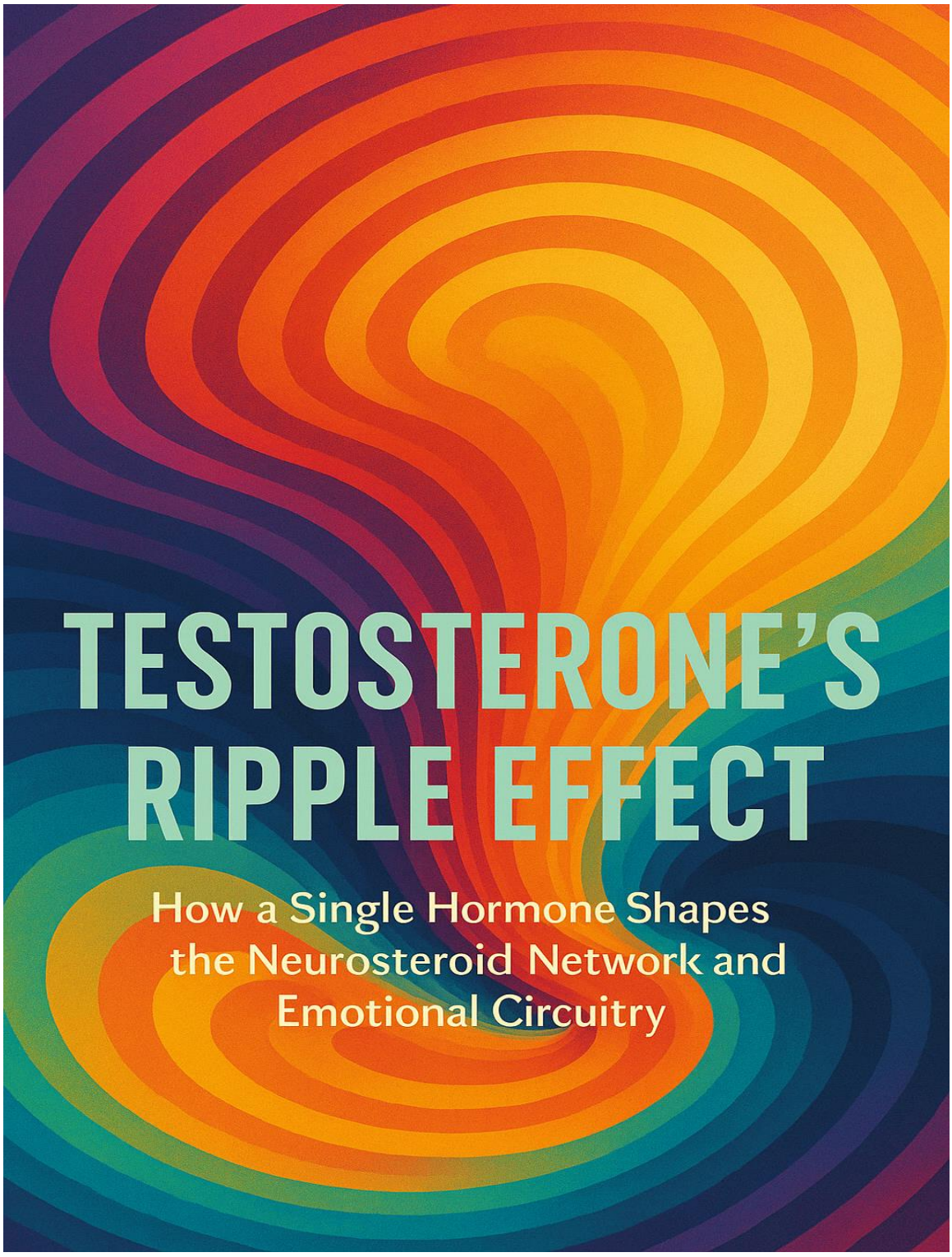

TESTOSTERONE'S
RIPPLE EFFECT
How a Single Hormone Shapes
the Neurosteroid Network and
Emotional Circuitry

Testosterone's Ripple Effect: How a Single Hormone Shapes the Neurosteroid Network and Emotional Circuitry

Introduction

Testosterone is often introduced as the quintessential male sex hormone, driving the development of secondary sexual characteristics and sustaining libido. Yet its physiological reach extends far beyond reproduction and sexual health. In both men and women, testosterone functions as a biochemical hub—a central node in the body's steroid hormone network that bridges endocrine signaling with brain chemistry and emotional regulation.

