CLINICAL MONOGRAPH · HORMONE OPTIMIZATION

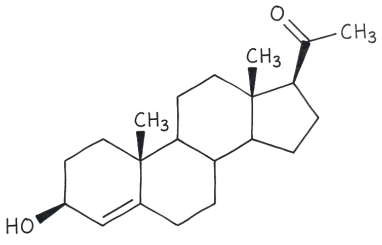
Pregnenolone

Upstream precursor to all major steroid hormones

Pregnenolone is a steroid molecule the body makes from cholesterol. It sits at the top of the steroid family tree, your cells use it to build progesterone, DHEA, testosterone, estrogen, cortisol, and a group of brain-active steroids called neurosteroids. Because every other steroid hormone is downstream of pregnenolone, it is sometimes called the 'master steroid' or 'parent prohormone'.

Pregnenolone is sold over the counter in the United States as a dietary supplement under DSHEA. There is no FDA-approved prescription product. Researchers have studied oral pregnenolone, mostly at 30, 500 mg per day, as an add-on treatment in schizophrenia (cognitive and negative symptoms), as a stand-alone treatment for bipolar depression in a single trial, and in smaller imaging and biomarker studies in PTSD and traumatic brain injury [marx2014poc; ritsner2014kreinin; brown2014bipolar]. Results are mixed and trials are generally small.

RonanRx compounds pregnenolone on a patient-specific prescription when the OTC supplement market does not meet a documented clinical need, for example a custom strength, verified API purity for a clinical research context, an alternative dosage form, or a preparation without a specific excipient [marx2011candidate]. Compounded pregnenolone is not FDA-approved and is not a substitute for FDA-approved therapy for any condition [fda503a].



EVIDENCE POSTURE EMERGING

REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Pregnenolone (3β-hydroxy-5-pregnen-20-one) is the proximal product of mitochondrial cholesterol side-chain cleavage by CYP11A1 and the obligate precursor to every other endogenous steroid hormone class, progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens, as well as to the GABA-A-active neurosteroid allopregnanolone via the progesterone → 5α-dihydroprogesterone → allopregnanolone pathway [marx2011candidate, boero2020allopreg] [fda503a]. Pregnenolone sulfate, the sulfated metabolite, is a negative allosteric modulator of GABA-A receptors and a positive modulator of NMDA receptors; this dual modulation is implicated in cognitive and synaptic-plasticity effects [holsboer1994steroid, marx2006neurosteroids] [marx2009poc].

Clinical evidence is emerging and almost entirely concentrated in the adjunctive psychiatric literature. Four small randomized placebo-controlled trials evaluated oral pregnenolone as an adjunct to antipsychotic therapy in schizophrenia, with two additional trials adding pregnenolone-plus-DHEA [ritsner2010preg_dhea] or pregnenolone-plus-L-theanine [kardashev2018ltheanine] regimens, and one risperidone-adjunct trial in women [kashani2017risperidone]. Signals include modest improvements in negative symptoms and selected cognitive domains; effect sizes vary by trial and overall evidence remains preliminary [kreinin2017cognition]. A single 12-week RCT in bipolar depression [brown2014bipolar] reported greater depressive-symptom reduction on pregnenolone vs placebo [marx2014poc; ritsner2014kreinin]. Functional MRI work [sripada2013allopreg, sripada2014amygdala] documents that oral pregnenolone administration elevates allopregnanolone and modulates emotion-regulation neurocircuitry in healthy adults, supporting a CNS-active mechanism at orally administered doses [fda503a].

There is no FDA-approved pregnenolone product [fda503a]. Pregnenolone is marketed OTC as a dietary supplement under DSHEA; compounded preparations have a legitimate 503A role only when a documented patient-specific need cannot be met by the supplement market, typical reasons include verified API purity for a clinical-care context, custom strengths outside available supplement increments, exclusion of specific excipients, or alternative dosage forms such as sublingual troches. RonanRx does not compound pregnenolone as a direct substitute for an OTC supplement absent such documented need.

Why Personalized Pregnenolone

The published pregnenolone trials picked doses, 30 to 500 mg per day of an oral capsule, that fit the average adult enrolled in an adjunct-to-antipsychotic protocol or a 12-week bipolar-depression study. Those schedules were not calibrated to your baseline neurosteroid pool, your age (pregnenolone and DHEA decline measurably across the adult lifespan), your concurrent psychiatric regimen, whether you are using pregnenolone for cognition versus mood versus a cannabinoid-axis indication, or whether oral first-pass metabolism is the right route for what your prescriber is trying to achieve. The dietary supplement aisle is calibrated for even less than that, the doses available are whatever the brand decided to make.

That is the gap a compounding pharmacy fills on a patient-specific prescription. A clinician who knows the chart can write a strength outside the OTC increments (10 mg increments below the supplement floor for a careful titration, or trial-range doses with verified API potency for a clinical-research context), switch the dosage form to a sublingual troche when oral first-pass is the wrong fit, exclude an excipient the patient does not tolerate, or blend pregnenolone with related neurosteroid precursors when the protocol calls for it. Compounded preparations are not FDA-approved and the evidence base remains emerging, so the prescriber and pharmacist together carry the documentation that a specific patient's need is not met by the supplement market.

This is the older arrangement, a doctor who knows the patient, a pharmacist who prepares the medicine for that named person, a prescription that ties the two together. Modern 503A oversight, state licensure, named-on-label dispensing, and pharmacist review, keeps it honest.

Quick Facts About Pregnenolone

Category: Endogenous neurosteroid; upstream precursor to all major steroid hormones

Common aliases: 3β-hydroxy-5-pregnen-20-one; the 'master steroid' or 'parent prohormone' in lay literature

Biological role: Synthesized from cholesterol in mitochondria via CYP11A1; precursor to progesterone, allopregnanolone, DHEA, androgens, estrogens, and cortisol

Routes studied in humans: Oral capsule (clinical-trial standard at 30, 500 mg/day); sublingual tablet/troche used clinically though less directly studied

Evidence posture: Emerging. Multiple small randomized trials as adjunct in schizophrenia (cognitive and negative symptoms) with mixed signals; single RCT in bipolar depression; preclinical and small clinical work in PTSD, cannabis-related psychosis, and traumatic brain injury

FDA-approval status: Not FDA-approved for any indication. Marketed over the counter as a dietary supplement under DSHEA. No branded prescription product exists in the US.

Compounded under: 503A, patient-specific prescription only

Compounded role: Pregnenolone exists as an OTC dietary supplement, so compounded preparations are appropriate when a documented patient need is not met by the supplement market, custom strengths, verified API purity and potency for a clinical context, exclusion of specific excipients, or alternative dosage forms such as sublingual troches.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Pregnenolone described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Pregnenolone?

