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REVIEW ARTICLE

Pharmacokinetics of testosterone therapies in relation to diurnal variation of serum testosterone levels as men age

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Abstract

Background: To improve symptoms associated with testosterone deficiency, many testosterone therapies are available that aim to restore serum testosterone (T) levels to the normal physiologic range. The magnitude, frequency, and duration between peak and trough T concentrations vary with route of administration, and none reflect normal endogenous daily diurnal T variations.

Objective: To compare pharmacokinetic profiles of serum T from approved T formulations with endogenous diurnal T variations in young and older men, and to consider whether there may be value in mimicking the diurnal T rhythmicity with exogenous testosterone therapies as men age.

Materials and methods: A literature search of studies examining the diurnal variation of endogenous T in healthy men and men with testosterone deficiency was performed using PubMed in January 2020. Additional searches for serum T pharmacokinetic profiles of various testosterone therapy formulations were also conducted. Prescribing information for various T formulations was also reviewed.

Discussion and conclusion: Endogenous diurnal T variation is well described and appears to be blunted naturally as men age. Men with testosterone deficiency lack diurnal T variation and exhibit a flatter T profile compared with eugonadal men. Some T replacement options provide intraday T level variations similar to normal circadian secretion, and others provide a flatter exposure profile reflective of depot release. Others provide profiles that exceed the frequency and physiologic range of the natural diurnal variation of T. All exogenous T replacement dosing targets an increase in average T levels to within the normal physiologic range and improves symptoms associated with low T, but no single testosterone therapy can exactly mimic the normal diurnal T patterns seen in younger men and the blunted circadian T secretion of older men.

KEYWORDS
diurnal variation, testosterone deficiency, testosterone therapy

1 | INTRODUCTION

The United States Food and Drug Administration (USFDA) approves use of various formulations for testosterone therapy (TTh) for men with testosterone deficiency (TD) associated with certain medical conditions to achieve eugonadal levels of T seen in healthy men.[1] The Endocrine Society clinical practice guideline and American Urological Association recommend diagnosing TD in men with presence of clinical signs and symptoms of TD and testosterone (T) levels consistently <10.4 nmol/L (300 ng/dl).[2,3] Societies outside the United States largely are in agreement with the clinical practice guideline set by the Endocrine Society, with most societies recommending a cutoff of either 10.4 nmol/L (300 ng/dl) or 12–12.1 nmol/L (346–350 ng/dl) as the mean total T cutoff for TD diagnosis and during follow-up. There are slight differences in diagnostic workup and follow-up[4]; for example, the Endocrine of Society of Australia has recommended separate mean total T (TT) cutoffs to diagnose TD for young men and men older than 70 years, possibly to reflect the lower mean total T levels seen in older men.[5–8] In addition, "adult-onset hypogonadism" or "late-onset hypogonadism" (LOH), as defined by the Sexual Medicine Society of North America (SMSNA), is a syndrome characterized by clinical and biochemical evidence of low T with advancing age.[7] Currently, only the European Academy of Andrology (EAA) and the SMSNA have provided recommendations for the short-term treatment of LOH with TTh. Nevertheless, overall, these societies recommend that pre-treatment serum T levels should be obtained and T levels should be regularly assessed following TTh.[9–12]

In 2016, it was estimated that 2.4 million men in the United States 40 to 69 years old have symptomatic TD.[13] Globally, this prevalence ranges from 2% to 6%.[6,14] Results from the Hypogonadism in Males (HIM) study estimated that approximately 40% of men aged ≥45 years had T levels <10.4 nmol/L (300 ng/dl) and that a patient's risk for TD was estimated to increase by 17% for every 10-year increase in age. Age-related decline in T levels may be attributed to variances in T levels observed in men over 40.[15] TD may negatively impact men's health and quality of life, as symptoms of TD include impaired sexual function, depressed mood and fatigue, changes in bone mineral density, and body composition, and increased body fat.[2,16] The presence of certain comorbidities, such as obesity, type 2 diabetes mellitus, atherosclerotic cardiovascular disease, and metabolic syndrome, are also associated with low T levels, which may be ameliorated with long-term TTh.[17–23] To improve symptoms associated with TD, many TTh are available to restore serum T levels to the middle tertile of the normal physiologic range (450–600 ng/dl).[3,24] Men across a wide age range seek treatment for low T, with an estimated 2.3% of men in their 40s and 3.8% of men in their 60s receiving some form of TTh in 2011.[25] When used appropriately, TTh can ameliorate signs and symptoms associated with hypogonadism.[26,27] There are many routes of administration for TTh approved for use by the FDA. Depending on the route of administration, the varying T formulation pharmacokinetics (PKs) contribute to the differences in time when improvements begin to take effect (ranging between 3 and 6 weeks), with maximum effects achieved within 6 months to 1 year after initiating therapy.[13,28,29] Furthermore, the amplitude between peak T (C_{max}) and trough T (C_{min}) concentrations following TTh may also vary widely from what is observed in daily diurnal endogenous T variations. In this review, we sought to compare the PK profiles of serum T from different exogenous T formulations with diurnal variations in endogenous serum T levels and consider whether, as men age, there may be clinical value in mimicking the diurnal T rhythmicity with exogenous TTh.

2 | MATERIALS AND METHODS

A literature search using PubMed was performed in January 2020 with the following search terms: "diurnal variation" or "circadian rhythm," and "testosterone," "testosterone deficiency," or "testosterone treatment." Studies evaluating diurnal T variation in healthy young and older men, as well as men with low T, were reviewed. This article reviewed the prescribing information for various T preparations currently approved by the FDA, and additional searches were conducted using PubMed to identify primary PK studies for each TTh. Studies with clinical importance and T PK assessments were included. This review was funded by Antares Pharma, Inc., who provided review for medical accuracy.

3 | PK PROFILES OF APPROVED EXOGENOUS T FORMULATIONS

3.1 | Subcutaneous injections

In September 2018, the FDA approved subcutaneous (SC) testosterone enanthate (TE) as an option for TTh for men with TD. This product is supplied as a single-dose auto-injector that patients self-administer in the abdominal region once a week. The recommended starting dose is 75 mg and may be adjusted in 25 mg increments to 50 or 100 mg based on trough-concentration-guided dosing.[30]

In an open-label, single-arm, dose-blinded, 52-week phase 3 study, 150 patients were initiated on 75 mg SC TE administered weekly, with trough-concentration-guided dose adjustment.[31] At baseline, TT was 8.0 ± 3.3 nmol/L (230.4 ± 94.0 ng/dl). The primary endpoint was met, with 92.7% of overall patients achieving T levels within physiologic range of 10.4 to 38.1 nmol/L (300–1100 ng/dl). There were no patients with a measured TT C_{max} ≥52 nmol/L (1500 ng/dl) at week 12. Mean C_{trough} values >10.4 nmol/L (300 ng/dl) were maintained from week 6 (17.4 ± 6.0 nmol/L, or 501.9 ± 172.7 ng/dl) through week 52 (16.9 ± 5.3 nmol/L, or 487.2 ± 153.3 ng/dl) of the study. Following 12 weeks on SC TE treatment, the 7-day mean total T concentration ($C_{avg0\text{-}168h}$) was 19.2 ± 4.4 nmol/L (553.3 ± 127.3 ng/dl). The C_{max} (27.4 ± 7.5 nmol/L, or 789.8 ± 215.4 ng/dl; Table 1) and C_{min} (15.1 ± 3.8 nmol/L, or 435.6 ± 109.2 ng/dl) measured during the 7-day period at week 12 yielded a peak-to-trough ratio of 1.8. During the week 12 dosing interval, there was little fluctuation in dihydrotestosterone (DHT) and estradiol (E_2).

