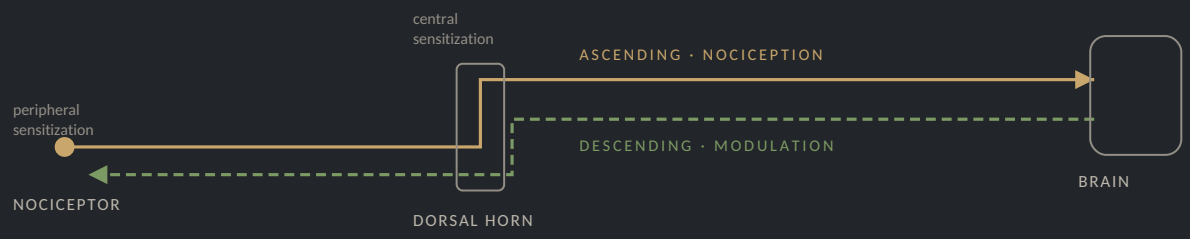
THE PHYSICAL ROOT

CLINICIAN GUIDE · EVIDENCE-BASED

What Pain Science *Actually* Tells You About Your Patient

A working field guide to nociception, sensitization, descending modulation, and mechanistic pain descriptors — built from the JOSPT *Pain Science in Practice* series and written for the clinician who has to use it on Monday morning.



PERIPHERAL SENSITIZATION · CENTRAL SENSITIZATION · DESCENDING MODULATION · NOCIPLASTIC PAIN

Audience Physical therapists, PTAs, and movement-based clinicians

Format Long-form clinical read with pull-out action blocks

Evidence level Research-backed, with limitations named explicitly

Reading time About 25 minutes · Clinic card on the final page

CONTENTS

What's in here

Every section ends with something you can do in the room. If you only have five minutes, read the boxes.

SECTION 01

The gap this fills

Most of us were trained to find the dysfunction and correct it. That model is not wrong so much as it is incomplete — and the incompleteness shows up in the patients who don't get better.

I was taught the biomechanical model well. Find the movement fault, restore the mechanics, the pain resolves. It works often enough that it feels like a law. Then you accumulate a caseload, and you start collecting the patients it does not explain: the imaging-negative back that has hurt for four years, the post-op knee whose swelling resolved but whose pain did not, the shoulder that hurts more with light touch than with load, the ankle that is objectively stable and subjectively terrifying.

The proposed linear relationship between movement and chronic musculoskeletal pain does not fit contemporary pain science.[1,2] That is not a rhetorical statement — it is the reason a whole editorial series exists in *JOSPT*. Morten Hoegh and colleagues wrote nine pieces between 2022 and 2025 whose entire purpose was to give clinicians the neuroscience underneath the clinical picture, in a form we can reason with.[3]

> **SET EXPECTATIONS HONESTLY**
>
> Pain is far more than neuronal activity. This guide covers only what neuroscience contributes. Psychological, social, occupational, and biographical factors are not a footnote to the mechanism — they are co-equal drivers, and the neuroscience does not fully embrace the lived experience of chronic pain.[8] Read this as one column of a wider account, not the account.

This guide is my synthesis of that series, reorganized around what a clinician actually does in an hour with a patient. I have kept the mechanisms because mechanisms are how you reason when the protocol runs out. I have kept the limitations because a mechanism you overstate becomes a mechanism you misuse.

Why not just teach metaphors?

Pain neuroscience education has been in our vocabulary for two decades, and metaphors are essential to it. But there is a real dispute in the literature about whether metaphors alone serve patients well, and a good argument that clinicians should understand the scientific principles rather than the metaphorical stand-ins.[4,5] The clearest evidence of that problem is the most common misuse in our profession: attempting to *diagnose* "central sensitization syndrome," which continues to lack scientific support.[6,7]

You cannot recognize a misuse of a concept you only know as a metaphor. That is the case for learning the underlying science.

IN THE ROOM

Three sentences that change the tone of a first visit, and are all defensible:

- "Pain is real whether or not I can find damage on a scan. Those are two different questions."
- "Hurt and harm are related, but they're not the same signal."
- "My job is to figure out what's driving this — and there's usually more than one thing."

What follows is organized in the order the science builds: what a signal is, how it gets amplified in the periphery, how it gets amplified centrally, how the body turns the volume down, how researchers measure any of it, and finally how all of that collapses into the three clinical labels you will actually write in a note.

SECTION 02

The vocabulary that changes your reasoning

Nociception is not pain. Get this one distinction fully into your clinical reasoning and half of the confusing patients stop being confusing.

Stimulus and perception are different objects

Hoegh opens the series with the falling tree.[9] A tree falls in an empty forest: particles move, and that is measurable and quantifiable. But sound is a feature of a conscious mind. The moving particles are the *stimulus*. The experience of sound is the *perception*. Stimuli can be objectively measured. Perception is subjective, always.

Map that onto us. Nociception — the neural process of encoding noxious stimuli — is the stimulus side. Pain is the perception side. Activating a nociceptor does not produce pain the way pressing a key produces a note. Nociceptive stimuli do not equal pain; they activate nociceptors. That is it.

> *You can try to rule out nociception in the clinic. You can never disqualify the experience of pain described by a patient.*
>
> HOEGH, JOSPT 2022 — PAIN SCIENCE IN PRACTICE, PART 1

The four verbs

Transduction is the conversion of one form of energy — chemical, thermal, mechanical — into an electrical signal. This is where the "alarm system" metaphor comes from: specific, intense stimuli open receptors. Transduction produces hyperexcitability through ion flux or through metabolic changes inside the neuron.

Transmission is the action potential and what follows it. If transduction depolarizes the membrane enough, a voltage-gated ion channel along the axon opens and an action potential fires. When it reaches the central terminal in the dorsal horn, voltage-gated channels admit calcium, vesicles of neurotransmitter release into the synaptic cleft, and a second-order neuron may fire — projecting via the lateral spinothalamic tract toward the thalamus.

Modulation is the healthy nervous system adapting to changes in and around the body. It can go either way — pro-nociceptive or anti-nociceptive — and it is more transient than most clinicians assume. Sensitization phenomena live here.

Perception is the conscious experience. It is not a readout of the other three.

