Pinealon (EDR)

A Clinical Learning Guide for Medical Providers

Synthetic Tripeptide Bioregulator (Glu-Asp-Arg) • Neuroprotective • DNA / Epigenetic • Circadian

Evidence base at a glance: A tiny synthetic tripeptide (EDR, ~418 Da) small enough to enter the nucleus and act DIRECTLY on DNA and histones — a receptor-independent epigenetic bioregulator rather than a classic signaling peptide. Three facts dominate: (1) its mechanism is gene-expression regulation — it upregulates endogenous antioxidant enzymes (SOD2, GPx1, catalase), retimes MAPK/ERK stress signaling toward survival, and restores dendritic spines in Alzheimer's and Huntington's models; (2) within this circadian group its role is nighttime DNA repair and recovery — it supports the tryptophan→serotonin→melatonin cascade and is, in the lecturer's clinical experience, often the strongest of these peptides for sleep; and (3) the human evidence is minimal — NO RCTs, no human PK, with essentially all data from a single Russian institute (Khavinson group) without independent replication, plus one 72-patient open-label TBI study. NOT FDA-approved (research compound). Derived from Cortexin, a bovine cortical polypeptide drug used in Russia.

1. Peptide Profile

Name: Pinealon / EDR peptide (also "Pinealon" after its cortical-pineal context)

Classification: Synthetic short-peptide (tripeptide) bioregulator; neuroprotective epigenetic regulator that interacts directly with DNA rather than via receptor-mediated pathways

Structure: Tripeptide — 3 amino acids (Glu-Asp-Arg); ~418 Da — small enough to cross cellular AND nuclear membranes

Source: Synthetic; isolated from Cortexin, a polypeptide drug derived from young bovine cerebral cortex used clinically in Russia for neurological conditions (often alongside Cerebrolysin). Developed by Khavinson et al., St. Petersburg Institute of Bioregulation & Gerontology

Primary mechanisms: Direct DNA/histone binding (epigenetic gene regulation); antioxidant-enzyme upregulation; MAPK/ERK timing modulation; anti-apoptotic (↓ caspase-3/p53); dendritic-spine restoration; serotonin-pathway and PPARα/γ modulation

Routes: Subcutaneous (the lecturer's preferred route); oral and sublingual described in Russian protocols (oral bioavailability documented — unusual for a peptide)

Regulatory status: NOT FDA-approved; not approved by any Western agency. In Russia it is a component of the approved drug Cortexin, but EDR as a standalone is unregistered (research/supplement use)

A Note on Naming and Class

Pinealon belongs to the family of "ultrashort" peptide bioregulators distilled from Russian glandular extracts (the same research program that produced Epitalon from pineal extract). Its defining class feature is that, because of its small size and lack of receptor dependence, it translocates into the nucleus and engages DNA and histones directly — placing it

mechanistically closer to an epigenetic regulator than to a conventional signaling peptide. It is grouped here with the circadian-rhythm peptides because its core value — DNA repair, antioxidant defense, and melatonin/serotonin support — maps onto the nighttime recovery-and-repair window of the circadian clock.

2. Modes of Action & Mechanisms

Pinealon acts as a multi-target, receptor-independent epigenetic regulator. It enters the nucleus, binds DNA and histones, and shifts the transcriptional program of stressed neurons toward survival, antioxidant defense, and synaptic maintenance — rather than scavenging radicals or activating a single receptor.

Direct DNA Binding & Epigenetic Regulation

- **Nuclear entry & DNA binding:** at ~418 Da it crosses cellular and nuclear membranes and binds the DNA minor groove at CG-rich sequences (docking ΔG ≈ −7.5 kcal/mol), destabilizing secondary structure and compacting the molecular coil
- **Histone interactions:** binds linker/core histones H1, H2B, H3, H4 at N-terminal peptide-binding motifs; binding histone H1.3 remodels chromatin at the Fkbp1b locus (a peptidyl-prolyl isomerase regulating neuronal Ca^{2+})
- **Promoter binding sites:** EDR has identified binding sites in the promoters of genes including CASP3, SOD2, GPX1, PPARA (3 sites), PPARG (5 sites), TPH1, APOE, NES (nestin), GAP43, and IGF1 — a coordinated antioxidant, anti-apoptotic, anti-inflammatory, and neuroplasticity program

MAPK/ERK Stress-Response Retiming

Under oxidative stress (homocysteine exposure) in cerebellar granule cells, Pinealon delays ERK1/2 activation from ~2.5 minutes to ~20 minutes. This temporal shift converts a rapid, transient response that favors the apoptotic cascade (high caspase-3) into a sustained, adaptive one that favors survival — effectively giving the cell time to catch up with the oxidative insult.