Pregnenolone is a 21-carbon steroid with the systematic name 3β-hydroxy-5-pregnen-20-one [fda503a]. It is the immediate product of cholesterol side-chain cleavage catalyzed by CYP11A1 (also called P450scc) on the inner mitochondrial membrane, the rate-limiting and committed step of steroidogenesis. Once formed, pregnenolone exits the mitochondrion and is metabolized along multiple downstream pathways: to

progesterone by 3β-hydroxysteroid dehydrogenase (and from progesterone onward to mineralocorticoids, glucocorticoids, and the neuroactive 5α-reduced steroid allopregnanolone); to 17α-hydroxypregnenolone and then DHEA by CYP17A1; and from DHEA onward to androgens and estrogens [marx2011candidate].

Pregnenolone is synthesized not only in the adrenal cortex and gonads but also locally in the brain by neurons and glia [fda503a]. Brain-synthesized steroids, including pregnenolone, pregnenolone sulfate, progesterone, allopregnanolone, and DHEA, are termed neurosteroids. They act through both classical nuclear receptors (after downstream conversion) and rapid, non-genomic modulation of ligand-gated ion channels, principally the GABA-A and NMDA receptors [holsboer1994steroid, boero2020allopreg].

Pregnenolone has been available pharmaceutically and as a dietary supplement since the 1940s. In the United States it is currently sold over the counter under DSHEA, typically as oral capsules at 10, 100 mg. There is no FDA-approved prescription pregnenolone product. Compounded oral capsules and sublingual troches are dispensed under 503A on patient-specific prescriptions where the OTC supplement market does not meet a documented clinical need [fda503a].

How Pregnenolone Works

Pregnenolone has two mechanistically distinct roles that the literature does not always cleanly separate. First, it is the upstream precursor to most physiologically important steroid hormones, so administered pregnenolone can in principle raise downstream steroid pools, progesterone, allopregnanolone, DHEA, and the steroids further downstream [marx2011candidate]. Second, pregnenolone and its sulfate metabolite have direct neuromodulatory activity at GABA-A and NMDA receptors, independent of conversion [holsboer1994steroid].

Allopregnanolone, a downstream metabolite of pregnenolone via progesterone and 5α-dihydroprogesterone, is one of the most potent endogenous positive allosteric modulators of GABA-A receptors known [boero2020allopreg]. Sripada and colleagues demonstrated in healthy adults that a 400 mg oral dose of pregnenolone meaningfully elevates serum allopregnanolone and shifts activation of cortical and subcortical emotion-regulation circuits, providing direct evidence that oral pregnenolone reaches the CNS and engages the downstream neurosteroid pathway in humans [sripada2013allopreg, sripada2014amygdala].

Pregnenolone sulfate is a different molecule pharmacologically. It is a negative allosteric modulator of GABA-A receptors and a positive modulator of NMDA receptors, and it has been studied preclinically for cognition-enhancing effects [rajagopal2018ps_aug]. The relative contributions of unconjugated pregnenolone, pregnenolone sulfate, allopregnanolone, and other downstream steroids to any clinical effect of administered pregnenolone are not fully resolved and likely differ by indication.

Biological Role of Pregnenolone

Endogenous pregnenolone is synthesized continuously from cholesterol in the adrenal cortex, gonads, placenta during pregnancy, and locally within the central nervous system by neurons and glia. The brain-synthesized pool, together with downstream conversion products allopregnanolone, pregnenolone sulfate, DHEA, and DHEA-sulfate, comprises the principal endogenous neurosteroid pool [marx2011candidate, boero2020allopreg].

Serum and CSF pregnenolone fluctuate with normal hormonal physiology and decline with age, paralleling the well-described age-related decline in DHEA and DHEA-sulfate. Altered neurosteroid levels have been documented in major psychiatric and neurological disorders including schizophrenia, bipolar disorder, major depression, PTSD, and traumatic brain injury [marx2006neurosteroids; cruz2019ptsd_ofc]. Whether these alterations are causal, compensatory, or epiphenomenal is not resolved.

Because pregnenolone sits at the top of the steroidogenic cascade, exogenous administration in principle expands all downstream steroid pools, including progesterone, allopregnanolone, DHEA, and the sex steroids and glucocorticoids downstream of those [george1994csf_affective]. The clinical consequence in humans of supplementation is incompletely characterized: the directly demonstrated effect in healthy adults is elevation of allopregnanolone with corresponding fMRI changes in emotion-regulation circuits [sripada2013allopreg], but broader endocrine effects of sustained pregnenolone supplementation across the population have not been systematically mapped [ritsner2007blood_levels].

Detailed Mechanism of Pregnenolone

Steroidogenesis and the position of pregnenolone. CYP11A1, expressed on the inner mitochondrial membrane of steroidogenic cells in the adrenal cortex, gonads, placenta, and central nervous system, cleaves the side chain of cholesterol to yield pregnenolone, isocaproaldehyde, and water. This is the rate-limiting and committed step of de novo steroidogenesis: every other steroid hormone class, progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens, is synthesized from pregnenolone by tissue-specific complements of downstream enzymes. The traditional 'master steroid' framing reflects this anatomical position in the pathway [marx2011candidate].

Downstream neurosteroid pathway. Pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase, progesterone to 5α-dihydroprogesterone by 5α-reductase, and 5α-dihydroprogesterone to allopregnanolone (3α,5α-tetrahydroprogesterone) by 3α-hydroxysteroid oxidoreductase. Allopregnanolone binds at a steroid-recognition site distinct from the benzodiazepine and barbiturate sites on the GABA-A receptor and enhances both phasic and tonic GABAergic inhibition. Allopregnanolone-mediated GABAergic tone is the proximate mechanism shared by zuranolone and brexanolone, the two FDA-approved neurosteroid therapeutics for postpartum depression, and is the rationale for testing pregnenolone, as a

precursor, in stress-related, mood, and cognitive indications [boero2020allopreg, marecki2023zuranolone].

Direct receptor pharmacology. Beyond serving as a precursor, pregnenolone and pregnenolone sulfate have direct effects on ligand-gated channels. Pregnenolone sulfate is a negative allosteric modulator of GABA-A receptors (opposite in sign to allopregnanolone) and a positive modulator of NMDA receptors; it has been associated with enhanced long-term potentiation in hippocampus and pro-cognitive effects in animal models [holsboer1994steroid, rajagopal2018ps_aug]. Pregnenolone itself signals through the microtubule-associated protein MAP2 and modulates microtubule dynamics, a non-receptor pathway implicated in neurite outgrowth and possibly in some of pregnenolone's cognitive effects in preclinical models [marx2011candidate].

Cannabinoid axis. Pregnenolone is also an endogenous, allosteric negative feedback signal at the CB1 cannabinoid receptor. Vallée and colleagues demonstrated that THC raises brain pregnenolone, which then binds an allosteric site on CB1 and dampens THC's downstream signaling, a feedback loop that pregnenolone administration can amplify [busquets_garcia2017]. Subsequent preclinical work reported that pregnenolone administration blocked and reversed cannabinoid-induced psychotic-like states in mice, attenuated the hyperdopaminergic phenotype of prenatal-THC-exposed offspring, and modulated the neurosteroid-endocannabinoid cross-talk implicated in cannabis use disorder [frau2019_thc; frau2023_thc; raux2023_crosstalk]. This mechanism positions pregnenolone as a candidate adjunct in cannabis-related psychiatric phenotypes, though human trial evidence remains limited.