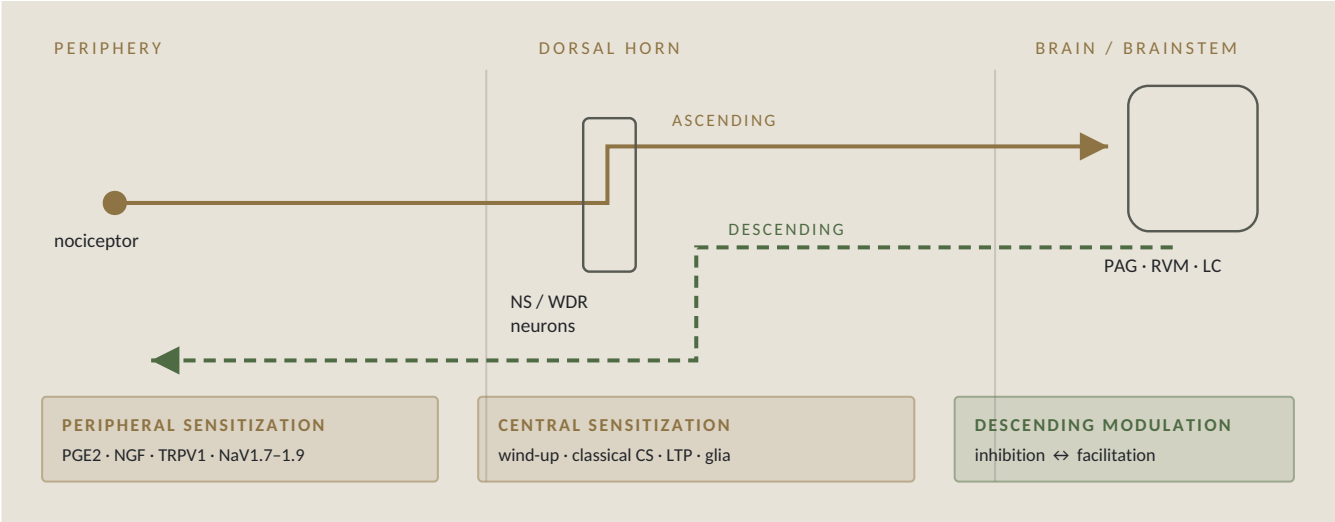


FIGURE 1 · THE ORIENTATION MAP. Three zones, two directions. Everything in this guide sits somewhere on this diagram. Peripheral sensitization lowers the threshold at the nociceptor. Central sensitization increases synaptic efficacy in the dorsal horn. Descending modulation is the brainstem's bidirectional control over the whole thing — and it is the system your exercise prescription is aimed at.

The fibers, in the only detail that matters clinically

C fibers, A-delta fibers, and A-beta fibers respond in varying degrees to chemical, thermal, and mechanical energy. The clinically useful distinction is not the letter — it is the threshold. Some neurons fire to gentle stimuli. Others fire only to intense stimuli, because they carry high-threshold receptors. Those are nociceptors.

One genetics finding is worth carrying because it settles an argument you will eventually have. NaV1.7 is a voltage-gated sodium channel on nociceptive neurons. Mutations in *SCN9A*, which encodes it, can produce congenital insensitivity to pain or, in the other direction, erythromelalgia.[10,11] The nociceptive system is real, physical, and consequential. Nothing in modern pain science says "it's all in your head" — the opposite, in fact.

> **A LIMITATION WORTH REMEMBERING**
>
> Most human research on nociception comes from studies of intact or damaged **skin**, not deep tissue. We treat muscle, tendon, joint, and bone. When you extrapolate a skin finding to a rotator cuff, you are extrapolating — say so in your own head before you say it to a patient.

TERMINOLOGY — IASP DEFINITIONS, VERBATIM WHERE IT MATTERS

Sensitization
Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.

Peripheral sensitization
Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to stimulation of their receptive fields.

Central sensitization
Increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input.

Hyperalgesia
Increased pain from a stimulus that normally provokes pain.

Allodynia
Pain in response to a stimulus that does not normally provoke pain.

Primary vs. secondary hyperalgesia
Primary is hyperalgesia in the injured area; secondary is hyperalgesia in an *uninjured* area surrounding it.

Phenotypic change
A change in observable characteristics — e.g., light touch that used to be felt as touch is now felt as pain.

MONDAY MORNING

- Stop writing "pain generator" as if you located one. Write what you actually observed: "local tenderness over the lateral epicondyle, reproduced with resisted extension."
- When a patient reports sensory change — numbness, tingling, burning, patches of altered feeling — follow it with a neurological exam. Do not file it under "irritability."[12]
- Remember that not all sensory change is pathological. Modulation is part of a functioning nervous system, not evidence of a broken one.

SECTION 03

Receptors and ion channels — why "nonspecific" isn't nothing

Pharmacology gets to claim specificity. We usually can't. That is a real difference — and it is a much smaller problem than it sounds.

What a receptor actually is, in three types

An ion channel is a gated protein that lets hydrophilic molecules cross the lipid membrane and change the membrane potential. A receptor is a protein complex that recognizes a specific signaling molecule. Sensory neurons carrying receptors and channels instead of an encapsulated sensory organ are the free nerve endings — some with high-threshold receptors (nociceptors), some with low.

RECEPTOR TYPE	HOW IT WORKS	WHY YOU CARE
Ligand-gated	Key-in-lock. A ligand binds and directly opens an ion channel. Fast, highly specific.	NMDA (glutamate) — central to wind-up and to spinal "memory."
Metabotropic (GPCR)	Acts via second messengers — enzymes and ions. Can rapidly change how the cell behaves.	EP2 (prostaglandin) — involved in both peripheral *and* central sensitization.
Receptor tyrosine kinase (Trk)	Responds to growth factors via complex signaling cascades; governs neuroplasticity and regeneration.	TrkA (nerve growth factor) and TrkB (BDNF) — the maintenance and adaptation machinery.

The specificity argument, and the answer to it

An NSAID inhibits cyclooxygenase metabolites including prostaglandin E2, which is an agonist at the EP2 receptor, which is pivotal in sensitization.[13] That is a clean causal chain, and it is why pharmacology can say exactly what it did.

Nonpharmacological therapy almost certainly targets several mechanisms at once, and it is unclear exactly how our therapies work at a molecular level. That is not the same as saying they don't work. It means the specific effect is unknown.[14] And the nonspecific portion is not trivial: expectation effects can be large enough to abolish or amplify the measurable analgesic benefit of an intravenous opioid.[15] Meanwhile, the recommended nonpharmacological options — education, exercise, manual therapy — carry a markedly lower risk of adverse events.[16]

> *Education, exercise, cognitive behavioral therapy, manual therapy, and pharmacotherapy may work on the same system — alternate routes to the same goal.*
>
> ADAPTED FROM HOEGH, JOSPT 2022 — PART 2

"Why does it hurt to move?"

Mechanical transduction was the last piece to fall into place. Piezo ion channels are now well established as central to it — the 2021 Nobel Prize covered TRPV1 and Piezo2 — but how much Piezo contributes to musculoskeletal pain conditions specifically is still unknown. Which means the best scientific answer to the most common question your patients ask remains **sensitization**: activity- or transcription-dependent changes in nociceptive neurons. Pain is a dynamic process, not a fixed property of a tissue.

IN THE ROOM

When a patient asks how manual therapy or exercise "works," you do not have to bluff a specific mechanism and you do not have to shrug. Try:

"We know these treatments change how the nervous system processes signals — probably through several pathways at once. We can't point to one molecule the way a drug company can. What we can say is that the effect is real, the risk profile is very low, and we can measure whether it's helping *you* in a few weeks."

That answer is honest, it respects the patient's intelligence, and it sets up an outcome-based conversation instead of a mechanism-based one.

MONDAY MORNING

- Stop over-claiming mechanism in your patient education. "This releases the adhesion" is a claim you cannot support. "This changes how sensitive the area is right now" is one you can.
- Deliberately use the context you have — clear rationale, confident delivery, a plan the patient believes in. Context effects are physiology, not deception. Do not fabricate; do frame well.
- Judge your interventions on measured effect and safety, not on mechanistic elegance.

SECTION 04

Peripheral sensitization — the mechanism behind "it's tender right there"

In most cases, tissue injury leads to inflammation, and inflammation leads to sensitization. That is the neuroscience explanation for why we hurt when we're injured — and it is the most clinically legible mechanism in the whole series.

Sensitization is a term, not a diagnosis

This is the first thing to get right. Sensitization is a neurophysiological term that can only be applied when both the input and the output of the neural system under study are known. Input means quantifying the stimulus and the resulting action potentials. In human research that is rare; in the clinic it is impossible. What IASP allows is that hyperalgesia and allodynia can be considered *clinical correlates* of sensitization — correlates, not equivalents.

