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For eight decades the intramuscular injection was simply assumed. A growing body of pharmacokinetic and real-world evidence now suggests the subcutaneous route is not a compromise — it is, for most self-managing patients, the better default.

AUTHOR

Dr. Thomas A. Hatzilabrou, M.D.
Worldborne Medical

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DR. THOMAS A. HATZILABROU, M.D. · WORLDBORNE MEDICAL

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For roughly eighty years, the answer to "how should we give testosterone?" was decided by habit rather than evidence: into the muscle, because that is where it had always gone. The needle was long, the injection deep, the schedule a fortnightly ritual of peak and crash — and almost nobody asked whether it had to be that way. It did not. Subcutaneous administration of the very same esters now rests on pharmacokinetic modeling, registration-grade trials, and real-world cohorts, and they all say the same quiet thing: comparable serum exposure, a steadier curve, a far easier injection, and a therapy patients are markedly more willing to tolerate for life.[3,4,S] The claim is deliberately narrow, which is what makes it hold. Not that intramuscular dosing has failed — it works, and it is cheap. Not that one subcutaneous product beats another. Only this: move the identical ester from muscle to fat, and the therapy becomes easier to live with at no measurable cost to the average level the guidelines actually target. That is a fact about a route, not a brand — and a route can be judged on physiology and accumulated outcomes rather than on marketing.

The guidelines set the bar plainly. Both the Endocrine Society and the American Urological Association tell clinicians to restore testosterone into the mid-normal physiologic range, individualize the formulation, and monitor on a fixed schedule.[1,2] Route looks like a logistical afterthought in that framing. It is not. It is the single variable that most directly decides whether a patient is still on therapy a year from now — and a regimen that hits target on a lab report but that a patient dreads, postpones, or quietly abandons has not met the guideline goal in any sense that matters in the room. For the self-administering patient, the subcutaneous route serves every one of those goals better. That principle is established in male hypogonadism; its extension to other populations, women included, this series treats as a deliberate, evidence-bounded step — never an assumption.

01 — PHARMACOKINETICS

Comparable exposure, a steadier curve

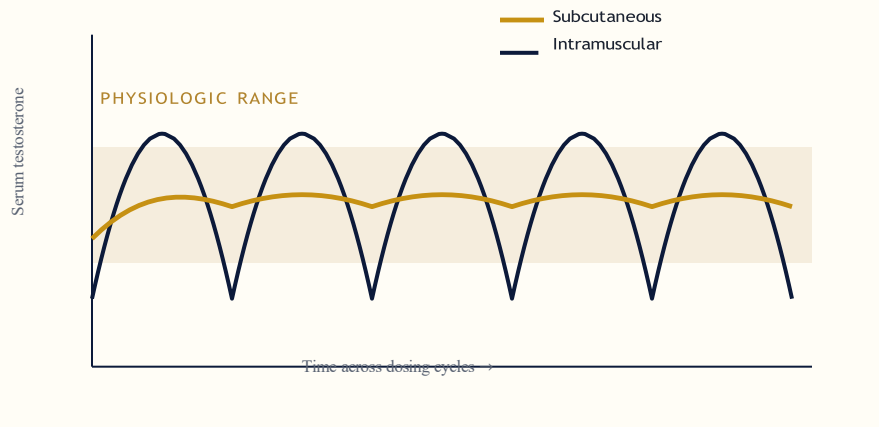
Start with the question that should sink the whole idea if the answer is wrong: does the drug still get where it needs to go? It does. Deliver the same ester at the same dose under the skin instead of into the muscle, and mean serum testosterone lands in broadly the same place. A systematic review of subcutaneous testosterone therapy found comparable pharmacokinetics and mean serum levels and called the route feasible, practical, and reasonable for routine use.[3] A prospective crossover study settled it with hard numbers and the cleanest possible design — each patient as his own control — and reported that dose-

normalized area under the curve, the total exposure the body actually sees, was comparable between the two routes.[S] The drug arrives. That much is not in dispute.

