NEUR 1520 Neuroscience Study Guide for Exam 2: Book 5.2: Pain

Source: The Mind's Machine, Chapter 5 (no Chapter 5 lecture slides are posted yet). Nothing else.
Each heading is one book learning objective. [MM p148] = book page 148.
(teal italics) = plain meaning of the word before it. ⚠ **Do not mix up = a look-alike pair to keep apart.** **Amber dotted words** = names printed on the figure beside them.

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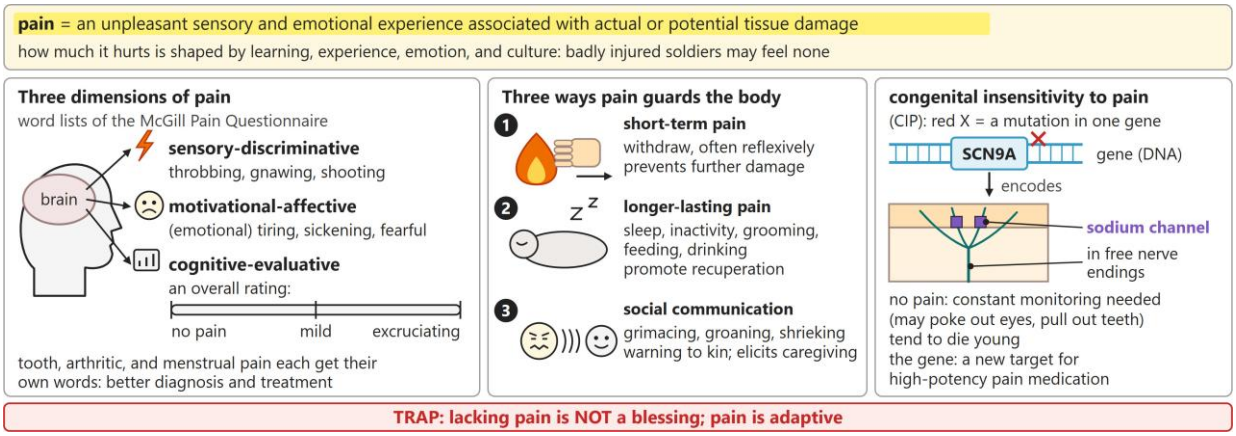
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5.2.1 List and describe the three separate components of pain experience

⚠ **Do not mix up: Motivational-affective = emotional words (sickening, fearful); cognitive-evaluative = overall rating (mild, excruciating).** [MM p154]

Pain: an unpleasant sensory and emotional experience tied to actual or potential tissue damage. [MM p154]
Glossary definition of **pain**: the discomfort normally associated with tissue damage. [MM p154]
Pain is at best a mixed blessing: unpleasant but adaptive. [MM p154]
Pain forcefully guides behavior in ways that minimize risk to the body. [MM p154]
Immediate, short-term pain: we withdraw from the source, often reflexively, preventing further damage. [MM p154]
Longer-lasting pain: encourages sleep, inactivity, grooming, feeding, and drinking, which promote **recuperation** *(recovery)*. [MM p154]
Pain-related **social communication** (grimacing, groaning, shrieking) warns kin. [MM p154]
These signals also draw caregiving from kin: grooming, defending, and feeding. [MM p154]
Learning, experience, emotion, and culture all strongly affect how we perceive pain. [MM p154]
Example: badly injured soldiers and athletes may show an apparent absence of pain. [MM p154]
Opposite example: a child may be anguished by a paper cut. [MM p154]



Pain dimensions in the McGill Pain Questionnaire, uses of pain, and CIP [MM p154]

On the figure: McGill Pain Questionnaire · sensory-discriminative · motivational-affective · cognitive-evaluative · recuperation · social communication · congenital insensitivity to pain

McGill Pain Questionnaire: widely used pain measure; people pick words tapping three pain dimensions. [MM p154]