TABLE 1 Comparison of testosterone PK profile of different TTh preparations

Route	Formulation	Dose	Mean C_{max}	Time to C_{max}	Mean C_{min}	Mean C_{avg} Between Treatment Doses	Recommended Starting Dose
SC	TE[31,32] (XYOSTED®)[30]	50 mg/week	29.5 ± 9.5 nmol/L (849.6 ± 274.8 ng/dl)	12.0 h (median)	15.9 ± 4.9 nmol/L (458.2 ± 139.9 ng/dl)	20.7 ± 6.2 nmol/L (598.2 ± 177.7 ng/dl)	75 mg every week[30]
		75 mg/week	26.3 ± 6.4 nmol/L (758.2 ± 185.9 ng/dl)	11.9 h (median)	14.9 ± 3.4 nmol/L (431.2 ± 97.5 ng/dl)	18.6 ± 3.7 nmol/L (537.6 ± 108.1 ng/dl)	
		100 mg/week	30.0 ± 8.3 nmol/L (866.3 ± 238.6 ng/dl)	24.1 h (median)	14.8 ± 4.2 nmol/L (427.7 ± 120.9 ng/dl)	19.8 ± 4.4 nmol/L (571.1 ± 127.2 ng/dl)	
		Overall	27.4 ± 7.5 nmol/L (789.8 ± 215.4 ng/dl)	11.9 h (median)	15.1 ± 3.8 nmol/L (435.6 ± 109.2 ng/dl)	19.2 ± 4.4 nmol/L (553.3 ± 127.3 ng/dl)	
IM	TC[35] (Depo®-Testosterone)[34]	200 mg/2 weeks	38.6 ± 10.3 nmol/L (1112 ± 297 ng/dl)	4–5 days	n/a	n/a	50–400 mg every 2–4 weeks[34]
	TE[36] (DELATESTRYL®)[37]	100 mg/week	>41.6 nmol/L or 1200 ng/dl	24 h	n/a	36.6 nmol/L (1055 ng/dl)	50–400 mg every 2–4 weeks[37]
		200 mg/2 weeks	>41.6 nmol/L or 1200 ng/dl	48 h	n/a	32.7 nmol/L (943 ng/dl)	
		300 mg/3 weeks	>41.6 nmol/L or 1200 ng/dl	36–48 h	n/a	30.6 nmol/L (883 ng/dl)	
		400 mg/4 weeks	~55.5 nmol/L or 1600 ng/dl	36–48 h	n/a	25.3 nmol/L (729 ng/dl)	
	TU[38,39] (AVEED®)[40]	750 mg	30.9 ± 12.0 nmol/L (890.6 ± 345.1 ng/dl)	10 days post-injection	Week 14: 11.8 ± 4.3 nmol/L (339.5 ± 122.7 ng/dl) Week 24:11.2 ± 3.4 nmol/L (323.5 ± 99.1 ng/dl)	17.1 ± 4.9 nmol/L (494.5 ± 141.5 ng/dl)	750 mg (3 ml) injected at initiation, at 4 weeks, then every 10 weeks thereafter[40]
	TU (REANDRON®/NEBIDO®[97])	1000 mg	45 nmol/L (1298 ng/dl)	7 days	17 nmol/L (490 ng/dl)	n/a	1000 mg every 10 to 14 weeks
Subdermal implantation	T pellets[50] (TESTOPEL® at days 1–113[45])	900 mg (12 pellets)	35.4 ± 0.9 nmol/L (1021.6 ± 24.9 ng/dl)	13.5 days (median)	n/a	22.1 ± 4.3 nmol/L (638.3 ± 124.2 ng/dl)	150–450 mg SC every 3–6 months[45]
	T pellets—retrospective study[48]	6–7 pellets (450–525 mg)	33.5 nmol/L (966 ng/dl)	1 month	8.1 nmol/L (233 ng/dl)	24.7 nmol/L (712 ng/dl)	
		8–9 pellets (600–675 mg)	37.4 nmol/L (1078 ng/dl)	1 month	7.7 nmol/L (221 ng/dl)	24.9 nmol/L (719 ng/dl)	
		10–12 pellets (750–900 mg)	61.1 nmol/L (1762 ng/dl)	1 month	8.9 nmol/L (257 ng/dl)	27.6 nmol/L (795 ng/dl)	
Transdermal patch	TE patch[52] (ANDRODERM®)[51]	5 mg/day (no longer available)	26.5 ± 9.6 nmol/L (765 ± 277 ng/dl)	8.2 ± 2.0 h	9.7 ± 5.1 nmol/L (280 ± 146 ng/dl)	17.9 ± 6.1 nmol/L (517 ± 176 ng/dl)	4 mg/day applied nightly for 24 h delivering 4 mg of T/day[51]
Topical gels and solutions	1% T gel[64] (AndroGel® 1% at day 90)[62]	50 mg/day	29.3 ± 1.9 nmol/L (845 ± 55 ng/dl)	4.0 h	12.3 ± 0.6 nmol/L (355 ± 17 ng/dl)	19.2 ± 1.1 nmol/L (554 ± 32 ng/dl)	50 mg applied topically 1× in the morning[62]
		100 mg/day	41.7 ± 2.3 nmol/L (1203 ± 66 ng/dl)	7.9 h	17.4 ± 0.8 nmol/L (502 ± 23 ng/dl)	27.5 ± 1.1 nmol/L (793 ± 32 ng/dl)	

(Continues)

TABLE 1 (Continued)