Stress and PTSD biology. Stress-related disorders are associated with altered neurosteroid biology. Locci and Pinna characterized a stress-induced down-regulation of neurosteroid biosynthesis paired with changes in GABA-A receptor subunit composition, a biomarker axis relevant to cognitive and emotional impairment [locci2017stress]. PTSD cohorts show altered CSF and post-mortem neurosteroid levels [cruz2019ptsd_ofc], serum pregnenolone, allopregnanolone, and DHEA track with cortical-thickness and white-matter MRI markers in stress-exposed populations [morey2019cortical_thickness], and traumatic-brain-injury rodent models show acute and chronic neurosteroid changes [servatius2016tbi_androsterone]. Peltier and colleagues' 2024 review consolidated a decade of clinical neurosteroid data in PTSD and alcohol use disorder, framing pregnenolone and allopregnanolone as candidate biomarkers and modulators [peltier2024ptsd_aud].

Schizophrenia rationale. Pregnenolone, DHEA, allopregnanolone, and related steroids are altered in postmortem and serum samples from individuals with schizophrenia and bipolar disorder [marx2006neurosteroids, ritsner2007blood_levels] [mason2017bipolar_cud]. Marx and colleagues' clinical program in schizophrenia rests on three convergent rationales: replacement of altered endogenous neurosteroid tone, GABA-A enhancement via allopregnanolone, and NMDA-receptor modulation via pregnenolone sulfate (relevant to the NMDA-hypofunction model of schizophrenia) [marx2011candidate]. Preclinical work supports the rationale: pregnenolone rescues schizophrenia-like behavior in dopamine-transporter-knockout mice [wong2012dat_ko] and pregnenolone sulfate reverses phencyclidine-induced

cognitive and social deficits [rajagopal2018ps_aug]; an early-life psychosocial-stress model showed that targeting neurosteroid synthesis ameliorated schizophrenia-related alterations [frau2015stress].

Pregnenolone Research History

Pregnenolone was isolated and named in the 1930s during the early steroid-biochemistry era. Through the 1940s and 1950s, pregnenolone was investigated clinically in arthritis and as a general fatigue or 'tonic' remedy, with mixed and largely uncontrolled results; this body of work fell out of mainstream pharmacology when more specific steroid therapies (cortisone, estrogens, testosterone esters) became available [marx2011candidate]. The molecule remained available pharmaceutically and, after DSHEA passed in 1994, as a dietary supplement.

Modern interest in pregnenolone as a clinical agent dates to the neurosteroid era opened by Baulieu and colleagues in the 1980s, who demonstrated that the brain synthesizes pregnenolone and its sulfate ester locally [marx2011candidate]. Pharmacological characterization of pregnenolone sulfate as a positive modulator of NMDA receptors and a negative modulator of GABA-A receptors, and of allopregnanolone (a downstream metabolite) as a potent positive modulator of GABA-A receptors, was completed across the 1990s and 2000s [holsboer1994steroid].

George and colleagues in 1994 reported altered CSF pregnenolone, progesterone, and DBI in affective disorders [george1994csf_affective]. Marx and colleagues at Duke and the Mid-Atlantic MIRECC published a key 2006 paper demonstrating altered neuroactive steroid levels in schizophrenia and bipolar disorder, providing the rationale for the subsequent randomized trials [marx2006neurosteroids]. Ritsner and colleagues characterized blood pregnenolone and DHEA differences between schizophrenia patients and healthy controls in 2007 [ritsner2007blood_levels] [marx2011candidate].

The clinical-trial era for pregnenolone in schizophrenia opened with Marx and colleagues' 2009 proof-of-concept randomized placebo-controlled trial of adjunctive pregnenolone (up to 500 mg/day) in 18 adults with schizophrenia or schizoaffective disorder, which reported improvement in negative symptoms and selected cognitive domains [marx2009poc]. Ritsner's 2010 8-week randomized trial of pregnenolone, DHEA, pregnenolone + DHEA, and placebo as augmentation in schizophrenia and schizoaffective disorder followed [ritsner2010preg_dhea]. Marx and colleagues' 2014 follow-on multi-site proof-of-concept RCT in Singapore [marx2014poc], and Ritsner and Kreinin's 8-week recent-onset schizophrenia trials of pregnenolone for negative symptoms [ritsner2014kreinin] and cognitive deficits [kreinin2017cognition], extended the evidence base [marx2011candidate]. Kashani 2017 reported a risperidone-adjunct trial in women [kashani2017risperidone] and Kardashev 2018 a pregnenolone + L-theanine combination trial [kardashev2018ltheanine]. Heringa 2015 published a quantitative review of sex-hormone augmentation strategies in schizophrenia [heringa2015review]; Ritsner 2010 had earlier reviewed the broader pregnenolone/DHEA schizophrenia literature [ritsner2010review].

Brown and colleagues at UT Southwestern published the only randomized placebo-controlled trial of pregnenolone in bipolar depression in 2014 [brown2014bipolar]. fMRI work from Sripada and the Liberzon group at Michigan demonstrated in 2013 and 2014 that oral pregnenolone administration in healthy adults elevates allopregnanolone and modulates emotion-regulation neurocircuitry and resting-state amygdala connectivity [sripada2013allopreg, sripada2014amygdala], providing mechanistic human imaging evidence [marx2011candidate].

The cannabinoid-axis work is more recent. Vallée and colleagues at INSERM demonstrated that pregnenolone is an endogenous CB1 negative allosteric modulator and that pregnenolone administration blocked cannabinoid-induced acute psychotic-like states in mice [busquets_garcia2017] [wong2012dat_ko]. Frau and colleagues in 2019 showed that pregnenolone reverses the hyperdopaminergic phenotype of prenatal-THC-exposed offspring [frau2019_thc], with sex-specific extension in 2023 [frau2023_thc]. Mason and colleagues' 2017 study of neurosteroid levels in bipolar disorder with cannabis use disorder highlighted the same axis clinically [mason2017bipolar_cud]; Raux and Vallée reviewed the neurosteroid-endocannabinoid cross-talk in 2023 [raux2023_crosstalk]. Tomaselli and Vallée's 2019 review consolidated the pregnenolone-progesterone-allopregnanolone pathway in stress and addiction [tomaselli2019pathway].

PTSD and TBI neurosteroid research has remained largely observational. Marx and colleagues at the Mid-Atlantic MIRECC have published a series of post-mortem and CSF studies, neurosteroid levels in PTSD orbital frontal cortex [cruz2019ptsd_ofc], cortical thickness associations [morey2019cortical_thickness], and TBI rodent neurosteroid changes [servatius2016tbi_androsterone]. Peltier and colleagues' 2024 review consolidated the decade of clinical neurosteroid data in PTSD and alcohol use disorder [peltier2024ptsd_aud]. There is no completed adequately powered RCT of pregnenolone for PTSD, TBI, or cannabis use disorder. The FDA approvals of brexanolone (2019) and zuranolone (2023) for postpartum depression, both downstream allopregnanolone-pathway therapeutics, have intensified interest in the broader neurosteroid program but do not extend to pregnenolone itself [marecki2023zuranolone] [marx2011candidate].