1. **Sensory-discriminative** dimension *(what the pain feels like)*: throbbing, gnawing, shooting. [MM p154]
2. **Motivational-affective** dimension *(the emotional side)*: tiring, sickening, fearful. [MM p154]
3. Overall **cognitive-evaluative** dimension *(judging how bad overall)*: no pain, mild, excruciating. [MM p154]

Different pains get different descriptor sets: tooth, arthritic, and menstrual pain are described differently. [MM p154, MM p155]

This detailed analysis gives better information for diagnosing and treating illness. [MM p155]

Congenital insensitivity to pain *(born unable to feel pain)*: people tend to die young from repeated injuries. [MM p154]

Review, why pain is a positive adaptation: it drives withdrawal, **recuperation**, and caregiving, limiting damage. [MM p154]

5.2.2 Describe the neuronal receptor cells that detect painful stimuli and the molecular receptor proteins they use

⚠ Do not mix up: First sharp pain is NOT from C fibers: it is fast A delta via TRPM3. [MM p156]

Most tissues of the body, but not all, contain receptors for painful stimuli. [MM p155]

These pain receptors are best studied in the skin. [MM p155]

Nociceptor *(pain receptor)*: receptor responding to stimuli that damage tissue or threaten damage. [MM p155]

Nociceptors sit on **free nerve endings** *(bare nerve tips)* specialized to detect damage. [MM p155]

Free nerve ending: an axon ending in the skin with no specialized cell attached. [MM p147]

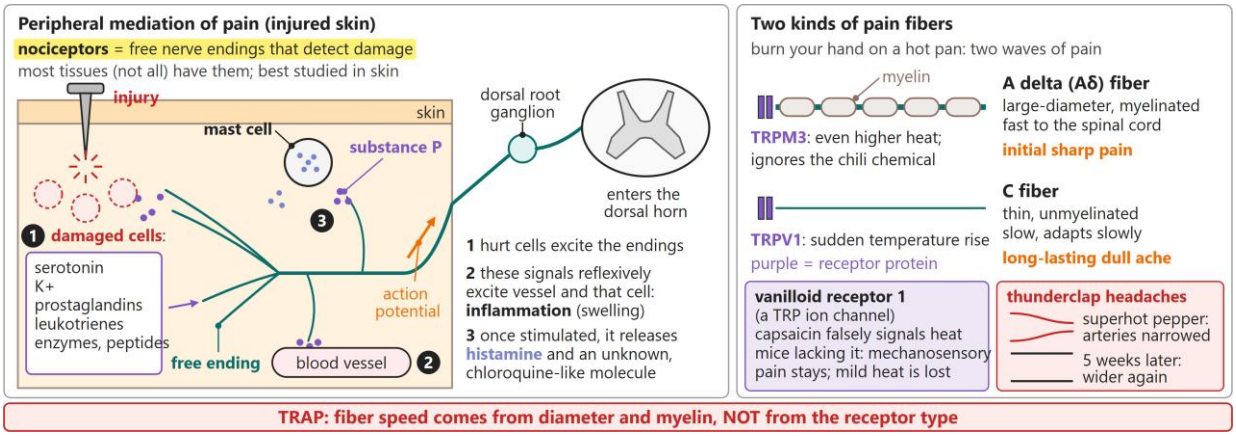
Free nerve endings in the skin detect pain, itch, heat, and cold. [MM p146, MM p147]

Injured cells release chemicals that activate nearby nociceptors. [MM p155]

The same chemicals also cause **inflammation** *(injury swelling)*. [MM p155]

Nociceptor stimulants in injured tissue include serotonin, histamine, and various enzymes and peptides. [MM p155]

Different nociceptors respond to different stimuli, such as pain and/or temperature changes. [MM p155]



Injury chemicals excite nociceptors, then pain fibers A delta and C with TRPM3 and TRPV1 [MM p155]

On the figure: nociceptors · mast cells · substance P · dorsal root ganglion · A delta · C fiber · TRPM3 · TRPV1