Route	Formulation	Dose	Mean C_{max}	Time to C_{max}	Mean C_{min}	Mean C_{avg} Between Treatment Doses	Recommended Starting Dose
Topical gels and solutions, *continued*	1.62% T gel (AndroGel® 1.62% at day 112/TESTOGEL®)[63]	20.25–81 mg	29.3 ± 16.6 nmol/L (845 ± 480 ng/dl)	8 h	n/a	19.5 ± 9.0 nmol/L (561 ± 259 ng/dl)	40.5 mg (2 pump actuations, or single 40.5 mg packet) applied topically 1× in the morning[63]
	2% T gel (FORTESTA®)[67]	40 mg/day	29.6 ± 14.5 nmol/L (855 ± 417 ng/dl)	2–4 h	n/a	15.4 ± 6.1 nmol/L (444 ± 176 ng/dl)	40 mg (4 pump actuations) applied 1× daily in the morning[67]
	2% T gel (TESTAVAN®/ TESTARZON®)[74,98]	23 mg/day	25 ± 8.8 nmol/L (721 ± 254 ng/dl)	4 h	n/a	12.8 ± 4.2 nmol/L (369 ± 121 ng/dl)	23 mg (1 pump actuation) applied 1× daily in the morning
	1% T gel (TESTIM®/ VOGELXO®)[71,72]	50 mg/day	18.7 ± 12.9 nmol/L (538 ± 371 ng/dl)	8 h	7.7 ± 4.4 nmol/L (223 ± 126 ng/dl)	12.7 ± 6.5 nmol/L (365 ± 187 ng/dl)	50 mg applied once daily
		100 mg/day	31.1 ± 19.6 nmol/L (897 ± 565 ng/dl)	4–8 h	13.7 ± 6.6 nmol/L (394 ± 189 ng/dl)	21.2 ± 9.9 nmol/L (612 ± 286 ng/dl)	
	2% T solution[76] (AXIRON® at day 120)[61] [DSC]	30 mg/day	27.0 ± 14.4 nmol/L (779 ± 416 ng/dl)	n/a	10.1 ± 6.1 nmol/L (291 ± 175 ng/dl)	17.1 ± 8.3 nmol/L (493 ± 239 ng/dl)	60 mg (1 pump or 1 twist actuation to each axilla) applied 1× daily in the morning[61]
		60 mg/day	29.1 ± 15.1 nmol/L (839 ± 436 ng/dl)	n/a	10.0 ± 4.0 nmol/L (288 ± 115 ng/dl)	17.5 ± 6.1 nmol/L (506 ± 175 ng/dl)	
		90 mg/day	23.0 ± 11.6 nmol/L (664 ± 336 ng/dl)	n/a	8.0 ± 4.1 nmol/L (230 ± 119 ng/dl)	14.4 ± 5.7 nmol/L (415 ± 165 ng/dl)	
		120 mg/day	22.8 ± 12.2 nmol/L (658 ± 353 ng/dl)	n/a	9.1 ± 3.8 nmol/L (262 ± 111 ng/dl)	13.5 ± 5.5 nmol/L (390 ± 160 ng/dl)	
		Overall	27.5 ± 14.5 nmol/L (792 ± 417 ng/dl)	2 h	n/a	16.6 ± 6.1 nmol/L (480 ± 177 ng/dl)	
Nasal T gel	4.5% T nasal gel[79] (NATESTO®)[77]	22 mg/day	36.3 ± 16.2 nmol/L (1045.7 ± 467.1 ng/dl)	1.4 h	6.5 ± 3.2 nmol/L (186.3 ± 92.6 ng/dl)	13.0 ± 4.5 nmol/L (375.3 ± 128.9 ng/dl)	
		33 mg/day	32.4 ± 13.2 nmol/L (934.9 ± 381.2 ng/dl)	1 h	7.0 ± 2.5 nmol/L (200.9 ± 72.7 ng/dl)	13.4 ± 3.9 nmol/L (386.9 ± 111.9 ng/dl)	3 × 11 mg (3 daily dose; 2 pump actuations, 1 pump actuation in each nostril)[77]
Buccal T muco-adhesives	T buccal system[83] (STRIANT®)[82] [DSC]	30 mg/twice per day	33.6 ± 15.3 nmol/L (969 ± 441 ng/dl)	10.5 ± 9.3 h	10.1 ± 4.5 nmol/L (291 ± 130 ng/dl)	18.4 ± 7.1 nmol/L (531 ± 205 ng/dl)	30 mg to the gum region twice daily (12 h apart)[82]
Oral T	TU capsules (JATENZO®)[89]	158–396 mg taken orally twice daily	34.9 ± 20.1 nmol/L (1008 ± 581 ng/dl)	2 h	n/a	14.0 ± 4.4 nmol/L (403 ± 128 ng/dl)	237 mg taken orally twice daily (once in the morning and once in the evening)[89]
	TU capsules (Andriol® Testocaps®)[99]	80–160 mg/day for 2–3 weeks	40 nmol/L (1154 ng/dl)	4–5 h	n/a	n/a	120–160 mg/day for 2–3 weeks

DSC, discontinued.

The mean DHT:TT ratio was 7.4 ± 2.7 at week 12. Consistent with a previous study of SC TE,[32] SC weekly dosing achieves stabilized physiologic T levels over a one-week dosing interval after injection, and minimizes large peak and trough differences as seen with some other TTh.[31]

3.2 | Intramuscular injections

Intramuscular (IM) injection of T esters has been widely used as TTh. Unlike non-esterified T, which has a short half-life of 10 min when injected, esterification of T at the 17β-carbon prolongs the duration of action. Esterification increases the solubility of T in oil, allowing for slower release of T with IM injection.[13,33] The three IM formulations that are approved by the FDA for use as TTh are testosterone cypionate (TC), TE, and testosterone undecanoate (TU). Depending on the formulation and dosage, following IM injection of TE or TC, supraphysiologic levels occur within a week after administration, decreasing to sub-therapeutic levels in between dosing intervals, resulting in large TT peak-to-trough ratios. A longer interval to reach steady state is observed with IM TU. The Endocrine Society Clinical Practice Guideline for TTh recommends measuring serum T levels midway between injections for IM TE or TC and at the end of the dosing interval prior to the subsequent injection for IM TU, adjusting dose or frequency to target the low-mid physiological range (12.1–20.8 nmol/L, or 350–600 ng/dl).[2]

3.2.1 | Testosterone cypionate

TC is available in two strengths, 100 and 200 mg/ml concentrations prepared in cottonseed oil.[34] The recommended dose is 50 to 400 mg administered every 2 to 4 weeks for IM TC. In a study of 11 men with hypogonadism, every-other-week administration of 200 mg IM TC caused a threefold rise in serum T, with peak values occurring between 2 to 3 days (38.4 ± 15.3 nmol/L; 1108 ± 440 ng/dl) and 4 to 5 days (38.6 ± 10.3 nmol/L, or 1112 ± 297 ng/dl) post-injection.[35] Similarly, E_2 levels also increased almost threefold. Within 2 weeks, mean T C_{avg} approached 13.9 nmol/L (400 ng/dl). These large fluctuations in serum T over the 2-week dosing period differ greatly from what is observed in normal, diurnal T variation of healthy young or older men.

3.2.2 | Testosterone enanthate

A study evaluated the relative efficacy of four different dosage regimens in 23 men with primary hypogonadism.[36] The men received one of the four following regimens—100 mg weekly, 200 mg every 2 weeks, 300 mg every 3 weeks, or 400 mg every 4 weeks—and mean serum T concentrations were assessed once weekly during the initial 12-week treatment period. For all dosing regimens, the mean C_{max} was >41.6 nmol/L (1200 ng/dl) and occurred between 24 and 48 h. After the last dose of each regimen, mean C_{avg} values were 36.6 nmol/L (1055 ng/dl), 32.7 nmol/L (943 ng/dl), 30.6 nmol/L (883 ng/dl), and 25.3 nmol/L (729 ng/dl) for the 100, 200, 300, and 400 mg doses, respectively. Treatment with either 100 mg/week or 200 mg every 2 weeks was able to lower the initially elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations. Based on these results, the authors recommend 200 mg IM TE injections every 2 weeks or 300 mg every 3 weeks, which seem to be effective to keep mean serum T levels within normal range (10.4–41.6 nmol/L, or 300–1200 ng/dl). The manufacturer of TE, supplied as 5 ml (200 mg/ml) in sesame oil and available in multiple-dose vials, recommends that the starting dose of IM TE injections be 50 to 400 mg every 2 to 4 weeks.[37]

