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BRIEF COMMUNICATION

Prescription Patterns and Testosterone Concentrations Achieved With AndroForte 5% Testosterone Cream in Transgender and Gender Diverse Individuals

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ABSTRACT

Background: Masculinizing hormone therapy with testosterone is used to align an individual's physical characteristics with their gender identity in trans and gender diverse individuals. Standard testosterone doses and formulations recommended for hypogonadal cisgender men are typically administered. 100 mg AndroForte 5% testosterone cream is the recommended starting dose in hypogonadal cisgender men but there are no data evaluating the use of AndroForte 5% testosterone cream in gender-affirming hormone therapy regimens.

Aim: To assess the prescription patterns and serum total testosterone concentrations achieved with AndroForte 5% testosterone cream in trans and gender diverse individuals.

Methods: A retrospective analysis was undertaken of trans and gender diverse individuals at a primary and secondary care clinic in Melbourne, Australia. Seventy-two individuals treated with AndroForte 5% testosterone cream to the torso were included.

Outcomes: Testosterone dose and serum total testosterone concentration.

Results: Median age was 26 years (IQR 22−30) and median duration of testosterone therapy was 14 months (7−24). Fifty (69%) individuals had a non-binary gender identity. Initial median testosterone dose was 50 mg (50−100) daily. Thirty-eight (53%) commenced doses <100 mg daily, the recommended starting dose for hypogonadal cisgender men. Median total testosterone concentration achieved from 186 individual laboratory results was 11.9 nmol/L (8.1−16.4). Polycythemia was documented in 5 (7%) individuals.

Clinical Implications: AndroForte 5% testosterone cream can be used in individuals with a binary and/or non-binary gender identity seeking masculinization. It can be commenced at a lower dose than that administered to hypogonadal cisgender men for individuals seeking slow masculinization goals.

Strengths & Limitations: Limitations include the retrospective study design, lack of clinical end points and lack of standardization of timing of laboratory tests in relation to the last dose. This is the first study to evaluate AndroForte 5% testosterone cream in trans and gender diverse individuals and provides insights into prescription patterns in individuals with a non-binary gender identity.

Conclusion: AndroForte 5% testosterone cream represents an alternative formulation of testosterone administration for trans and gender diverse individuals seeking masculinization. **Nolan BJ, Zwickl S, Locke P, et al. Prescription Patterns and Testosterone Concentrations Achieved With AndroForte 5% Testosterone Cream in Transgender and Gender Diverse Individuals. J Sex Med 2021;XX:XXX−XXX.**

Key Words: Transgender; Gender Identity; Non-Binary; Testosterone; Transdermal

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INTRODUCTION

Testosterone therapy is a necessary component of management for some transgender (trans) individuals (including those with a binary and/or non-binary gender identity) to permit development of physical characteristics to align with their gender identity. Standard doses of parenteral or transdermal testosterone used to treat hypogonadal cisgender men are recommended in consensus guidelines.[1,2]

AndroForte 5% is a white, opaque, non-alcohol-based cream presented as single boxed 50 mL tube (50 mg testosterone per 1 mL of cream) with a graduated syringe-style measuring device to allow for dose titration. The recommended starting dose in trans and gender diverse individuals and hypogonadal cisgender men is 2 mL of cream by measured applicator per day applied to the upper body (torso, abdomen and sides of the body) or in hypogonadal cisgender men, 0.5 mL applied to the scrotal skin. AndroForte 5% testosterone cream is approved for use in Australia and is one testosterone formulation recommended in the Endocrine Society of Australia position statement for treatment of male hypogonadism,[3] and the position statement on the hormonal management of adult trans and gender diverse individuals.[4] Despite this, there are currently no published data evaluating the serum total testosterone concentrations achieved with AndroForte 5% testosterone cream in trans and gender diverse individuals.

As such, in this retrospective study in adult trans and gender diverse individuals on testosterone therapy, we aimed to evaluate the prescription patterns of AndroForte 5% testosterone cream, the serum total testosterone concentrations achieved, and the prevalence of polycythemia.