Pregnenolone Timeline

- **1930s** — Pregnenolone first isolated and characterized during the early steroid-biochemistry era; named for its progesterone relationship
- **1940s, 1950s** — Pregnenolone investigated clinically in arthritis and as a general 'tonic' agent; results largely uncontrolled and the molecule falls out of mainstream pharmacology when more specific steroid therapies become available
- **1980s** — Baulieu and colleagues establish that the brain synthesizes pregnenolone and pregnenolone sulfate de novo, opening the modern neurosteroid era

1994 • DSHEA passes; pregnenolone becomes a dietary supplement in the US [holsboer1994steroid; george1994csf_affective]. Holsboer and colleagues publish steroid effects on central neurons; George and colleagues report altered CSF pregnenolone/progesterone/DBI in affective disorders

2006 • Marx et al publish 'Neuroactive steroids are altered in schizophrenia and bipolar disorder' (Neuropsychopharmacology), anchors the rationale for the subsequent schizophrenia adjunct trials [marx2006neurosteroids]

2007 • Ritsner et al characterize differences in blood pregnenolone and DHEA between schizophrenia patients and healthy controls [ritsner2007blood_levels]

2009 • Marx et al publish the first proof-of-concept RCT of adjunctive pregnenolone in schizophrenia (Neuropsychopharmacology), reporting improvement in negative symptoms and selected cognitive domains [marx2009poc]

2010 • Ritsner et al publish 8-week randomized trial of pregnenolone, DHEA, and pregnenolone + DHEA as augmentation in schizophrenia and schizoaffective disorder [ritsner2010preg_dhea]

2011 • Marx et al publish 'Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence' (Neuroscience), comprehensive mechanism + clinical synthesis [marx2011candidate]

2012 • Wong et al show pregnenolone rescues schizophrenia-like behavior in dopamine-transporter knockout mice (PLoS One) [wong2012dat_ko]

2013 • Sripada et al publish fMRI study showing oral pregnenolone elevates allopregnanolone and enhances emotion-regulation neurocircuit activation in healthy adults (Biol Psychiatry) [sripada2013allopreg]

2014 • Marx et al publish multi-site RCT of pregnenolone in schizophrenia (Psychopharmacology); Ritsner-Kreinin 8-week recent-onset schizophrenia negative-symptom trial; Brown et al publish the only RCT of pregnenolone in bipolar depression (Neuropsychopharmacology); Sripada et al publish allopregnanolone/DHEA amygdala connectivity fMRI work [marx2014poc; ritsner2014kreinin; brown2014bipolar; sripada2014amygdala]

2015 • Heringa et al publish quantitative review of sex-hormone augmentation strategies in schizophrenia; Frau et al show that targeting neurosteroid synthesis ameliorates schizophrenia-related alterations from early psychosocial stress [heringa2015review; frau2015stress]

2017 • Kreinin/Ritsner publish 8-week recent-onset schizophrenia cognition trial (positive cognitive signal); Kashani et al publish risperidone-adjunct trial in women with schizophrenia; Mason et al examine neurosteroid levels in bipolar disorder with cannabis use disorders; Busquets-Garcia/Vallée show pregnenolone blocks cannabinoid-induced acute psychotic-like states in mice (Mol Psychiatry); Locci and Pinna characterize stress-induced neurosteroid down-regulation and GABA-A subunit changes [kreinin2017cognition; kashani2017risperidone; mason2017bipolar_cud; busquets_garcia2017; locci2017stress]

2018 • Kardashev et al publish pregnenolone + L-theanine adjunct trial in schizophrenia; Rajagopal et al show pregnenolone sulfate augmentation reverses PCP-induced cognitive and social deficits preclinically [kardashev2018ltheanine; rajagopal2018ps_aug]

2019 • Frau et al show prenatal THC produces a hyperdopaminergic phenotype rescued by pregnenolone (Nat Neurosci); Cruz et al examine neurosteroid levels in the orbital frontal cortex of subjects with PTSD; Morey et al associate cortical thickness with neuroactive steroid levels; Tomaselli and Vallée publish a comprehensive pregnenolone-progesterone-allopregnanolone pathway review [frau2019_thc; cruz2019ptsd_ofc; morey2019cortical_thickness; tomaselli2019pathway]

2020 • Boero et al publish 'Pleiotropic actions of allopregnanolone underlie therapeutic benefits in stress-related disease' (Neurobiol Stress), consolidates downstream neurosteroid pharmacology [boero2020allopreg]

2023 • Frau and Melis publish sex-specific susceptibility to prenatal THC and reversal by pregnenolone; Raux and Vallée review cross-talk between neurosteroid and endocannabinoid systems in cannabis addiction; Marecki et al publish a narrative review on zuranolone, synthetic neurosteroid context for the broader pathway [frau2023_thc; raux2023_crosstalk; marecki2023zuranolone]

2024 • Peltier et al publish 10-year clinical review of neurosteroids in PTSD and alcohol use disorder [peltier2024ptsd_aud]

Off-Label Uses of Pregnenolone

Adjunct in schizophrenia (negative symptoms and cognition) EMERGING

Studied as an add-on to antipsychotic therapy in several small randomized placebo-controlled trials; signals are mixed and effect sizes vary by trial. Evidence remains preliminary.

Marx 2009 (n=18) reported improvement in negative symptoms and selected cognitive domains on adjunctive pregnenolone up to 500 mg/day [marx2009poc; marx2014poc]. Ritsner 2010 (n=58) compared pregnenolone, DHEA, the combination, and placebo over 8 weeks [ritsner2010preg_dhea]. Marx 2014 (n=120) was a multi-site RCT with a more modest signal. Ritsner-Kreinin 2014 and Kreinin 2017 reported negative-symptom and cognitive improvements in recent-onset schizophrenia [ritsner2014kreinin; kreinin2017cognition]. Kashani 2017 added pregnenolone to risperidone in women [kashani2017risperidone]. Kardashev 2018 combined pregnenolone with L-theanine [kardashev2018ltheanine]. Heringa 2015's quantitative review of sex-hormone augmentation in schizophrenia integrated the data and concluded the evidence remains preliminary [heringa2015review].

Bipolar depression (adjunct) EMERGING

Single 12-week RCT supports an exploratory signal; no replication.

Brown et al (2014) randomized 80 adults with bipolar depression to pregnenolone 500 mg/day or placebo over 12 weeks [brown2014bipolar]. Pregnenolone produced a greater reduction in depressive symptoms than placebo. No replication trial has been published; the signal sits in the same exploratory tier as the schizophrenia adjunct literature.

PTSD and trauma-related disorders EMERGING

Mechanistic and biomarker work supports an association between altered neurosteroid biology and PTSD; no adequately powered RCT of pregnenolone is completed.

