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Testosterone Therapy in Women

The evidence for one problem — distressing low desire — is now solid. The harder and more useful conversation is everything around it: which women, which route, and how much.

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WOMEN'S HEALTH · ANDROGEN REPLACEMENT

Testosterone Therapy in Women

The evidence for one problem — distressing low desire — is now solid. The harder and more useful conversation is everything around it: which women, which route, and how much.

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

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Testosterone is not a male hormone that women happen to carry in trace amounts. Across most of adult life a woman's ovaries and adrenals produce more testosterone than estrogen by mass, and that output falls with age until, by the late fifties, it sits near its lifetime floor.[9,30] For one consequence of that decline — distressing low sexual desire after menopause — the evidence is now strong enough that every major menopause and endocrine society has signed the same position statement, with a meta-analysis of randomized trials underneath it.[1,3] The argument worth having is no longer whether testosterone works in women. It is how to deliver a genuinely supported therapy to the right woman, by a route that fits her physiology, at a dose that lands inside her own normal range — and how to be honest about the wide territory the trials have not yet mapped.[2]

This article takes all of that territory, not just the part after menopause. It walks the one solid indication and its evidence, then the thinner ground on either side of it — premenopausal desire, surgical menopause, primary ovarian insufficiency — before turning to the two questions a prescriber actually has to answer: which route, and what dose. The governing principle never changes: restore testosterone to the physiologic range a healthy young woman carries, and not one step beyond it.[1,2]

It is worth naming why this clarity took so long. Testosterone in women spent decades caught between clinicians who watched real responses in individual patients and clinicians who could point to no adequately powered trial — neither able to win the argument on the other's terms.[3,&] What broke the deadlock was not one landmark study but enough randomized data, pooled, to support a statement the major societies could endorse together.[1,3] That history still matters at the bedside, because it explains both why the core indication is firm and why its edges were drawn so deliberately narrow.[2]

01 — THE INDICATION

Where testosterone earns its place — and where it doesn't

One use stands on Level I evidence: hypoactive sexual desire disorder in postmenopausal women. The diagnosis turns on distress — a persistent, unwanted loss of desire that troubles the woman herself, rather than a quiet fading she does not mind — and that single criterion is what separates a treatable disorder from an ordinary turn in the life course.[1,S] Where it is met, the data are unusually firm: pooled across dozens of randomized trials in roughly eight thousand women, testosterone improved desire, arousal, orgasm, pleasure, and satisfaction and lowered sexual distress, with effects that are moderate but consistent.[3,10,20,21,22] The primary-trial record beneath that estimate is deep — placebo-controlled patch and cream studies in surgically and naturally menopausal women, from the first oophorectomy trials through APHRODITE in women taking no estrogen at all.[12,13,1&,1S,1S,17,18,19]

Precision about that effect is what keeps a real benefit from being oversold: the gains are statistically robust and clinically meaningful on validated instruments, but moderate rather than transformative, and they sit against a substantial placebo response.[3,10] Counseling toward a realistic, bounded benefit is part of delivering the therapy honestly — not a hedge.[2,10]

What gets lost when that one indication dominates the conversation is that testosterone is, in fact, prescribed off-label to women for a range of other reasons — and a clinician is better served by knowing where each of those actually stands than by pretending only one exists. The rest of this section maps them honestly, strongest evidence first.[11,23]

Beyond desire, the most common off-label rationale is the broader cluster of menopausal complaints — low energy, flagging well-being, mood. Here the evidence is genuinely mixed, and worth seeing in full rather than dismissed. Early and small studies were encouraging: a placebo-controlled crossover trial of transdermal testosterone in premenopausal women improved well-being and mood scores,[39] and several menopause trials reported well-being gains as secondary findings.[12] But the signal has not held where it was tested most rigorously — the best dedicated trial, testosterone added for antidepressant-resistant depression in women, found no benefit over placebo on mood, fatigue, or sexual function,[&0] the large pooled analysis found no robust effect on well-being, mood, or cognition,[3] and dedicated systematic reviews of cognition, mood, and muscle reach the same null.[2&,2S,2S,27,28] The honest read is a real but inconsistent signal that no society endorses as an indication: worth knowing, not worth promising.[23,38]