The cascade, in the order it happens

Tissue damage releases algogens (prostaglandins), cytokines (TNF-alpha), and neurotrophic factors (nerve growth factor). These bind receptors on the neuron surface and activate second messenger systems — calcium, cyclic AMP, inositol triphosphate — which are the communication channel between the cell's environment and its interior. Those messengers switch on enzymatic processes: protein kinase A, phospholipase A2 and C, calcium/calmodulin-dependent kinase.

In C fibers the downstream effect is phosphorylation of TRPV1 receptors and facilitation of voltage-gated sodium channels NaV1.7–1.9. Net result: a lower threshold and more action potentials for the same stimulus. That barrage of input into the dorsal horn is what kickstarts secondary hyperalgesia mechanisms centrally.

Neurogenic inflammation and the axon reflex

Part of the inflammatory response is generated by the nerve itself. When peptidergic C fibers are activated, an antidromic signal travels from branch points *back out* to the peripheral terminals, releasing calcitonin gene-related peptide and substance P into the tissue. Those peptides cause vasodilation, smooth muscle contraction, and increased capillary permeability — local edema and erythema — and they recruit mast cells to degranulate, activate macrophages and glia, and attract more immune cells.

You have seen this a thousand times: scratch skin, watch the flare spread beyond the scratch. That is the axon reflex. And critically, neurogenic inflammation is **vital for tissue healing** and for resolving the inflammatory response. Negative feedback loops mean it does not continue without relevant stimuli — it dissipates.

> *Inflammation is not the enemy. It is the repair process, and the nerve is a participant in it — not just a bystander reporting on it.*

Silent nociceptors and the chili receptor

Nearly all human C fibers express TRPV1, the transient receptor potential vanilloid receptor 1 — the same receptor capsaicin activates. Most C fibers are also mechanosensitive. But a subset are mechanoinsensitive: in their naïve state they do not respond to stimuli at all, and they only begin responding to noxious stimuli, including mechanical ones, once sensitized. These are the "silent nociceptors," and they are a clean explanation for why an area can become painful to pressure that never used to be.

TRPV1 also runs in the other direction. Intense, prolonged stimulation desensitizes it — which is the basis for high-concentration capsaicin patches in neuropathic pain, where depending on concentration the effect ranges from inactivating channels to ablating axon terminals.[17]

What this means for palpation

Peripheral sensitization is never visible to the naked eye. What you can look for is hyperalgesia — abnormal evoked pain — and then place it in the context of the patient's history. Local, relevant pain responses plus a relevant history can be interpreted as a strong clinical suspicion of inflammation from overloading, injury, or pathology.[18] Note what that sentence does *not* say: it does not say you have found the tissue. Many orthopaedic tests are not tissue-specific. Test structural integrity separately when it is relevant.

IN THE ROOM — EXPLAINING TENDERNESS WITHOUT FRIGHTENING ANYONE

Do not say: "You're really tender there — that tells me there's a lot of damage."

Say: "That area is more sensitive than it should be right now. That's your nervous system turning up the gain on the tissue while it settles down — it's a normal part of healing, and it's not a measure of how much damage there is."

Then, if you tested integrity: "I also checked whether the structure itself is holding up, and that part looks fine. Those are two separate questions and they got two separate answers."

WHEN A PATIENT ASKS ABOUT NSAIDS

You can explain the mechanism: NSAIDs partly work by blocking the synthesis of prostaglandin E2, reducing the pain associated with inflammation and peripheral sensitization. You should also know, and can say, that even short-term NSAID use is associated with increased thrombotic risk.[19] Then route the decision to their prescriber. Being able to discuss the mechanism without prescribing is exactly the interdisciplinary posture the series argues for.

MONDAY MORNING

- **Map the tender area, don't just note it.** Where the hyperalgesia sits relative to the injury is diagnostic information (see Section 05).
- **Separate the two exams.** Pain provocation tests and structural integrity tests answer different questions. Document them separately.
- **Reframe soreness as expected, not as damage** — but only when the integrity testing supports it.

- **Consider silent nociceptors** when a patient reports new pain to pressure in an area that was previously fine and imaging is unremarkable. That is a mechanism, not a mystery.

SECTION 05

Central sensitization — what it is, and what it is not

This is the most important discovery in contemporary pain science and the most abused term in our profession. Both statements are true, and holding them together is the whole skill.

The anatomy you need

Most nociceptive input arrives in laminae I–II of the dorsal horn — the superficial laminae — and is transmitted to subcortical areas via the spinothalamic tract, mainly by **nociceptive-specific (NS) neurons**, which respond only to high-threshold stimuli. In lamina V, high-threshold input *and* low-threshold input (light touch) converge onto **wide-dynamic-range (WDR) neurons**. That convergence is the anatomical basis for a great deal of clinical confusion, and once you see it, referred pain and spreading pain stop being mysterious.

When NS or WDR neurons are stimulated repeatedly, they undergo physiological changes that leave them sensitized — outlasting the initial stimulus by seconds, hours, or longer. This is activity-dependent central sensitization: driven and maintained by input.

Two kinds of plasticity, three named phenomena

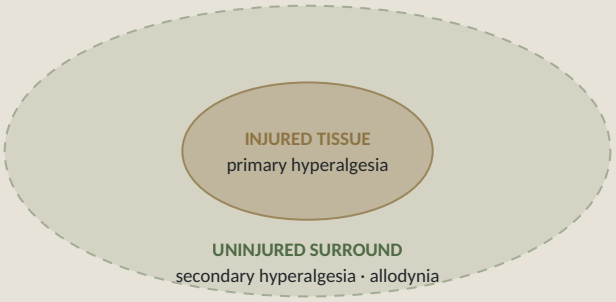
Homosynaptic plasticity means a specific synapse got stronger — the same pathway, facilitated. **Heterosynaptic** plasticity means the sensitization spreads to inputs that were *not* stimulated, so fibers that previously could not depolarize the second-order neuron now can. That is how an A-beta fiber carrying light touch ends up producing pain.

PHENOMENON	TYPE	DURATION	WHAT IT MEANS CLINICALLY
Wind-up	Homosynaptic	Seconds	Repetitive low-frequency C-fiber input (<5 Hz) progressively removes the Mg^{2+} block on NMDA receptors; more action potentials for the same stimulus. Human correlate: temporal summation. **Very short-lived and unlikely to play a substantial role in chronic MSK pain.**
Classical central sensitization	Homo- *and* heterosynaptic	Tens of minutes; as long as inflammation persists	Woolf, 1983. Spreads to A-beta inputs. **Secondary hyperalgesia and allodynia are its clinical signs.** Plausibly involved in chronic pain.
Long-term potentiation (LTP)	Homosynaptic	30 min – 3 h (early phase)	Driven by intracellular calcium rise and kinase activation. Requires high-frequency C-fiber input (~100 Hz) that may not be physiological in an intact animal. Plausibly involved in chronic pain.

The map on the skin

Injure a patch of skin and you get a predictable geography. The *damaged* area becomes sensitive to light touch (allodynia), heat (heat hyperalgesia), and pinprick (primary hyperalgesia) — likely a

consequence of both peripheral and central sensitization. Evoked pain in the *surrounding, uninjured* skin — secondary hyperalgesia and allodynia — is closely linked to central sensitization.



INSIDE THE ZONE

Allodynia to light touch, heat hyperalgesia, pinprick hyperalgesia. Both peripheral and central mechanisms contribute.

OUTSIDE THE ZONE

Evoked pain in tissue that was never injured. Closely linked to central sensitization. This is the finding to map.

