“Transgender” serves as the umbrella term for individuals whose gender identity or gender expression differs from the sex that they were assigned at birth (i.e. male, female or intersex), which is typically based on external genital anatomy. Alternatively, “cisgender” individuals are those whose gender identity matches their sex assigned at birth. Gender identity refers to an individual’s self-perception as a man, woman, or non-binary. Gender expression refers to the external manifestation of a person’s gender identity, which may or may not conform to the socially-defined behaviors (e.g. speech patterns, voice, mannerisms, movements, social interactions, etc.) and external characteristics (e.g. dress, grooming, hairstyles, jewelry, physical characteristics, etc.) commonly attached to masculinity or femininity.

Depending on the individual patient’s goals and desires, transgender and non-binary individuals may seek a variety of hormonal therapies and/or gender affirming procedures to better align their physical traits with their gender identity. Masculinizing hormone therapy (MHT) represents a common intervention for both transgender men and non-binary individuals. Individuals receiving MHT may experience a number of dermatologic side effects, including the development and/or worsening of acne vulgaris. While standard guidelines for management of acne vulgaris remain largely applicable, there are several important and unique considerations that dermatologists should be aware of when caring for acne patients receiving MHT.

In this article, we discuss the management of acne vulgaris among patients receiving MHT. Of note, there is a general lack of research surrounding management of acne vulgaris specifically in patients receiving MHT, and further research is needed to better define the optimal management strategies for acne vulgaris in these patients. Accordingly, while we attempt to provide evidence-based recommendations whenever possible, some of these recommendations are based on research conducted among cisgender individuals and/or the clinical experience of the authors.

**WHAT IS MASCULINIZING HORMONE THERAPY AND HOW DOES IT IMPACT ACNE?**

The overall goals of masculinizing hormone therapy (MHT) are to enhance internal feelings of masculinity, to promote the development of male secondary sex characteristics (e.g. increased facial and body hair, increased muscle mass, deeper voice), to minimize the appearance of female secondary sex characteristics, and ultimately, to decrease gender dysphoria. The typical approach to MHT comprises the use of testosterone therapy in topical, oral or injected forms.

MHT can result in the development and/or worsening of acne vulgaris due to impact of androgens on the pilosebaceous unit. Eccrine and sebaceous glands account for the majority of androgen metabolism in the skin with high levels of 5a-reductase enzymes that convert weaker androgens into more potent ones (e.g. dihydrotestosterone). Through the peroxisome proliferator activated receptor-γ (PPARγ), these androgens stimulate sebum production and thus contribute to the pathogenesis of acne vulgaris.

In one prospective study of patients receiving MHT, 82% demonstrated facial acne and 88% demonstrated back and/or chest acne after 6 months of MHT. While most patients receiving MHT develop mild to moderate acne, some patients may develop more severe acne with risk for permanent scarring.
WHAT IS CHEST BINDING?

Binding, or chest binding, represents a common practice of transgender men and non-binary individuals who desire a more masculine chest appearance. This practice involves the use of tight fitting sports bras, elastic bandages, ace or plastic wrap, duct tape, or designated binders to limit the appearance of female breasts and to create a flat chest contour. When binding is used for longer periods in persons with larger breasts, compression and prolonged occlusion can result in the development or worsening of acne vulgaris.1,2,3 Dermatologists should be cautious about recommending discontinuation of binding, as this practice can help mitigate gender dysphoria and significantly improve quality of life for transgender patients. Rather, they should counsel patients to consider taking days off from binding and avoid use of plastic wrap, ace wrap, or duct tape in favor of less occlusive methods, such as sports bras.

WHAT ARE RECOMMENDED TOPICAL TREATMENTS FOR MILD TO MODERATE ACNE?

For treatment of mild to moderate acne among patients receiving MHT, we recommend starting monotherapy with a topical retinoid for those with primarily comedonal acne. For patients with papulopustular and/or inflammatory lesions, we recommend the addition of either (1) topical benzoyl peroxide +/- topical antibiotic, or (2) topical dapsone.10 The latter option may represent a particularly effective combination for patients receiving MHT with inflammatory lesions. Topical dapsone has both anti-inflammatory and anti-androgen properties, and has demonstrated greater therapeutic potential for treatment of hormone-related, inflammatory acne in cisgender women.10 However, no study has yet evaluated the use of topical dapsone in the treatment of acne vulgaris specifically among patients receiving MHT.