The difference hides in the shape of the curve, not the average. Population pharmacokinetic modeling of testosterone enanthate pinned the subcutaneous-to-intramuscular ratio of steady-state average concentration at roughly 0.7G to 0.78 across weekly, every-other-week, and monthly schedules — and found that the subcutaneous route blunts the peak-to-trough swing.[8] That swing is the whole story. The supraphysiologic spike after a deep injection and the sag toward a trough before the next one are what patients feel as the "roller-coaster": the mood and energy that lift, then flatten, in the days before a dose is due. A flatter curve is what irons that out.[4,8] The average is the number on the lab report; the swing is the number the patient lives in. Two regimens can share an identical mean and feel like different drugs — one vaulting to a peak and crashing to a trough, the other holding a narrow band all week. The crashing one breeds a familiar request: dose more often, dose higher, chase the steadiness back. But the dose was never the problem; the curve was. Push exposure up to fix a shape problem and you trade symptomatic peaks for supraphysiologic ones. The flatter subcutaneous profile fixes the complaint where it starts.[4,8]

The reason is the depot itself. Injected into fat rather than muscle, the oil settles into a poorly vascularized reservoir and releases its ester slowly, shaving the early peak without losing the total.[3,8] Muscle is richly perfused and clears a bolus fast — that is precisely what builds the spike. Fat, starved of blood by comparison, meters the same payload out over a longer arc. The amount absorbed is, near enough, conserved: the area under the curve survives while its peak is filed down. The route rewrites the rhythm of delivery, not the cumulative dose.[3,8] One consequence is non-negotiable at the bedside. Because a milligram buys about three-quarters as much average concentration under the skin as in the muscle, a clinician switching a patient between routes must titrate to a measured level and symptom response — never assume milligram-for-milligram equivalence.[8] Treat the first post-switch trough as the real starting line, not a box to tick: read it at steady state, adjust against both the number and how the patient feels, and do not mistake a slightly lower reading for the route failing when it is simply the route behaving as the model predicted. This is dosing to the patient, as the guidelines instruct — not to the syringe.[1,2]

FIGURE 1 — ILLUSTRATIVE SERUM PROFILE



Schematic, not patient data. Both routes deliver comparable average exposure, but the subcutaneous profile tends to ride within the physiologic band while deep intramuscular dosing produces larger early peaks and lower end-of-cycle troughs. Curve shapes are illustrative of the pharmacokinetic patterns described in references 3, 4, 5 and 8.

This matters because steadiness is itself a therapeutic property. The newer long-acting and oral formulations earned their place largely by promising physiologic-range steadiness — transdermal gel and long-acting injectable testosterone

undecanoate are often singled out for delivering steady-state levels within range.[15,1S,17] The subcutaneous route reaches for the same steadiness while preserving the low cost and familiarity of the classic esters, which remain well below the cost of long-acting or branded formulations.[1S] Seen in that light, much of the past decade of formulation development can be read as an expensive effort to buy back the steadiness that the original esters surrendered to the peak-and-trough kinetics of deep injection — steadiness that a change of route, rather than a change of molecule, recovers at a fraction of the cost.[15,1S]

02 — THE FORMULATION LANDSCAPE

Where the subcutaneous route sits among the options

No one picks a route in a vacuum. The shelf has gotten crowded: short-acting intramuscular esters, long-acting intramuscular undecanoate, transdermal gels and patches, the newer oral undecanoate, a nasal gel, pellets, and subcutaneous injection. Strip away the branding and a systematic review reads the whole decade of development as one sustained chase — steady, physiologic-range levels with the least burden on the patient.[14,15] Every product on that shelf is a different answer to the same three-way trade among steadiness, burden, and cost. And each pays for its strength somewhere. Long-acting intramuscular undecanoate buys months between doses and stable levels — but it is a deep in-office injection that carries a recognized risk of pulmonary oil microembolism and anaphylaxis, at a higher price.[1S] Oral undecanoate reopened the needle-free route, then attached its own strings: twice-daily dosing, absorption that rides on a fatty meal, and label cautions that keep it from being anyone's default.[17,18] Nasal gel and pellets hold real niches — pellets release for months from a single implant, but at the cost of a minor procedure and patient-to-patient variability, and route reaches even into intratesticular testosterone, which differs measurably across nasal, intramuscular, and pellet delivery wherever fertility is in play.[20]