FIGURE 2 · THE MAP YOU CAN DRAW WITH A FINGERTIP. Tenderness confined to the symptomatic tissue points toward peripheral mechanisms. Tenderness that extends well beyond it points toward central ones. Outline it, date it, and re-test it — a shrinking secondary zone is real clinical information. You are observing a correlate, not measuring sensitization.

That distinction is the most portable idea in this section. Tenderness confined to the injured tissue points toward peripheral mechanisms. Tenderness that spreads well beyond it points toward central ones. You are not measuring central sensitization; you are observing a correlate. But it is a correlate you can map with a fingertip in ninety seconds.

Glia — the half of the story we ignored

The importance of non-neuronal cells in pain is now beyond speculative. Astrocytes influence synaptic transmission — clearing unused neurotransmitter from the cleft — and form the structural part of the blood-brain barrier. Microglia are the CNS counterpart to macrophages, responding to threat signals by releasing cytokines that further activate neuronal and non-neuronal cells.

Both homosynaptic and heterosynaptic LTP between C fibers and NS neurons depend to varying degrees on microglial and astrocytic activation.[20] Glia can trigger long-lasting changes in nociceptive pathways that then persist independently of glial activation — a possible mechanism for widespread pain, and the closest thing we have to an explanation for how nociception leaves a "memory trace" in nociceptive pathways.

THE FIVE CAVEATS — READ THESE BEFORE YOU USE THE TERM WITH A PATIENT

- **You cannot measure it.** Central sensitization cannot be directly measured in humans; it requires recording the neural event. Everything clinical is a surrogate.
- **The surrogates aren't exclusive.** Temporal summation, secondary hyperalgesia, and allodynia are typical of central sensitization but not unique to it.
- **It is not static or permanent.** It is essentially considered reversible, and in the absence of a continuing trigger it may return to normal thresholds.
- **The system fights back.** When LTP is produced by C fibers, a countermeasure is produced in the same synapse — homeostatic mechanisms that may prevent or limit central sensitization.

- **It is not a diagnosis.** Attempts to diagnose "central sensitization syndrome" continue to lack scientific support.[6,7,21] It is unlikely to be the single cause of chronic pain, and it is unclear that reversing it — if we could measure and treat it — would help people with chronic musculoskeletal pain.[22]

Pain reduction and management of disability should remain the clinical goals. Correlates of central sensitization are, at best, indirect measures of treatment effect.

HOEGH, JOSPT 2023 — PART 4

IN THE ROOM — WHAT TO SAY INSTEAD OF "YOU HAVE CENTRAL SENSITIZATION"

"Your nervous system has gotten better at producing this pain signal — the same way it gets better at anything you practice. That's a real, physical change in how signals get processed in your spinal cord. It's also the kind of change that can go the other direction, which is what we're going to work on."

You have described the mechanism accurately, given it legitimacy, and left the door open. You have not handed the patient a label that implies a permanent condition, and you have not claimed a measurement you did not take.

MONDAY MORNING

- **Map primary vs. secondary distribution.** Outline where evoked pain sits relative to the injured or symptomatic tissue. Reassess it. A shrinking secondary zone is meaningful clinical information.
- **Stop diagnosing "central sensitization."** Describe findings — "allodynia to light touch extending 6 cm proximal to the incision" — and let the findings do the work.
- **Track pain and function, not surrogates.** If your outcome measure is a sensitization proxy, you have chosen the wrong outcome measure.
- **Do not tell patients this is permanent.** The science does not support that, and the message itself is a pro-nociceptive intervention.

SECTION 06

Descending modulation — the system your treatments actually recruit

If Sections 04 and 05 were about the volume going up, this is the section about the knob that turns it down — and it is the section with the most direct implications for how you prescribe exercise.

The system

The descending pain modulatory system (DPMS) comprises many, likely functionally overlapping, pathways descending from cortical and subcortical regions — anterior cingulate cortex, midbrain, pons, medulla — to the dorsal horn. Recurring names: the periaqueductal gray, the rostral ventromedial medulla including the nucleus raphe magnus, the locus coeruleus (A6), the A5 nucleus, and the subnucleus reticularis dorsalis.

Two features matter more than the anatomy:

It is bidirectional. The pathways are both facilitatory and inhibitory. In healthy individuals the balance is dynamic, so the organism can adapt to ongoing stimuli and context. Descending modulation is not an on/off phenomenon — it is a balance, and that balance is what allows a person to experience the world normally.

Neurotransmitters are not inherently inhibitory or facilitatory. This is a correction worth internalizing, because our profession is full of "serotonin is calming" reasoning. Whether a transmitter inhibits or facilitates is determined by the receptor subtype and by the location of the receptor. Labeling a neurotransmitter's action as inhibitory or facilitatory is misleading.[23] And disease state can flip the balance: the 5-HT7 receptor may be upregulated in the dorsal horn in rodents with nerve injury, so injury can change the response to serotonin toward pro-nociceptive.

Two findings that established the system exists

Placebo analgesia is opioidergic. In the late 1970s, volunteers who had undergone molar extraction were given placebo and then naloxone. About one in three reported stable or decreased pain after placebo. When those responders received naloxone, their pain rose to match the non-responders'. Placebo analgesia was mediated by endogenous opioids.[24] That study is the origin of the claim that we have an endogenous pain control system — and it is physiology, not a rhetorical flourish about the mind.

Diffuse noxious inhibitory controls (DNIC). In 1979, recordings from WDR neurons in anesthetized rats showed that the response to one noxious stimulus was inhibited when a second noxious stimulus was applied concurrently to a remote body region.[25] Pain inhibits pain, and it does so across dermatomes — hence "diffuse." The circuit is subserved mainly by noradrenaline, historically considered antinociceptive via the spinal alpha-2 adrenergic receptor.

Exercise-induced hypoalgesia — read this part carefully

Most people without chronic pain experience increased tolerance to noxious stimuli after even a single bout of exercise. This is exercise-induced hypoalgesia (EIH), and it is believed to reflect DPMS activity. But the honest version has three qualifiers a PT needs:

- **It is short-lived.** Like DNIC, the effect can only be measured for a few minutes once exercise stops.
- **It is not a useful standalone measure** of the effect of exercise on chronic pain.[26] It may, however, be a proxy for flare-up during activity — impaired EIH has been found in individuals reporting increased low back pain during acute exercise.[27]
- **Phenotype matters at group level.** There is a proposed spectrum from pro-nociceptive to anti-nociceptive phenotypes, which partly explains group differences between athletes and people with chronic pain.[28]

Here is the part that should change your practice. For many people living with chronic pain, exercise without pain is not an option. But sedentary behavior is a poor alternative — it can lead to DPMS dysfunction, with dominant descending facilitation, reduced inhibition of nociception, and reduced efficacy of the opioidergic system.[29]

> *Regular physical activity is beneficial even if immediate pain relief does not follow. Inactivity is likely to make things worse.*
>
> HOEGH & BANNISTER, JOSPT 2024 — PART 6

That single sentence resolves the most common impasse in chronic pain rehab. The patient exercises, does not feel better, and concludes exercise is not for them. You now have a mechanistic answer: the benefit you are building is in the modulatory system, it accrues over time, and the absence of an immediate analgesic response is not evidence of failure.

And if the barrier is that they cannot tolerate the activity at all, there is a therapeutic window worth using. A rigorous trial with more than 300 participants found that TENS — but not sham-TENS or no TENS — reduced movement-evoked pain and fatigue in people with widespread pain.[30] Not a cure. A door-opener.

