DSIP

A Clinical Learning Guide for Medical Providers

Delta Sleep-Inducing Peptide • Nonapeptide (WAGGDASGE) • Sleep / Stress-Adaptogen / Neuroprotective

Evidence base at a glance: A multifunctional nonapeptide named for sleep — but its biology remains, after ~50 years, a genuine "riddle." Three facts dominate: (1) despite the name, its SLEEP evidence is real but modest and inconsistent in humans (small 1980s trials; the strongest RCT showed weak effects), and the DSIP–sleep link is openly debated; (2) its BEST-documented effects — replicated across multiple labs — are stress adaptation, mitochondrial protection, and antinociception, not sleep; and (3) its fundamental biology is unresolved — no gene, no receptor, and no precursor protein have ever been identified. NOT FDA-approved; the FDA flags immunogenicity risk and (per the lecturer) has currently REMOVED it from the Category 1 bulk list, so it should not be compounded at present, pending re-evaluation. A non-sedative peptide best viewed as an intermittently-used adaptogen with possible sleep, withdrawal, and pain applications — all investigational.

1. Peptide Profile

Name: DSIP — Delta Sleep-Inducing Peptide

Classification: Multifunctional regulatory nonapeptide; non-sedative sleep modulator, stress adaptogen, and neuroprotective/antinociceptive agent. Structure is unique among known peptide families

Structure: Nonapeptide — 9 amino acids (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu; WAGGDASGE); ~849 Da; amphiphilic; crosses the blood–brain barrier

Discovery & source: Isolated 1977 by the Schoenenberger–Monnier group (Basel) from the cerebral venous blood of sleeping rabbits

Distribution: Found (free and bound) in hypothalamus, limbic system, pituitary, peripheral organs, plasma, CSF, and human breast milk; co-localizes with ACTH/MSH/TSH/MCH in pituitary and with glucagon in pancreas

Half-life: ~15 minutes in vitro; rapidly degraded by aminopeptidases; may complex with carrier proteins in vivo

Regulatory status: NOT FDA-approved; flagged for potential immunogenicity. Per the lecturer, currently removed from the FDA Category 1 bulk-substances list (not compoundable at present) and under re-evaluation

The Unresolved "Riddle"

DSIP is unusual among therapeutic peptides in that, despite nearly five decades of study, no DSIP gene, no specific receptor, and no precursor protein has ever been identified. It exists in free and protein-bound forms and acts on multiple systems, yet how it is made and how it signals remain undefined — a point reviewers (Kovalzon & Strekalova, 2006) summarize bluntly

as a “still unresolved riddle.” This uncertainty is the backdrop for every claim that follows: the effects are observed empirically, but the underlying biology is incompletely understood.

2. Modes of Action & Mechanisms

DSIP acts across several systems at once — balancing excitation and inhibition, engaging the endogenous opioid system, modulating neuroendocrine output, and supporting mitochondrial/antioxidant function. Many actions are inferred (no receptor is known), so mechanisms are best read as well-observed effects rather than fully mapped pathways.

Excitation–Inhibition Balance (NMDA / GABA)

- **NMDA modulation:** blocks NMDA-activated potentiation in cortical and hippocampal neurons, reducing excessive excitatory neurotransmission (possible anti-excitotoxic neuroprotection)
- **GABA enhancement:** potentiates GABA-activated inhibitory currents in hippocampus and cerebellum
- **Net effect:** dual GABA enhancement + NMDA blockade shifts neural tone toward inhibition — an adaptogen-like rebalancing that underlies both sleep induction and anticonvulsant/neuroprotective effects

Endogenous Opioid System (Antinociception)

- No direct binding to opioid receptor subtypes; instead stimulates calcium-dependent Met-enkephalin release from the brainstem (in vitro)
- Antinociception is supraspinal (ICV/IC routes effective, intrathecal not), naloxone-blockable, and absent in morphine-tolerant mice — consistent with indirect opioid-system engagement

Neuroendocrine Signaling

Axis / Hormone	Effect	Evidence
Growth hormone	Dose-dependent GH release (ICV, rats) via a dopaminergic mechanism + direct pituitary action; anti-DSIP antiserum blocks sleep-related GH release	Animal
Somatostatin	Inhibits somatostatin secretion (disinhibiting GH)	Animal
LH	Stimulates LH release	Animal
HPA / ACTH-cortisol	Decreases basal corticotropin in animals, BUT a human study showed no effect on CRH-induced ACTH/cortisol — conflicting	Conflicting