3.2.3 | Testosterone undecanoate

Esterification of T at the 17β-position with undecanoic acid results in a longer-acting IM TTh option that increases treatment intervals compared with that of other T esters.[33,38] The efficacy and safety of 750 mg IM TU were evaluated in an open-label, 84-week, phase 3 clinical trial of 130 men with TD.[39] Enrolled men received 750 mg TU in 3 ml of castor oil (250 mg/ml) by deep IM injections administered at baseline, week 4, and every 10 weeks thereafter through 9 injections. Serum T levels peaked approximately 7 days after each injection, with a mean C_{max} of 30.9 ± 11.9 nmol/L (890.6 ng/dl) after the third IM TU injection. Serum T profiles were nearly identical after the third and fourth injection. Mean C_{min} levels remained within the reference range (10.4–34.7 nmol/L, or 300–1000 ng/dl) at every time point measured throughout the study, and a peak-to-trough ratio was maintained around 2.6 to 2.8. During the 10 weeks after the third injection, 94% of patients treated with 750 mg IM TU had T C_{avg} levels within 10.4 to 34.7 nmol/L, or 300 to 1000 ng/dl (mean C_{avg}: 17.2 nmol/L or 494.9 ng/dl), which is consistent with a previous study where T levels were achieved within the normal range during a 10-week dosing period.[38,39] The PK profile of IM TU does not demonstrate the supraphysiological peaks observed with IM TE and TC injections, and C_{min} levels occur at later intervals after each injection. With fewer peaks and troughs, IM TU may be more acceptable for men with TD seeking TTh than IM TC or TE. Patients treated with IM TU also demonstrated average levels of DHT and E_2, and DHT:T and E_2:T ratios were within the reference range. The recommended dose of IM TU is an initial 750 mg injection, followed by 750 mg 4 weeks later, and 750 mg every 10 weeks thereafter, injected in the gluteus medius.[40]

3.2.4 | Testosterone ester mixtures

Globally, a variety of T ester mixtures are available for TTh outside of the United States (e.g., Testoviron Depot: T propionate and TE; Sustanon 250: 30 mg T propionate, 60 mg T phenylpropionate, 60 mg T isocaproate, and 100 T decanoate)[41,42]; however, in silico simulations

suggest that injections of T ester mixtures produce wider fluctuations of serum T concentrations than IM TE injections alone. These mixtures have not been recently studied, but in a 1974 study, 3 men with TD treated with 115.7 mg TE and 20 mg T propionate reported approximately 40 nmol/L (1154 ng/dl) increase of serum T over baseline 1 day post-IM injection, suggesting combining these so-called "short-acting" T esters only worsens the PK profile and increases the initial undesired T peak.[33,43]

3.3 | Subdermal T pellets

Subdermal T pellet implantation was among the earliest methods developed for clinical applications of TTh since the late 1930s, and the original pellets were usually implanted under the skin of the lower abdominal wall.[44] Currently available T pellets require office visits and a minor procedure for T pellet implantation into the hip area.[33] These T pellets consist of crystalline T and are synthesized by high-temperature molding which allows prolonged, steady, and low concentrations of T to be released over an extended period.[33,45] In an early crossover study, 43 men with primary or secondary hypogonadism were randomized to 1 of 3 initial dosing regimens (6 pellets x 100 mg; 6 pellets x 200 mg; 3 pellets x 200 mg).[46] Men were sequentially treated with the next regimen following an interval of ≥6 months until T levels returned to hypogonadal levels and completed all three dosing regimens. For all treatment regimens, peak T levels occurred at the first month after pellet insertion; serum T levels gradually declined to baseline by 6 months for the two 600 mg regimens, but remained significantly elevated after 6 months at the 1200 mg dose. The 75 mg implantable subdermal T pellet (TESTOPEL®) received FDA approval in 1972, and the recommended dosing regimen is 150 to 450 mg (2–6 pellets) implanted subcutaneously every 3 to 6 months; dosing is adjustable depending on the patient's age and diagnosis, and how the patient responds to treatment.[45] However, data from the medical literature suggest that insertion of at least 10 pellets (≥750 mg) may be common in clinical practice.[47–50]

In a retrospective review of medical records collected from 6 different institutions from 380 men, the mean C_{max} occurred 1 month post-implantation, regardless of the number of pellets implanted (T C_{avg} for 6–7 pellets, 24.7 nmol/L [712 ng/dl]; 8–9 pellets, 24.9 nmol/L [719 ng/dl]; ≥10 pellets, 27.6 nmol/L [795 ng/dl]).[48] The more T pellets (10–12; 750–900 mg) that were implanted, the higher and more sustained levels of T that could be achieved and maintained. A retrospective study of 273 men with TD treated with T pellets revealed that patients with 6 to 9 pellets implanted had significantly lower total T levels than men receiving 10 to 12 pellets (21.3 nmol/L [614 ng/dl] vs. 28.1 nmol/L [811 ng/dl]; $p = 0.0006$).[49] In an open-label, three-center study, implantation of 12 T pellets (900 mg) resulted in peak serum T levels within 2 weeks, with a mean C_{max} of 35.4 nmol/L (1021.6 ng/dl) and a mean C_{avg} of 22.1 nmol/L (638.3 ng/dl) by month 4.[50] Most patients (93%) did not have C_{max} levels >52 nmol/L (1500 ng/dl), and 71% of patients had total T levels >10.4 nmol/L (300 ng/dl) for at least 3 months, consistent with results from an open-label study in which 86% (24/28) of patients received 6 to 12 pellets (450–900 mg), maintaining T levels >10.9 nmol/L (315 ng/dl) at 4 months.[47,50]

3.4 | Transdermal T patch

The FDA originally approved ANDRODERM®,[51] a non-scrotal transdermal T patch, in 1995, with the 2.5 mg/day and 5.0 mg/day systems. This method of delivery allows T to be continually absorbed without dose accumulations for 24 h.[52–56] In a 24-week, multicenter, randomized 1:1, parallel-group study comparing the PK, efficacy, and safety of a transdermal T system with IM TE injections in 66 men with TD, daily application of 2 transdermal T patches (5.0 mg/day total) resulted in morning T levels within the defined normal physiologic range (10.6–35.7 nmol/L, or 306–1031 ng/dl) in 96% of patients over weeks 2 to 24.[54] At week 16, T C_{avg} was 17.9 ± 6.1 nmol/L (517 ± 176 ng/dl) compared with 1.9 ± 2.2 nmol/L (55.4 ± 62.8 ng/dl) at baseline. Peak T levels were reached approximately 8.2 h after application, with a C_{max} of 26.5 ± 9.6 nmol/L (765 ± 277 ng/dl). In 34 men from a multicenter, phase 3 study of a transdermal T patch system for TD, nightly applications of 2 patches (5.0 mg/day) resulted in peak levels occurring in the morning after application and decreasing slowly until system removal, mimicking the circadian patterns reported in healthy, young men.[52]

A reduced dosing regimen for either 2.0 mg/day or 4.0 mg/day systems applied nightly was evaluated in an interventional study enrolling 40 men with TD for 4 weeks (Clinicaltrials.gov identifier: NCT01104246). This reduced dosing regimen was approved in 2011, and manufacturer data show that following 28 days of transdermal T application, 97% (34/35) men with TD were able to achieve C_{avg} within 10.4 to 35.7 nmol/L (300–1030 ng/dl).[51] Mean C_{max} values with 2.0 mg/day and 4.0 mg/day treatment were 22.5 ± 5.0 nmol/L (648 ± 145 ng/dl) and 24.1 ± 5.5 nmol/L (696 ± 158 ng/dl), respectively. Similar to the 2.5 mg/day and 5.0 mg/day systems, peak T levels occurred 8 h post-application, mimicking diurnal variation when the patch is applied at night.