Antioxidant, Anti-Apoptotic & Neuroplastic Effects

Pathway / Action	Effect
Antioxidant gene upregulation	Raises endogenous SOD2, glutathione peroxidase (GPx1), and catalase at the transcriptional level (not direct radical scavenging); levels restored toward those of hypoxia-resistant animals; normalized in hypoxic neurons
Anti-apoptotic	Reduces caspase-3 and p53 pro-apoptotic activity under stress, shifting the balance toward neuronal survival
Dendritic-spine restoration	Restores mushroom (active-synapse) spines in amyloid- and Huntington-stressed neurons — the morphological basis of learning and memory (see Evidence Profile for figures)
Serotonin pathway	Increases serotonin synthesis in cortical neuron cultures via a binding site in the TPH1 (tryptophan hydroxylase) promoter —

Pathway / Action	Effect
	supporting the tryptophan→serotonin→melatonin cascade relevant to mood, sleep, and AD
PPARα / PPARγ modulation	Normalizes PPARA/PPARG expression under stress; PPARα curbs inflammation and Aβ42 production, PPARγ activation reduces BACE1 (β-secretase) — limiting amyloid-plaque formation

What makes Pinealon distinctive: it is a receptor-independent epigenetic regulator that works from inside the nucleus, simultaneously tuning antioxidant, anti-apoptotic, anti-inflammatory, serotonergic, and neuroplasticity genes. Its circadian relevance comes from supporting nighttime DNA repair and the serotonin→melatonin cascade — the recovery-and-repair half of the clock — rather than from acting as a melatonin agonist itself.

3. Points of Clinical Relevance

1. Its mechanism is gene regulation, not receptor signaling — effects build over weeks

Because Pinealon works by entering the nucleus and reprogramming gene expression (antioxidant enzymes, anti-apoptotic and neuroplasticity genes), its benefits accrue over weeks of cumulative transcriptional change rather than producing an acute, perceptible effect. Set patient expectations accordingly: this is long-term neural resilience, not same-day cognitive enhancement.

2. Effects are sub-perceptual — frame it as neuroprotection, not a nootropic "boost"

Patients typically feel no acute subjective change. The intended outcome is protection and repair (reduced oxidative DNA damage, preserved dendritic spines), so the honest framing is neuroprotective support rather than a stimulant-like cognitive enhancer. This also shapes monitoring — track biomarkers and longitudinal cognition, not day-to-day "feel."

3. Its circadian role is nighttime DNA repair and the serotonin→melatonin cascade

Within this peptide group, Pinealon's place is the night-time recovery window: DNA repair, antioxidant defense, and support of the tryptophan→serotonin→melatonin pathway. In the lecturer's clinical experience it has often produced better sleep benefit than Epitalon — though he notes the opposite is true for some patients and that the question genuinely needs more data.

4. Subcutaneous is more reproducible than oral, despite documented oral activity

Oral bioavailability is reported (unusual for a peptide), but the lecturer does not use the oral route and finds subcutaneous dosing more powerful and reproducible — noting that even a tripeptide remains susceptible to GI peptidases and degradation. His clinical dosing centers on

~3 mg/day SC. He is explicit that he is not dismissing oral use by those who get results, but that SC is where he has seen the clearest effect.

5. Oxidative-stress / DNA-damage states are where it is most useful — track 8-OHdG and MDA

Pinealon's clearest rationale is in states of significant oxidative stress and DNA damage — fatigue, mitochondrial strain, and the epigenetic changes that accompany them. The key biomarkers to follow are 8-hydroxydeoxyguanosine (8-OHdG, oxidative DNA damage) and malondialdehyde (MDA, lipid peroxidation), supplemented by inflammatory cytokines (IL-1β, IL-6, TNF-α).

6. It pairs naturally with Epitalon (and Semax/Selank) — but combination data are theoretical

Mechanistically, Pinealon (downstream neuronal protection) and Epitalon (upstream pineal/circadian restoration) are complementary and come from the same research program — a pairing the lecturer finds especially compelling, with intermittent rather than daily use to allow adaptation. Other rational pairings include Vesugen (vascular delivery), and Semax/Selank (acute cognitive/anxiolytic support). No controlled combination studies exist.