Once secreted by the testes, ovaries, and adrenal glands, testosterone enters a dynamic metabolic web. Within peripheral tissues and the central nervous system, it can be reduced by 5α-reductase to dihydrotestosterone (DHT)—a potent androgen critical for structural integrity and sexual function—or aromatized to estradiol, an estrogen essential for neuroprotection, synaptic plasticity, and mood stability. But the story does not stop there. Testosterone also exerts powerful regulatory influence on upstream precursors and downstream neurosteroids, including dehydroepiandrosterone (DHEA), its sulfated reservoir DHEA-S, pregnenolone, progesterone, allopregnanolone, and pregnanediol. These molecules are not simply hormonal by-products; they are active neuromodulators that shape neurotransmission, dampen inflammation, and fine-tune the brain's response to stress.

This interconnected network means that testosterone therapy or dysregulation—whether from aging, chronic illness, or supraphysiologic supplementation—can reshape the neuroendocrine landscape in ways that directly affect mood, cognition, resilience, and sexual desire. Optimal levels help preserve neurosteroid balance, sustain motivation, and maintain healthy emotional circuitry. In contrast, excess testosterone can suppress precursor production, downregulate androgen receptors, and deplete key neurosteroids such as DHEA and allopregnanolone, leading paradoxically to anxiety, irritability, or diminished libido despite elevated serum testosterone.

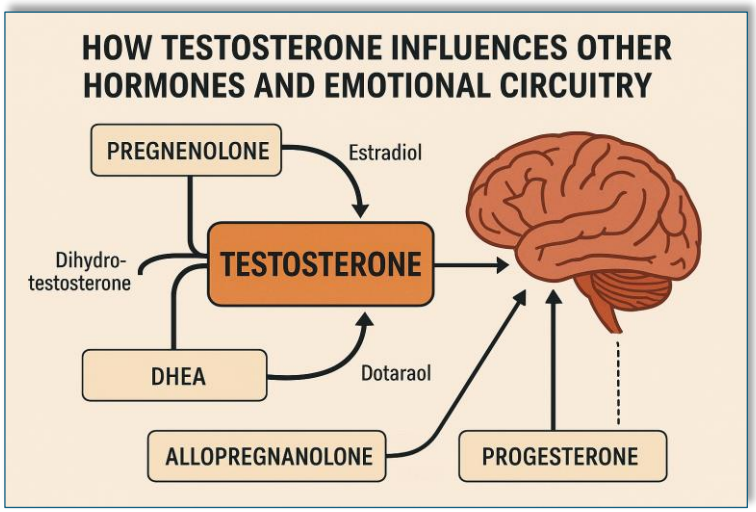
Understanding testosterone as more than a simple androgen—and instead as the conductor of a complex neurosteroid orchestra—is critical for clinicians seeking to optimize hormone therapy. It reframes the conversation from "replace what is low" to "balance the system for emotional and cognitive vitality."

Testosterone and Its Neurosteroid Family

Testosterone does not operate in isolation; it interacts with a family of neurosteroids that profoundly influence brain function and emotional health. One of the most important of these is pregnenolone, often called the "grandmother" hormone because it is the first step in the synthesis of nearly all steroid hormones. Produced from cholesterol inside mitochondria, pregnenolone serves as a crucial precursor for many downstream pathways. Physiologic testosterone levels tend to help maintain and stabilize pregnenolone production. However, when exogenous testosterone is used long-term or at high doses, it can suppress the hypothalamic-pituitary-gonadal (HPG) axis. This suppression may reduce upstream pregnenolone synthesis and, in turn, decrease the availability of vital neurosteroids that support cognition, emotional stability, and stress resilience.

Another critical pair of molecules influenced by testosterone are dehydroepiandrosterone (DHEA) and its sulfated form DHEA-S. These adrenal and gonadal steroids act as resilience factors in the brain, offering neuroprotection, modulating inflammation, and enhancing the stress response. Testosterone therapy—particularly when administered in higher doses—can suppress adrenal DHEA production through negative

feedback on adrenocorticotropic hormone (ACTH) and by reducing the body's need to convert DHEA into downstream androgens. Clinically, men on high-dose testosterone replacement therapy (TRT) often show low circulating DHEA/DHEA-S, which may contribute to fatigue, decreased stress tolerance, and mood flatness, even when total testosterone levels appear optimal.



