SECTION 1

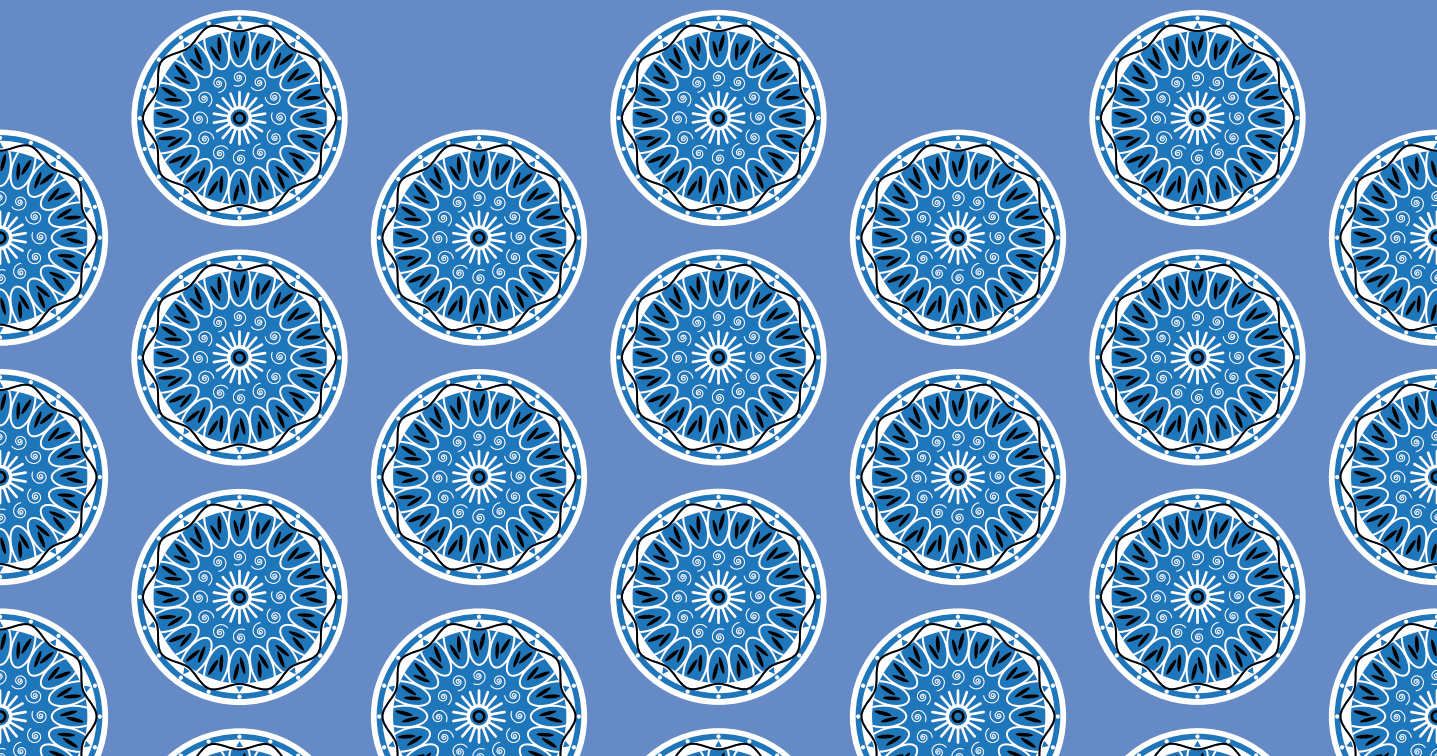
The nuts and bolts of pain

Section editors

Romy Parker
Jocelyn Park-Ross

Authors

Romy Parker
Tory Madden
Gill Bedwell
Brett Mason
Luyanduthando Mqadi
Murray McDonald
Claire-Louise Pfister
Jocelyn Park-Ross
Dawn Ernstzen
Cameron Reardon
Marisa Coetzee
Johannes Stofberg
Johan van Der Walt



Published in 2024
by University of Cape Town Libraries,
Rondebosch, Cape Town, 7700, South Africa.

ISBN: 978-0-7961-8936-3 (print)
ISBN: 978-0-7961-8937-0 (e-book)

DOI: 978-0-7912-3456-7

Acknowledgements:

This book has been funded by an International Association for the Study of Pain Developing Countries Education Grant.