3.5 | Topical T gels and solutions

Because of their convenience and ease of application, transdermal T gels and solutions are among the most commonly used formulations and have been preferred by many patients.[57,58] Users of T gel have indicated a preference for a gel formulation that can dispense accurate T doses in a small gel volume in the inner thigh/abdomen and one with a shorter waiting time after application before showering and/or swimming.[59] Currently, there are four branded, FDA-approved hydroalcoholic T gels available: AndroGel®, FORTESTA®, TESTIM®, and VOGELXO®. Despite its convenience, for most patients, serum T levels fall under the normal range within 24 h of applying transdermal 2% T gel, requiring daily application of product.[60] In addition to T gels, AXIRON® was offered as a T topical solution.[61]

3.5.1 | AndroGel®

AndroGel® is available in 1.0% and 1.62% concentrations.[62,63] Topical AndroGel® 1.0% is offered as a unit-dose packet containing 2.5 g or 5.0 g of gel, equivalent to 25 or 50 mg of T, respectively.[62] A randomized, 180-day study of 227 men with TD evaluated the PK profile and tolerability of AndroGel® 1.0% at two dosages (50 and 100 mg/day) compared with the T patch (5 mg/day).[64] The study was double-blinded until day 90 for the T gel groups, after which patients could elect to continue with the long-term follow-up study and receive any dose adjustments as necessary. After the first application of either 5 g or 10 g T gel, mean C_{avg}, C_{max}, and C_{min} T levels were within the normal physiological range (values ranged from 7.9 ± 0.5 to 25.9 ± 1.4 nmol/L; 228 ± 14 to 747 ± 40 ng/dl).[64] The C_{avg}, C_{max}, and C_{min} following 90 days of 10 g T gel application were 27.5 nmol/L (793 ng/dl), 41.7 nmol/L (1203 ng/dl), and 17.4 nmol/L (502 ng/dl), respectively, compared with 19.2 nmol/L (554 ng/dl), 29.3 nmol/L (845 ng/dl), and 12.3 nmol/L (355 ng/dl) with 5 g T gel.[64] At day 90, peak T levels were reached after 4 and 8 h with 5 g and 10 g T gel application, respectively. Steady-state serum T levels were achieved within a few days, and these levels were maintained with once-daily applications. AndroGel® 1.62% is also available as unit-dose packets (20.25 mg T in 1.25 g gel, or 40.5 mg T in 2.5 g gel), as well as a metered-dose pump delivering 20.25 mg T in 1.25 g gel.[63] Compared with AndroGel® 1.0%, this formulation reduces the volume of gel and total mass of gel applied.[65] Efficacy and safety of 1.62% topical T gel at the initial dose of 2.5 g were evaluated in a two-phase, 364-day, randomized, double-blind, placebo-controlled study in 234 men with TD.[65,66] Serum T levels were assessed on days 14, 28, and 42, and adjustments to dose were made (increased or decreased) in 1.25 mg increments if TT levels were not within the pre-specified range (12.1–26.0 nmol/L, or 350–750 ng/dl). The primary endpoint was met, with 81.6% (146/179) of patients achieving C_{avg} within the pre-specified range (10.4–34.7 nmol/L, or 300–1000 ng/dl) on day 112. Doses were distributed as follows after titration: 1.25 g (7.3%, 17/234), 2.5 g (25.6%, 60/234), 3.75 g (28.2%, 66/234), and 5.0 g (38.9%, 91/234). Combining all four doses on day 112, C_{avg} and C_{max} levels were 19.5 nmol/L (561 ng/dl) and 29.3 nmol/L (845 ng/dl), respectively.[63] Mean E_2 mirrored changes observed in TT levels, but LH, FSH, and sex hormone binding globulin (SHBG) significantly decreased from baseline following T gel use. In a long-term follow-up to this study, DHT levels were generally within the normal reference range (0.4–3.3 nmol/L, or 11.2–95.5 ng/dl), and 77.9% of patients continuing with AndroGel® 1.62% treatment maintained C_{avg} within the normal range on day 364 (mean total T concentration, 15.8 nmol/L, or 455 ng/dl), confirming the results observed in the double-blind phase of the study.[66]

3.5.2 | FORTESTA®

FORTESTA® is available with a metered-dose pump delivering 0.5 g gel (10 mg of T) per pump actuation, with the recommended starting dose of 40 mg of T (4 pump actuations) applied once daily to the thighs in the morning.[67] The PK profile and safety of FORTESTA®, a 2% T gel, were evaluated in a multicenter, 90-day, open-label non-comparative trial of 149 men with TD.[68] Men started with a 40 mg dose, and adjustments were made on days 14, 35, and 60 in 10 mg increments to between 10 and 70 mg/day. The primary efficacy endpoint was met, with 77.5% (100/129) of patients achieving C_{avg} within the normal range, defined as 10.4 to 39.5 nmol/L (300–1140 ng/dl), on day 90. Overall, C_{avg} was 15.2 nmol/L (438.6 ng/dl) and C_{max} was 28.7 mol/L (827.6 ng/dl) on day 90, with 94.6% (122/129) of patients with a C_{max} ≤52.0 nmol/L (1500 ng/dl) and 2 patients with C_{max} between 62.4 and 86.7 nmol/L (1800 and 2500 ng/dl). The 24-h PK profile showed that peak T levels were reached approximately 2 to 4 h post-application.[67,68]