Bone is the one non-sexual endpoint with a positive randomized result behind it. In a two-year controlled trial, adding a testosterone implant to estradiol raised bone density at the spine, hip, and total body faster than estradiol alone, alongside the expected gains in sexual function.[3S] It is a genuine finding — and a thin reed: the trial was small, decades old, used supraphysiologic implants, and was never powered for fractures, which is why every guideline still declines to list bone as an indication.[23] Body composition and lean mass, usually invoked in the same breath, showed no significant effect in the pooled trial data at all.[3]

A separate and frequently muddled use is local rather than systemic. Vaginal testosterone has been studied for the genitourinary syndrome of menopause — the dryness, atrophy, and painful intercourse that systemic therapy does not target — and it occupies a real niche in one hard situation: breast-cancer survivors on aromatase inhibitors, for whom vaginal estrogen is usually avoided. Small trials, including a randomized comparison against a low-dose estradiol ring, improved atrophy and sexual symptoms without meaningfully raising serum estradiol.[&1,&2] The evidence is thin and the use off-label, but it is a legitimate option where first-line therapy is contraindicated — and it should never be confused with treating low desire, which is a systemic question.[S]

The edges of the desire indication matter as well. Premenopausal women with distressing low desire show a benefit signal in small trials, but the evidence is graded inconclusive and no society endorses the use.[1,39] Surgical menopause is the mirror image — removing the ovaries strips out a gland that makes testosterone for years, producing an abrupt, marked fall in circulating levels, which is precisely why oophorectomized women supplied much of the original trial population.[30] And women with primary ovarian insufficiency or adrenal failure carry a real physiologic-replacement rationale the evidence has simply never caught up to, which is why guidelines stop short of recommending it and warn against diagnosing a “female androgen deficiency” from a low number alone.[23]

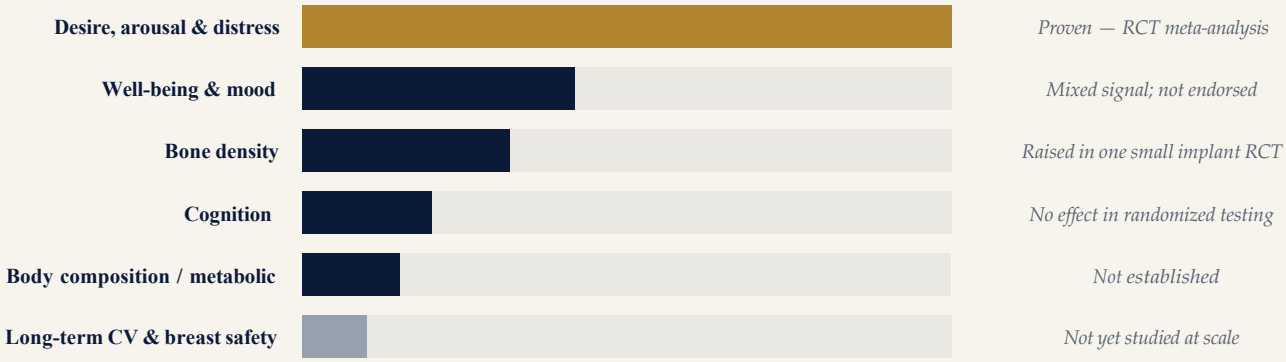
Three further uses round out the map, named precisely so they are not misapplied. Androgens were, historically, an endocrine therapy for metastatic breast cancer — inducing remission in a substantial minority before tamoxifen and the aromatase inhibitors made them obsolete; history, not current practice.[&3] Testosterone reliably stimulates red-cell production, which is a monitoring concern at higher doses far more than an anemia treatment in women.[&S] And masculinizing testosterone for

transmasculine patients is well-established off-label care — but at male-range targets under dedicated guidelines, a different clinical problem from everything else here, and not to be reasoned about with female physiologic dosing.[&&,&S]

Underneath the supported uses is a coherent mechanism, reassuring but not a license. Endogenous androgen tracks several domains of female sexual function across the lifespan, so restoring it toward premenopausal concentrations has biological logic behind it.[9] But the trials measured sexual outcomes, and it is sexual outcomes — not mood, cognition, or vitality — that mechanism and evidence jointly support.[3,9,11]

It helps to see the whole map at once — what testosterone has actually been shown to do, and how firmly. Desire and its associated distress are the proven center. A few effects beyond it carry a real but lighter signal worth knowing about; the rest remain unproven or simply unstudied, and honesty about which is which is what separates a supported therapy from a wellness pitch.[3,11]

FIGURE 1 — WHAT THE EVIDENCE SUPPORTS, BY OUTCOME



Bar length reflects the strength of the evidence, not the size of any effect. Sexual function is the one outcome carried by pooled randomized trials; well-being shows an inconsistent secondary signal and bone density rose in a single small implant trial, but neither is an approved indication; cognition and metabolic endpoints are null or unestablished; long-term safety is unstudied. Illustrative of references 3, 11, 23, 24, 25 and 35.