Professor Romy Parker romy.parker@uct.ac.za
Jocelyn Park-Ross jo.park-ross@uct.ac.za

Design: Gaelen Pinnock | polygram.co.za

Suggested citation:

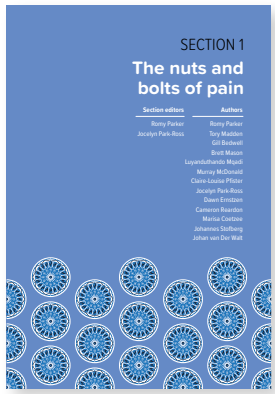
> *Parker P, Park-Ross J. Understanding Pain: unravelling the physiology, assessment and treatment of pain through South African stories. 2024. Cape Town: University of Cape Town Press.*

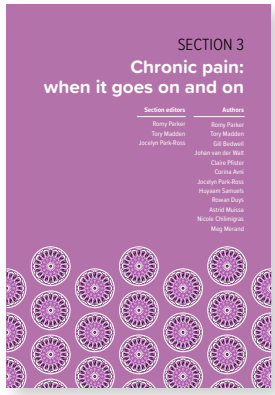
www.uct.ac.za

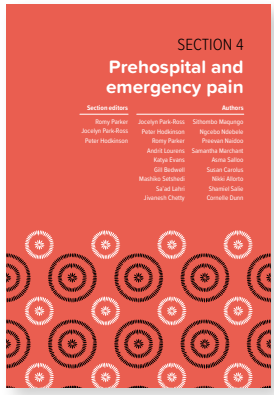
About the book

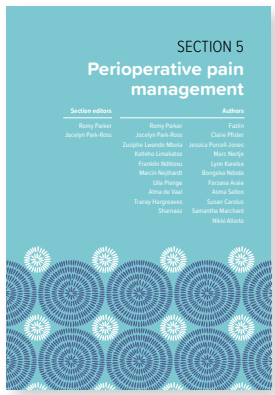
This open access textbook is aimed at all healthcare disciplines, including nurses, doctors, rehabilitation and allied healthcare and prehospital care providers.

Throughout the book, essential evidence-based pain knowledge is interwoven with contextual case studies and patient stories, centering the patient experience to enhance understanding of the physiology, assessment, and treatment of pain.









Authors' information and affiliations

Professor Romy Parker BSc (Physiotherapy); BSc (Med)(Hons) Ex. Sci (Phys); MSc (Pain), PhD

- *Physiotherapist*
- *Director: Pain Management Unit, Department of Anaesthesia and Perioperative Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

Associate Professor Victoria (Tory) J Madden BSc (Physiotherapy); PhD

- *Physiotherapist and researcher*
- *African Pain Research Initiative, Department of Anaesthesia and Perioperative Medicine, Neuroscience Institute, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

Gillian J Bedwell BSc (Physiotherapy); PGDip Interdisciplinary Pain Management; MSc (Physiotherapy)

- *Physiotherapist*
- *Pain Management Unit, Department of Anaesthesia and Perioperative Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

Brett Mason BSc (Physiotherapy); MSc (Disability Studies); PGDip Interdisciplinary Pain Management

- *Physiotherapist*

Luyanduthando Mqadi BSc (Hons Neuroscience); MSc (Neuroscience)

- *Neuroscientist*
- *Pain Management Unit, Department of Anaesthesia and Perioperative Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

Dr Claire-Louise Pfister BSc; MBBCh; DA; DCH (SA); FCA (SA); MMed Anaesthesia

- *Specialist Anaesthetist*
- *Department of Anaesthesia and Perioperative Medicine, University of Cape Town*

Dr Murray McDonald MTech (Chiropractic); PGDip Interdisciplinary Pain Management

- *Chiropractor*
- *Pain Management Unit, Department of Anaesthesia and Perioperative Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

Jocelyn Park-Ross NDip (Emergency Medical Care); BTech (Emergency Medical Care); MPhil (Emergency Medicine)

- *Paramedic*
- *Department of Anaesthesia and Perioperative Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*
- *Clinical Skills Unit, Department of Health Sciences Education, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

Professor Dawn Ernstzen BSc (Physiotherapy); MPhil (Higher Education); PhD (Physiotherapy)

- *Physiotherapist and Professor*
- *Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University*

Cameron Reardon BSc (Physiotherapy); MSc (Physiotherapy).

- *Physiotherapist and Lecturer*
- *Division of Physiotherapy, Department of Health and Rehabilitation Sciences. Faculty of Medicine and Health Sciences. Stellenbosch University*

Marisa Coetzee BSc (Physiotherapy) MSc (Physiotherapy).