3.5.3 | TESTIM® and VOGELXO®

TESTIM® 1% gel is available as a unit-dose tube containing the recommended starting dose of 50 mg of T in 5 g of gel.[69] Serum T level measurements should be performed 14 days after starting treatment, and daily doses may be increased to 100 mg (2 tubes) if serum T levels are below the normal range (10.4–34.7 nmol/L, or 300–1000 ng/dl). VOGELXO® 1% gel is available as unit-dose tubes, packets, or a multi-dose metered pump containing the recommended starting dose of 50 mg of T, with the multi-dose metered pump delivering 12.5 mg of T per actuation.[70] In 2015, VOGELXO® received an AB rating from the FDA, deeming it therapeutically equivalent to TESTIM® when substituted and used as indicated. The PK and clinical profile of TESTIM®/VOGELXO® 1% gel were evaluated in men with TD against other TTh in various studies.[71–73] There were 3 concentration maxima observed with both TESTIM®/VOGELXO® 1% and AndroGel® 1%; peak T levels were reached at 3 to 4 h, 8 to 10 h, and 18 to 24 h post-application. However, with TESTIM®/VOGELXO® 1%, the C_{max} was approximately 30% higher than with AndroGel® 1%.[71] In a randomized, blinded, parallel treatment group study of 406 men with TD, treatment with TESTIM®/VOGELXO® 1% gel normalized serum T levels with fewer skin irritations than the T patch. Within 30 days of treatment, the increase in mean C_{avg} from baseline was similar in the 50 mg gel and T patch groups (50%). Treatment with the 100 mg gel resulted in a 173% increase in mean C_{avg} from baseline compared with the T patch group, with 95% of patients in the 100 mg gel group achieving mean C_{avg} above 10.4 nmol/L (300 ng/dl). At day 30, daily peak-to-trough ratios were 2.4 and 2.3 in patients treated with 50 mg and 100 mg gel, respectively, which was less than the fluctuation observed with the T patch (3.0). At day 90, more patients in both T gel groups had mean C_{avg} values (50 mg: 75%; 100 mg: 80%) above 10.4 nmol/L (300 ng/dl) compared with the T patch-treated patients (57%), and peak-to-trough ratios remained around 2.2 for both T gel groups but increased slightly, to 3.2, in the T patch group. Mean changes in DHT C_{avg} from baseline to day 30 were four- to sevenfold greater for the 50 mg and 100 mg gel, respectively, than that observed for the T patch treatment group. While

T gel treatment produced higher serum DHT levels at day 30 and day 90, DHT:T ratios remained stable and similar to that reported in normal men. In these studies, treatment with TESTIM® gel increased and maintained serum T levels to within the normal range, improved sexual function, and resulted in fewer application site reactions than patch formulations of TTh.[72]

3.5.4 | TESTAVAN®/TESTARZON®

TESTAVAN®/TESTARZON® 2% T gel (available outside the United States) is administered on the upper arm or shoulder with a cap applicator; the recommended starting dose is 23 mg (1 pump actuation) applied once daily, preferably in the morning.[74] The dose can be titrated based on serum T levels and presence of clinical signs and symptoms associated with TD.[74] This gel uses a hydroalcoholic and highly viscous topical formulation, and includes a cap applicator for hands-free dispensing and application. In a phase 3 study evaluating the efficacy and safety of TESTAVAN® 2% gel over 90 days, 76.1% of men achieved average T concentration of 10.4–36.4 nmol/L (300–1050 ng/dl) on day 90.[75] Depending on dose, T levels peaked approximately 2–4 h post-application and decreased to pre-application levels within 12 h, mirroring the natural diurnal rhythm of male T.

3.5.5 | AXIRON®

AXIRON® was supplied in a metered-dose pump delivering 30 mg of T per pump applied once daily with an applicator to the underarms, with a recommended starting dose of 60 mg T (1 pump or twist actuation per axilla).[61] This delivery route with an applicator prevents users from touching the solution and minimizes the risk of transfer of T to others. The efficacy and safety of the 60 mg/day 2% topical T solution were evaluated in an open-label trial enrolling 155 men with TD. Of the 155 enrolled men, 135 men completed the 120-day study.[76] On day 15, 76.1% of patients had C_{avg} within the pre-defined normal range (10.4–36.4 nmol/L, or 300–1050 ng/dl), which increased to 84.1% by day 120. With the 60 mg/day dose, mean TT concentrations were 15.8 nmol/L (456 ng/dl) and 17.6 nmol/L (508 ng/dl) on days 15 and 120, respectively; peak T levels were reached at 2 h post-application, and T peak-to-trough ratios were maintained around 3 from day 15 to 120. There were similar proportions of men with a C_{max} <52.05 nmol/L (1500 ng/dl) on day 15 (95.6%) and day 120 (94.8%). At day 120, most men (n = 97) remained on the 60 mg/day dose; 3 had decreased to 30 mg/day, 25 patients increased to 90 mg/day, and 10 patients titrated up to receive 120 mg/day. By day 120, steady-state levels of serum T, free T, and DHT were attained, and the DHT:T ratio was within the expected range of 0.05 to 0.33. This axillary application of T solution was well tolerated, and 84% of men achieved serum T within the normal range by day 120.[76] This product has since been discontinued.

3.6 | Nasal administration

Approved by the FDA in May 2014, the nasal gel formulation of TTh (NATESTO®) is a product using a metered-dose pump delivering 5.5 mg of T per pump actuation, with the recommended dosing of 2 pumps (11 mg; 1 actuation/nostril) administered intranasally 3 times daily (total 33 mg/day) 6 to 8 h apart.[77] Absorption occurs through the nasal mucosa, thereby avoiding hepatic first-pass metabolism, with approximately 75% of administered T entering the blood.[78] Peak serum T levels were reached approximately 60 min post-application and declined to near baseline before the next dose.[79,80] In a randomized, dose-ranging, open-label phase 3 study of 306 men with TD (ClinicalTrials.gov NCT01446042), 11 mg nasal T dosed two times or three times daily resulted in between 71% and 91% of patients achieving serum TT concentrations within the defined range (10.4–36.4 nmol/L; 300–1050 ng/dl). At day 90, mean TT C_{avg} values were 13.0 and 14.6 nmol/L (375 and 421 ng/dl) for 11 mg dosed two or three times daily, respectively.[79] Compared with other routes of T delivery, nasal T gel administration results in rather low C_{avg} and C_{max} TT levels, as well as DHT and DHT:T ratios, even with administering 11 mg three times daily. While patients experience 3 C_{max} peaks in 1 day because of the required 3 daily doses, only 3.3% of patients had a C_{max} between 62.4 and 86.7 nmol/L (1800–2500 ng/dl). At day 90, the C_{max} and C_{min} were 32.4 nmol/L (934.9 ng/dl) and 7.0 nmol/L (200.9 ng/dl), respectively, with a peak-to-trough ratio of 4.7. Furthermore, an ongoing phase 4 clinical trial suggests that not only can T nasal gel increase serum T over time, but it can also maintain FSH, LH, and semen parameters.[81]

3.7 | Buccal mucoadhesives

A testosterone buccal system (TBS) was approved by the FDA in June 2003 (STRIANT®, Endo Pharmaceuticals).[82] Each TBS contains 30 mg T and is designed as a tablet-like mucoadhesive system applied to the gum region twice daily. As the buccal system hydrates, it slowly forms a gel to allow sustained and controlled-release of T over 12 h through the buccal mucosa. This transbuccal route bypasses liver metabolism and delivers T directly into the systemic circulation.[83] The efficacy and the PK profile of TBS were evaluated in a phase 3 study in 82 men with TD. Following 12 weeks of applying TBS twice daily, the mean T C_{avg} increased to 20.1 to 24.9 nmol/L (580–718 ng/dl) at weeks 4, 8, and 12 from baseline levels of 5.2 ± 3.1 nmol/L (150 ± 89 ng/dl). At week 12, steady-state T concentrations within 20.1 to 24.9 nmol/L (580–718 ng/dl) were achieved by 87% (71/82) of patients, a slightly lower percentage than in another study where 92% of men achieved a C_{avg} within the normal range following TBS application.[84] The time-averaged steady-state C_{avg} measured over the two consecutive 12-h dosing intervals was 18.7 ± 5.9 nmol/L (540 ± 170 ng/dl), with a peak-to-trough ratio of 3.3 (C_{max} of 34.3 ± 12.5 nmol/L, or 990 ± 360 ng/dl; C_{min} of 10.4 ± 4.2 nmol/L, or 300 ± 120 ng/dl). Physiologic levels of T can be sustained with continued use, with peak T levels reached in the morning 10 to 12 h after evening application, mimicking circadian