> IN THE ROOM — THE EXERCISE CONVERSATION FOR A PATIENT WHO "TRIED EXERCISE AND IT DIDN'T HELP"
>
> "There's a system in your brainstem and spinal cord whose whole job is turning pain signals down. It works better in people who move regularly — and it works worse in people who've had to stop moving, which is most people with long-standing pain. That's not a character flaw, it's a physiological consequence."
>
> "So here's the deal I'm making with you: I'm not promising you'll feel better after each session. Some days you won't. What I'm telling you is that regularity is what rebuilds that system, and the payoff shows up over weeks, not minutes. Our job together is to find a dose you can repeat."

MONDAY MORNING — DOSING EXERCISE THROUGH A DPMS LENS

- **Prioritize repeatability over intensity.** The mechanism you're targeting responds to regular activity over time. A dose that gets done four times a week beats a dose that gets abandoned.
- **Set the expectation explicitly at visit one** that immediate relief is not the criterion for success. If you don't say it, the patient's own experience will teach them the wrong lesson.
- **Use flare-up patterns as data, not failure.** Someone whose pain reliably increases during acute exercise may have impaired EIH — that changes your entry point, not your destination.
- **Use modalities as windows, not as treatment.** TENS, heat, manual therapy — if it lets someone complete the activity that actually builds the system, it earned its place. Say that out loud so the patient doesn't mistake the window for the room.
- **Treat prolonged sedentary behavior as an active clinical problem** with its own mechanism, not as a lifestyle footnote.

SECTION 07

How modulation is measured — and why none of it is a clinic tool yet

You will see these acronyms in papers and in course marketing. Knowing what they measure — and what they don't — is how you avoid buying a device that cannot do what it claims.

Measuring the activity of individual DPMS circuits in humans is not currently possible. What researchers can test is the *net* response of inhibitory and facilitatory actions, using standardized paradigms.

PARADIGM	HOW IT WORKS	WHERE IT STANDS
Conditioned pain modulation (CPM)	A test stimulus alone, then the test stimulus concurrent with or immediately after a remote noxious conditioning stimulus. The difference is the CPM effect. Human proxy for DNIC.	~80% of healthy individuals show a positive effect; ~20% show none or worse. Pressure-cuff versions have excellent reliability. But variability exceeds the factors normally controlled for, and a recent review could not establish clinically relevant predictive value. **Not a clinic tool.**
Temporal summation of pain (TSP)	~10 pinpricks delivered faster than one per second produce disproportionately more pain than one prick. Proposed proxy for wind-up.	Not purely spinal — the PAG and anterior cingulate cortex participate. Unclear whether it can measure treatment effect, predict outcomes, or guide treatment choices.
Offset analgesia	Three heat stimuli; the middle one ~1°C hotter. Most healthy people report disproportionate relief when it steps back down.	Mechanisms unknown; likely activates pathways distinct from CPM. Research use only.
Stress-induced analgesia	Cognitive or social stressors — timed arithmetic, public speaking — rather than sensory stimuli. A "top-down" paradigm.	Results have not supported the hypothesis: neither pain threshold nor CPM response changed in healthy students exposed to a stressful task. May be more variable, or may influence pain in a way evoked-pain testing does not capture.
Placebo analgesia	Verbal suggestion, conditioning, or both. Reliable across methods; boosted when suggestion and conditioning are combined.	Opioidergic; involves the dorsolateral funiculus plus multiple cortical and subcortical areas. Notably, the circuits underpinning placebo analgesia and the CPM response are *different*.

TWO WORDS PEOPLE USE INTERCHANGEABLY AND SHOULDN'T

Placebo response
An improvement in pain observed after a treatment intended to be a placebo — e.g., the placebo arm of a trial.

Placebo effect
The *difference* in pain reduction between no treatment and the placebo condition. This isolates the analgesic effect from natural history, regression to the mean, and other confounders.

> *CPM, EIH, TSP and offset analgesia appear to work on different neural pathways — not the same one. No single paradigm characterizes "this patient's modulation."*

That finding is the practical bottom line of this section. It is why a course that sells you a bedside "central sensitization test" is selling you more certainty than exists. It is also why, given how complex the organism is, it is not surprising that any one paradigm has different efficacy in different people.

IF YOU ARE CONSIDERING QUANTITATIVE SENSORY TESTING IN YOUR CLINIC

It is legitimate to use simple sensory testing to *describe* a patient — mapping allodynia, noting hyperalgesia, comparing side to side. That is clinical examination and it belongs in your practice.

It is not currently legitimate to use it to classify a patient into a mechanism, predict their treatment response, or select their intervention. The predictive validity for individual decisions has not been established. Describe; don't classify.

MONDAY MORNING

- Add a cotton wisp and a neurological pin to your table. Two minutes of sensory mapping tells you more than most special tests.
- Always compare to the contralateral side and to a remote uninvolved area. A finding without a comparison is a number without units.
- Record findings descriptively and re-test them. Change over time is the useful part.
- When you read a study using CPM or TSP, check whether the authors are describing a group difference or claiming an individual prediction. Those are very different claims.

SECTION 08

What patients ask about drugs — and what you should be able to answer

We don't prescribe. We do get asked, constantly, and we are often the clinician a patient sees most often. Understanding the mechanism of what they're taking is part of interdisciplinary competence — and it reduces the risk of monotherapy.

CLASS	MECHANISM RELEVANT TO THE DPMS	WHAT YOU SHOULD KNOW CLINICALLY
Opioids	Bind receptors throughout the neuroaxis; the dominant one is the mu-opioid receptor (MOR). Spinally, they attenuate input presynaptically (C fiber) and inhibit action potentials postsynaptically (NS neuron). Closely tied to the RVM, whose "ON" cells correlate with hyperalgesia and "OFF" cells with hypoalgesia. During inflammation, OFF cells may become hyperpolarized while ON cells are hyperactivated — driving hyperalgesia.	Effects are dose-dependent on *all* cells expressing MOR, including respiratory and digestive systems. That is the mechanistic account of the risk profile, and it is a better patient explanation than moralizing about opioids.
Gabapentinoids (gabapentin, pregabalin)	Despite the name, no direct effect on GABAergic mechanisms. They inhibit trafficking of voltage-gated calcium channels to the membrane of spinal neurons, and have supraspinal effects including inhibiting descending facilitation via spinal 5-HT3 receptors.	Consistently antinociceptive in animal models; **variable in human and clinical studies**, with dose-dependent side effects. Discontinuing pregabalin is associated with withdrawal symptoms in many patients — relevant if your patient mentions stopping abruptly.
SNRIs (e.g., duloxetine)	Inhibit presynaptic reuptake of noradrenaline and serotonin, prolonging their availability in the synapse — including in the dorsal horn. Both are essential components of the DPMS.	The precision-medicine hypothesis is attractive but unresolved: duloxetine appeared more efficacious in painful diabetic neuropathy with lower-than-average CPM responses, but CPM did not correlate with duloxetine's effect in painful knee osteoarthritis. It is unclear whether SNRIs work by enhancing CPM-pathway activity.

IN THE ROOM — THE SCRIPT FOR "SHOULD I TAKE THIS?"

"That's your prescriber's call and I won't get in the middle of it. What I can tell you is roughly how it's supposed to work, so the conversation you have with them is a better one."

Then give the mechanism in one sentence, name the trade-off honestly, and finish with: "Bring that up with them and tell me what they say — it changes how I dose your program."

That last clause is not filler. It is true, it signals that you are on the same team as the prescriber, and it makes the patient the courier of information rather than the arbiter of it.