4. General Dosing & Delivery Options

No FDA-approved dosing exists; all protocols are empirical, from published Russian protocols and open-label clinical use, with no Western RCTs and no human PK to validate them. For educational context only.

Routes & Protocols (empirical)

Route	Dose	Frequency	Duration / Cycle
Subcutaneous (preferred)	1–2 mg (up to ~3 mg/day in clinical use)	Once daily	10–20 days; the lecturer often runs ~3 mg/day SC over longer cycles (up to ~6 wk or 3 mo)
Oral	0.2 mg	Twice daily	10–20 days (oral bioavailability documented; less favored by the lecturer)
Sublingual	0.2 mg	Twice daily	10–20 days
Cycling	—	Every 3–6 months	Repeat course; e.g. 12 weeks on / ~6 weeks off, or intermittent (non-daily) dosing to allow adaptation

Administration Notes

- **Timing:** morning for cognitive-support emphasis; evening for sleep emphasis — used both ways depending on the dominant goal
- **Onset:** antioxidant-gene upregulation builds over weeks; benefits are best understood as long-term neural resilience rather than acute effects
- **Route caveat:** as a small peptide it is still vulnerable to GI peptidases — the SC route is regarded as more reproducible than oral
- **Combination practice:** the lecturer favors intermittent use and pairings (Pinealon + Epitalon; Pinealon + Semax/Selank) tailored to the endpoint, especially for sleep and neuroprotection

Research Concentrations (for context)

Study Model	Conc / Dose	Key Result
Hippocampal neurons (AD)	200 ng/mL	+71% mushroom spines
5xFAD mice (AD)	400 µg/kg IP	+11% CA1 spine density (p=0.039)
YAC128 neurons (HD)	200 ng/mL	Spine density restored to wild-type
Induced neurons (aging)	10 µg/mL	−23% oxidative DNA damage; +46% dendrite length
TBI patients (n=72)	0.2 mg oral BID	Memory improved in 59.4%

5. Evidence Profile

Evidence tier distribution (7 references): 0 RCTs; 1 open-label human study (72 patients, TBI/cerebrasthenia); the remainder in vitro and animal, with reviews. The entire base originates from the Khavinson group / St. Petersburg Institute, with no independent replication and no human pharmacokinetics.

Antioxidant & DNA Protection (in vitro / animal)

- Transcriptional upregulation of SOD2, GPx1, and catalase, with enzyme levels in hypoxic neurons restored toward hypoxia-resistant baselines
- In aged induced neurons (2024): ~23% reduction in oxidative DNA damage (8-OHdG) and ~46% increase in dendrite length

Dendritic-Spine Restoration (in vitro / animal)

Model	Finding
Hippocampal neurons + Aβ42 (AD, in vitro)	EDR 200 ng/mL increased mushroom spines by 71%, returning counts to normal; comparator KED gave only ~20%
5xFAD mice (AD, animal)	400 µg/kg IP daily × 2 months increased CA1 dendritic spine density by 11% (p=0.039); LTP tended to increase

Model	Finding
YAC128 striatal neurons (HD, in vitro)	EDR 200 ng/mL restored spine density to wild-type levels with functional mushroom morphology

Neuroendocrine / Gene-Regulatory (in vitro)

– Increased serotonin synthesis via TPH1 promoter binding (supporting the serotonin→melatonin cascade); MAPK/ERK retiming toward survival; normalization of PPARα/PPARγ expression with downstream reduction of Aβ42/BACE1 signaling

Human / Clinical (limited)

Study Type	Population	Key Finding
Open-label (n=72)	TBI / cerebrasthenia	Memory improved in 59.4% of patients; no adverse events reported
Primate study (2025)	Aging laboratory primates	Confirmed cognitive improvement with EDR (emerging, single-group)

Critical gaps: ZERO randomized controlled trials and NO human pharmacokinetic data; no independent replication outside the originating institute; no long-term safety data; no characterized drug interactions; and no pregnancy/lactation or pediatric data. The single human study is open-label and unblinded. The oral-versus-subcutaneous efficacy question is unresolved and, per the lecturer, needs delineation — with SC appearing more reproducible.

6. Clinical Considerations

Contraindications & Cautions

– **Pregnancy & lactation:** no safety data — avoid
– **Active autoimmune neurological disease:** unknown immune modulation — avoid
– **Concurrent immunosuppressive therapy:** unknown interaction — caution
– **Patients requiring evidence-based treatment:** no RCTs exist — not an appropriate substitute for validated therapy
– **Pediatric:** not studied — avoid

Drug Interactions

No interaction database or human PK exists; interactions are entirely uncharacterized. Use caution with immunosuppressants and any agents affecting neurological or immune function, and document all concurrent peptides given the lecturer's emphasis on combination use.