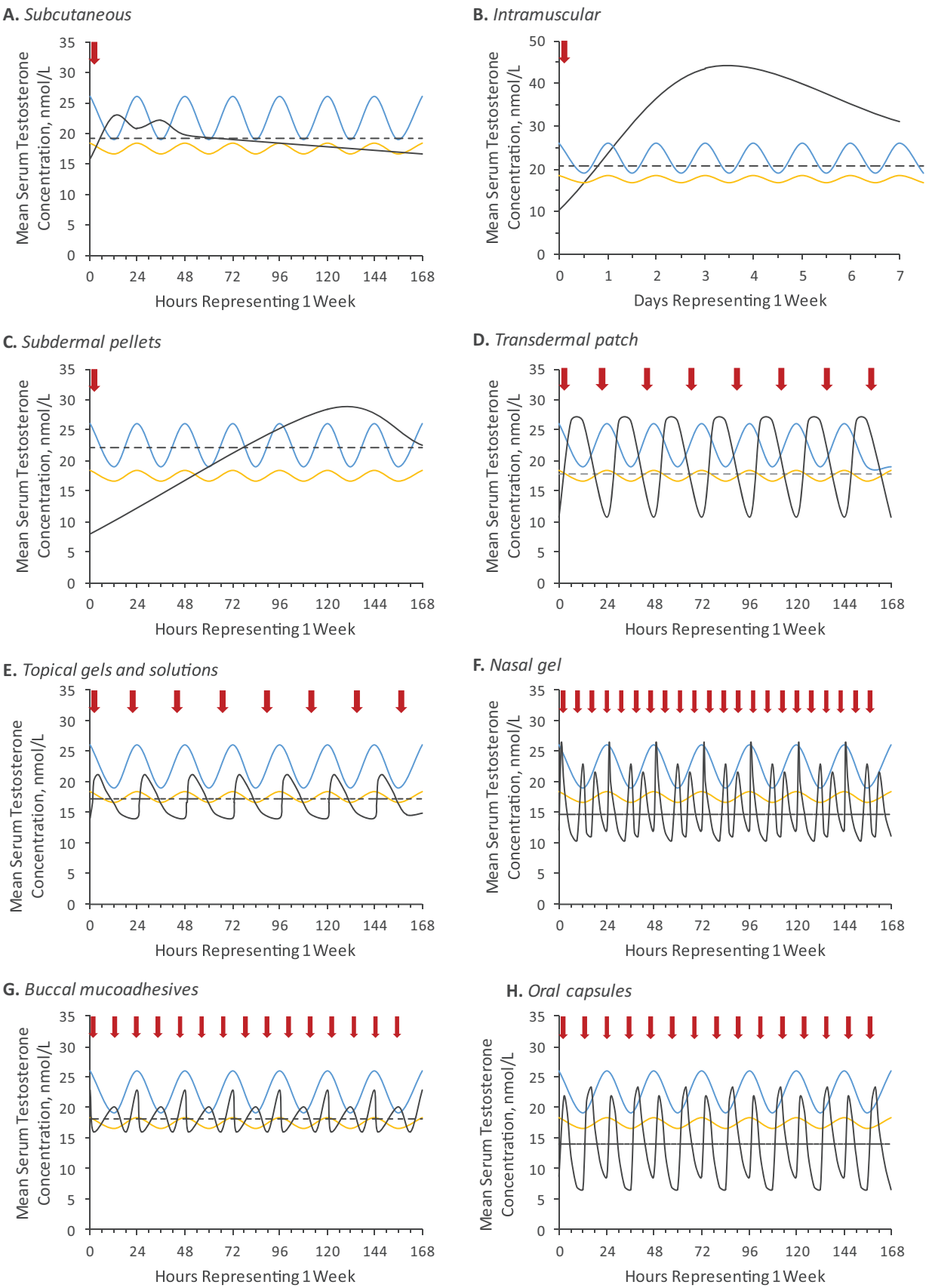

FIGURE 1 Extrapolated[a] mean steady-state serum total testosterone concentrations. Estimated diurnal T in young men (blue, range: 23–28 years) and older men (age range 58–82 years). Red arrows indicate time of T administration. Dotted lines indicate C_{avg} over a dosing interval of 168 h. Black lines in each panel represent mean steady-state T profiles of: (A) weekly SC TE administration; (B) average mean T profiles for IM TC,

TE, and TU over 2 weeks; (C) 900 mg subdermal T pellets; (D) 4.0 mg daily transdermal patch; (E) average mean T profiles of 100 mg TESTIM®/VOGELXO®, 40 mg FORTESTA®, 1.62% AndroGel®, and 2% AXIRON®; (F) nasal gel T at day 90 three times daily; (G) 30 mg buccal mucoadhesives applied twice daily; and (H) twice daily 200 mg oral TU capsules. [a]For products with ≥1 daily dose, we extrapolated data over 1 week to compare all PK profiles consistently. For products with dosing regimens of longer than a week (eg, IM injections and T pellet implantation), only the PK profile in the first week following dosing is presented; these data do not reflect average concentrations throughout the entire dosing interval. IM, intramuscular; SC, subcutaneous; T, testosterone; TC, testosterone cypionate; TE, testosterone enanthate; TU, testosterone undecanoate

T patterns. Mean serum DHT and E_2 levels were within the upper limit of the normal range. While men experience two C_{max} peaks daily produced from two daily doses, there does not appear to be an accumulation of T over time.[85] This product has since been discontinued.

3.8 | Oral testosterone undecanoate (TU)

Historically, oral TTh with non-esterified T has been unsuccessful in delivering physiological T because of first-pass hepatic metabolism; to overcome this, high doses were needed to achieve measurable serum T levels.[86] A new, oral TU formulation delivered via a self-emulsifying drug delivery system was developed to promote solubilization and absorption of the lipophilic TU in the gastrointestinal tract, and in March 2019, became the first oral TTh approved by the FDA. In a phase 2 study, 200 mg oral TU administered twice a day resulted in 87% of men achieving average serum T levels within the physiological range (10.4–34.7 nmol/L, or 300–1000 ng/dl), and none of the men had serum T levels >52 nmol/L (1500 ng/dl).[87] Peak T levels were reached 4 to 5 h after administration, and levels steadily decreased to baseline at approximately 12 h unless a second dose was administered. As oral TU capsules are recommended to be taken with a meal, serum T levels appear to be modulated by dietary fat content.[88] C_{avg} and mean C_{max} serum T levels were approximately 2-fold higher when 200 mg oral TU was administered with food compared with fasting.[87] Dietary fat was found to affect mean serum T levels achieved with oral TU; meals with higher fat content increased serum T concentrations. In a phase 3 study comparing the efficacy and safety of 237 mg oral TU given twice daily with once daily 60 mg topical T solution, 87% (145/166) of men with TD treated with oral TU were able to achieve a mean C_{avg} within 8.7 to 31.4 nmol/L (252–907 ng/dl), meeting the primary objective.[89] At the final study visit on day 105, the mean C_{avg} was 14.0 nmol/L (403 ng/dl) and C_{max} was 34.9 nmol/L (1008 ng/dl). As oral TU is given twice daily, there were 2 serum T peaks between 20.8 and 24.3 nmol/L (600 and 700 ng/dl) approximately 4 h after administration, 2 sub-therapeutic troughs (<6.9 nmol/L or <200 ng/dl) 12 h after administration, and a peak-to-trough ratio approaching 4.