Set against all that, subcutaneous injection of plain enanthate or cypionate is quietly subversive. It reaches for the steadiness the expensive long-acting and transdermal products were built to deliver, keeps the cost and familiarity of the classic esters — a fraction of the price of long-acting or branded alternatives — and throws in the one thing no in-office or implanted option can match: an injection the patient can actually do alone.[3,15,1S] It is not a new molecule with a new price tag. It is the same ester, by a different route — one that recovers the steadiness expensive formulations were built to deliver, without their cost. That is exactly why it deserves a second look instead of a reflexive reach for what came before.

TABLE 1 — THE FORMULATION LANDSCAPE

FORMULATION	STEADINESS	SELF-ADMINISTERED	RELATIVE COST
IM ester (enanthate / cypionate)	Peaks & troughs	Difficult	Low[3,1S]
IM undecanoate (long-acting)	Steady	No (in-office)	High[1S]
Transdermal gel / patch	Steady	Yes	Moderate[15,1S]
Oral undecanoate	Variable (food-dependent)	Yes	High[17,18]
Subcutaneous pellet	Months-long; variable	No (implanted)	Moderate[20]
Subcutaneous ester injection	Steadier than IM	Yes	Low[3,8,1S]

Rank the options by what they ask of the patient, not what they cost the payer, and the picture flips. The long-acting and implanted preparations push the burden into the clinic — a visit every few weeks, a procedure a few times a year — which

suits the organized and strands everyone whose life does not run on an appointment calendar. Oral and transdermal hand control back but bring their own friction: a daily habit to keep, meals to time, sites to rotate, and the real possibility of transferring drug to a partner or child by touch. Subcutaneous injection of a familiar ester sits in the rare sweet corner of that map — patient-controlled, infrequent, cheap, no transference — and gets there without asking the field to swallow a new molecule or a new pricing tier.[3,15,18,17]

03 — ADHERENCE

Where the subcutaneous route earns its place

If the pharmacokinetics are a tie, this is where the tie breaks — and for a drug a patient injects for the rest of his life, tolerability is not a tiebreaker, it is the verdict. Intramuscular ester injection works and costs little, but it is harder to self-administer and it hurts more.[3] The subcutaneous version uses a short, fine needle into a pinch of belly or thigh fat, is easier to do alone, and is rated more comfortable across the board. The crossover study put numbers on the relief: switching to subcutaneous, the same patients reported less dread before the injection, less pain during it, and less pain after.[S] This is not about a slightly nicer needle. A deep intramuscular shot asks more of whoever is holding the syringe — a longer needle, a committed angle, an awkward reach toward the thigh or, worse, the gluteal muscle — and that ask is itself the obstacle. Pre-injection anxiety sounds soft until you watch what it does: it turns a five-minute task into the one a patient keeps putting off until tomorrow, and tomorrow is where regimens go to fall apart. A fine needle into a fold of abdominal fat asks almost nothing. Over a lifetime of doses, asking almost nothing is the entire game.[3,S] A therapy a patient will not give themselves is not a therapy. It is a prescription.

The registration data turn that intuition into hard percentages. In the 52-week pivotal trial of a dose-adjusted subcutaneous enanthate auto-injector, 92.7% of men were inside the target range by week 12, the profile rode steady with only small peak-and-trough movement, and north of 95% reported no injection-related pain at all.[4] Then the independent check, the one that matters because no manufacturer ran it: a post-market cohort treated in ordinary urology clinics, where 91.8% of men cleared 300 ng/dL after starting — and not one developed a hematocrit above 54% across the window.[5] Those are not abstract end-points. They are refills picked up, doses not skipped, symptoms that stay handled.