1. Damaged cells release substances (serotonin, K+, **prostaglandins** *(chemical injury signals)*, leukotrienes) exciting nociceptor endings. [MM p155]

2. Action potentials from the periphery reflexively excite blood vessels and **mast cells** *(cells that release histamine)*: inflammation. [MM p155]

3. Stimulated mast cells release histamine and an unknown, chloroquine-like molecule. [MM p155]

Nerve endings release **substance P** onto mast cells and blood vessels, promoting swelling. [MM p155]

4. Signal passes the **dorsal root ganglion**, enters the dorsal root, synapses in the dorsal horn. [MM p155]

5. Pain fibers release **glutamate** (transmitter) and **substance P** (neuromodulator) in the spinal cord. [MM p155]

6. Dorsal horn cells send the signal across the midline and up to the thalamus. [MM p155]

Congenital insensitivity to pain (CIP) *(born unable to feel pain)*: linked to a mutation in the gene **SCN9A**. [MM p155]

Clue case: a boy who could feel no pain died performing dangerous pranks. [MM p155]

Studying the boy's family helped identify the nociceptor that detects physical damage. [MM p155]

Children with CIP need constant monitoring so they do not poke out eyes or pull teeth. [MM p155]

SCN9A encodes a **sodium channel** *(gate letting sodium in)* expressed in nociceptor free nerve endings. [MM p155]

The SCN9A sodium channel offers a new target for high-potency pain medication. [MM p155]

Some free nerve endings detect temperature changes. [MM p155]

Capsaicin: the chemical that makes chili peppers spicy hot. [MM p155]

Capsaicin studies revealed the receptor signaling sudden temperature **increases**; why spicy food seems to burn. [MM p155]

TRPV1 (transient receptor potential vanilloid type **1,** or vanilloid receptor **1**): reports a temperature rise. [MM p156]

TRPV1 belongs to the **transient receptor potential (TRP)** family of **ion channels** *(gates letting ions cross)*. [MM p156]

Mice lacking the TRPV1 gene: still respond to mechanical pain, but not mild heat or capsaicin. [MM p156]

TRPV1 normally warns of danger from rising temperature. [MM p156]

Chili peppers evolved capsaicin to ward off mammal predators by falsely signaling burning heat. [MM p156]

TRPM3 (transient receptor potential type M3): free nerve ending receptor; channel opens as temperature rises. [MM p156]

TRPM3 detects even higher temperatures than TRPV1 but does **NOT** respond to capsaicin. [MM p156]

TRPM3 sits on **A delta fibers**; TRPV1 sits on **C fibers**. [MM p156]

A delta (Aδ) fiber: moderately large, **myelinated** *(fat-insulated)*, fast-conducting axon usually carrying pain. [MM p156]

Large diameter plus myelination let A delta action potentials reach the spinal cord very quickly. [MM p156]

C fiber: small, **unmyelinated** *(no insulating fat)* axon that conducts pain slowly and adapts slowly. [MM p156]

Hand burned on a hot pan: initial sharp pain = fat A delta fibers via TRPM3. [MM p156]

The long-lasting dull ache that follows comes from slower C fibers via TRPV1. [MM p156]

C fibers adapt slowly. [MM p156]

Other TRP receptors detect coolness and spices such as oregano, cloves, garlic, and wasabi. [MM p156]

How those other TRP receptors relate to pain receptors is still unknown. [MM p156]

Overstimulating TRPV1 can be hazardous to health. [MM p156]

Case: a **34**-year-old professional eater ate a whole Carolina Reaper pepper. [MM p156]

Result: dry heaves, neck pain, then a series of **thunderclap headaches**. [MM p156]

Thunderclap headache: excruciating, sudden-onset headache peaking in a minute, subsiding, then returning. [MM p156]

MRI of the brain: no abnormalities. [MM p156]

CAT scan of blood vessels: several arteries supplying the brain had narrowed remarkably. [MM p156]