- *Physiotherapist, lecturer and PhD student*
- *Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faulty of Medicine and Health Sciences, Stellenbosch University.*

Dr Johannes PJ Stofberg MBChB; MMed; Dip (HIV Management)

- *Specialist Family Physician*
- *Western Cape Department of Health*

Dr Johan Van Der Walt MBCHB; MMED; FCA

- *Specialist Anaesthetist*
- *Department of Anaesthesia and Perioperative Medicine, University of Cape Town*

Contents

1 What is this thing called pain?

Romy Parker
Gill Bedwell
Tory Madden
Cameron Reardon
Brett Mason
Dawn Ernstzen

Pain is a normal everyday life experience. Have you ever stubbed your toe? Really painful, isn't it? Let's think about stubbing your toe on a good day, though - you know, a beautiful, happy day when you are with people you love, you feel like life is good, and you are smiling, just because it's a good day. Let's say it's a warm sunny day, and you are walking barefoot in your home and talking with your friends and family. There is music, there is laughter, and as you are walking you catch your toe on the door, and it bends sideways – OUCH! How much does it hurt? For how long does it last? What do you do? Sure, it hurts, but not much, and only for a few moments, and you might shout or swear or even laugh, and then it's all over and you carry on with your good, happy day.

Pain is a sensory and emotional construct of the conscious brain.

What about stubbing your toe on a bad day? One of *those* days: it's cold, and you feel so alone and sad or stressed. You've had a fight with someone you love, you are hating your job or your studies, your bank account is empty, you're tired, and life just feels so hard right now. You have to get out of your warm bed and get ready for work, and you walk barefoot to the bathroom on the cold floor and as you walk you catch your toe on the door, and it bends sideways – OUCH! How much does it hurt? For how long does it last? What do you do? It's agony! You sit on the ground and grab your toe - you shout, you might cry, you check to see if it's broken. It is so painful you limp into the bathroom; you keep checking it, you struggle to put your shoe on because it's so sore and it throbs all day long, adding to your misery.

What does this tell us about pain? Pain is about more than what is going on in your toe (or any other part of your body). On each of these occasions, the damage to your toe was exactly the same, but the pain was completely different. When you stub your toe, the nerves in your toe carry danger messages, known as nociception, to the spinal cord and then up to the brain. But pain is about more than just nociception (those danger messages). Your brain receives those danger messages and evaluates them in context i.e., it evaluates what else is going on at that time, and the pain we experience is the result of putting all of this information together. Pain is a sensory and emotional construct of the conscious brain. It is a sensory emotion that the brain has created in response to a perception of (potential) threat or danger – and how much danger our brain generates depends on more than just nociception.

We all experience pain regularly, but what is it that motivates us to attend a clinic, to see a nurse or doctor or pharmacist or other healthcare professional for help? Let's keep thinking about stubbing your toe. When might you decide to see a healthcare professional about your sore toe? If the pain didn't settle down the way you expected it to? If it swelled up so much you couldn't get your shoe on? If it was so sore, you could only hobble? If it was still sore that night and you couldn't

sleep? If you remember your aunty who injured her toe and her toe had to be amputated? If it was stuck bent sideways?! Any of these symptoms or signs might worry you, might increase the amount of danger you felt you were in. And if the danger was greater than your own knowledge and skills to cope with it, you would seek help somewhere or from someone who is easy for you to access. That might be Google, a friend, your mother, or a healthcare professional. It is often not the pain alone which motivates us to seek help; we are motivated to seek help when we interpret the pain as being threatening or dangerous to us as human beings. As healthcare professionals, it is important to keep this in mind, and to assess beyond the pain to establish what the person with pain is worried is wrong, and what the person with pain is doing, or not doing, because of their pain.

DON'T MISS THIS

When it comes to pain, context counts!

Pain is a normal and helpful experience which motivates us to take action that will protect us.

Nociception is a message about potential danger in the body. It is not the same as pain. The amount of pain we feel (and whether we do actually feel pain) depends on context.

We are motivated to seek help when we interpret pain as being threatening or dangerous to us as human beings.

DEEP DIVE

What is the point of pain?

What would happen if you couldn't feel pain? There actually are a few people in the world who are unable to feel pain, and typically they don't live for very long. Pain warns us about danger so that we can protect ourselves. That's genuinely helpful when we have an injury, or even if we are at risk of an injury – if you jump into a bath that is hot enough to burn you, you need to get out of there fast! Pain is a potent way to get you to jump straight back out of the bath and avoid a burn. If you've had surgery and your wound needs time to heal, pain will remind you to protect the wound by moving more carefully. That is helpful, because it allows you to heal.