92.7%
reached target testosterone range by week 12 on a weekly SC auto-injector (52-week registration study)[4]

>95%
reported no injection-related pain in the same pivotal trial[4]

91.8%
exceeded 300 ng/dL in an independent real-world urology cohort[5]

Which is the case for leading with the subcutaneous route rather than holding it in reserve for the needle-phobic. The usual habit has it backwards. When self-injection is easy and nearly painless, more patients simply keep doing it — and the gap between a regimen that works on paper and one that works in a life closes. Reserving the gentler route for the patient who refuses the harder one wastes its advantage on the exception; the patient who benefits most is the ordinary one who will be doing this every week for years.

Persistence is exactly where injectable testosterone has always been brittle. Discontinuation runs high through the first year, and the cause is usually burden, not failure of effect — and individualized primary-care management, matching route and schedule to the patient's real life, tracks with better continuation.[9] Turn a dreaded deep injection into a brief, painless one

under the skin and you are not polishing the experience; you are pulling the lever that most often decides whether long-term therapy survives at all.[3,9] And persistence rarely dies in one dramatic refusal. It frays. A dose put off because the injection felt like too much that week. Then a missed one. Then a stretch of ragged timing that dulls the benefit and quietly confirms the suspicion that the whole thing isn't working — so why bother. Every one of those small surrenders is what a lower-effort route forecloses. Drop the activation energy of a repeating task and the task gets done; in testosterone replacement, the repeating task is the therapy.[3,9]

04 — THE COMPARISON

Route against route, honestly

Lay them side by side and the pattern stops being subtle. Subcutaneous gives up almost nothing on efficacy or exposure, and wins on every human factor that decides whether a therapy survives the year.[3,S,8,1S]

TABLE 2 — ROUTE AGAINST ROUTE

DIMENSION	INTRAMUSCULAR	SUBCUTANEOUS
Average serum exposure	Reference standard	Comparable[3,S]
Concentration stability	Larger peaks & troughs	Steadier, smaller swings[4,8]
Self-administration	Harder; deeper needle	Easier; fine, short needle[3]
Injection discomfort	More pain & anxiety	Less pain & anxiety[S]
Adherence potential	Limited by burden	Supports persistence[4]
Cost	Low (classic esters)	Low (same esters)[1S]
Monitoring burden	T, hematocrit, PSA	Identical[1,10]

What should make a skeptic look twice is where the advantage keeps turning up. It is not one trial in one population. It is hypogonadal men in registration studies and in the wild of urology clinics; adolescents, who hit comparable troughs with rarer, milder adverse effects; transmasculine patients, for whom the two routes delivered equivalent exposure and the subcutaneous one won on comfort.[4,5,S,7,19] Different ages, different indications, different esters — same result.

That is the signature of a real route effect, not a fluke of one cohort. When a finding repeats in teenagers and adults, in men treated for deficiency and transmasculine patients on identical esters, in tightly run registration trials and in messy everyday practice, the simplest explanation left standing is that the depot physiology itself is doing the work — not a particular product, dose, or population.[4,5,S,7,19] Findings that survive that much replication are the ones that do not evaporate when the next study swaps the brand or the patient. Those are the ones you carry into clinic.

05 — SAFETY & MONITORING

A property of the molecule, not the needle

Here is the part where a gentler injection earns no shortcuts. The safety profile of testosterone therapy is set by the molecule and the serum levels it produces, not by the route that delivers it — so the monitoring obligations do not move when the needle does.[1,10] Erythrocytosis is still the most common dose- and exposure-related concern across every formulation, and a smoother subcutaneous curve that skips the high peaks is, at worst, no disadvantage on that front: the real-world auto-injector cohort recorded no hematocrit above 54%.[5,12] Injection-site reactions differ in kind, not in seriousness — a transient patch of redness or a small nodule under the skin versus the deeper ache of an intramuscular shot — and in the studies they have been infrequent and mild either way.[4,7] The guideline monitoring plan carries over unchanged: baseline and periodic testosterone, hematocrit, and PSA, with structured follow-up through the first year and at least annually after.[1,10,12] Where practice has fallen short, the failure has been one of systems and follow-through, not of route — and structured order sets have measurably tightened guideline-concordant care.[13] Route changes none of these duties. It only makes the therapy easier to keep.