The narrowed arteries may have caused the headaches; more seconds-long headaches followed over days. [MM p156]

Five weeks later, headaches gone: brain arteries had expanded to a more normal size. [MM p156]

Superhot chili peppers have caused severe, even fatal, heart attacks. [MM p156]

Review, how pain receptors work: injury chemicals or heat activate receptor proteins on free nerve endings. [MM p155, MM p156]

Review, pain vs touch receptors: pain uses free nerve endings with no specialized cell. [MM p146, MM p155]

Touch uses specialized receptors: the onion-like **Pacinian corpuscle** (vibration and pressure), **Meissner's corpuscles**. [MM p146, MM p155]

Other touch receptors: **Merkel's discs** (edges and points) and **Ruffini corpuscles** (skin stretch). [MM p146, MM p155]

Summary: free nerve endings detect damage or temperature through specialized receptor proteins. [MM p174]

A delta vs C fibers

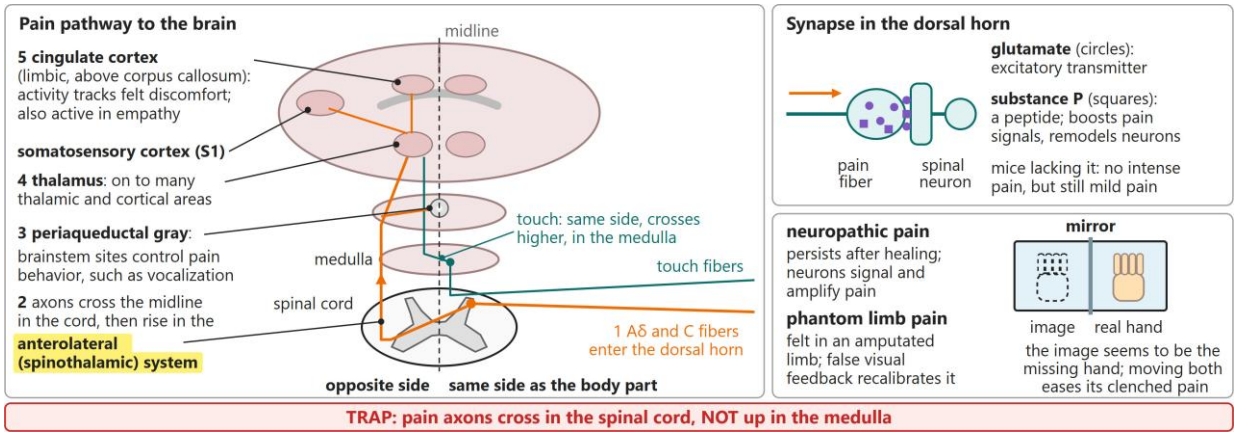
Feature	A delta (Aδ) fiber	C fiber
Size	large diameter	small, thin
Myelin	myelinated	unmyelinated
Speed	fast	slow
Heat receptor	TRPM3 (higher heat, no capsaicin)	TRPV1 (heat and capsaicin)
Pain felt	initial sharp pain	long-lasting dull ache

Table source: [MM p156]

5.2.3 Trace the neuronal pathway that transmits pain information from the periphery to the brain, as well as the neuronal pathway by which the brain can modulate pain

⚠ **Do not mix up: Pain pathway crosses the midline in the SPINAL CORD; touch (dorsal column) crosses in the MEDULLA.** [MM p157, MM p151]

Anterolateral system (also **spinothalamic system**): carries most pain information from body to brain. [MM p157]



Pain pathway crossing in the spinal cord, substance P synapse, and mirror box [MM p157]

On the figure: cingulate cortex · periaqueductal gray · anterolateral · midline · substance P · glutamate · neuropathic pain · phantom limb pain