The priority, of course, is survival – so if there's uncertainty, your system will probably err on the side of assuming you're in danger (and generate pain), rather than wrongly assuming you're safe. If it assumes you're safe when you're actually in danger, you could die – and that wouldn't be especially helpful, would it?

This idea that we are biased towards protection might be why chronic or persistent pain is such a big problem: when our protective bias goes into overdrive, we can get stuck with pain when it's not actually helpful.

Communication about pain

Let's talk about communication. What do you do when you feel pain? How do you choose who to tell, and what to tell them? Most of us will tell people who we think can help us, perhaps with advice on how to look after the painful body part, or perhaps by giving us emotional support. In this way, we can understand that our communication strategies are shaped by our needs. Sometimes we don't recognise our own needs, but they are always there under the surface, and it's *completely normal* – even helpful – for our actions to be shaped by our needs. Some researchers refer to this as goal-directed communication about pain.

In turn, needs are shaped by context, and so they can change from moment to moment, and are often different between people. When Lethabo first felt pain in his stubbed toe, his most immediate need was to find out how badly his toe was injured. His first action was to inspect his toe. Once he could see that it wasn't even red, his need changed – he needed to get to work on time, so he continued walking briskly. When Junior first felt pain in his stubbed toe, his most immediate need was to get help – he yelled out, and his friend came running. Next, he needed to gauge the damage, so he inspected his toe. Having verified that there was no injury, he needed to release his discomfort (he was embarrassed about yelling so loudly over a non-injury), and he burst out laughing, which his friend took to mean that Junior was fine. Interestingly, even though Lethabo and Junior's actions and communication were shaped by their needs, it's likely that neither of them would have been able to pick out and name each need. Much of this process happens implicitly – almost automatically - and our control over it is limited.

Let's play a mind game. Picture Junior as coming from an exuberant, talkative family. When they eat together, the conversation gets louder and louder, everyone interrupting the next person to add parts to the story that is being told. Hands fly; gestures tell the story as much as the words do. Junior is immersed in this way of life; when he speaks, his face is animated, he speaks loudly, attracting the attention of the whole room. When you see him stub his toe and yell out, how severe do you interpret his pain to be? Maybe you don't think it is that severe because you know him: he's always loud and animated, it's not that bad.

Now, picture Junior as quiet, reserved, and careful with his words. He was taught never to exaggerate. He is a gentle person who has plenty of stories to tell but is careful not to take up too much time to tell them. With this Junior, when you see him stub his toe and yell out, how severe do you interpret his pain to be? Maybe you think it is really bad: he's always so quiet and reserved, so if he is being loud now it must be really severe.

The way we communicate about pain is intimately influenced by ourselves, who we are, and *how* we are in the world. The way our communication is received and interpreted is subject to the same features of ourselves - *and* of the receiver. There are many layers here – country, culture, sub-culture, schooling, family values and roles, social and work roles, and our level of comfort and familiarity within the context in which we are trying to communicate – and that's not even a complete list. Different people understand pain differently. For some, it's an indication of injury.

For others, sickness. For others, vengeful action by someone else. For others, personal weakness. Our interpretation of pain influences how we communicate about it – and if we acknowledge it at all.

The context of each interpersonal interaction also influences how we communicate about pain. Let's say you stub your toe as you're walking out of a job interview. You feel that you messed up and the interview didn't go well, but you are determined to hold onto your dignity as you exit the room. You stub your toe – OUCH! – but do you yell out or cry? Probably not! Another time, you stub your toe while you're walking with your best friend, who happens to be a kind and gentle person who is endlessly invested in your happiness. You stub your toe – OUCH! – and now, do you yell out or cry? Probably yes! We are all sensitive to what seems appropriate or acceptable in different situations. The same is true in a clinical encounter: many of us will unconsciously adopt the role that seems appropriate to the situation. This is one of the reasons why different people express pain differently.

Let's also remember: words are not the only way we communicate. Pain changes the way we behave – that's why it's so powerfully useful and why it can be powerfully disabling. There are many factors that influence the way we *behave in response to* pain. When you stub your toe painfully, do you stop walking? Hold it? Rub it? Ignore it and keep walking? If you keep walking, do you do so cautiously, or do you walk hard until the pain goes away? Your response to a painfully stubbed toe may be different to your response to a painful back, or a painful surgical wound: context is a rich and complex thing and can produce different behaviours in subtly different situations.

DON'T MISS THIS

Communication happens with and without words.

When we are in pain, the way we communicate about it is shaped by our needs. Different people will communicate about pain differently at different times and in different circumstances – this is normal. The way we interpret others' communications about pain is shaped by ourselves; it's not an objective process.