MATERIALS AND METHODS

A retrospective audit of electronic medical records was performed of consultations for trans and gender diverse individuals at a primary care clinic and an endocrine clinic in Melbourne, Victoria, Australia. Data were collected from consecutive new consultations between 22 February 2016 and 22 July 2021. The study was approved by the Austin Health Human Research Ethics Committee (Audit/21/Austin/69) and Thorne Harbor Health (THH/CREP 19/015) and the nature of the study did not require informed consent.

This retrospective longitudinal analysis included trans and gender diverse individuals treated with AndroForte 5% testosterone cream (AndroForte 5, 5% w/v (50 mg/mL); Lawley Pharmaceuticals, West Leederville, Australia) who had at least one total testosterone concentration available whilst on therapy. Individuals were excluded if they did not have laboratory results available after initiation of testosterone therapy or if they were concurrently prescribed another testosterone formulation.

The primary outcome of interest was serum total testosterone concentration. The target range of 10−30 nmol/L was defined from a previous reference range obtained from healthy eugonadal cisgender men.[5] We also analyzed the testosterone dose, prescription patterns by gender identity, and prevalence of polycythemia. We defined polycythemia as hematocrit >0.5, as described in the Endocrine Society clinical practice guidelines of gender-dysphoric/gender-incongruent persons.[1]

Gender identity was obtained from intake forms and medical records. Classification of binary and/or non-binary gender identity was as previously described.[6] In short, binary gender identity was defined as identification as exclusively male (including trans male, trans man, and transgender male), and non-binary gender identity encompassed all other identities (including non-binary, transmasculine, genderqueer, and agender). If an individual reported more than one gender identity, and one of which was categorized as non-binary, they were categorized as having a non-binary gender identity for the analysis.

As data were obtained retrospectively, total testosterone concentrations were measured using immunoassays available as standard care for clinical decision-making. All laboratories were accredited by National Association of Testing Authorities (NATA, the national accreditation body for Australia).

Statistical analyses were performed using STATA version 17.0 software (StataCorp. 2021. *Stata Statistical Software: Release 17.* College Station, TX: StataCorp LLC). Data were not normally distributed so median (IQR) are reported. Differences in testosterone dose by gender identity were compared using Mann-Whitney *U* test. For individuals with more than one serum total testosterone concentration available, the data were averaged. $P < .05$ was considered statistically significant.

RESULTS

Data were collected from 92 individuals prescribed AndroForte 5% testosterone cream, of whom 72 had laboratory results available for analysis. Seventeen individuals did not have follow-up laboratory studies available in our database, 2 individuals had recently commenced testosterone therapy and did not have follow-up laboratory results, and 1 individual was co-prescribed intramuscular testosterone enanthate.

The median age was 26 years (22−30) and median duration of testosterone therapy was 14 months (7−24). Baseline total testosterone concentration was 1.1 nmol/L (0.8−1.6) and baseline body mass index 27 kg/m^2 (22−34). Fifty (69%) individuals had a non-binary gender identity (Table 1).

Initial median AndroForte 5% testosterone dose was 50 mg (50-100) daily applied to the torso. Thirty-eight (53%) individuals commenced doses <100 mg daily, the recommended starting dose for hypogonadal cisgender men of 100 mg daily. There was no difference in initial testosterone dose between individuals with a binary or non-binary gender identity (100 mg (50−100) vs 50 mg (50−100), $P = .17$). Some individuals had dose adjustment over their follow-up, however there was no difference in

Table 1. Gender identity (N = 72)

Gender identity	Number*	%
Agender	2	2.8
Genderqueer	4	5.6
Male	24	33.3
Non-binary	31	43.1
Trans	1	1.4
Trans male/trans man	2	2.8
Transmasculine	21	29.2

*Individuals could indicate more than one gender identity, so total number exceeds number of individuals included in this analysis. Gender identities for those indicating more than one gender identity: transmasculine/non-binary (n = 8), male/transmasculine (n = 3), male/non-binary (n = 1), trans/non-binary (n = 1).

median dose between individuals with a binary or non-binary gender identity at last follow-up (100 mg (50−100) vs 50 mg (50−100), $P = .06$).