1. Pain travels on fast myelinated A delta fibers and slow unmyelinated C fibers. [MM p157]
2. Pain and temperature fibers enter the **dorsal horns** *(back gray matter of cord)* of the spinal cord. [MM p157]
3. They synapse onto spinal neurons there. [MM p157]
4. Dorsal horn neuron axons cross the **midline** to the opposite side in the spinal cord. [MM p157]
5. They ascend the cord in the **anterolateral quadrant** *(front side part of cord)*. [MM p157]
6. Brainstem sites receive pain information and control pain behavior such as vocalization. [MM p157]
7. Reaches **thalamic nuclei**; pain is distributed to many thalamic and cortical areas, including S1. [MM p157]
8. **Cingulate cortex** is especially activated; pain information is eventually integrated there. [MM p157]

The anterolateral system is distinct from the touch **dorsal column system**. [MM p157]

Like touch, each hemisphere receives pain inputs from the **contralateral** *(opposite)* body side. [MM p157]

In the spinal cord, pain fibers release excitatory **glutamate** plus the peptide **substance P**. [MM p157]

Substance P: a peptide transmitter involved in pain transmission. [MM p157]

Substance P selectively boosts pain signals and remodels pain pathway neurons. [MM p157]

Mice lacking substance P cannot feel intense pain but still feel mild pain. [MM p157]

Cingulate cortex (also **cingulum**): medial cortex dorsal to the **corpus callosum** *(band joining the hemispheres)*; limbic system. [MM p157]

Same mildly painful stimulus: more cingulate and S1 activation goes with more reported discomfort. [MM p157]

Different cingulate subregions seem to handle emotional versus sensory aspects of pain. [MM p157, MM p158]

One cingulate part activates even when we just empathize with a loved one in pain. [MM p158]

Descending control, one possibility the book gives: [MM p159]

1. Opiates or endorphins bind opioid receptors in the brainstem **periaqueductal gray** *(midbrain gray area)*. [MM p159, MM p157]
2. The periaqueductal gray brainstem system sends descending projections to the spinal cord. [MM p159]
3. The projections activate the spinal cord pain-gating mechanism. [MM p159]
4. Gates close: transmission of pain signals to the brain is blocked. [MM p159, MM p158]

Central modulation: descending brain connections inhibit ascending sensory and pain axons at lower levels. [MM p150]

Neuropathic pain: pain persisting long after the injury that started it has healed. [MM p158]

Neuropathic pain is a disagreeable example of **neuroplasticity** *(nervous system change)*. [MM p158]

Neurons keep signaling, even amplifying, pain with no tissue damage at all. [MM p158]

Phantom limb pain: neuropathic pain that seems to come from an amputated limb. [MM p158]

Phantom limb pain is notoriously difficult to treat. [MM p158]

Mirror box: the mirror makes both limbs look intact. [MM p158]

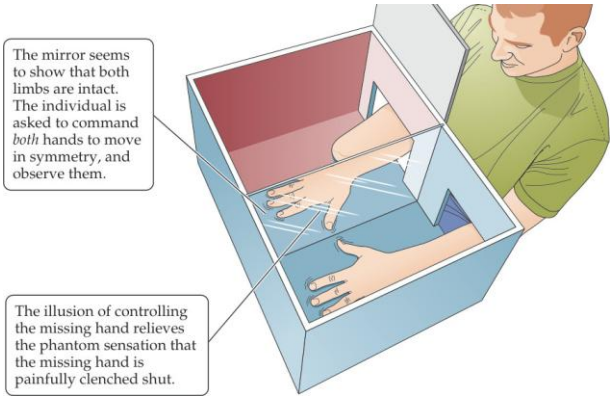
The person commands **both hands** to move in symmetry and watches them. [MM p158]

Illusion of controlling the **missing hand** relieves the feeling it is painfully clenched shut. [MM p158]

Visual feedback, even false, apparently lets the brain recalibrate the pain signal. [MM p158]

Review, sketch: fibers, dorsal horn, cross midline, anterolateral cord, brainstem, thalamus, S1 and cingulate. [MM p157]

Summary: pain, temperature, and itch enter the cord, cross, and ascend the anterolateral system. [MM p174]