Cruz 2019 documented altered neurosteroid levels in PTSD orbital frontal cortex [cruz2019ptsd_ofc]. Morey 2019 associated serum neuroactive steroids, including pregnenolone, with cortical-thickness MRI markers in stress-exposed populations [morey2019cortical_thickness]. Sripada 2013/2014 demonstrated that exogenous pregnenolone elevates allopregnanolone and modulates emotion-regulation and amygdala-connectivity fMRI signatures in healthy adults [sripada2013allopreg; sripada2014amygdala]. Peltier 2024 consolidated 10 years of clinical neurosteroid data in PTSD and AUD [peltier2024ptsd_aud]. The PTSD literature remains primarily biomarker- and imaging-driven; clinical efficacy of pregnenolone in PTSD is not established.

Cannabis-related psychiatric phenotypes EMERGING

Strong preclinical mechanistic basis via CB1 allosteric modulation; clinical evidence in humans remains preliminary.

Pregnenolone is an endogenous negative allosteric modulator at CB1. Busquets-Garcia/Vallée 2017 reported that pregnenolone administration blocked cannabinoid-induced acute psychotic-like states in mice [busquets_garcia2017; frau2023_thc]. Frau 2019 and Frau-Melis 2023 demonstrated rescue of prenatal-THC-induced hyperdopaminergic phenotypes [frau2019_thc]. Mason 2017 documented altered neurosteroid levels in bipolar disorder with co-occurring cannabis use disorders [mason2017bipolar_cud; tomaselli2019pathway]. Raux and Vallée 2023 and Tomaselli-Vallée 2019 reviewed the cross-talk [raux2023_crosstalk]. Adequately powered human RCTs in cannabis use disorder or cannabis-related psychosis are not yet completed.

Traumatic brain injury PRECLINICAL

Rodent stress + mTBI models show neurosteroid changes; clinical translation is preliminary.

Servatius 2016 documented elevation of brain and serum androsterone in response to stress in rats with mild TBI [servatius2016tbi_androsterone]. Marx and colleagues have published a series of post-mortem and biomarker studies on neurosteroid changes after brain injury. There is no published completed randomized trial of pregnenolone for traumatic brain injury in humans.

Compounded Pregnenolone (503A)

Pregnenolone is sold over the counter in the United States as a dietary supplement under DSHEA, typically as oral capsules at 10, 100 mg. There is no FDA-approved prescription pregnenolone product. The 'essentially-a-copy' framing that governs much of 503A compounding does not apply here in the usual way, there is no FDA-approved branded product to copy [fda503a].

Compounded pregnenolone has a legitimate 503A role when a documented patient-specific clinical need cannot be met by the OTC supplement market [peltier2024ptsd_aud]. Common reasons include: a custom strength outside available supplement increments; verified API purity, potency, and identity for a clinical-care context where supplement-grade verification is insufficient; exclusion of specific excipients (fillers, dyes, or allergens present in the patient's available supplement options); or an alternative dosage form, such as a sublingual troche, that the supplement market does not offer. RonanRx does not compound pregnenolone as a routine substitute for a commercially available OTC supplement absent such documented patient-specific need.

Patients and prescribers should also recognize that any decision to administer pregnenolone, compounded or supplement, sits on an emerging evidence base. The principal psychiatric trials are small, often single-site, and concentrated in the schizophrenia adjunct space with one bipolar depression trial; cognitive-aging, PTSD, TBI, and cannabis-related indications have either no completed RCT or only exploratory biomarker

work [brown2014bipolar]. Pregnenolone is not a substitute for any FDA-approved therapy for any psychiatric, neurological, or endocrine condition [marx2014poc].

Pregnenolone Formulations and Routes

Form	Concentration	Description
Oral capsule	Custom; published trial strengths span 30, 500 mg/day	Custom-strength oral capsules, the dose form used in essentially all published randomized clinical trials of pregnenolone, including the Marx and Ritsner schizophrenia program and Brown's bipolar depression RCT
Sublingual troche or tablet	Custom	Alternative dosage form prepared on patient-specific prescription when oral capsule administration is not appropriate; less directly studied in randomized trials but used clinically

Routes used in published literature: oral, sublingual, troche.

Pregnenolone Dosing

Route	Population	Range	Duration	Study type
oral capsule	adults with schizophrenia (adjunct)	30, 500 mg/day, titrated; Marx 2009 used 500 mg/day, Marx 2014 used 500 mg/day, Ritsner studies used 50, 150 mg/day	8, 12 weeks (trial protocols)	randomized double-blind placebo-controlled trial
oral capsule	adults with bipolar depression (adjunct)	500 mg/day	12 weeks	randomized double-blind placebo-controlled trial
oral capsule	healthy adults (single-dose fMRI study)	400 mg single dose	single dose	randomized double-blind crossover fMRI

Doses listed reflect published clinical-trial protocols, not RonanRx prescribing recommendations. The prescribing doctor selects route, dose, frequency, and duration based on the patient's clinical context, indication, and goals.

Pregnenolone trial-dose ranges are wide (30, 500 mg/day) and indication-dependent. The schizophrenia adjunct trials clustered at 50, 500 mg/day; the only bipolar depression RCT used 500 mg/day; the human fMRI mechanistic work used 400 mg single doses. Optimal dose for any other indication is not established

by published clinical data. Doses listed should not be presented to patients as instructions, patient instructions originate from the prescribing physician's prescription.

Pregnenolone Safety

Across the randomized clinical trials of oral pregnenolone in schizophrenia and bipolar depression, pregnenolone has been generally well-tolerated at trial doses (up to 500 mg/day for 8, 12 weeks) with adverse-event rates comparable to placebo in most studies [5] [12]. Reported adverse effects are typically mild, drowsiness, headache, occasional gastrointestinal upset, and have not differentiated pregnenolone from placebo in a clinically meaningful way in the published trials [16].

The principal theoretical safety consideration is that pregnenolone is upstream of every steroid hormone class. Sustained supraphysiologic dosing could in principle elevate progesterone, allopregnanolone, DHEA, androgens, estrogens, and glucocorticoids, with associated downstream endocrine effects. The clinical trials reviewed have been too short and too small to characterize chronic endocrine effects of sustained pregnenolone supplementation, and routine monitoring practice for chronic exogenous pregnenolone has not been standardized [5] [34]. Patients with hormone-sensitive conditions (history of breast, prostate, or other steroid-responsive cancers; estrogen-dependent disorders; androgen-related dermatologic conditions) require particular clinical caution and prescriber-directed monitoring.

Contraindications

Honest gap. No FDA-approved prescription pregnenolone product exists, so no FDA-defined contraindications. Documented hypersensitivity to any component of a particular preparation is a relative contraindication for that preparation. Theoretical contraindications, derived from pregnenolone's upstream position in the steroid cascade, include pregnancy and lactation (unknown effects on fetal/neonatal steroid biology), hormone-sensitive cancers, and other steroid-responsive disorders pending prescriber-directed risk assessment.

Searched: PubMed, DailyMed on 2026-05-11 · terms *pregnenolone contraindications; pregnenolone adverse effects; pregnenolone hormone-sensitive cancer*.