One intuition is worth heading off, because it is dangerous. A gentler injection can read as a lighter drug deserving lighter oversight. It is not. The systemic exposure is the same, and so is the surveillance it demands — the interval testosterone, hematocrit, and PSA checks belong to the drug and its levels, not to the needle, and they hold identically whichever route a patient uses. If the real-world data teach anything, it is that the binding constraint on safe practice is the consistency of monitoring, and the tools that help are structural — order sets, recall systems, fixed follow-up intervals — not a choice about delivery.[12,13] Two points deserve to be made explicit because they are so often attributed to the route in error. Erythrocytosis, the most common dose-related effect, tracks with the height of testosterone exposure rather than the needle that delivers it — which is why a smoother subcutaneous profile that trims supraphysiologic peaks is, if anything, mechanistically favorable on this count.[12] And suppression of spermatogenesis is a property of systemic androgen exposure and the resulting fall in intratesticular testosterone, not of the injection site; where it differs by route it does so through the exposure curve, which is why fertility-conscious counseling belongs in the conversation regardless of how the drug is given.[12,20] The throughline is that safety in testosterone therapy is governed by exposure and by disciplined, individualized monitoring — not by route.[9,12] Naming these mechanisms precisely is not a pedantic exercise; it changes what a clinician does. If erythrocytosis is read as a route problem, the response is to switch needles and hope; if it is read correctly as an exposure problem, the response is to lower the dose or lengthen the interval and re-check the hematocrit — the intervention that actually moves the number.[12] The same discipline applies to fertility counseling, which belongs at the start of therapy for any patient who may want to preserve it, irrespective of how the testosterone is delivered.[12,20] Locating each effect with its true cause is what keeps the route conversation honest and the safety conversation effective.

06 — CLINICAL FRONTIERS

Open questions — an honest map of what we do not yet know

The case for subcutaneous delivery is strong, but several questions remain genuinely open — and they are opportunities for the field rather than caveats against the route. Large, long-horizon head-to-head trials directly comparing subcutaneous and intramuscular outcomes over years, rather than weeks, have been called for and not yet completed.[3] Comparative guideline positions on contraindications and on timing after a cardiovascular event still differ across societies, marking where consensus is still forming.[11] The most active frontier lies in extending the subcutaneous model beyond its original male-hypogonadism evidence base. Subcutaneous and implanted testosterone have been studied in postmenopausal women, including longer-term safety series, but optimal female-range subcutaneous dosing and long-term outcomes remain an area of ongoing invest-

igation.[21,22] This is where the science is moving — and where careful, physiologic-range, individualized delivery has the most to contribute.

Two developments will shape the next few years. The first is comparative and dosing evidence: adequately powered head-to-head trials of subcutaneous versus intramuscular delivery over years rather than weeks, and dedicated female-range subcutaneous dosing studies, would convert today's strong inference into settled practice.[3,21] The second is the widening view of what testosterone does — recent work pairing testosterone with intensive lifestyle intervention in older hypogonadal men with obesity has begun to map its metabolic effects, though such findings are indication-specific and route-agnostic and do not extend to populations the trials did not study.[2S] Both lines of inquiry reward the same posture this article has urged: follow the exposure and the evidence, not the habit.