Mitochondrial, Antioxidant & Stress-Response Pathways

- **Oxidative phosphorylation:** raises phosphorylating respiration (V3) ~10–20% and ADP phosphorylation ~10–30% in rat brain mitochondria; improves respiratory control; pretreatment fully prevented hypoxia-induced mitochondrial dysfunction
- **Antioxidant enzymes:** increases SOD and glutathione peroxidase activity and inhibits lipid peroxidation (especially under stress)

- **Metabolic switch:** shifts metabolism from anaerobic back to aerobic (oxidative phosphorylation) under hypoxia — central to its adaptogenic profile
- **MAPK / GILZ homology (mechanistic theory):** DSIP is regulated by glucocorticoids and is homologous to glucocorticoid-induced leucine zipper (GILZ), which blocks Raf-1→ERK activation — a possible anti-inflammatory link to the MAPK cascade (direct evidence limited)

Sleep Induction (a non-sedative mechanism)

For sleep specifically, the proposed mechanism is the GABA/NMDA rebalancing above (more inhibitory tone, less excitatory drive), supported by influence on pineal N-acetyltransferase (the melatonin pathway) and on circadian locomotor/transmitter rhythms. The defining feature is that DSIP promotes delta (slow-wave) sleep WITHOUT classic sedation — distinct from benzodiazepines and barbiturates. Importantly, reviewers note the DSIP–sleep link itself is "extremely poorly documented and still weak," and animal data conflict (slow-wave promotion in some studies, REM effects in cats, no effect in others; a U-shaped dose-response; synthetic analogues stronger than native DSIP).

Mechanistic takeaway: DSIP's through-line is rebalancing — of excitation/inhibition, of stress metabolism, and of neuroendocrine tone — which is why its most reproducible effects are adaptogenic (stress and mitochondrial protection) rather than narrowly hypnotic. The sleep effect is real but mechanistically softer and less consistent than the name implies.

3. Points of Clinical Relevance

1. It is named for sleep, but sleep is NOT its strongest evidence

The most reproducible, multi-lab DSIP effects are stress adaptation, mitochondrial protection, and antinociception — not sleep. Human sleep data come from small 1980s trials, and the strongest randomized controlled trial (Bes 1992) showed weak, equivocal effects. Frame DSIP to patients as a multifunctional adaptogen that may aid sleep, not as a reliable sleep drug.

2. It is non-sedative — a different tool than hypnotics

DSIP promotes delta (slow-wave) sleep without the sedation, dependence, or next-day grogginess profile of benzodiazepines/barbiturates. This makes it conceptually attractive but also means it does not "knock a patient out"; the effect is a gentle shift toward sleep-permissive neural tone.

3. Not first-line for sleep — layer it after the fundamentals

The lecturer is explicit that DSIP is not a first-line sleep intervention: sleep hygiene, CBT-I, and evidence-based pharmacotherapy come first. DSIP is positioned as an adjunct to consider after those foundations, used judiciously rather than indiscriminately.

4. Tolerance appears to develop — cycle it, don't dose it nightly

A practical clinical observation: used too frequently, DSIP seems to lose effect (possible receptor attenuation, though no receptor is known). Because effects can persist for multiple nights after a single dose, the lecturer suggests a loading approach — perhaps daily for the first

3–5 days, then spacing to roughly twice weekly — rather than continuous nightly use. Intermittent use is framed as the key to keeping it effective.

5. The most compelling signals are adaptogenic and (historically) in withdrawal/pain

Where DSIP looks most interesting is as a stress/mitochondrial adaptogen and in two striking but dated open-label datasets: opioid and alcohol withdrawal (97% and 87% symptom relief in 1980s series) and chronic pain (~90% pain reduction in an open pilot). These are low-tier designs, but the effect sizes are notable enough that the lecturer flags them as deserving renewed study.

6. Sourcing and the current FDA status are gating issues

DSIP is not FDA-approved, the FDA flags immunogenicity risk, and — per the lecturer — it has been removed from the Category 1 bulk list (so it should not be compounded at present, pending re-evaluation). Research-grade material raises purity and immunogenicity concerns. Practically: confirm current regulatory status, source only pharmaceutical-grade peptide with a certificate of analysis, document investigational use, and monitor for immunogenic reactions early.