As a second line treatment, especially for patients who cannot tolerate or fail to respond to traditional topical therapies, dermatologists may consider the use of superficial chemical peels, such as glycolic acid, salicylic acid, or trichloroacetic acid peels. These have demonstrated efficacy for treatment of mild to moderate comedonal, papulopustular, and inflammatory acne and are generally well tolerated.11 Furthermore, many superficial chemical peels are available in over-the-counter formulations, are relatively inexpensive, and can be performed at home, if needed.

WHAT ARE RECOMMENDED SYSTEMIC TREATMENTS FOR MODERATE TO SEVERE ACNE?

For patients receiving MHT who develop moderate to severe inflammatory, nodulocystic, or otherwise treatment-resistant acne vulgaris, systemic therapy must be considered. Systemic antibiotics, including tetracycline-class antibiotics such as doxycycline or minocycline, are reasonable first-line treatment options, especially for patients with moderate acne without scarring and/or those hesitant to start oral isotretinoin. Systemic antibiotics should be used for no more than 3-6 months and always in conjunction with topical therapies. However, as systemic antibiotics do not routinely provide prolonged clearance once the drug is discontinued, oral isotretinoin may ultimately be required.

Isotretinoin is a reasonable first line treatment option, especially for patients with scarring and/or severe inflammatory or nodulocystic acne. A more detailed explanation of use of oral isotretinoin among patients receiving MHT is discussed later in this article.

Pseudotumor cerebri (PTC) is a rare adverse event associated with both tetracycline antibiotics and isotretinoin.12 Recent case reports have also identified a possible association between PTC and testosterone therapy.13,14 Consequently, before starting a tetracycline antibiotic or oral isotretinoin, patients receiving MHT should be counseled on this rare but potentially serious side effect.
WHAT IS THE ROLE OF HORMONAL AGENTS?
Systemic hormonal agents, including combination oral contraceptive pills (OCPs) and spironolactone, should generally not be used for treatment of acne vulgaris in patients on MHT. From the patient perspective, most patients receiving MHT will likely oppose any estrogen-containing contraceptive over concerns that it may result in feminization and/or counteract MHT. Unfortunately, there is little empirical data to support or refute this perception. Of note, drosperinone, a synthetic progestin often used for hormonal acne given its unique antiandrogenic activity, is available only in combination with estradiol and, therefore, may not be an appropriate option for patients receiving MHT. Spironolactone, an aldosterone antagonist with potent anti-androgenic activity, can result in gynecomastia and vaginal bleeding. These potential side effects are often unacceptable for patients receiving MHT who typically desire both a flat chest contour and amenorrhea. In the unlikely scenario that a patient receiving MHT is willing or interested in starting systemic hormonal agents for treatment of acne vulgaris, the dermatologist should consult with the physician managing their MHT before starting treatment.

HOW DO I REGISTER TRANSGENDER PATIENTS FOR THE iPLEDGE PROGRAM?
Based on the current iPLEDGE classification system, dermatologists are often confronted with the choice of registering transgender men and non-binary individuals with childbearing potential as either (a) male or (b) female of childbearing potential. Neither option is ideal as (a) respects the individual’s gender identity while increasing the potential risk of fetal isotretinoin exposure and (b) appropriately addresses pregnancy prevention but disregards the patient’s gender identity. Advocacy efforts argue for a revision of the classification system to separate gender from child-bearing potential. Until such changes are implemented, dermatologists should have an honest and empathetic conversation with patients receiving MHT about the limits of the current iPLEDGE classification system in addition to the risk of teratogenicity associated with isotretinoin use.