4 | DIURNAL VARIATION IN SERUM T LEVELS

Diurnal variation in endogenous serum T levels in healthy men is well documented, with highest T levels in the morning and lowest values in the afternoon and early evening, although the amplitudes of peak and trough levels vary by age. In 1983, a study by Bremner et al. showed that there was a clear difference between serum T levels in normal young men (mean age 25.2 years) and older men (mean age 71.0 years).[5] In young men, serum T levels were highest in the morning, falling to their lowest levels approximately 12 h later and gradually increasing again to peak levels the next morning. Furthermore, a study to determine how endogenous T levels vary over clinic hours revealed that in 30- to 40-year-old men, morning total T levels are 30% to 35% higher than levels measured in the mid to late afternoon. This amplitude in daily endogenous T variation decreases with age, with a morning-to-afternoon difference of only 10% in 70-year-old men.[90] The morning-to-afternoon total T ratios in young and older men were approximately 1.3 and 1.1, respectively, similar to what was observed in the Bremner study. These observations have led to recommendations in various clinical guidelines, including those of the American Urology Association in 2018, to obtain early morning blood tests for the diagnosis of TD, a threshold defined as <10.4 nmol/L (300 ng/dl).[3] While endogenous serum T exhibits a clear diurnal pattern in young men that appears to be blunted naturally as men age, there does not appear to be much diurnal variation for DHT, SHBG, LH, FSH, or E_2, regardless of age.[90]

Diurnal variation appears to be absent in men with TD. Using a population mixed-effect analysis, Gupta et al. showed that no circadian rhythm was detected in men with TD, and the mean endogenous T levels in men with TD (serum T levels <10.4 nmol/L, or 300 ng/dl) were much lower than in healthy young (mean age, 28 years) or older (mean age, 71 years) men.[91] Consistent with the literature, their modeling of circadian T in healthy young and older men revealed peak-to-trough ratios of 1.3 and 1.2, respectively. Additionally, univariate analysis of cross-sectional data from 3007 older men (≥40 years) showed that the proportion of men with serum T levels <10.4 nmol/L (300 ng/dl) did not significantly change during the day ($p < 0.11$), further supporting that endogenous T diurnal variation is absent in men with TD.[92] Results from a study by Shlykova et al. evaluating endogenous T levels over a 24-h period in 21 healthy male volunteers showed that men with baseline serum T levels <10.4 nmol/L (300 ng/dl) did not demonstrate diurnal variation within the 24-h sampling period.[93] To understand the circadian rhythmicity of T levels in men with TD, a population kinetic model built by Gonzales-Sales et al., using baseline T profiles from 859 men with TD, predicted a base T value of 8.3 nmol/L (239 ng/dl), with the amplitude of oscillation estimated to be 1.1 nmol/L (32.4 ng/dl).[94] Their model also predicted that a stretched cosine function was more suitable to describe the circadian behavior of T levels of men with TD, as trough levels occurred approximately 5 h after peak T levels, and levels then increased until the next peak occurred approximately 19 h later.[94]

A variety of exogenous TTh are available to increase serum T to physiologic levels in males with TD and may alleviate symptoms associated with TD.[2] Some T replacement options more closely mimic the circadian levels of T identified in older men, whereas other options seem to provide PK profiles closer to those of younger men (Figure 1 and Table 1). Some TTh options provide profiles that exceed the frequency of the natural T circadian rhythmicity. Once-weekly SC TE injections bring mean T levels into the physiologic range within 24 h after the first dose, with a total T C_{max}/C_{min} ratio of 1.8. The PK profile appears to mimic the flatter profile of older males' endogenous T.[95] IM T injections can cause both supratherapeutic T levels postinjection and subtherapeutic levels during the dosing interval, and depending on the formulation and dosage, peak-to-trough ratios of IM TC and TE range between 2 and 5.3. Longer-lasting TU injections do not demonstrate the supratherapeutic peaks of other IM formulations, with trough levels occurring at later time points after each injection and a peak-to-trough ratio of approximately 2.6 to 2.8. All IM TTh preparations result in PK profiles that are unlike those of the normal diurnal variation of healthy young or older men. Daily transdermal gels and solutions, and nasal and oral T products, provide a consistent serum T level within physiologic range in most patients. The daily dosing frequency of the topical gel products results in a PK profile with a resemblance to that of endogenous T in younger males. Men using nasal and oral T products are able to achieve mean serum T levels that are within the normal range, but they experience several T peaks and troughs throughout the day because of the multiple daily dosing regimens required (2 or 3 times/day). This results in a PK profile that significantly deviates from the endogenous PK profiles of both younger and older patients. No single formulation appears to provide an exposure profile that would resemble diurnal variation of both young and older men. The importance of diurnal variation of endogenous T is not fully understood, but there may be additional factors (eg, sleep quality and duration) that may influence endogenous T levels.[96] However, further clarification is needed for the association between the circadian timing of sleep loss and its effect on T levels.

5 | CONCLUSION

With testosterone therapy, serum T may be returned to levels within the normal physiologic range, and symptoms associated with low T may be improved. However, no testosterone therapy product precisely simulates the endogenous diurnal T variation observed in young and older men, and more clarification is needed on the impact of the variability in range between peak and trough exposure with each different testosterone therapy.

DATA AVAILABILITY STATEMENT

All data analyzed during this review are included in this article or in the data listed in the References.

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CONFLICT OF INTEREST

Alexander W. Pastuszak: consultant, speaker, research support, Endo Pharmaceuticals; founder and leadership role, Woven Health; leadership role, Vault Health; speaker, Bayer AG; advisor, Allotrope Medical, Inherent Biosciences. **Marc Gittelman**: consultant, speaker, research support, Clarus. **James P. Tursi**: former employee, Antares Pharma, Inc. **Jonathan S. Jaffe**: employee, Antares Pharma, Inc. **David Schofield**: employee, Antares Pharma, Inc. **Martin M. Miner**: leadership role, Vault Health; research support, Acerus Pharmaceuticals.

AUTHOR CONTRIBUTIONS

Alexander W. Pastuszak: conceptualization, methodology, investigation, writing—original draft, writing—review & editing; **Marc Gittelman**: conceptualization, methodology, investigation, writing—original draft, writing—review & editing; **James P. Tursi**: conceptualization, methodology, investigation, writing—original draft, writing—review & editing; **Jonathan S. Jaffe**: conceptualization, methodology, investigation, writing—original draft, writing—review & editing, funding acquisition, resources, supervision; **David Schofield**: conceptualization, methodology, investigation, writing—original draft, writing—review & editing, funding acquisition, resources, supervision; **Martin M. Miner**: conceptualization, methodology, investigation, writing—original draft, writing—review & editing.

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