1
consensus-endorsed indication — postmenopausal HSDD with distress[1,S]

0
FDA-approved testosterone products for women[3,S]

3–S
months to judge response before applying the stop rule[2,3]

02 — THE ROUTE QUESTION

Where the evidence actually sits

Start with the fact that flatters our instincts least and matters most: the randomized efficacy evidence in women is almost entirely transdermal. The pivotal Phase III program ran on a patch, creams and gels filled in later, and the surgical-menopause trials and APHRODITE — the study in postmenopausal women taking no estrogen at all — established the benefit the consensus now rests on, every one of them delivering the hormone through the skin.[3,S,S,12,13,18] That is the honest starting point. It is worth stating once, cleanly, so the rest of the section can do something more useful than repeat it.

The more revealing question is why the evidence ended up transdermal — and the answer is mostly history, not physiology. Oral testosterone was ruled out early: it runs the liver-first gauntlet of first-pass metabolism and pushes lipids the wrong way,

while every non-oral route tested came back lipid-neutral.[3,7] What the field needed next was a way to deliver a very small, steady, physiologic female dose — roughly a tenth of a man's — without the supraphysiologic spikes that male-oriented injectables and fixed pellets throw off. A patch did that, and, just as decisively, it was the product a manufacturer chose to carry through Phase III. When the FDA declined that patch in 2004 for want of long-term cardiovascular and breast-safety data, the commercial pipeline narrowed further, and the only licensed female testosterone product anywhere today is still a transdermal cream.[S,38] So "the evidence is transdermal" is largely a statement about which delivery system got commercialized and studied — not a finding that skin is the only route physiology will accept.

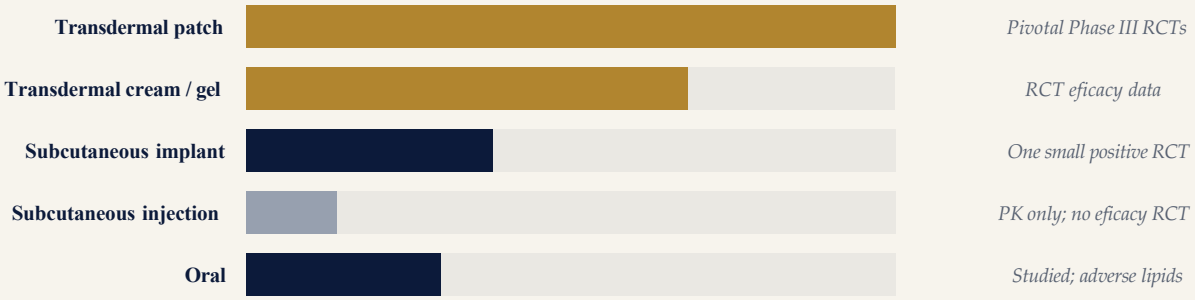
That distinction opens ground the route debate usually skips past. The one randomized trial of subcutaneous testosterone in women is, in fact, positive: adding a testosterone implant to estradiol improved desire, activity, and satisfaction and raised bone density over two years.[3S] The physiologic logic runs the same direction — a steady subcutaneous depot can hold a low, flat concentration inside the female range as faithfully as a patch, and far more faithfully than fixed-dose pellets, which spike to three or four times the upper limit of normal in the first weeks and vary several-fold between patients.[8] The real contrast is not transdermal versus subcutaneous; it is a titratable subcutaneous dose versus an un-titratable pellet.

A periodic self-administered injection asks nothing of a daily routine, leaves no drug on the skin to transfer to a partner or a child, and sidesteps the adhesion and site reactions that make patches quietly unpopular.

None of which erases the gap, and the gap belongs on the table once, plainly: outside that lone implant trial, subcutaneous delivery in women has no dedicated efficacy RCT, and no study has ever published a dose-equivalence between a patch and a subcutaneous injection. A clinician who chooses this route is extrapolating deliberately and dosing to a measured serum level rather than to any milligram analogy — which, as the next section argues, is the only defensible way to dose testosterone in a woman by any route.[2,8]

The route that matters is the one that holds a woman's testosterone inside her own range — steadily, and without overshoot. Transdermal delivery proved it can be done. Physiology gives no reason to think it is the only route that can.