MONDAY MORNING

- Ask what they're taking, at what dose, and whether it's helping — every intake. It is DPMS-relevant information, not just a checkbox.

- Flag abrupt discontinuation of gabapentinoids back to the prescriber rather than reassuring the patient yourself.
- Know that "the drug didn't work" is common and mechanistically unsurprising — the number needed to treat with 600 mg pregabalin for neuropathic pain in polyneuropathy is 6.
- Never characterize a medication as unnecessary. Characterize your own contribution as complementary.

SECTION 09

Mechanistic descriptors — nociceptive, neuropathic, nociplastic

This is where all of the above turns into something you write in a note. It is also where the honest answer is "partly."

Descriptors are not mechanisms

Keep these separate or you will misuse both. **Pain mechanisms** are the biological and physiological processes that generate or maintain pain — wind-up, LTP, peripheral sensitization. They exist at a molecular, cellular, and systems level, and they are studied to develop treatments. **Mechanistic pain descriptors** are labels used to sort clinical presentations into clusters presumed to share underlying mechanisms. They are studied to figure out how best to subgroup patients so treatment can be matched.

The descriptors are presumed to be associated with different mechanisms. They are not mechanisms themselves.

DESCRIPTOR	IASP DEFINITION	THE CLINICAL READING
Nociceptive	Pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors.	Contrasts with neuropathic. Describes pain occurring with a *normally functioning* somatosensory nervous system. Note that the contemporary use conflates the older "inflammatory" and "nociceptive" categories.
Neuropathic	Pain caused by a lesion or disease of the somatosensory nervous system.	The best-defined descriptor and the most straightforward to *rule out*. It is a clinical description, not a diagnosis, and requires a demonstrable lesion or disease meeting established neurological criteria. **Symptoms or signs alone — including touch-evoked pain — do not justify the term.**
Nociplastic	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage activating peripheral nociceptors, and no evidence of disease or lesion of the somatosensory system causing the pain.	Introduced by IASP in 2016, originally as a placeholder for pain best explained by altered nociceptive function with hypersensitivity. Patients can have a combination of nociceptive and nociplastic pain.

Grading neuropathic pain — the one algorithm worth memorizing

Neuropathic pain is the descriptor where the clinical criteria are actually usable, and where a PT can add real value by grading rather than guessing.[31] The pain must have persisted at least three months before the grading system is applied, and alternative plausible causes must first be excluded.

GRADE	WHAT IT REQUIRES
Possible	A history of pain in a neuroanatomically plausible distribution, with a history suggestive of a relevant lesion or disease of the somatosensory nervous system.
Probable	The above, plus clinical examination findings: one or more assessments demonstrating **partial or complete loss of function** (e.g., hypoesthesia) corresponding to the suspected lesion or pathology.
Definite	Confirmation by a diagnostic test demonstrating the lesion or disease. This criterion can be met even if the examination criterion is not, when the lesion or disease clearly explains the symptoms.

Notice what the examination criterion is looking for. Not pain. **Loss** of function — hypoesthesia, reduced pinprick, reduced cold sensation, reduced vibration — in a distribution that matches a plausible lesion. This is where the profession most often goes wrong: burning pain, shooting pain, and touch-evoked pain get labeled neuropathic on the strength of the descriptor words alone, without any sensory loss and without a plausible lesion.

FIVE REASONS DESCRIPTORS ARE NOT YET A CLEAN CLASSIFICATION SYSTEM

- **Animal-to-human translation.** Mechanistic research uses "clean" models — sciatic nerve ligation, joint injury — that ignore the mixed, messy reality of human pain, and species differences in how pain is expressed, and how age, sex, gender, context and learning act differently across species.
- **They overlap.** There is currently no consensus or evidence that nociceptive and neuropathic pain can be discriminated from nociplastic pain. Mixed presentations are the norm, and a condition can start nociceptive-dominant and develop nociplastic features over time.
- **They capture only part of the lived experience.** Descriptors alone cannot explain why some people respond well when most do not.
- **The clinical tests don't exist.** Nociception and sensitization cannot be directly measured in living humans; we rely on indirect signs like allodynia and secondary hyperalgesia.
- **"Nociplastic" risks staying a placeholder.** If pain is called nociplastic merely by excluding the other two, the term does no mechanistic work — and its enigmatic character makes it impossible to measure clinically. Published clinical criteria have been criticized on exactly these grounds.

So what are descriptors good for?

Two things, both real.

First, ruling out neuropathic pain. The grading algorithm works, it is defensible, and getting it right changes management and referral. This is the highest-yield thing in this section.

Second, choosing a toolbox. Identifying the predominant descriptor informs which category an intervention should come from — for example, treatments that address the source of nociception when the picture is nociceptive-dominant. It tells you which shelf to reach for. It does not tell you which tool.

And nociplastic pain, whatever its limitations as a mechanism, already earns its keep as something else: *an evidence-based explanation that helps make sense of pain in the absence of known pathology.* That is not nothing. For a patient who has been told for years that their scans are clean and

therefore nothing is wrong, a legitimate physiological account is itself a clinical intervention. Just don't treat it as a target you know how to hit.

IN THE ROOM — EXPLAINING NOCIPLASTIC PAIN WITHOUT HEDGING OR OVERCLAIMING

"Your imaging is clean, and I believe your pain. Those two things aren't in conflict. There's a recognized category — the technical term is nociplastic pain — for pain that comes from changes in how the nervous system processes signals rather than from damage in the tissue. It's a real, named, researched category, not a way of saying we can't find anything."

"What I'll be honest about is that we don't yet have a way to measure it directly, and we don't have a treatment aimed specifically at it. What we do have is a lot of evidence about what helps people in your situation function better — and that's what I'm going to work on with you."

MONDAY MORNING

- **Run the neuropathic grading on anyone with pain of 3+ months and a plausible nerve story.** Test for sensory *loss*, not just sensory unpleasantness.
- **Write "predominantly" or "features of," not a category.** "Predominantly nociceptive presentation with features suggesting nociplastic contribution" is accurate. "Nociplastic pain" as a stand-alone diagnosis is not.
- **Re-evaluate the descriptor over time.** Presentations migrate. A descriptor set at intake and never revisited is a stale assumption.
- **Use the descriptor to pick a toolbox, then judge the tool by the patient's response.**

SECTION 10

Monday morning — putting it together

Everything above collapses into a reasoning sequence, a short list of exam additions, and a set of sentences. This is the part I'd actually hand a new grad.

The reasoning sequence

STEP	THE QUESTION	WHAT IT CHANGES
1	Are there red flags or signs of serious pathology?	Everything. Screen first, always. Nothing in this guide replaces that.
2	Is the structure intact? Test integrity separately from provocation.	Determines whether "tender" can be safely reframed as sensitivity rather than damage.
3	Where does evoked pain sit relative to the symptomatic tissue — confined, or spreading well beyond it?	Primary vs. secondary distribution. Points toward peripheral vs. central contribution. Map it; re-test it.
4	Is there sensory *loss* in a neuroanatomically plausible distribution, with a plausible lesion or disease?	Runs the neuropathic grading. Changes management, referral, and often prognosis conversation.
5	Is there ongoing nociceptive drive that plausibly explains the presentation? Load history, inflammatory pattern, mechanical behavior, 24-hour pattern.	If yes, the nociceptive toolbox comes first — load management, tissue capacity, inflammation.
6	If neuropathic is excluded and nociceptive drive doesn't account for the picture — what's left?	Nociplastic features. Use it as an explanation and a framing, not as a treatment target.
7	What is this person's activity history, sleep, and load tolerance?	DPMS capacity. Drives dosing, expectation-setting, and the timeline you promise.
8	What outcome will I actually measure?	Pain and function. Not surrogates. Set it at visit one and re-measure on schedule.