Monitoring Parameters (theoretical — not trial-validated)

Biomarker / Test	Rationale	Frequency
8-OHdG (urine/serum)	Oxidative DNA damage — the key mechanistic marker	Baseline + post-cycle

Biomarker / Test	Rationale	Frequency
MDA (malondialdehyde)	Lipid peroxidation / oxidative-stress progression	Baseline + post-cycle
Melatonin (salivary)	Circadian rhythm / pineal function	Baseline + post-cycle
Cognitive testing (e.g. MoCA)	Memory, attention, executive function	Baseline + every 3 months
EEG alpha index	Neuroplasticity / integrative function	Baseline + post-cycle
Inflammatory cytokines	IL-1β, IL-6, TNF-α — inflammatory load	Baseline + post-cycle

Typical cadence: establish baseline (oxidative-stress and inflammatory markers, cognition, melatonin, EEG if available), reassess at the end of each 10–20 day cycle (sleep, tolerability), and repeat biomarkers/cognition across 3-month cycles to gauge individual response. The lecturer stresses documenting route, dose, cycle duration, and observations for every patient so the field can eventually accumulate replicable data.

Safety Profile

- No significant adverse effects reported in preclinical (cell-culture/animal) studies; no AEs in the 72-patient open-label study; oral 0.2 mg BID × 10–20 days well tolerated
- Effects are sub-perceptual with no acute subjective changes reported
- Long-term human safety is unknown; all reassurance derives from a single research group without independent replication

Regulatory Status

Pinealon is NOT FDA-approved and is not reviewed by any Western regulator. In Russia it exists as a component of the approved drug Cortexin, but EDR as a standalone is unregistered. Any human use is investigational/off-label and requires explicit, documented informed consent — including that all data come from a single institute without independent replication.

7. Final Note

Pinealon is the neuroprotective, DNA-repair member of this circadian peptide group: a tripeptide small enough to enter the nucleus and act directly on DNA and histones, retuning the transcriptional program of stressed neurons toward antioxidant defense, anti-apoptosis, and synaptic maintenance. Its circadian relevance is the nighttime recovery window — DNA repair and the serotonin→melatonin cascade — and in clinical practice it is often a strong sleep-supportive option, sometimes outperforming Epitalon, sometimes not. Its mechanistic story is genuinely distinctive: a receptor-independent epigenetic regulator with a coordinated, multi-gene neuroprotective signature and reproducible dendritic-spine restoration in Alzheimer's and Huntington's models.

The honest framing is that Pinealon sits almost entirely in the preclinical realm. There are no RCTs, no human pharmacokinetics, and essentially all data come from a single Russian institute without independent replication — the lone human study being a 72-patient open-label TBI trial. Practical uncertainties remain, most notably whether oral delivery matches subcutaneous; the

lecturer favors SC at ~3 mg/day as more reproducible, while explicitly respecting practitioners who get results orally and inviting them to contribute data.

For the clinician, Pinealon is best understood as a research-stage neuroprotective bioregulator with a compelling epigenetic mechanism and a defensible role in oxidative-stress and DNA-damage states (tracking 8-OHdG and MDA), most naturally used short-term and cyclically — often paired with Epitalon — and only investigationally, with full informed consent and careful documentation of route, dose, and response.

Bottom line: A tiny synthetic tripeptide (EDR, Glu-Asp-Arg) that enters the nucleus and acts as a receptor-independent epigenetic regulator — upregulating antioxidant genes (SOD2, GPx1, catalase), retiming MAPK/ERK toward survival, reducing caspase-3/p53, restoring dendritic spines in AD/HD models, and supporting the serotonin→melatonin cascade for nighttime repair and sleep — but with ZERO RCTs, no human PK, and all data from a single institute without independent replication (one 72-patient open-label TBI study). Subcutaneous (~3 mg/day) appears more reproducible than oral. Pairs naturally with Epitalon. Research/investigational only; NOT FDA-approved.

Selected References

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For educational and research purposes only. Not medical advice. Pinealon (EDR) is NOT FDA-approved and is a research compound; in Russia it exists only as a component of Cortexin, not as a registered standalone drug. There are no randomized controlled trials, no human pharmacokinetic data, and essentially all evidence derives from a single research group without independent replication (one 72-patient open-label study). Long-term safety is unknown. Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.