From 72 individuals, 186 individual total testosterone concentration results were available following initiation of testosterone therapy. Median total testosterone concentration achieved was 11.9 nmol/L (8.1−16.4). Serum total testosterone concentrations for each AndroForte 5% testosterone cream dose are shown in Figure 1. There was no difference in serum total testosterone concentration achieved in individuals with a binary or non-binary gender identity (11 nmol/L (7.3−15.4) vs 12.1 nmol/L (8.1−16.8), $P = .64$) (Figure 2). There was no difference in serum total testosterone concentration between individuals prescribed ≥100 mg testosterone, compared to those prescribed <100 mg testosterone (11.9 nmol/L (9.1−17.0) vs 11.2 nmol/L (5.7−16.2), $P = .19$). Including all laboratory results, 98 (53%) were in range 10−30 nmol/L, with 76 (41%) <10 nmol/L and 8 (4%) >30 nmol/L.

Of 171 full blood examination results, polycythemia (defined as hematocrit >0.5) was documented in 9 (5%) results from 5 (7%) individuals, with 5 ≥0.52 (3%). The maximum hematocrit was 0.53. Of these results with hematocrit >0.5, 6 total testosterone concentrations were in range 10-30 nmol/L, with 2 <10 nmol/L and 1 >30 nmol/L. No individual had haemoglobin >180, the upper limit of the cisgender male reference range.

DISCUSSION

In this retrospective analysis of trans and gender diverse individuals, AndroForte 5% testosterone cream achieved serum testosterone concentrations within the male reference range, though was frequently initiated at a lower dose than that recommended for cisgender hypogonadal men. A non-binary gender identity was reported in 69% of individuals in this analysis. Polycythemia was recorded in 5% of laboratory results.

Pharmacokinetics of AndroForte 5% Testosterone Cream

Initial pharmacokinetic evaluation of AndroForte 5% testosterone cream in hypogonadal cisgender men revealed that 100 mg and 200 mg daily doses were able to achieve serum total testosterone concentrations within the male reference range for