4. General Dosing & Delivery Options

No FDA-approved dosing exists; all dosing is from research literature and empirical clinical practice. Note the route discrepancy: the IV research dose (25 nmol/kg) extrapolates to ~1,600 µg SC in an 80 kg adult, far above the 100–500 µg SC range used in practice — so doses across routes are not directly comparable. For educational context only.

Dosing by Route

Route	Dose	Context / Notes
Subcutaneous (clinical practice)	100–500 µg daily	Common empirical range; morning, or after dinner/before bed for sleep emphasis
Intravenous (research)	25 nmol/kg	Used in human sleep & withdrawal studies; ≈ ~1,600 µg in an 80 kg adult
Intranasal (research)	120 µg/kg	Rat stroke study; crosses the blood–brain barrier

Cycling & Timing (the practical key)

- **Anti-tolerance cycling:** consider daily for the first ~3–5 days, then space to roughly twice weekly — effects can persist for multiple nights after a single dose; continuous nightly use risks loss of effect
- **Timing:** can be given any time of day; dose in the evening/before bed when sleep is the goal
- **Pairing:** sometimes rotated with sleep/repair peptides (e.g. Epitalon, Pinealon) within a broader sleep program — combinations are empirical, with no controlled data

Administration & Sourcing Notes

- **Reconstitution:** lyophilized powder reconstituted with bacteriostatic water (some products supplied pre-buffered); handle gently
- **Sourcing:** pharmaceutical-grade peptide with a certificate of analysis is essential — research-grade material carries purity and immunogenicity concerns
- **Regulatory check:** verify current FDA/compounding status before use, given the Category 1 removal noted above

5. Evidence Profile

Evidence tier distribution (17 references): a mix of small human clinical trials (mostly 1980s, small n, often open-label), animal studies, in vitro work, and reviews — with NO large-scale RCTs and no long-term safety data. The strongest, most replicated findings are preclinical (stress/mitochondrial adaptation); the human sleep evidence is the weakest part of the picture.

Sleep — Human (small, dated, mixed)

Study	Design	Key Finding
Schneider-Helmert 1981	6 volunteers, IV, double-blind crossover	Increased total sleep time, faster onset, better efficiency
Kaeser 1984	7 severe insomniacs, open-label, 10 injections	Sleep normalized in 6/7; benefit lasted 3–7 months; better daytime mood
Bes 1992	16 chronic insomniacs, double-blind, placebo-controlled	Higher efficiency / shorter latency vs placebo — but weak, equivocal (strongest RCT)

Sleep — Animal (conflicting)

- Iyer 1988: in sleep-deprived rats, recovery slow-wave sleep and GH both rose and BOTH were blocked by anti-DSIP antiserum — implicating DSIP as a physiological stimulus for SWS and sleep-related GH (in rats)
- Conflicting reports: SWS promotion with REM suppression in some studies; more pronounced REM effects in cats; no sleep correlation in others; U-shaped dose-response; synthetic analogues stronger than native DSIP

Non-Sleep Applications (often the stronger signal)

Domain	Finding	Tier
Withdrawal (Dick 1983/1984)	Opiate 97% / alcohol 87% symptom relief; benefit in 48/49 (98%) in earlier series; rapid onset	Clinical (open-label)
Chronic pain (Larbig 1984)	~90% reported significant pain reduction; depressive episodes also fell	Clinical (open pilot)

Domain	Finding	Tier
Stroke (Tukhovskaya 2021)	Intranasal DSIP recovered motor coordination by day 7 (rat MCAO); infarct smaller but NS	Animal
Anticonvulsant (Stanojlovic 2004/05)	DSIP and analogues raised delta/theta power and cut seizure incidence/grade; DSIP-12 > native	Animal
Stress / mitochondria	Stress-protective across many models; antioxidant enzyme ↑; anaerobic→aerobic switch — best-replicated effects	Animal / In vitro
Geroprotection (single study)	Lifetime dosing: −2.6x tumor incidence, −22.6% chromosome aberrations, +24.1% max lifespan (mice)	Animal (needs replication)

Critical gaps: No DSIP gene, receptor, or precursor protein identified after ~50 years; NO large-scale RCTs; no long-term safety data; no standardized pharmaceutical-grade formulation; and conflicting sleep data across species. The striking withdrawal/pain results are open-label and decades old, never replicated in controlled trials. The geroprotective/anticancer data rest on a single mouse study. The best-supported claims (stress/mitochondrial adaptation) remain preclinical.