Progesterone, although traditionally labeled a "female hormone," is critically important for men as well. It plays key roles in neuroprotection, myelin repair, and the modulation of GABAergic tone—helping to calm neural activity and stabilize mood. Testosterone indirectly influences progesterone production by altering luteinizing hormone (LH) and follicle-stimulating hormone (FSH) signaling, as well as testicular steroidogenesis. One of progesterone's most important metabolites is allopregnanolone, one of the brain's most potent natural positive modulators of the GABA-A receptor. Adequate allopregnanolone levels help reduce anxiety and promote a sense of emotional stability. When exogenous testosterone suppresses the body's own progesterone production, the downstream production of allopregnanolone can fall, eroding the brain's natural anxiolytic and mood-stabilizing defenses.

Finally, pregnanediol—a urinary metabolite of progesterone metabolism—can provide clues about neurosteroid balance. In men using aggressive TRT regimens, pregnanediol levels often decline. This drop signals reduced progesterone turnover and can be viewed as another marker of disrupted neurosteroid homeostasis. Such findings reinforce the importance of understanding testosterone's broad influence: it is not only an androgen but also a regulator of the entire neurosteroid network, with far-reaching effects on cognition, emotional health, and overall vitality.

Emotional Circuitry: How Testosterone and Neurosteroids Shape the Brain

The brain is richly sensitive to androgens and their neurosteroid derivatives, and the way testosterone interacts with different regions helps explain its profound effects on mood, motivation, and sexual drive. In the amygdala, testosterone enhances vigilance, threat detection, and the drive for dominance—behaviors that can be adaptive when balanced. Importantly, it works in concert with the neurosteroid allopregnanolone, which calms over-reactivity and promotes emotional stability. When allopregnanolone levels are reduced, as can occur with long-term or high-dose testosterone therapy, the amygdala may shift toward a state of heightened irritability, anxiety, and reactivity rather than confident composure.

In the prefrontal cortex (PFC), moderate, physiologic testosterone levels help improve motivation, goal-directed behavior, and executive control, partly by modulating dopaminergic signaling. However, when testosterone levels become supraphysiologic, this balance can be lost. Excess androgen signaling may disrupt PFC-mediated inhibition, contributing to impulsivity, poor decision-making, or emotional blunting—an effect often reported by men who use high-dose testosterone.

The hippocampus, a key structure for memory formation and stress regulation, also depends on balanced androgen and estrogen activity. Testosterone that is locally aromatized to estradiol helps sustain neurogenesis, synaptic plasticity, and cognitive resilience. When pregnenolone and its derivative allopregnanolone decline, the hippocampus becomes less resilient to chronic stress, which can manifest as

memory difficulties, reduced stress tolerance, or depressive symptoms despite adequate circulating testosterone.

Finally, the hypothalamus plays a central role in regulating libido and reproductive drive. Testosterone and DHEA influence hypothalamic circuits through kisspeptin and dopamine signaling, maintaining healthy sexual motivation. However, when testosterone levels become excessively high, androgen receptor desensitization and disrupted feedback within these circuits can paradoxically diminish sexual desire, a phenomenon sometimes seen in individuals using supraphysiologic testosterone therapy.

Together, these regional effects illustrate that testosterone's impact on emotional and sexual health depends not only on its own levels but also on the balance of neurosteroids that shape and refine its actions within the brain.

When More Testosterone Becomes Too Much

Optimal testosterone replacement or carefully titrated optimization can enhance libido, elevate mood, and strengthen emotional resilience. However, when testosterone levels are driven too high—especially through supraphysiologic dosing—the expected benefits may reverse, leading to unexpected emotional and sexual difficulties.

One key mechanism is androgen receptor downregulation. Chronic overstimulation from excessive testosterone reduces the sensitivity and number of androgen receptors, blunting the hormone's own effectiveness. At the same time, high-dose testosterone can suppress the production of upstream precursors such as DHEA and pregnenolone, cutting off critical neurosteroid pathways that support emotional depth, stress buffering, and cognitive vitality.

Another consequence is the reduction of allopregnanolone, a potent GABA-A receptor modulator that normally provides calming, anxiolytic effects within the brain. When this neurosteroid declines, the nervous system becomes more prone to anxiety, irritability, and mood instability despite elevated serum testosterone. In parallel, supraphysiologic testosterone may disrupt dopamine and serotonin signaling, altering reward sensitivity and motivation and paradoxically reducing sexual desire.