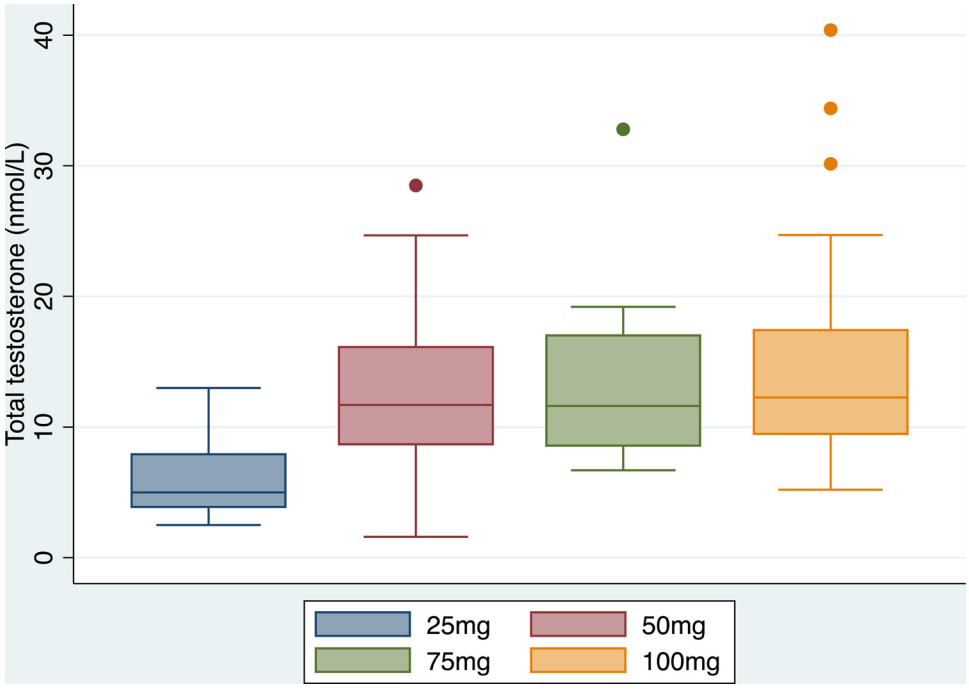

Figure 1. Serum total testosterone concentration by AndroForte 5% testosterone cream dose. Figure 1 is available in color online at www.jsm.jsexmed.org.

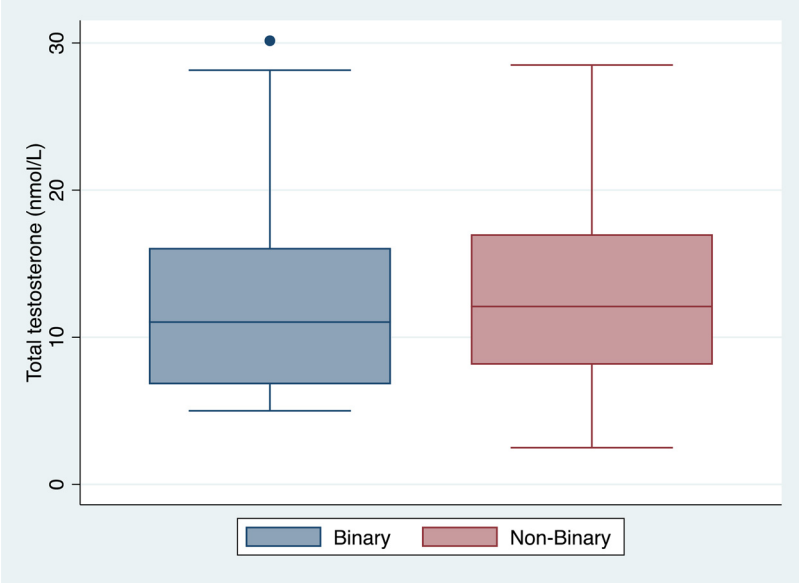

Figure 2. Serum total testosterone concentration by gender identity. Figure 2 is available in color online at www.jsm.jsexmed.org.

12 hours after application to the torso.[7] A subsequent 12-week pharmacokinetic study demonstrated that most cisgender men were able to maintain serum total testosterone concentrations within the male reference range.[8] Of thirty individuals in the 12-week study, the final titrated dose was <100 mg per day in 5 men, 100 mg per day in 15 men and 150 mg per day in 10 men. Notably, some cisgender men treated with 150 mg per day did not achieve target serum testosterone concentrations, potentially related to poor absorption or increased metabolism. AndroForte 5% testosterone cream has been shown to be bioequivalent to 1% testosterone gel in a randomized, open-label cross-over trial in 16 hypogonadal cisgender men.[9]

Testosterone Concentrations in Trans and Gender Diverse Individuals

Typically, testosterone concentrations in the male reference range are targeted for trans and gender diverse people desiring full masculinization (typically 320−1,000 ng/dL (11.1−34.7 nmol/L)).[1] To our knowledge, no previous study has evaluated the use of AndroForte 5% testosterone cream in trans and gender diverse individuals. Serum total testosterone concentrations with other testosterone formulations have been reported in a previous retrospective analysis of our databases.[10] In this analysis, median total testosterone concentration measured 11.5 nmol/L (1.5−21.1) with intramuscular testosterone undecanoate, 12.1 nmol/L (1.35−20.45) with intramuscular testosterone enanthate and 5.6 nmol/L (1.1−17.1) with transdermal testosterone. In another retrospective analysis involving 62 trans men in the United States, individuals treated with transdermal testosterone had a lower serum concentration than those receiving intramuscular testosterone (11.3 nmol/L vs 18.2 nmol/L, $P = .018$).[11] However, in a randomized, open-label study enrolling 45 transgender men, mean total testosterone concentration in individuals treated with transdermal testosterone was 5.89 ng/mL (18.7 nmol/L), with no between-group difference compared to short-acting and long-acting intramuscular formulations.[12]