Mirror box: seeing both hands move relieves phantom limb pain [MM p158]

On the figure: mirror · both hands · missing hand · phantom

Touch pathway vs pain pathway

Feature	Touch	Pain
System	dorsal column system	anterolateral (spinothalamic) system
Receptors	specialized skin receptors	free nerve endings (nociceptors)
First synapse	dorsal column nuclei, medulla	dorsal horn, spinal cord
Crosses midline in	medulla	spinal cord
Ascends in	dorsal columns	anterolateral quadrant
Relay	thalamus	brainstem sites, thalamus
Cortex	somatosensory cortex	S1 and cingulate cortex
Body side served	contralateral	contralateral

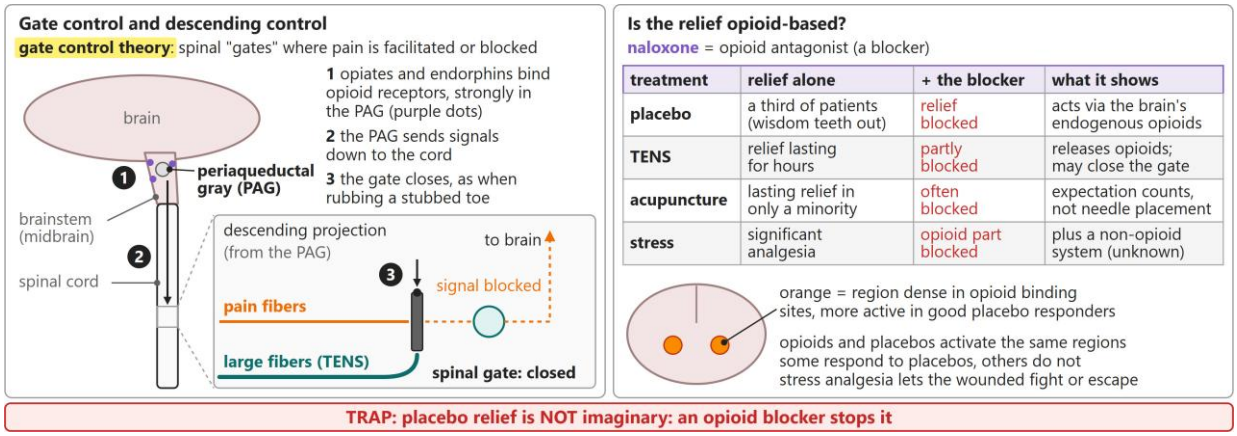
Table source: [MM p146, MM p150, MM p151, MM p155, MM p157]

5.2.4 Discuss the various methods for controlling pain, including advantages and disadvantages of each

⚠ Do not mix up: Naloxone does NOT relieve pain: it BLOCKS opioid-based relief (opiates, placebo, acupuncture). [MM p159, MM p160]

Pain control is hard: even cutting nerves may give **only** temporary relief. [MM p158]

The pain system eventually finds a way to restore its signal to the brain. [MM p158]



Gate control and descending control, and which reliefs a naloxone blocker stops [MM p159]

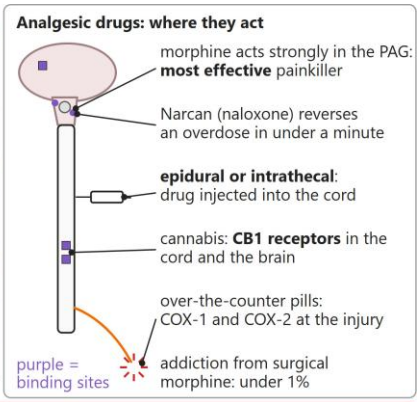
On the figure: gate control theory · periaqueductal gray · naloxone · placebo · TENS · acupuncture · endogenous opioids · stress

Gate control theory: spinal gates, where pain is facilitated or blocked, control signals reaching the brain. [MM p158]