Exam add-ons that take under three minutes

- **Light touch mapping** with a cotton wisp — outline any area where touch is unpleasant or painful. Compare to contralateral.
- **Pinprick** with a neurological pin — looking for both increased (hyperalgesia) and *decreased* (hypoalgesia) response. The decrease is the neuropathic-relevant finding.
- **Cold** — a cold metal object or cold roller. Note altered or absent perception.
- **Vibration** where a nerve lesion is plausible.
- **Tenderness geography** — outline the tender zone with a washable marker or on a body chart, relative to the symptomatic structure. This is the single highest-yield addition on this list and it takes ninety seconds.

- **Remote comparison site** — always test one uninvolved region so your findings have a reference.

Language: the swap table

RETIRE THIS	USE THIS
"You have central sensitization."	**"Your nervous system has become more efficient at producing this signal — and that can change."**
"Your pain is out of proportion to the findings."	**"The amount of pain and the amount of tissue change are two different measurements. Both are real."**
"There's nothing structurally wrong, so…"	**"The structure is holding up well — which tells us the problem is in how the signal is being processed, not in the tissue failing."**
"This releases the adhesion / resets the joint."	**"This changes how sensitive the area is right now, which gives us a window to load it."**
"You need to push through the pain."	**"We're looking for a dose you can repeat. Some sessions won't feel better afterward — that's expected and it's not failure."**
"Your pain is chronic, so it's permanent."	**"These changes are considered reversible. That's the whole reason we're working on it."**
"It's neuropathic — it's burning and shooting."	**"Let me check whether there's actual sensory loss here, because that's what distinguishes nerve involvement from nerve-sounding pain."**

What to stop doing

- **Stop diagnosing central sensitization.** It cannot be measured in humans, and the syndrome construct lacks scientific support.
- **Stop equating tenderness with tissue damage.** Peripheral sensitization is the more parsimonious explanation for most local tenderness, and it is not a measure of damage.
- **Stop using a single questionnaire to declare a patient "central."** The surrogates aren't exclusive and the paradigms don't converge.
- **Stop over-claiming your mechanism.** Claim the effect and the safety profile — those you can defend.
- **Stop treating the absence of immediate analgesia as treatment failure** in someone you're rebuilding activity tolerance in.
- **Stop calling pain neuropathic on the basis of descriptor words.** Grade it.

DOCUMENTATION PHRASING YOU CAN PASTE

- "Hyperalgesia to pressure localized to [structure]; no extension into surrounding uninvolved tissue. Integrity testing [negative/positive] for [structures tested]."
- "Allodynia to light touch extending approximately [X] cm beyond the symptomatic region, consistent with secondary hyperalgesia distribution. Mapped and to be re-assessed [date]."
- "Sensory examination: [intact / reduced pinprick and cold perception] in [distribution]. Neuropathic pain grading: [possible / probable / definite / criteria not met]."

- "Presentation is predominantly [nociceptive/neuropathic] with features suggestive of [nociplastic] contribution. Descriptor to be re-evaluated at reassessment."
- "Patient educated that immediate post-exercise analgesia is not the criterion for program success; expectation set for benefit accruing over weeks with regular activity."

SECTION 11

What we still cannot do

A guide that only tells you what the science supports is half a guide. Here is the honest ledger — and I'd rather you carry these limits than carry false precision.

WE CANNOT MEASURE NOCICEPTION IN THE CLINIC

Nociception is almost impossible to measure objectively in a clinical setting. You can build a case that nociception is or is not a dominant driver from history and examination. You cannot demonstrate it.

WE CANNOT MEASURE SENSITIZATION IN LIVING HUMANS

Central sensitization requires recording the neural event. There is no way to measure whether the responsiveness of nociceptive neurons in the CNS has changed in a living person. Every clinical claim about it is an inference from a non-exclusive surrogate.

MOST HUMAN NOCICEPTION DATA COMES FROM SKIN

We treat deep tissue. The extrapolation is usually reasonable and it is still an extrapolation.

ANIMAL MODELS DON'T CARRY OVER CLEANLY

The assumption that targeting a molecular mechanism of nociception will produce effective pain treatment is generally tested in clean, single-injury models. That ignores mixed mechanisms in humans, species differences in pain behavior, the gap between acute pain models and lived chronic pain, and differential effects of age, sex, gender, context and learning.

WE CANNOT YET DISCRIMINATE THE THREE DESCRIPTORS

There is no consensus or evidence that nociceptive and neuropathic pain can be reliably discriminated from nociplastic pain. Work is ongoing.

METHOD CHOICES CHANGE THE FINDINGS

High-frequency and low-frequency stimulation of C fibers sensitize different projection neurons — one projecting to the periaqueductal gray, the other to the parabrachial area. The consequences are unknown, but it means the method used to study central sensitization shapes the result, and therefore shapes what we believe about clinical practice.

THE NEUROSCIENCE DOES NOT CAPTURE THE LIVED EXPERIENCE

DPMS dysfunction is an essential part of how neuroscience explains chronic musculoskeletal pain, and the current understanding does not fully embrace what it is like to live with chronic pain. All treatment of individuals with chronic pain should be person-centered. The mechanism is a tool for reasoning, not a substitute for the person.

> *Not being able to measure what is important does not make the things we can measure important.*
>
> HOEGH, SCHMID, HANSSON & FINNERUP — PAIN, 2022

That line is the discipline this whole field asks of us. It is very easy to build a practice around the things that are easy to measure — range of motion, pressure pain thresholds, a questionnaire score — and to let those quietly become the goal. The goal is that the person hurts less and does more.

PULL-OUT

The clinic card

Print this page. Tape it inside a cabinet door. Everything on it is defensible.

THE EIGHT-STEP SEQUENCE

1	Screen for red flags.
2	Test structural integrity separately from pain provocation.
3	Map evoked pain: confined to the tissue, or spreading beyond it?
4	Test for sensory *loss*. Run the neuropathic grading if 3+ months.
5	Is there ongoing nociceptive drive that explains the picture?
6	If not, and neuropathic is excluded — nociplastic features. Explain; don't target.
7	Assess activity history and load tolerance. That's DPMS capacity.
8	Choose the outcome measure: pain and function. Re-measure on schedule.

NEUROPATHIC GRADING — 3+ MONTHS, ALTERNATIVES EXCLUDED

Possible	Neuroanatomically plausible pain distribution + history suggestive of a relevant lesion or disease.
Probable	+ examination showing partial or complete **loss of function** corresponding to the lesion.
Definite	+ diagnostic test confirming the lesion or disease.

THREE-MINUTE SENSORY ADD-ON

Cotton wisp (allodynia) · pin (hyper- *and* hypoalgesia) · cold · vibration if a lesion is plausible · outline the tender zone relative to the structure · always compare contralateral and a remote site.

THE FOUR SENTENCES

> - "Tender doesn't mean damaged. Those are two separate questions and I checked both."
> - "Your nervous system got better at producing this signal. That's a physical change — and it goes both directions."
> - "I'm not promising relief after every session. Regularity is what rebuilds the system; the payoff is in weeks."
> - "Your scans are clean and I believe your pain. Those aren't in conflict."

NEVER SAY

"You have central sensitization." · "Your pain is out of proportion." · "There's nothing wrong." · "It's permanent." · "This releases the adhesion." · "Push through it."