Drug interactions

Honest gap. No specific drug-drug interactions are formally established for pregnenolone. Theoretical interactions, derived from pregnenolone's metabolism through CYP and 3β-/17β-HSD enzymes, include other steroid hormone therapies (testosterone, estradiol, progesterone, DHEA, glucocorticoids) where supplementation may shift the balance between the administered hormone and the endogenous steroid pool. Patients taking antipsychotics, antidepressants, mood stabilizers, or other CNS-active medications should have any pregnenolone use coordinated with the prescribing psychiatrist or neurologist; the

published adjunct trials specifically combined pregnenolone with antipsychotic or antidepressant base therapy under protocol supervision.

Searched: PubMed, DailyMed on 2026-05-11 · terms *pregnenolone drug interactions; pregnenolone CYP; pregnenolone hormonal therapy*.

Adverse events

In the published randomized trials of oral pregnenolone at trial doses (30, 500 mg/day for 8, 12 weeks), adverse-event rates did not differ clinically meaningfully from placebo [5] [3][16]. Most-commonly reported mild adverse events across studies include drowsiness, headache, transient gastrointestinal upset, and dizziness; serious adverse events have been rare and not consistently attributable to pregnenolone.

Longer-term adverse-event characterization is limited. Theoretical endocrine consequences of sustained supplementation, through expansion of downstream steroid pools, have not been systematically mapped in the trial literature. Reports of mood disturbance, headache, irritability, or breast or skin changes attributed to pregnenolone supplements appear in the broader OTC literature but are not consistently reproduced in controlled trials [5] [12].

Monitoring Pregnenolone Therapy

Routine laboratory monitoring is not standardized for pregnenolone supplementation or compounded use. The prescribing clinician may monitor disease-specific outcomes (psychiatric symptom scales, PTSD or depression rating instruments, cognitive testing) at clinically appropriate intervals consistent with the prescribed indication.

Where there is concern about downstream endocrine effects, particularly with sustained higher-dose use or in patients with hormone-sensitive conditions, the prescribing clinician may consider baseline and on-therapy steroid panels (pregnenolone, DHEA-sulfate, progesterone, testosterone, estradiol, cortisol) at intervals consistent with the patient's clinical context. Standardized monitoring intervals are not established in the published trial literature.

Pregnenolone Evidence Quality

Evidence for pregnenolone as a therapeutic agent is emerging across all indications. The strongest signal, adjunct use in schizophrenia for negative symptoms and selected cognitive domains, rests on four small randomized placebo-controlled trials [marx2009poc], one combination-augmentation trial (Ritsner 2010 pregnenolone + DHEA), one risperidone-adjunct trial [kashani2017risperidone], and one combination trial [kardashev2018ltheanine]. Heringa's 2015 quantitative review of sex-hormone augmentation strategies integrated these data and concluded the evidence remained preliminary [heringa2015review]. Effect sizes

vary by trial; pivotal multi-site trials of pregnenolone alone in schizophrenia have not been completed [marx2014poc; kreinin2017cognition; ritsner2010preg_dhea].

Bipolar depression rests on a single 12-week RCT [brown2014bipolar] with a positive signal that has not been independently replicated [ritsner2014kreinin]. PTSD evidence is observational, imaging-based, and biomarker-focused [cruz2019ptsd_ofc]. Cannabis-axis evidence is preclinical and mechanistic (Busquets-Garcia/Vallée 2017, Frau 2019, Frau-Melis 2023, Raux-Vallée 2023). Traumatic brain injury is rodent-stage. Cognitive aging and broader mood indications are anecdotal and supplement-market-driven rather than trial-supported.

Mechanism is reasonably well established at the biochemical level, CYP11A1-mediated synthesis, downstream conversion to allopregnanolone and other neurosteroids, GABA-A and NMDA receptor modulation by pregnenolone sulfate, CB1 allosteric modulation [sripada2014amygdala]. Human imaging work [sripada2013allopreg] confirms that orally administered pregnenolone reaches the CNS and engages the downstream neurosteroid pathway [busquets_garcia2017; frau2019_thc]. The gap between mechanism and confirmed clinical benefit is real and should be communicated clearly to patients considering use [morey2019cortical_thickness; peltier2024ptsd_aud].

Major Pregnenolone Clinical Studies

Study	Design	Participants	Duration	Finding
Marx et al (2009, Neuropsychopharmacology), Proof-of-concept trial of pregnenolone in schizophrenia	Randomized double-blind placebo-controlled adjunct trial	18	8 weeks	Adjunctive pregnenolone (up to 500 mg/day) produced improvement in negative symptoms and selected cognitive domains in adults with schizophrenia or schizoaffective disorder on stable antipsychotic therapy [marx2009poc].
Ritsner et al (2010, J Clin Psychiatry), Pregnenolone and DHEA augmentation in schizophrenia	Randomized double-blind placebo-controlled four-arm trial	58	8 weeks	Compared pregnenolone, DHEA, pregnenolone + DHEA, and placebo as augmentation in schizophrenia and schizoaffective disorder; pregnenolone-containing arms produced measurable changes in selected outcomes vs placebo, with overall effect size modest [ritsner2010preg_dhea].
		120	8 weeks	

Study	Design	Participants	Duration	Finding
Marx et al (2014, Psychopharmacology Berl), Multi-site RCT of pregnenolone in schizophrenia	Randomized double-blind placebo-controlled multi-site adjunct trial			Adjunctive pregnenolone in adults with chronic schizophrenia on antipsychotic therapy; modest signals on selected cognitive and symptom outcomes; effect size smaller than the 2009 proof-of-concept trial [marx2014poc].
Ritsner-Kreinin (2014, Psychiatry Clin Neurosci), Pregnenolone in recent-onset schizophrenia	Randomized double-blind placebo-controlled add-on two-center trial	—	8 weeks	Pregnenolone reduced severity of negative symptoms in adults with recent-onset schizophrenia [ritsner2014kreinin].
Kreinin/Ritsner (2017, Clin Schizophr Relat Psychoses), Pregnenolone and cognition in recent-onset schizophrenia	Randomized double-blind placebo-controlled adjunct trial	—	8 weeks	Adjunctive pregnenolone ameliorated cognitive deficits in adults with recent-onset schizophrenia across selected neurocognitive domains [kreinin2017cognition].
Kashani et al (2017, J Psychiatr Res), Pregnenolone + risperidone in women with schizophrenia	Randomized double-blind placebo-controlled adjunct trial	—	8 weeks	Adjunctive pregnenolone added to risperidone produced improvement on selected symptom dimensions in women with schizophrenia [kashani2017risperidone].
Kardashev et al (2018, Clin Schizophr Relat Psychoses), Pregnenolone + L-theanine in schizophrenia	Randomized double-blind placebo-controlled adjunct trial	—	8 weeks	Pregnenolone combined with L-theanine relieved negative and anxiety symptoms in adults with schizophrenia [kardashev2018ltheanine].
Brown et al (2014, Neuropsychopharmacology), Pregnenolone in bipolar depression	Randomized double-blind placebo-controlled trial	80	12 weeks	Pregnenolone 500 mg/day produced greater reduction in depressive symptoms than placebo in adults with bipolar depression. Only RCT of pregnenolone in bipolar depression to date [brown2014bipolar].