6. Clinical Considerations

Contraindications & Cautions

- **Pregnancy & lactation:** theoretical — avoid (no safety data)
- **Cancer history:** theoretical concern — avoid
- **Concurrent sedatives / anxiolytics:** unknown interactions — use caution given additive CNS effects
- **Pediatric / other populations:** not established (a small Deltaran series in children exists but is not a safety basis)

Drug Interactions

Drug interactions are unstudied and no interaction database exists. Exercise particular caution with other CNS depressants (sedatives, anxiolytics, alcohol). Document all concurrent agents.

Monitoring Parameters

Parameter	Target / Note	Rationale
Immunogenic reactions	Watch early in treatment	FDA-flagged immunogenicity; higher with research-grade material
Sleep quality	Sleep diary / scale; pre/post	Primary subjective endpoint for sleep use
Tolerability	Headache, nausea, vertigo	Reported transient effects

Parameter	Target / Note	Rationale
Tolerance / response	Effect maintained across cycles?	Apparent tolerance — guides cycling
Stress / fatigue markers	Subjective + oxidative markers if used	Adaptogenic/mitochondrial use case

Cadence: baseline (sleep or stress/fatigue measures as appropriate, regulatory/source verification), reassess after the initial loading days and across cycles for both response and possible tolerance, and monitor for immunogenic reactions throughout — especially early. Document route, dose, cycle structure, and observations for every patient.

Safety Profile

- Described as “incredibly safe” (Pollard & Pomfrett, 2001); no lethal dose found in animal studies; no significant adverse effects in the small clinical trials
- Minor, transient effects reported in humans: headache, nausea, vertigo
- Key caveats: FDA-flagged immunogenicity risk; long-term safety entirely unknown; no standardized formulation; tolerance reports conflict

Regulatory Status

DSIP is NOT FDA-approved and has no validated clinical indication. The FDA has flagged potential immunogenicity, and — per the lecturer — DSIP has been removed from the Category 1 bulk-substances list, meaning it should not be compounded at present and is under re-evaluation (status could change). Any human use is investigational and off-label and requires explicit, documented informed consent; verify current status before use.

7. Final Note

DSIP is one of the more paradoxical peptides in this field: named for sleep, yet its sleep evidence is the weakest part of its profile, while its best-replicated effects — stress adaptation, mitochondrial protection, and antinociception — have little to do with the name. Mechanistically it works by rebalancing rather than suppressing: enhancing GABAergic tone while dampening NMDA-driven excitation, engaging the endogenous opioid system indirectly via Met-enkephalin, modulating GH and other neuroendocrine axes, and — most durably — supporting mitochondrial oxidative phosphorylation and antioxidant defense under stress and hypoxia. It promotes delta sleep without sedation, which is conceptually appealing, but the human sleep data are small, old, and inconsistent.

The honest framing is that DSIP’s fundamental biology is still unsolved — no gene, receptor, or precursor after roughly fifty years — and its most eye-catching clinical results (near-total relief in opioid and alcohol withdrawal; ~90% pain reduction) come from uncontrolled 1980s studies that were never followed up. As a sleep tool it is not first-line and appears to develop tolerance, so it is best used intermittently and after sleep-hygiene fundamentals. As an adaptogen for stress and mitochondrial resilience — the lecturer’s area of greatest interest — it has the strongest preclinical support and the clearest rationale for renewed study.

For the clinician, DSIP is a research-stage, multifunctional peptide to be used — if at all — investigationally, with current regulatory status confirmed, pharmaceutical-grade sourcing,

intermittent dosing, and monitoring for immunogenic reactions. Its promise lies less in being a sleep aid than in being a stress/mitochondrial adaptogen whose biology we still do not fully understand.

Bottom line: A unique multifunctional nonapeptide (WAGGDASGE) that promotes delta sleep WITHOUT sedation but whose human sleep evidence is small, dated, and weak. Its best-replicated effects are stress adaptation, mitochondrial protection, and antinociception; its most striking (open-label, 1980s) results are in opioid/alcohol withdrawal and chronic pain. No gene, receptor, or precursor identified after ~50 years; no large RCTs; no long-term safety data. NOT FDA-approved — immunogenicity-flagged and currently off the Category 1 compounding list (per the lecturer), pending re-evaluation. Not first-line for sleep; appears to develop tolerance, so use intermittently. Research/investigational only.

Selected References

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