Clinically, these neurochemical shifts explain why some men who escalate their testosterone replacement therapy (TRT) doses experience flattened libido, emotional dullness, or increased anxiety, even though their laboratory values show "high T" levels. The issue is not a lack of testosterone but rather a disrupted neurosteroid balance and receptor adaptation caused by excess. This underscores the importance of maintaining testosterone within physiologic ranges and supporting the broader neurosteroid network to preserve emotional and sexual health.

Clinical Translation

Successful testosterone therapy goes beyond simply normalizing serum levels; it requires an understanding of how testosterone interacts with the broader neurosteroid network. One important step is to measure upstream precursors such as pregnenolone and DHEA/DHEA-S. These neurosteroids often decline with long-term or high-dose testosterone replacement therapy (TRT) because of hypothalamic-pituitary-gonadal axis suppression. Routine monitoring can help identify when supplementation is needed to maintain cognitive and emotional resilience.

Clinicians can also support neurosteroid balance directly. In men on TRT who report mood flattening or loss of libido, physiologic doses of pregnenolone (10–50 mg daily) or DHEA (10–25 mg daily) may help restore emotional depth, stress buffering, and sexual desire. These doses aim to replace what is physiologically lost rather than push levels beyond normal.

It is equally important to avoid supraphysiologic testosterone dosing. Maintaining testosterone within mid-to-upper physiologic ranges preserves androgen receptor sensitivity and allows normal conversion to essential neurosteroids. Overshooting these ranges may reduce the very hormones and neuromodulators that sustain emotional well-being and libido.

Finally, therapy should always be individualized. Numbers on a lab report—while useful—do not fully predict a patient's emotional and sexual outcomes. Changes in mood, motivation, stress tolerance, and libido often serve as more reliable indicators of therapeutic success than serum testosterone alone. A patient-centered, symptom-informed approach helps ensure both hormonal optimization and preservation of healthy brain chemistry.

Neurotrauma and Neuroendocrine Disruption

Subconcussive and concussive brain trauma do more than cause mechanical injury; they fundamentally alter the brain's steroidogenic capacity. After a traumatic brain injury (TBI)—even one considered mild—the hypothalamic–pituitary axis and local cholesterol metabolism can be disrupted. Cholesterol transport into neuronal mitochondria, mediated by the steroidogenic acute regulatory (StAR) protein, is often impaired, which in turn limits the conversion of cholesterol into pregnenolone, the first and rate-limiting step of neurosteroid synthesis.

Reduced pregnenolone availability has a ripple effect: levels of DHEA and DHEA-S, key resilience and anti-inflammatory hormones, frequently decline after TBI. These molecules normally protect neurons by modulating glutamate toxicity, supporting mitochondrial function, and dampening microglial activation. When they drop, the injured brain becomes more susceptible to chronic inflammation and oxidative stress.

Similarly, the production of progesterone and its neuroactive metabolite allopregnanolone is often blunted after both concussive and repetitive subconcussive injuries. Progesterone and allopregnanolone are critical for myelin repair, axonal integrity, and GABA-A–mediated neuroprotection. Their loss contributes to post-traumatic anxiety, irritability, sleep disruption, and vulnerability to long-term neurodegenerative changes.

Clinically, these deficiencies are seen in many patients with persistent post-concussive symptoms or those who have sustained repetitive subconcussive trauma, such as athletes and military personnel. Even in the absence of overt hypopituitarism, subtle reductions in pregnenolone, DHEA, and allopregnanolone can create a pro-inflammatory, hyperexcitable neural environment that fuels chronic mood disturbances and impaired resilience.

For clinicians managing hormone replacement after TBI, understanding these changes is vital. Addressing only testosterone deficiency may leave patients vulnerable to neurosteroid deficits that perpetuate anxiety, cognitive fog, and diminished libido. In some cases, supplementing pregnenolone or DHEA while carefully optimizing testosterone can help restore the neurochemical balance lost to trauma.