FIGURE 2 — STRENGTH OF RANDOMIZED EVIDENCE, BY ROUTE



Bar length reflects the depth of randomized eficacy evidence, not relative eficacy. Transdermal delivery carries the trials; subcutaneous delivery rests on a single positive implant RCT and sound physiologic rationale; oral is studied but lipid-adverse. Illustrative of references 3, 5, 7, 8, 13, 18 and 35.

TABLE 1 — ROUTE AND THE EVIDENCE BEHIND IT

ROUTE	EVIDENCE IN WOMEN	PRACTICAL NOTES
Transdermal (patch, cream, gel)	RCT-supported; basis of consensus	Neutral lipids; steady, low exposure; the proven route[3,S,7]
Oral	Studied; adverse lipids	First-pass lipid shift; not preferred[3,7]
Subcutaneous pellet / implant	One small positive RCT; otherwise observational	Implant trial favorable; fixed pellets overshoot the range and cannot be titrated[8,3S]
Subcutaneous injection	No dedicated efficacy RCT in women	Steady depot, titratable to level; dose to measured serum, not mg-equivalence[2,8]

03 — DOSING & THE PHYSIOLOGIC CEILING

Restore to the range, not beyond it

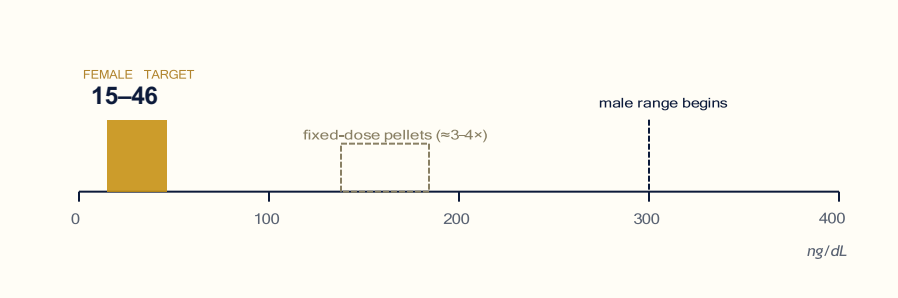
Every guideline says the same thing about dose, and it is worth saying with the numbers attached. A healthy young woman carries a total testosterone of roughly 15 to 4G ng/dL — about 0.5 to 1.G nmol/L, and somewhere between a tenth and a fifteenth of a man's 300-to-800.[3S] That figure is not fixed: it falls steeply through the early reproductive years — most sharply in the earlier decades — drifts to a lifetime low in the late fifties, and drops further still once the ovaries are removed.[9,30] The whole of the dosing task is to land a woman back inside that narrow band — and to stop there. Overshooting it is not a faster path to benefit; it is the mechanism by which androgenic side effects and the theoretical long-term risks appear.[1,2]

The doses that actually worked in the trials tell the same restraint story. The pivotal program standardized on a 300 µg/day patch; its own dose-ranging arm found 150 µg too little to register and 450 µg no better than 300 — a clean plateau, not a ladder.[13] The licensed 1% cream delivers a comparable physiologic dose at about 5 mg/day, and a separate dose-response study confirmed that pushing past the optimal exposure bought androgenic effects rather than extra desire.[29,37] Every one of those regimens is transdermal, daily, and low. None of them is a subcutaneous dose.

Which is the honest problem at the center of any non-transdermal prescription: no study has ever published a conversion between a 300 µg patch — or a 5 mg cream — and a subcutaneous dose, so there is no milligram figure to carry across.[2] The answer is not to invent one. It is to dose to the level rather than the label — start low, measure total testosterone at baseline

and a few weeks in, adjust against the number and the symptoms together, re-check after every change, and hold the result inside the 15-to-4G band.[2,8] That is good practice for a patch and the only defensible practice for a compounded injection, where the dose is set by titration to a measured serum level and nothing else.

FIGURE 3 — THE TARGET IS A NARROW BAND, NOT A DIRECTION



The female target sits low and narrow on any scale a lab report uses. The dosing goal is to reach the gold band and stay in it; fixed-dose pellets characteristically overshoot it for weeks. Illustrative; values per references 13, 30 and 35.