Notably, 69% of individuals in our analysis reported a non-binary gender identity, compared to a 14% prevalence of non-binary gender identity in a recent retrospective evaluation of our cohort.[6] There are currently limited data evaluating testosterone prescription patterns in individuals with a non-binary gender identity, though a recent analysis from the Netherlands has noted a higher proportion of "partial" hormone treatment amongst all individuals with a non-binary compared to binary gender identity (11% vs 4.7%, $P = .02$).[13]

Clinical Implications

AndroForte 5% testosterone cream achieved serum testosterone concentrations in the male reference range and represents an alternative testosterone formulation for trans and gender diverse individuals seeking masculinization. Given the option to commence low-dose testosterone therapy to target testosterone concentrations below the male reference range, this could be a consideration for individuals seeking slow or lower degrees of masculinization. Further research is required to elucidate the influence of serum testosterone concentrations on outcomes such as bone and cardiovascular health.

Intramuscular testosterone undecanoate is the preferred first-line treatment option for masculinizing hormone therapy amongst practitioners experienced in trans and gender diverse health in Australia,[14] and the most commonly prescribed formulation.[15] However, intramuscular formulations of testosterone have been associated with a higher prevalence of polycythemia.[10] AndroForte 5% testosterone cream therefore represents an

alternative formulation for individuals with a contraindication to intramuscular testosterone including hypersensitivity, or in those who develop polycythemia on parenteral testosterone.

Polycythemia was documented in 9 (5%) laboratory results from 5 (7%) individuals. This compares to a 23% prevalence with intramuscular testosterone enanthate (n = 31) and 15% prevalence with testosterone undecanoate (n = 125) in a previous cross-sectional analysis from Melbourne, Australia.[10] No individual treated with transdermal testosterone (n = 24) had polycythemia in this analysis. Similarly, another retrospective analysis reported an 11% prevalence of polycythemia in trans individuals treated with testosterone.[16]

Limitations

Limitations to this analysis include its retrospective design, with missing data given this was not collected in a standardized manner. Similarly, serum total testosterone concentration results were collected via different immunoassays available for routine clinical care, and not collected in a standardized time in relation to the timing of the last administered dose. Liquid chromatography-mass spectrometry (LC-MS) is considered the reference standard for sex steroid measurement but is not available in routine clinical care in Australia.[17] Given the retrospective analysis, we do not have data on clinically relevant end points such as masculinization, patient satisfaction or quality of life. Prescriber preference and the rationale for AndroForte 5% testosterone cream dose or prescription were not consistently documented.

CONCLUSIONS

AndroForte 5% testosterone cream achieves serum total testosterone concentrations within the male reference range and represents an alternative route of testosterone administration for trans and gender diverse individuals seeking masculinization. A high proportion of individuals had a non-binary gender identity, with over 50% commencing a lower dose than that administered to hypogonadal cisgender men.

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Conflict of Interest: ASC and BJN have received product from Besins Health Care for investigator-initiated clinical studies using estradiol and progesterone. No monetary support from Besins Health Care was received for these studies and Besins Health Care have had no input into the design, analysis or writing of any manuscripts.

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STATEMENT OF AUTHORSHIP

Brendan J. Nolan: Conceptualization, Data Curation Conceptualization, Methodology, Formal Analysis, Project administration, Writing-initial draft, Writing-review & editing; Sav Zwickl: Methodology, Writing-review & editing; Peter Locke: Resources, Writing-review & editing; Satu Simpson: Data Curation; Ling Li: Data Curation, Writing-review & editing; Jeffrey D. Zajac: Supervision, Writing-review & editing; Ada S. Cheung: Conceptualization, Methodology, Supervision, Writing-review & editing.

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