If the theory is right, effective relief may depend on keeping the gates closed. [MM p158]

Analgesia: absence of or reduction in pain (Greek an, not; algesis, feeling of pain). [MM p158]

Type	Mechanism
PSYCHOGENIC	
Placebo	May activate endorphin-mediated pain control system
Hypnosis	Alters brain's perception of pain
Stress	Uses both opioid and non-opioid mechanisms
Cognitive (learning, coping strategies)	May activate endorphin-mediated pain control system
PHARMACOLOGICAL	
Opiates	Bind to opioid receptors in periaqueductal gray and spinal cord
Spinal block	Blocks pain signals in spinal cord
Anti-inflammatory drugs	Block chemical inflammatory signals at the site of injury
Cannabinoids	Act in nociceptor endings, spinal cord, and brain
STIMULATION	
TENS/mechanical	On large fibers, blocks or alters pain signal to brain
Acupuncture	Activates endogenous opioids and/or placebo-like effect, possibly modulating effect on activity of peripheral pain pathways
Central gray	Electrically activates endorphin-mediated pain control systems, blocking pain signal in spinal cord



TRAP: aspirin and acetaminophen do NOT work like morphine; they act via COX enzymes

Types of pain relief and where analgesic drugs act [MM p160]

On the figure: opiates · naloxone · epidural · intrathecal · CB1 · COX-1 · TENS · acupuncture

Four categories: analgesic drugs, electrical stimulation, placebos, and activating **endogenous opioids**. [MM p158, MM p159, MM p160]

Opiates (opium-related drugs, like morphine): known for centuries to relieve pain. [MM p159]

Opiates and **endogenous opioids** *(the body's own painkillers)* bind specific brain receptors to reduce pain. [MM p159]

Endorphin: one of three kinds of endogenous opioids. [MM p159]

Opiate action is especially strong in the brainstem **periaqueductal gray** *(midbrain gray area)*. [MM p159]

Epidural or **intrathecal injection**: opiates injected carefully, directly into the spinal cord. [MM p159]

Advantage: opiates are the most effective painkillers; no other drug matches them. [MM p159]

People using painkillers for severe pain usually do not become addicted. [MM p159]

Addiction risk from morphine for surgical pain is vastly exaggerated: estimated under **1%**. [MM p159]

Disadvantage: the few who become addicted face a very real danger of overdose death. [MM p159]

Extremely potent opioids (OxyContin, fentanyl) worsened the opioid epidemic, causing more deaths. [MM p159]

Naloxone (Narcan): potent opiate **antagonist** *(blocker)*, often given after drug overdoses. [MM p159]

Given in time, naloxone saves lives; more public safety officers now carry it. [MM p159]

Naloxone, the Lazarus drug, can revive people dying of narcotic overdose in under a minute. [MM p159]

Aspirin and **acetaminophen** (Tylenol): over-the-counter, non-opiate; reduce pain and inflammation. [MM p159]

They act especially through **cyclooxygenase** *(pain and inflammation enzymes)* enzymes **COX-1** and **COX-2**. [MM p159]

Disadvantage: non-opiate drugs are less effective than opiates. [MM p159]

Cannabis: reduces pain by stimulating endogenous **CB1 cannabinoid receptors** in spinal cord and brain. [MM p159]

TENS (transcutaneous electrical nerve stimulation): mild electrical stimulation of nerves around injury sites. [MM p159]

TENS skin electrodes excite nerves supplying the region where pain is **referred** *(felt)*. [MM p159]

Exact mechanism unclear; one possibility is that TENS closes the spinal pain gate. [MM p159]

Everyday version: rubbing a stubbed toe brings a little relief. [MM p159]

TENS stimulates the nerves near the injury more efficiently than rubbing does. [MM p159]

Advantage: TENS may bring dramatic relief lasting for hours. [MM p159]

Naloxone partially blocks TENS: TENS works at least partly by releasing endogenous opioids. [MM p159]

