hormones and Epilepsy

Sex steroid hormones potentiate neuronal activity and thus could impact seizure frequency. This is best seen with catamenial epilepsy in which fluctuations in estrogen and progesterone levels during certain phases of the menstrual cycle trigger seizures. Estradiol is thought to be a proconvulsant via two mechanisms: glutamate transmission by potentiating N-methyl-D-aspartate receptor activity and anti-GABA activity.[74] The active metabolite of progesterone 3α,5α-tetrahydroprogesterone or allopregnanolone is an anticonvulsant by enhancing postsynaptic GABA activity. The NIH Progesterone Trial found decreased seizure frequency in cisgendered women with catamenial epilepsy treated with progesterone.[75] Androgen effects are more variable due to testosterone metabolism to both estradiol, a proconvulsant, and androstanediol and dihydrotestosterone, both of which are anticonvulsants mediated by enhancing GABA-A receptor activity. A small trial investigating anastrozole, an aromatase inhibitor that reduces the conversion of exogenous testosterone to estrogen, in seven cisgendered men with epilepsy over a 12-week period

resulted in a reduction in seizure frequency.[76] These studies suggest that there may be a subset of individuals who are sensitive to endogenous hormonal changes and may experience changes in seizure frequency with hormonal therapy. A recent systematic review of the impact of hormone replacement therapy (HRT) on seizure frequency in cisgendered women with epilepsy found three human studies with mixed results.[77] There are no available studies examining the effects GAHT in cisgendered or SGM individuals with epilepsy.

The Dynamic Interaction between Antiseizure Medications and Hormones

It is important for providers to be aware of potential drug interactions between ASMs and hormone levels. Some ASMs will lower the serum levels of exogenous hormones by increasing the activity of liver p450 enzymes, which metabolizes hormones and increases the production of steroid hormone-binding molecules. These ASMs are phenytoin, carbamazepine, oxcarbazepine, clobazam, eslicarbazepine, felbamate, lamotrigine, perampanel, phenobarbital, primidone, rufinamide, and topiramate (at high doses). Valproic acid and levetiracetam may increase the production of testosterone through nonenzymatic effects. Hormones can also affect the levels of ASMs. Estradiol can increase the metabolism of ASMs by inducing glucuronidation, particularly of lamotrigine and to a lesser degree valproic acid.[75]

Estrogen and testosterone are important for bone health. People with epilepsy are at risk for seizure-related injuries. Certain GAHT such as gonadotropin-releasing hormone therapies can alter the endogenous levels of these hormones and increase risk for osteopenia and osteoporosis. Enzyme-inducing ASMs, particularly phenytoin, phenobarbital, and primidone, also have increased risk of bone fractures through the induction of vitamin D metabolism leading to bone remodeling.[78] As such, providers should be vigilant using these ASMs in patients taking GAHT, with additional caution for adolescents[79] due to the pivotal time period for bone growth and remodeling.

Treatment Considerations

Monitoring levels of both GAHT and ASMs in SGM patients with epilepsy may be necessary to optimize hormonal effects while maintaining seizure control until evidence-based guidelines are available. Nonenzyme-inducing ASMs may be preferred. Regular screening of vitamin D levels and bone health with dual-energy X-ray absorptiometry should be obtained due to increased risk for osteoporosis.[75,78] Special considerations are needed for those with treatment-resistant epilepsy on multidrug regimens due to interactions with GAHT.

There are also limited data available regarding comorbid incidence of HIV and epilepsy in SGM populations. In 2012, the American Academy of Neurology and the American Epilepsy Society published guidelines[80] regarding ASMs for patients living with HIV/AIDS. Many ARVs also induce hepatic enzymes impacting the levels of ASMs, ARVs, and exogenous hormones. Providers should screen for potential drug interactions in SGM populations taking GAHT with epilepsy and HIV.

Movement Disorders

There are no quantitative studies regarding prevalence and phenomenology of movement disorders in SGM populations. However, there is growing body of literature regarding the impact of hormones on Parkinson's disease (PD). Both testosterone and estrogen are associated with modulation of nigrostriatal dopaminergic pathways. In preclinical studies, estrogen was shown to have antiapoptotic effects and inhibit alpha-synuclein fibril stabilization and aggregation.[81] Timing and length of estrogen exposure may play a critical role in the risk of developing PD, where higher total lifetime exposure is associated with decreased risk of developing PD in cisgendered women.[82] Estrogen fluctuations during menstrual cycles are also associated with worsening motor symptoms, whereas in postmenopausal cisgendered women with advanced PD, estrogen therapy is associated with worsening dyskinesias.[83] In non-PD patients, there are case reports of estrogen-induced chorea in women taking oral contraceptives or HRT and in pregnancy.[84,85] Further studies are needed to characterize the prevalence of other movement disorders in SGM populations and potential impact of GAHT.