Study	Design	Participants	Duration	Finding
Sripada et al (2013, Biol Psychiatry), Pregnenolone fMRI in healthy adults	Randomized double-blind placebo-controlled crossover fMRI study	—	Single dose	Single 400 mg oral dose of pregnenolone elevated serum allopregnanolone and enhanced activation of emotion-regulation neurocircuits (medial prefrontal cortex and amygdala) in healthy adults [sripada2013allopreg].
Sripada et al (2014, Hum Brain Mapp), Neurosteroid modulation of amygdala connectivity	Randomized double-blind fMRI study	—	—	Allopregnanolone and DHEA modulated resting-state amygdala connectivity in healthy adults, providing mechanistic-imaging evidence for downstream neurosteroid effects on stress-relevant neural circuits [sripada2014amygdala].
Marx et al (2006, Neuropsychopharmacology), Neuroactive steroids in schizophrenia and bipolar disorder	Post-mortem and serum neurosteroid measurement	—	—	Documented altered pregnenolone, allopregnanolone, and DHEA levels in postmortem brain tissue and serum from individuals with schizophrenia and bipolar disorder vs controls, anchors the rationale for the subsequent adjunct trials [marx2006neurosteroids].
Busquets-Garcia/Vallée et al (2017, Mol Psychiatry), Pregnenolone blocks cannabinoid-induced acute psychotic-like states	Preclinical (mice)	—	—	Pregnenolone administration prevented cannabinoid-induced acute psychotic-like states in mice, via CB1 allosteric negative modulation [busquets_garcia2017]. Defines the cannabinoid-axis mechanism for pregnenolone.
Frau et al (2019, Nat Neurosci), Prenatal THC rescued by pregnenolone	Preclinical (rats)	—	—	Prenatal THC exposure produced a hyperdopaminergic phenotype in offspring that was rescued by pregnenolone administration, supporting a clinical rationale in cannabis-

Study	Design	Participants	Duration	Finding
				related psychiatric outcomes [frau2019_thc].
Heringa et al (2015, Schizophr Res), Quantitative review of sex-hormone augmentation in schizophrenia	Quantitative review / meta-analysis	—	—	Integrated published trials of sex-hormone and neurosteroid augmentation strategies in schizophrenia (including pregnenolone, DHEA, estrogen, raloxifene, oxytocin); concluded the evidence remained preliminary and called for adequately powered trials [heringa2015review].
Peltier et al (2024, Front Neuroendocrinol), Decade review of neurosteroids in PTSD and AUD	Narrative review	—	—	Consolidated 10 years of clinical neurosteroid data in PTSD and alcohol use disorder; framed pregnenolone and allopregnanolone as candidate biomarkers and modulators but did not identify any completed adequately powered RCT of pregnenolone for PTSD or AUD [peltier2024ptsd_aud].
Boero et al (2020, Neurobiol Stress), Pleiotropic actions of allopregnanolone	Narrative review	—	—	Consolidated allopregnanolone pharmacology and therapeutic relevance across stress-related disease, frames the downstream pathway that pregnenolone supplementation engages [boero2020allopreg].

Pregnenolone Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Oral pregnenolone is absorbed but undergoes extensive first-pass metabolism through downstream steroidogenic pathways, so the principal pharmacologic exposure in humans is to a mixture of pregnenolone plus its metabolites, pregnenolone sulfate, progesterone, allopregnanolone, DHEA, DHEA-sulfate, and further downstream products. Direct measurement of the human PK of an oral pregnenolone

dose to all clinically relevant downstream pools is limited; the most quantitative human PK / PD work to date is Sripada and colleagues' 2013 demonstration that a single 400 mg oral dose meaningfully elevates serum allopregnanolone within hours and that the elevation correlates with measurable changes in emotion-regulation fMRI activation [sripada2013allopreg] [sripada2014amygdala].

Because every administered dose of pregnenolone enters the steroidogenic cascade, a 'selective' pregnenolone effect cannot be assumed from oral dosing. The clinical phenotype of supplementation reflects integrated effects across downstream pools, with relative contributions that depend on tissue-specific complements of conversion enzymes [marx2011candidate]. Sublingual administration is hypothesized to attenuate first-pass conversion, but direct human PK comparisons of oral capsule vs sublingual administration in clinically relevant doses have not been published.

Pregnenolone and pregnenolone sulfate are excreted primarily through hepatic metabolism with biliary and urinary elimination of conjugated metabolites. Half-life of unconjugated pregnenolone in plasma is on the order of hours, but the indirect pharmacologic exposure via downstream steroid pools (progesterone, allopregnanolone, DHEA) is longer [marx2011candidate].

Pharmacodynamics

Pharmacodynamic effects reflect contributions from pregnenolone itself, pregnenolone sulfate, and downstream metabolites, most notably allopregnanolone at GABA-A receptors and pregnenolone sulfate at GABA-A (negative modulation) and NMDA (positive modulation) receptors [holsboer1994steroid, boero2020allopreg, rajagopal2018ps_aug]. Direct measurement of human CNS pharmacodynamic effects of oral pregnenolone is limited to the Sripada 2013/2014 fMRI program, which demonstrated allopregnanolone elevation and modulation of emotion-regulation and amygdala-connectivity signatures after acute dosing [sripada2013allopreg; sripada2014amygdala].

Clinical pharmacodynamic endpoints studied in the randomized trials include psychiatric symptom rating scales (PANSS, MADRS, HAM-D), cognitive batteries (MATRICS, RBANS, selected MCCB domains), and global functioning measures [sripada2013allopreg]. The magnitude of pharmacodynamic effect varies by trial and indication and has not been integrated into a population-PK/PD model.

↓↑ Comparing Pregnenolone Formulations

The published clinical-trial literature is essentially limited to oral capsule administration. Marx and Ritsner's schizophrenia program, Brown's bipolar depression RCT, and the Sripada fMRI mechanistic work all used oral pregnenolone in micronized or USP-grade capsule form at 30, 500 mg/day [marx2009poc; marx2014poc; ritsner2014kreinin]. No randomized trial has directly compared oral capsule vs sublingual administration in a clinically relevant indication [brown2014bipolar].

Sublingual troches and tablets are prepared on patient-specific prescriptions where the prescribing clinician judges the alternative delivery preferable, for example to attenuate first-pass conversion, to

address swallowing difficulty, or to permit titration finer than oral capsule increments allow. The hypothesized PK rationale is plausible but not directly validated in human clinical studies. Patients and prescribers should not assume bioequivalence between oral capsule and sublingual administration [sripada2013allopreg].

Pregnenolone Storage and Handling

Compounded oral capsules and sublingual preparations of pregnenolone are stored at controlled room temperature (USP 20, 25 °C) in tight, light-resistant containers per dispensing pharmacy labeling. Beyond-use dates are assigned per USP General Chapter <795> for nonsterile compounded preparations and the specific stability data for each formulation [usp_795]. Pregnenolone is a stable steroid at room temperature in dry conditions; refrigeration is not required for typical solid dosage forms.