Placebo effect: symptom relief after a treatment known to be ineffective or inert. [MM p159]

In some people, simply believing they get a proven treatment relieves pain. [MM p159]

Wisdom teeth patients given morphine or placebo: fully a third on placebo felt relief. [MM p159]

Placebo given with naloxone (opioid receptor blocker): the placebo benefit disappeared. [MM p159]

Conclusion: placebos likely work by activating the brain's endogenous opioid system. [MM p159]

Brain imaging: opioids and placebos activate the same brain regions. [MM p159]

Disadvantage: for unknown reasons, some people consistently respond to placebos and others do not. [MM p159]

Acupuncture: inserting needles at designated skin points to relieve pain or neurological malfunction. [MM p160]

Acupuncture is ancient and very popular. [MM p160]

Disadvantage: **only** a minority of users get lasting relief from chronic pain. [MM p160]

When it works, endorphin release may be key: naloxone often blocks acupuncture. [MM p160]

So acupuncture resembles placebos. [MM p160]

Needle placement has little to do with the pain effect, despite many placement rules. [MM p160]

Expectation of relief seems to be the key, presumably releasing endogenous opioids. [MM p160]

Stressful events can produce significant analgesia: gravely wounded soldiers may feel no pain for a time. [MM p160]

Animal research: **stress** activates an opioid-dependent analgesia that naloxone blocks. [MM p160]

Stress also activates an uncharacterized non-opioid system, possibly using **endocannabinoids** *(body's own cannabis-like chemicals)*. [MM p160]

These built-in analgesic systems let a wounded individual fight or escape instead of being overwhelmed. [MM p160]

Chronic back pain: the prefrontal cortex shrinks much faster than normal, like rapid aging. [MM p160]

The wide range of relief strategies shows how elusive pain is. [MM p160]

Acupuncture may also modulate activity of peripheral pain pathways. [MM p160]

Review, most effective drugs: opiates; bind opioid receptors, especially periaqueductal gray, and spinal cord. [MM p159, MM p160]

Review, TENS: may close the spinal pain gate; partly releases endogenous opioids. [MM p159]

Review, placebo and acupuncture: naloxone blocks both, so both likely use endogenous opioids. [MM p159, MM p160]

Review, shared factor: expectation of relief; acupuncture needle placement barely matters. [MM p159, MM p160]

Summary: brain and spinal regions using endogenous opioids such as endorphins modulate pain. [MM p174]

Summary: opioid systems are also active in the placebo effect and acupuncture. [MM p174]

Types of pain relief

Type	Group	Mechanism
Placebo	Psychogenic	May activate endorphin pain control system
Hypnosis	Psychogenic	Alters brain perception of pain
Stress	Psychogenic	Uses opioid and non-opioid mechanisms
Cognitive (learning, coping strategies)	Psychogenic	May activate endorphin pain control system
Opiates	Pharmacological	Bind opioid receptors in periaqueductal gray, spinal cord
Spinal block	Pharmacological	Blocks pain signals in spinal cord
Anti-inflammatory drugs	Pharmacological	Block chemical inflammatory signals at injury site
Cannabinoids	Pharmacological	Act in nociceptor endings, spinal cord, brain
TENS/mechanical	Stimulation	On large fibers, blocks or alters pain signal
Acupuncture	Stimulation	Endogenous opioids and/or placebo-like effect
Central gray	Stimulation	Electrically activates endorphin system; blocks spinal pain signal

Table source: [MM p160]

Pain control: pros and cons

Method	Advantage	Disadvantage
Cutting nerves	may relieve pain	relief may be **only** temporary
Opiates	most effective painkillers	overdose death risk if addicted
Aspirin, acetaminophen	reduce pain and inflammation	less effective than opiates
TENS	dramatic relief lasting hours	exact mechanism unclear
Placebo	relieves a third in study	works in some people, not all
Acupuncture	very popular; may release endorphins	lasting relief **only** in a minority

Table source: [MM p158, MM p159, MM p160]