Neuromuscular Disorders

There is limited neuromuscular literature in SGM individuals. One case report described a transfeminine patient who developed spinal bulbar muscular atrophy despite undetectable androgen levels. The authors suggested that this was due to spironolactone, the antiandrogen she had taken for 15 years, which also has proandrogenic activity.[86] Another case report described a transgender man with hypokalemic thyrotoxic periodic paralysis exacerbated by testosterone therapy, suggesting that the androgenic effect of testosterone on the $Na+/K+$-ATPase pumps contributed to hypokalemia and requiring this patient to stop taking GAHT.[87]

Traumatic Brain Injury

A total of 50 to 60 million individuals a year experience traumatic brain injury (TBI) globally, with up to 50% of the world's population predicted to experience at least one event in their lifetime.[88] There is a lack of population studies describing the prevalence of TBI, risk factors, or outcomes in SGM individuals, despite this group experiencing violence and trauma at higher rates than heterosexual cisgender individuals due to stigma and discrimination. The 2015 Transgender Survey reported that of the 28,000 respondents, 9% experienced physical violence in the last year due to their gender identity, 33% experienced at least one negative interaction with a health care provider due to their gender identity, and 54% were victims of intimate partner violence at some point in their life, of which 24% experienced severe

violence involving their head, neck, or face.[89] No statistics are available for other SGM subpopulations.

In recent years, several research groups[90–92] have demonstrated the neuroprotective effect of female sex hormones in animal models of TBI. Proposed mechanisms include protective gene transcription, GABA-A activation, which increases cellular survival, scavenging oxygen free radicals, enhancement of astroglial metabolism and cycling, reduction of proinflammatory mediators, modulation of Aquaporin-4 channel expression resulting in reduced brain edema, and increased cerebral blood flow and promotion of angiogenesis. Unfortunately, clinical trials have not found a beneficial effect, although some researchers argue that study populations were too heterogenous. Small studies in cisgendered women and men found that the phase of menstrual cycle,[93] use of hormonal contraceptives at the time of injury,[94] and disruptions of the central hypothalamic–pituitary–ovarian axis post-TBI[95,96] could impact the development of postconcussive symptoms and recovery. Normal to high levels of testosterone was also associated with decreased risk of an unconsciousness state after TBI in some cisgendered males.[97,98] Studies evaluating the potential impact of GAHT in SGM populations with TBI are needed.

Small case series in adults with head injuries found changes in the notion of self as reduced perceived masculinity and perceived femininity at 1 year in cisgendered men and women, respectively,[99] and disparate coping strategies based on socioeconomic status led to strained marital and familial relationships.[100] Security in gender identity and social relationships are important for reintegration into society and willingness to access necessary care after TBI and may disproportionately impact SGM individuals experiencing additional stressors and barriers to care. SGM populations are understudied in TBI literature and require prioritization.

Conclusion

SGM populations have been historically excluded in public health and medical literature both actively (disregard due to stigma) and passively (lack of data collection or awareness). This article highlights the limited data and treatment considerations for common neurological conditions in SGM populations. There are multiple opportunities for improvement. There is an urgent unmet need for datasets that include SOGI information as well as funding for research that will characterize the prevalence of neurological conditions, unique risk factors, and health outcomes in SGM populations. Targeted studies of GAHT in SGM populations would provide evidence-based guidelines on how to effectively alter regimens to maximize benefits and reduce side effects. GAHT improves the quality of life for gender minority individuals that chose to integrate medication into their gender-affirming regimens, and every effort should be made to continue it. In the health care community, providers should address deficiencies in their professional training by seeking education in clinical competencies for SGM-related health. Providers should integrate inclusive language into their clinical skillset to build trust with SGM patients. We need to proactively engage SGM communities, collaborate to remove barriers to care, promote resilience, and develop targeted interventions to ensure high-quality, culturally competent care for SGM populations to improve neurological health for all.

Conflict of Interest
None declared.

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