1. Normal Physiological Daily Production

Hormone	Adult Male	Adult Female
Testosterone	~4–7 mg/day	~0.25–0.4 mg/day (ovarian + adrenal)

2. Replacement Targets & Clinical Goals

- Goal: Restore mid-physiologic serum levels, not to create supraphysiologic peaks.
    - Men: Total testosterone 400–700 ng/dL (14–25 nmol/L)

- Women: Total testosterone 15–60 ng/dL (0.5–2.0 nmol/L), free T within low–mid physiologic range
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3. Typical Male TRT Regimens

Formulation	Usual Starting Dose	Dosing Frequency	Clinical Notes
Testosterone cypionate / enanthate (IM/SQ)	75–100 mg weekly or 150–200 mg every 2 weeks	Weekly or every 10–14 days	Weekly is preferred to avoid peaks/troughs. Some use 50 mg twice weekly (SQ) for very steady levels.
Testosterone undecanoate (IM, long-acting)	750 mg at week 0 and 4, then every 10–12 weeks	Q10–12 weeks	Provides very stable levels but less flexible if dose needs titration.
Transdermal gel 1% / 1.62%	50–100 mg daily (delivers ~5–10 mg absorbed)	Daily	Mimics physiologic daily release; adjust dose by serum T.
Transdermal patch	4–6 mg nightly	Daily	Lower skin absorption in some; skin irritation possible.
Oral testosterone undecanoate	158–396 mg/day divided (varies by brand)	Daily	Variable absorption, generally less used in U.S.

4. Female Testosterone Replacement

Formulation	Typical Dose	Frequency	Goal
Transdermal cream/gel (compounded)	0.5–2 mg/day	Daily	Maintain total T ~20–60 ng/dL
Transdermal patch (where available)	300 µg/day	Daily	FDA-approved in some regions for HSDD
IM / SQ injections	5–15 mg every 10–14 days	Q2 weeks	Used cautiously; risk of virilization at higher doses

5. Clinical Consensus Points

- Men:
  - Most societies (Endocrine Society, AUA) recommend 75–100 mg weekly IM/SQ.
  - Weekly or twice-weekly dosing reduces peaks/troughs compared with biweekly injections. **Divided into 40mg every 72 hours**.
- Women:
  - Transdermal low dose is preferred.
  - Avoid long-acting injections unless carefully titrated; maintain female physiologic range.

Conclusion

Testosterone is far more than a solitary sex hormone; it is the conductor of a complex neurosteroid orchestra that shapes emotional balance, cognitive vitality, and sexual well-being. When maintained at physiologic, balanced levels, testosterone supports the synthesis and equilibrium of pregnenolone, DHEA, progesterone, and allopregnanolone—key neuroactive steroids that calm the amygdala, enhance prefrontal control, buffer the stress response, and sustain healthy libido.

Yet, the same hormone that restores drive and vitality at optimal levels can become disruptive when pushed beyond the body's adaptive range. Supraphysiologic testosterone suppresses upstream precursors, blunts neurosteroid tone, downregulates androgen receptors, and disturbs dopamine and GABAergic signaling. Clinically, this can present as flattened libido, emotional dullness, anxiety, or irritability—symptoms that contradict the simplistic idea that "more testosterone equals more masculinity or sexual desire."

Recognizing testosterone's networked influence allows clinicians to move beyond replacement alone and toward precision hormone optimization. By monitoring precursors such as pregnenolone and DHEA,

supporting neurosteroid balance when needed, and avoiding excessive dosing, practitioners can preserve both hormonal integrity and emotional resilience. Testosterone therapy, when used wisely, is not just about numbers on a lab report—it is about sustaining the neurochemistry of vitality, motivation, and human connection.

Comment by Gordon:

Many clinics focused on *men's health* or *steroid-based hormone therapy* have built their practices around the idea that low testosterone is the single root cause of fatigue, low libido, mood changes, and cognitive decline. While this approach may provide temporary improvement, the indiscriminate use of testosterone as a one-size-fits-all solution often overlooks the complex neuroendocrine network that drives true vitality.

At Millennium Health Centers, we routinely review laboratory panels from patients who were previously treated elsewhere. A striking number are missing critical upstream hormones—such as pregnenolone, DHEA, progesterone, and their neuroactive metabolites—that strongly influence mood, cognition, resilience, and sexual health. When these are ignored, symptoms frequently persist despite "optimal" testosterone levels.

Our mission is not to criticize but to elevate. By expanding beyond a testosterone-only model and incorporating a comprehensive, evidence-based assessment of the entire neurosteroid and endocrine system, clinics can dramatically improve outcomes, patient satisfaction, and long-term trust. This isn't about selling more products or chasing quick results; it's about building lasting health and delivering care that truly changes lives.

If you're a clinician or center interested in enhancing your protocols and achieving more reliable, sustainable results for your patients, I'm always open to discussion and collaboration: MillenniumCenters@gmail.com .

Mark L. Gordon, MD

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