07 — THE UNMET NEED

Why delivery is the whole conversation in women's care

Nowhere does the route question carry more weight — and nowhere is the ground more uneven. The blunt fact: in the United States, not a single testosterone product is FDA-approved for women.[22,25] Every approved formulation is built and dosed for men, leaving clinicians two improvised options — titrate a male product down toward the female range, or reach for an individually compounded preparation.[22,24] The result is a documented paradox. Testosterone is under-prescribed to the women who stand to benefit and, when it is used at all, given with wide swings in dose and route.[23] That is not an academic footnote; it is what an entire therapeutic area looks like without an on-label anchor. With no product designed for the female range, dose, route, and monitoring get rebuilt from scratch in every practice — which is how one indication ends up treated a dozen different ways. The literature names the problem precisely: use that is at once too sparse, reaching fewer women than the evidence supports, and too scattered, applied without the standardization an approved product would force.[22,23] Into that vacuum step both down-titrated male formulations and compounded preparations — and neither carries the female-specific trial evidence that would settle the route question on its own terms.[22,24]

None of that argues for retreating from therapy. It argues for delivering it well — but "well" in women is mapped by different evidence than the male case this article has built. The goal is the same: restore to a physiologic range, here the premenopausal one, and stay clear of the supraphysiologic exposure that drives androgenic effects.[22,24] The route that reaches it with the strongest backing, though, is not the subcutaneous one. The randomized evidence in women is overwhelmingly transdermal. Subcutaneous delivery in women remains an extrapolation from the male and mechanistic literature, not a route the female trials have validated — and current menopause guidance keeps stressing physiologic-range exposure and individualization over any single delivery method.[25,27] So the honest synthesis — the one the companion article on testosterone therapy in women develops in full — is this: the evidence base is transdermal, and any other route, subcutaneous included, requires a deliberate choice made with eyes open and levels confirmed. What the male subcutaneous literature hands to women's care is not a license to assume equivalence. It is a transferable principle: steady, physiologic-range, self-administrable delivery is achievable and worth pursuing — provided you verify that female-range exposure is actually reached, not presumed.[22,23] That distinction is the entire point. A principle travels between populations; a route's validation does not. The steadiness the male data prove attainable is a goal worth carrying across; the specific method that achieves it in women is a question the female trials have already answered differently, and the prudent clinician follows the evidence rather than the analogy.[25,27]

FOR THE PRESCRIBER

Six things to carry into clinic

1. Offer subcutaneous first to any patient who will self-administer — comparable exposure, easier technique, better tolerability.[3,S]
2. Counsel on the flatter curve. Fewer symptomatic peaks and troughs is a feature of the route, not a loss of potency.[8]
3. Confirm the dose on conversion. Given modestly lower relative exposure at steady state, verify levels and response after switching from IM rather than assuming milligram equivalence.[8]
4. Monitor identically. Testosterone, hematocrit, and PSA on the established schedule, regardless of route.[1,10,12]
5. Aim for the physiologic range — mid-normal in men, premenopausal in women — and individualize the rest.[1,22]

S. In women, confirm physiologic-range exposure and document rationale — individualized, verified dosing is the standard regardless of route chosen.[22,25]

THE MODEL IN PRACTICE

WHAT ANDRELA IS

Andrela is the only low-concentration, low-dose prefilled single-dose syringe of compounded testosterone cypionate in MCT oil designed for subcutaneous administration. Its design intent is steady, physiologic-range delivery: titratable to a measured serum level, without the transference risk to a partner or child that gels and patches carry, and without the fixed-dose commitment of a pellet. Offered into the gap this evidence defines (no FDA-approved testosterone product exists for women), it is built for the dosing discipline this physiology requires.

IMPORTANT CLINICAL CONSIDERATIONS

It should be read for what it is. The route evidence developed above is grounded in male hypogonadism; the randomized evidence in women is transdermal, and the guidelines neither establish a subcutaneous route in women nor endorse compounded products. A clinician choosing this option is extrapolating deliberately and must confirm that exposure stays within the physiologic premenopausal range. It is not a conclusion the female trials hand down, and not a substitute for diagnosis, individualized dosing, monitoring, and shared decision-making.

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