A target this narrow is only as real as the assay that reads it. Direct immunoassays were built for the male range and lose their footing at female concentrations, so liquid chromatography–tandem mass spectrometry, drawn at a consistent time of day, is the method the field endorses for both the baseline and the monitoring that follows.[31] Testosterone also sits within the rest of menopausal care, not on top of it. Where systemic estrogen is indicated for vasomotor symptoms or bone, testosterone does not replace it; where only desire and distress are at issue, it is not a general tonic for the menopause.[&,S] Keeping the indications separate is what stops one supported therapy from being stretched over problems another treats better.[1,2]

Dose to a level, not to a feeling: the milligrams are titrated against the physiologic range, while the symptom response is judged separately, against time.

One inversion trips clinicians up: the testosterone level that cannot diagnose HSDD is the very level that governs treating it safely. It earns no prescription on the way in, but once therapy begins it is the instrument that confirms exposure stayed physiologic and catches inadvertent excess.[2,9] That discipline bites hardest exactly when symptoms are slow to turn, because the reflex is to climb. But since both the androgenic effects and the long-term risks track how high exposure goes, adding dose against a level already in range buys a defined risk for no expected gain; when desire lags, the supported move is to wait and reassess, not to push past the ceiling.[2,3,8]

04 — CANDIDATE SELECTION & MONITORING

The treatment pathway in practice

The right candidate is easy to describe and easy to get wrong. She is a postmenopausal woman with HSDD and genuine distress, in whom the modifiable contributors — relationship strain, mood, desire-blunting medications, untreated genitourinary symptoms — have already been worked through rather than waved past.[2,S] Estrogen status shapes the conversation: much of the foundational evidence paired testosterone with estrogen, though the patch-without-estrogen trial shows

the testosterone effect standing on its own.[&,18] And consent should say plainly what this is — off-label use of a therapy with no FDA-approved female product.[1,2]

The assessment that precedes a prescription is mostly not about hormones. A structured history — screening for genuine distress, the medications that blunt desire (SSRIs above all), mood, relationship context, sleep, and genitourinary symptoms — reclassifies a meaningful share of apparent HSDD into something else, and treating that something else often restores desire with no testosterone at all.[2,S] Two contributors deserve particular vigilance: antidepressant-associated loss of desire, where the conversation belongs on the medication rather than on adding a hormone over it; and genitourinary syndrome of menopause, which masquerades as low desire when the real problem is pain that local estrogen, not a systemic androgen, is built to treat.[2,S] Working through them first is not procedural caution but accuracy — the woman whose real problem is named is often spared testosterone entirely, and the one who genuinely has the disorder is identified with more confidence once the alternatives are gone.[1,S]

FIGURE 4 — THE TREATMENT PATHWAY

Schematic of the consensus-described pathway. The number guides continuation, not initiation, and a defined stop rule replaces open-ended dose escalation. Illustrative of the approach described in references 1, 2, 3 and 5.

Monitoring follows the dosing logic. Establish a baseline, reassess testosterone after initiation to confirm a physiologic level, and review periodically for both response and signs of androgen excess — acne, unwanted hair growth, and, less commonly, voice change or alopecia.[2,8] A reasonable therapeutic trial is judged at three to six months: if distressing low desire has not meaningfully improved, the honest step is to stop rather than escalate beyond the physiologic range.[2,3]

Patients should know which signs to report. The androgenic effects to watch for — acne and increased facial or body hair most commonly, voice change or scalp hair loss only rarely — are dose-related and usually reversible if the dose is reduced promptly, which is exactly why scheduled reassessment matters.[2,8] A patient who knows what to look for becomes part of the monitoring system rather than a passive recipient of it.[2]

TABLE 2 — A MONITORING SCHEDULE

TIME POINT	WHAT TO CHECK	PURPOSE
Baseline	Total testosterone (LC–MS/MS); screen for pre-existing excess	Reference value to monitor against — not a diagnosis[2,9]
8–12 weeks	Total testosterone; symptom response; signs of excess	Confirm physiologic range; judge early effect[2,8]
Periodic / annual	Testosterone; acne, hirsutism, voice or hair changes	Sustain range; catch inadvertent excess[2,8]

Expectation-setting belongs in the same visit as the prescription. A realistic timeline — benefit, if it appears, builds over roughly two to three months rather than days — guards against both premature escalation and premature abandonment, and pairs naturally with the stop rule the guidelines describe.[2,3] Documenting the off-label rationale, the physiologic-range target, and the agreed reassessment point turns "individualization" from a slogan into a record a later reviewer can actually follow.[1,2]