Pregnenolone Compounding & Operations

503A compounding

RonanRx prepares pregnenolone under 503A on patient-specific prescriptions written by a licensed prescribing physician for an identified patient, consistent with section 503A of the Federal Food, Drug, and Cosmetic Act [fda503a]. Because pregnenolone is sold OTC as a dietary supplement and no FDA-approved prescription product exists, the 'essentially-a-copy' framework of 503A does not apply in the usual way; the compounded role is defined by patient-specific need not met by the supplement market, custom strengths, verified API identity and potency, excipient exclusion, or alternative dosage forms.

Bulk drug substance is sourced from FDA-registered API suppliers, with documented certificates of analysis confirming identity, purity, and potency. Nonsterile compounded preparations (oral capsules, sublingual troches and tablets) follow USP General Chapter <795> standards for nonsterile pharmaceutical compounding [usp_795]. Finished product lot records are retained per state board of pharmacy retention requirements, with full traceability from API lot through dispensing.

Pharmacist review

Each prescription for compounded pregnenolone undergoes pharmacist review prior to dispensing. The review confirms a documented patient-specific clinical reason that the OTC supplement market does not meet the patient's need (custom strength, verified API purity for the clinical context, excipient exclusion, or alternative dosage form); absence of disqualifying clinical concerns documented in the prescription record (hormone-sensitive cancer history, pregnancy/lactation, etc., pending prescriber risk assessment); appropriate concomitant medication review; and a prescribed regimen consistent with published clinical-trial protocols or with a prescriber-documented patient-specific rationale.

RonanRx does not fill prescriptions that read as routine substitution of compounded pregnenolone for an OTC supplement absent documented patient-specific clinical rationale. Pregnenolone is dispensed by patient-specific prescription only; RonanRx is not a direct-to-consumer storefront [fda503a].

Quality and traceability

Active pharmaceutical ingredient is sourced from FDA-registered facilities with documented certificates of analysis confirming identity, purity, and potency for each lot. Each compounded batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements with full traceability from API lot through dispensing.

Cold chain

Pregnenolone oral capsules and sublingual preparations are not cold-chain products. They ship at controlled room temperature in tight, light-resistant containers. Patients should store the preparation per pharmacy labeling at controlled room temperature and protect from excessive heat, humidity, and direct sunlight.

Frequently Asked Questions About Pregnenolone

Is pregnenolone FDA-approved?

No. Pregnenolone is not FDA-approved as a prescription drug for any indication [fda503a]. It is sold over the counter as a dietary supplement under DSHEA. Compounded pregnenolone is dispensed under 503A on a patient-specific prescription. Compounded drugs are not FDA-approved.

If pregnenolone is sold OTC, why would anyone get it compounded?

Most patients who take pregnenolone use the OTC supplement market. Compounded pregnenolone has a legitimate 503A role only when a documented patient-specific clinical need cannot be met by the supplement market, for example a custom strength outside available supplement increments, verified API purity and potency for a clinical-care context, exclusion of a specific excipient, or an alternative dosage form such as a sublingual troche. RonanRx does not compound pregnenolone as a routine substitute for a commercially available OTC supplement absent such documented need [fda503a].

Why is pregnenolone sometimes called the 'master steroid'?

Because pregnenolone sits at the top of the steroid family tree. It is the immediate product of CYP11A1 cleavage of cholesterol in mitochondria, and every other steroid hormone class, progesterone and the neurosteroid allopregnanolone, DHEA, testosterone, estrogen, cortisol and the other glucocorticoids,

aldosterone and the other mineralocorticoids, is built from pregnenolone by tissue-specific enzymes [marx2011candidate]. The 'master steroid' label reflects this anatomical position in the cascade.

What conditions has pregnenolone been studied in?

Published randomized clinical trials of pregnenolone are concentrated in schizophrenia as an adjunct to antipsychotic therapy, for negative symptoms and selected cognitive domains [marx2009poc; marx2014poc; ritsner2014kreinin]. One 12-week RCT examined bipolar depression [brown2014bipolar]. Smaller imaging and biomarker studies have addressed PTSD, traumatic brain injury, and cannabis-related psychiatric phenotypes [cruz2019ptsd_ofc]. Cognitive aging and general mood support are anecdotal and supplement-market-driven rather than trial-supported [kreinin2017cognition]. Evidence quality is emerging across all of these indications; pivotal multi-site trials have not been completed [peltier2024ptsd_aud].

Does pregnenolone work for memory or cognitive aging?

There is no completed adequately powered randomized trial of pregnenolone for healthy-adult cognitive aging or memory enhancement. The strongest cognitive signal in the human trial literature is the Kreinin 2017 trial in recent-onset schizophrenia, which reported improvement on selected cognitive domains in that specific clinical population [kreinin2017cognition]. Preclinical work on pregnenolone sulfate suggests NMDA-modulated cognitive effects, but that does not translate directly to clinical benefit in healthy adults [rajagopal2018ps_aug].

What about pregnenolone for PTSD or stress?

There is no completed adequately powered RCT of pregnenolone for PTSD. The clinical literature consists of biomarker and neuroimaging studies, neurosteroid levels in PTSD orbital frontal cortex, serum neuroactive-steroid associations with cortical-thickness MRI markers, and fMRI work showing that oral pregnenolone elevates allopregnanolone and modulates emotion-regulation neurocircuitry in healthy adults [cruz2019ptsd_ofc; morey2019cortical_thickness; sripada2013allopreg]. The mechanistic rationale is reasonable but clinical efficacy is not established [peltier2024ptsd_aud].

How does pregnenolone interact with the cannabis system?

Pregnenolone is an endogenous negative allosteric modulator at the CB1 cannabinoid receptor. Vallée and colleagues showed that THC raises brain pregnenolone, which then dampens THC's downstream signaling. In preclinical work, pregnenolone administration blocked cannabinoid-induced acute psychotic-like states in mice and reversed the hyperdopaminergic phenotype of prenatal-THC-exposed offspring [busquets_garcia2017; frau2019_thc; frau2023_thc]. Human clinical trials in cannabis use disorder or cannabis-related psychosis have not been completed [raux2023_crosstalk].

Is pregnenolone safe?

In published randomized trials at trial doses (30, 500 mg/day for 8, 12 weeks), oral pregnenolone has been generally well-tolerated with adverse-event rates comparable to placebo [marx2014poc; ritsner2014kreinin; brown2014bipolar]. The theoretical safety concern is that pregnenolone is upstream of every steroid hormone class, so sustained supplementation can in principle elevate downstream steroid pools [marx2009poc]. Long-term endocrine effects are not well characterized in the trial literature, and patients with hormone-sensitive conditions require particular clinical caution. Pregnancy and lactation are theoretical contraindications pending prescriber risk assessment.

Does RonanRx sell pregnenolone directly to patients?

No. Compounded pregnenolone, where dispensed, requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the OTC supplement market does not meet the patient's need, plus pharmacist review before dispensing. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Pregnenolone

Compounded Pregnenolone is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Pregnenolone, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)