WHAT COURSE OF ORAL ISOTRETINOIN IS MOST APPROPRIATE FOR PATIENTS ON MHT?
For the general population, current guidelines recommend a goal cumulative dose of oral isotretinoin between 120 and 150 mg/kg. There is also limited evidence that a higher cumulative dose of 220 mg/kg may result in lower rates of relapse. There is no empirical data or clinical consensus on the optimal cumulative dose of isotretinoin in patients receiving MHT. However, dermatologists may consider targeting higher cumulative doses of isotretinoin in patients on MHT as most individuals take MHT indefinitely and thus may be at higher risk of relapse.

WHAT CONTRACEPTION SHOULD I RECOMMEND FOR PATIENTS RECEIVING MHT (WITH CHILD-BEARING POTENTIAL) WHO ARE STARTING ISOTRETINOIN?
Many patients receiving MHT still retain internal female reproductive organs. Though some patients may achieve an anovulatory state, testosterone therapy alone is not an efficacious means of contraception as patients receiving MHT can still become pregnant. Because isotretinoin is a known teratogen, it is critical for dermatologists prescribing isotretinoin to assess the sexual behaviors of patients receiving MHT to identify those individuals who may require contraception. For patients receiving MHT who have female internal reproductive organs and engage in receptive penile-vaginal intercourse with a fertile partner, contraception is indicated.

The iPLEDGE program requires two forms of contraception, including a primary form of contraception, for individuals with reproductive potential. Most patients receiving MHT will elect for use of condoms or diaphragms in conjunction with a primary contraceptive method. Reasonable choices for the primary contraceptive method include the progestin IUD (Mirena), progestin implant, or the copper IUD. Many patients
receiving MHT will elect for the progestin IUD, as it has a favorable side effect profile that includes decreased vaginal bleeding and, in some cases, amenorrhea. In fact, 44% of cisgender women report amenorrhea after 6 months of use. The progestin IUD, however, has also demonstrated potential pro-androgenic properties and been associated with worsening of acne in some cisgender women. Patients should be counseled on these potential risks and benefits when discussing the progestin IUD. The progestin implant and copper IUD, in contrast, have not been found to have a significant impact on acne severity. However, the copper IUD can result in vaginal spotting and heavier menstrual flow and, therefore, may be undesirable to some patients receiving MHT.

Combined oral contraceptives are generally contraindicated in patients receiving MHT due to the potential they may result in feminization and/or counteract MHT. Progestin-only oral contraceptives may be reasonable options for contraception among patients receiving MHT. However, progestin-only oral contraceptives are not approved contraception methods under the iPLEDGE program.

**WHAT ABOUT THE RISK OF DEPRESSION IN PATIENTS RECEIVING MHT AND ISOTRETINOIN?**

Isotretinoin carries an FDA warning that it may cause depression, psychosis, and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behavior. A recent metaanalysis found that isotretinoin use in acne patients is not associated with an increased risk of depression and may actually improve depressive symptoms. Despite this, many patients seeking isotretinoin treatment present with higher baseline rates of depression and suicidal ideation due to the physical disfigurement and social isolation associated with having severe acne. For these reasons, providers prescribing isotretinoin should assess the patient’s psychiatric history and current mental health issues when discussing the potential risks and benefits of isotretinoin therapy. This is especially applicable to patients receiving MHT.

Sexual minorities with acne have recently been identified as a high-risk group for mental health issues, with over 1/3 reporting a history of depression and recent suicidal ideation. This may result from elevated baseline depression rates in addition to the importance of body image and appearance concerns among sexual minorities. While no study has assessed mental health issues specifically among transgender or non-binary patients with acne, sexual and gender minorities share an increased overall risk of developing mental health issues. Specifically, transgender youth have a 2- to 3-fold increased risk of depression, anxiety disorder, suicidal ideation, and suicide attempt when compared to cis-gender youth. Transgender adults also have an increased risk of depressive disorders, especially if not receiving appropriate treatment. Accordingly, patients receiving MHT with acne may also be a high risk group for developing mental health issues. It is thus important to discuss and monitor for signs and symptoms of depression and suicidal ideation in all transgender and other non-binary patients seeking treatment for acne vulgaris.
REFERENCES