Duration deserves a deliberate answer rather than drift. If the therapy works and is well tolerated, it is continued with periodic monitoring; if it does not meet the stop rule, it ends; and either way the decision is revisited rather than renewed by inertia, because the long-term safety data that would justify indefinite use do not yet exist.[2,3] The same discipline that governs starting the therapy governs staying on it.[1,2] In practice this means each renewal is a small re-decision — a confirmation that benefit persists, that exposure remains physiologic, and that the patient still judges the trade worthwhile — rather than an automatic continuation that quietly converts a bounded trial into an open-ended commitment.[2,3]

05 — SAFETY AND THE LONG VIEW

Practicing well inside the unknowns

The honest center of the safety conversation is an absence: the long-term cardiovascular and breast outcomes of testosterone therapy in women have not been settled by adequately powered trials, and that gap — not a positive safety signal — is the principal reason no female product has been approved.[3,S] Short- and medium-term data at physiologic doses are reassuring on the effects clinicians watch for day to day, but reassurance over months is not the same as evidence over years.[3,8]

That uncertainty does not forbid treatment; it shapes how treatment is offered. It argues for the lowest effective physiologic-range dose, for the route with the cleanest metabolic profile, and for especially explicit shared decision-making where baseline cardiovascular or breast-cancer risk is elevated and the long-term unknowns therefore weigh most heavily.[3,7] Practicing well here means treating the proven indication with confidence while declining to let a quality-of-life therapy quietly become a long-term commitment no one has yet shown to be safe.[1,3]

There is a particular discipline in holding two ideas at once: that the day-to-day safety data at physiologic doses are genuinely reassuring, and that this reassurance does not extend to the question that matters most over a lifetime. The androgenic effects clinicians monitor for are dose-related, usually reversible, and well characterized over the months the trials ran; the

cardiovascular and breast outcomes that would accrue over years are simply not yet measured at the scale required.[3,8] The longest controlled safety follow-up runs to about four years and remains reassuring on the effects it could detect, yet it was never powered for breast or cardiovascular endpoints; a randomized study of mammographic density found no increase, but over a span far too short to settle the breast question; and the dose-response relationship itself argues for restraint, since benefit plateaus while androgenic effects rise above the optimal exposure.[32,33,3&] A clinician who conflates the first kind of safety with the second will overstate what is known; one who lets the second erase the first will deny a supported therapy out of an uncertainty the evidence does not actually license.[3,S] The honest position sits between, and it is the position the shared-decision conversation should convey.[1,3]

This is also where documentation does real clinical work rather than merely satisfying a chart. Recording the off-label rationale, the physiologic-range target, the elevated baseline risks that were discussed, and the agreed reassessment point creates a record that a later clinician — or the patient herself, revisiting the decision — can actually follow and revise as new evidence arrives.[1,2] Because the long-term data are still being written, a therapy started today may need to be re-evaluated against findings that did not exist when it began, and only a clear contemporaneous record makes that re-evaluation possible rather than guesswork.[2,3]

OPEN QUESTIONS

What the evidence has not yet settled

The long-term safety of testosterone therapy in women — cardiovascular events and breast outcomes over years rather than months — has not been established in adequately powered trials, and remains the central reason no female product has been approved.[3,S] Benefits beyond sexual function are unproven.[3,11] Non-transdermal routes lack the randomized evidence the transdermal route enjoys, and current society guidance does not endorse compounded or subcutaneous testosterone for women.[8,38] And there is still no validated serum threshold that defines who is "deficient."[1,2] None of these gaps argues against treating the proven indication well; each argues against claiming more than the evidence supports.

FOR THE CLINICIAN

Five things to carry into clinic

1 Treat the proven indication. Postmenopausal HSDD with distress is the one consensus-endorsed reason to prescribe; address modifiable contributors first.[1,S]

2 Respect where the evidence lives. Transdermal carries the randomized trials and a neutral lipid profile; a subcutaneous route is a deliberate, physiologically reasonable choice — but dosed to a measured serum level, not a milligram analogy.[3,S,7]

3 Hold the physiologic ceiling. Dose to the premenopausal range and no further; overshoot is how harm, not benefit, appears.[1,2]

& Use the number to monitor, not to diagnose. Baseline and follow-up testosterone confirm physiologic exposure and catch excess.[2,9]

S Set a stop rule. Judge response at three to six months; if distress is unchanged, stop rather than escalate.[2,3]

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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