THE ONE THAT MATTERS MOST

Regular physical activity is beneficial even if immediate pain relief does not follow. Inactivity is likely to make things worse.

SOURCES

References & further reading

This guide is a clinical synthesis of the nine-part *Pain Science in Practice* editorial series in the *Journal of Orthopaedic & Sports Physical Therapy* (2022–2025), with primary sources cited where specific findings are referenced. The series is the recommended primary read; this document is a working translation of it, not a replacement.

THE SERIES

1. Hoegh M, Rathleff MS. Pain science in practice: linking basic pain science to the clinic and quality musculoskeletal rehabilitation care. *J Orthop Sports Phys Ther.* 2022;52(3):125-126. doi:10.2519/jospt.2022.10992
2. Hoegh M. Pain science in practice: what is pain neuroscience? Part 1. *JOSPT.* 2022;52(4):163-165. doi:10.2519/jospt.2022.10995
3. Hoegh M. Pain science in practice: what is pain neuroscience? Part 2. *JOSPT.* 2022;52(4):166-168. doi:10.2519/jospt.2022.10994
4. Hoegh M. Pain science in practice (part 3): peripheral sensitization. *JOSPT.* 2022;52(6):303-306. doi:10.2519/jospt.2022.11202
5. Hoegh M. Pain science in practice (part 4): central sensitization I. *JOSPT.* 2023;53(1):1-4. doi:10.2519/jospt.2023.11569
6. Hoegh M. Pain science in practice (part 5): central sensitization II. *JOSPT.* 2023;53(2):55-58. doi:10.2519/jospt.2023.11571
7. Hoegh M, Bannister K. Pain science in practice (part 6): how does descending modulation of pain work? *JOSPT.* 2024;54(2):97-100. doi:10.2519/jospt.2024.12112
8. Hoegh M, Bannister K. Pain science in practice (part 7): how is descending modulation of pain measured? *JOSPT.* 2024;54(3):155-160. doi:10.2519/jospt.2024.12113
9. Hoegh M, Hodges P. Pain science in practice (part 8): nociceptive, neuropathic, and nociplastic pain. *JOSPT.* 2025;55(9):555-560. doi:10.2519/jospt.2025.13335

NUMBERED CITATIONS IN THIS GUIDE

1. Hartvigsen J, Hancock MJ, Kongsted A, et al. What low back pain is and why we need to pay attention. *Lancet.* 2018;391:2356-2367.
2. Lin I, Wiles L, Waller R, et al. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines. *Br J Sports Med.* 2020;54:79-86.
3. Hoegh M, Rathleff MS. *JOSPT.* 2022;52(3):125-126.
4. Cayrol T, Draper-Rodi J, Fabre L, et al. Stuck in the middle with you: why a broad-brush approach to defining central sensitization does not help clinicians and patients. *JOSPT.* 2021;51:204-206.
5. van Griensven H, Schmid A, Trendafilova T, Low M. Central sensitization in musculoskeletal pain: lost in translation? *JOSPT.* 2020;50:592-596.
6. Nijs J, Goubert D, Ickmans K. Recognition and treatment of central sensitization in chronic pain patients: not limited to specialized care. *JOSPT.* 2016;46:1024-1028.
7. Curatolo M. Central sensitization: nice to know? *Eur J Pain.* 2018;22:214-215.
8. Marchand S. Mechanisms challenges of the pain phenomenon. *Front Pain Res.* 2021;1:574370.
9. Hoegh M. Part 1. *JOSPT.* 2022;52(4):163-165.
10. McDermott LA, Weir GA, Themistocleous AC, et al. Defining the functional role of NaV1.7 in human nociception. *Neuron.* 2019;101:905-919.e8.
11. Yang Y, Huang J, Mis MA, et al. Nav1.7-A1632G mutation from a family with inherited erythromelalgia. *J Neurosci.* 2016;36:7511-7522.
12. Schmid AB, Fundaun J, Tampin B. Entrapment neuropathies: a contemporary approach to pathophysiology, clinical assessment, and management. *Pain Rep.* 2020;5:e829.
13. Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesth.* 2010;105:i69-i85.
14. Bialosky JE, Bishop MD, Penza CW. Placebo mechanisms of manual therapy: a sheep in wolf's clothing? *JOSPT.* 2017;47:301-304.
15. Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med.* 2011;3:70ra14.
16. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. *Man Ther.* 2010;15:355-363.
17. Arora V, Campbell JN, Chung MK. Fight fire with fire: neurobiology of capsaicin-induced analgesia for chronic pain. *Pharmacol Ther.* 2021;220:107743.

18. Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed "Physical Stress Theory." *Phys Ther.* 2002;82:383-403.
19. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol.* 2020;17:574-584.
20. Kronschläger MT, Drdla-Schutting R, Gassner M, et al. Gliogenic LTP spreads widely in nociceptive pathways. *Science.* 2016;354:1144-1148.
21. Hoegh M, Schmid AB, Hansson P, Finnerup NB. Not being able to measure what is important, does not make things we can measure important. *Pain.* 2022;163:e963.
22. Quesada C, Kostenko A, Ho I, et al. Human surrogate models of central sensitization: a critical review and practical guide. *Eur J Pain.* 2021;25:1389-1428.
23. Kucharczyk MW, Di Domenico F, Bannister K. Distinct brainstem to spinal cord noradrenergic pathways inversely regulate spinal neuronal activity. *Brain.* 2022;145:2293-2300.
24. Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. *Lancet.* 1978;312:654-657.
25. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain.* 1979;6:283-304.
26. Wewege MA, Jones MD. Exercise-induced hypoalgesia in healthy individuals and people with chronic musculoskeletal pain: a systematic review and meta-analysis. *J Pain.* 2021;22:21-31.
27. Vaegter HB, Petersen KK, Sjodsholm LV, et al. Impaired exercise-induced hypoalgesia in individuals reporting an increase in low back pain during acute exercise. *Eur J Pain.* 2021;25:1053-1063.
28. Yarnitsky D, Granot M, Granovsky Y. Pain modulation profile and pain therapy: between pro- and antinociception. *Pain.* 2014;155:663-665.
29. Sluka KA, Frey-Law L, Hoeger Bement M. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. *Pain.* 2018;159:S91-S97.
30. Dailey DL, Vance CGT, Rakel BA, et al. Transcutaneous electrical nerve stimulation reduces movement-evoked pain and fatigue: a randomized, controlled trial. *Arthritis Rheumatol.* 2020;72:824-836.
31. Schmid AB, et al., as adapted in the neuropathic pain grading system presented in Hoegh M, Hodges P. *JOSPT.* 2025;55(9):555-560.

ALSO WORTH YOUR TIME

- Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain.* 2021;162:2629-2634. (Read alongside the published critiques.)
- Vaegter HB, Jones MD. Exercise-induced hypoalgesia after acute and regular exercise. *Pain Rep.* 2020;5:e823. (Open access.)
- Bannister K, Dickenson AH. The plasticity of descending controls in pain: translational probing. *J Physiol.* 2017;595:4159-4166. (Open access.)
- Sirucek L, Ganley RP, Zeilhofer HU, Schweinhardt P. Diffuse noxious inhibitory controls and conditioned pain modulation: a shared neurobiology? *Pain.* 2023;164:463-468. (Open access.)
- IASP terminology: iasp-pain.org/resources/terminology

This is the kind of thing I write here. The Physical Root is where I put the clinical reasoning that didn't fit in my CEU notes — pain science, functional labs, nutrition and inflammation, longevity, and the protocols I actually use. Written for clinicians, by a clinician who's still practicing.

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