Understanding that pain is about context means that we must consider multiple variables when we want to understand what might be contributing to someone's pain. Nociception is one of those variables, but only one of them. Have a look at these two infographics, we've changed the sizes of the bubbles to demonstrate what variables might have contributed to your pain when you stubbed your toe on different days! But notice: the bubble for nociception is the same!

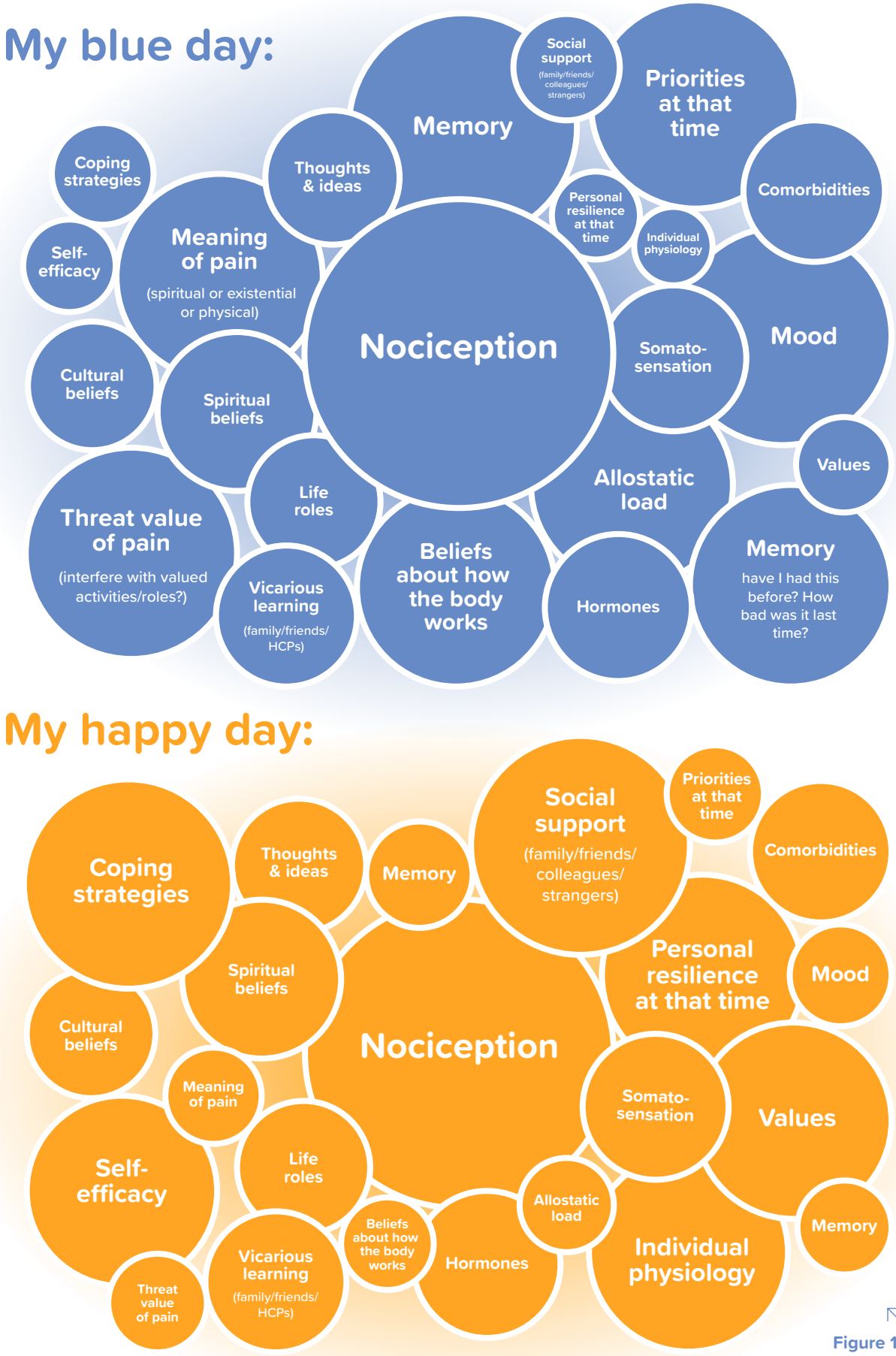


Figure 1.1: Contributors to pain

Pain language

In this book we will use some language and terminology for which you might not be familiar. We've tried to make a list of all the terms that we, as "pain nerds", use which you might not recognise.

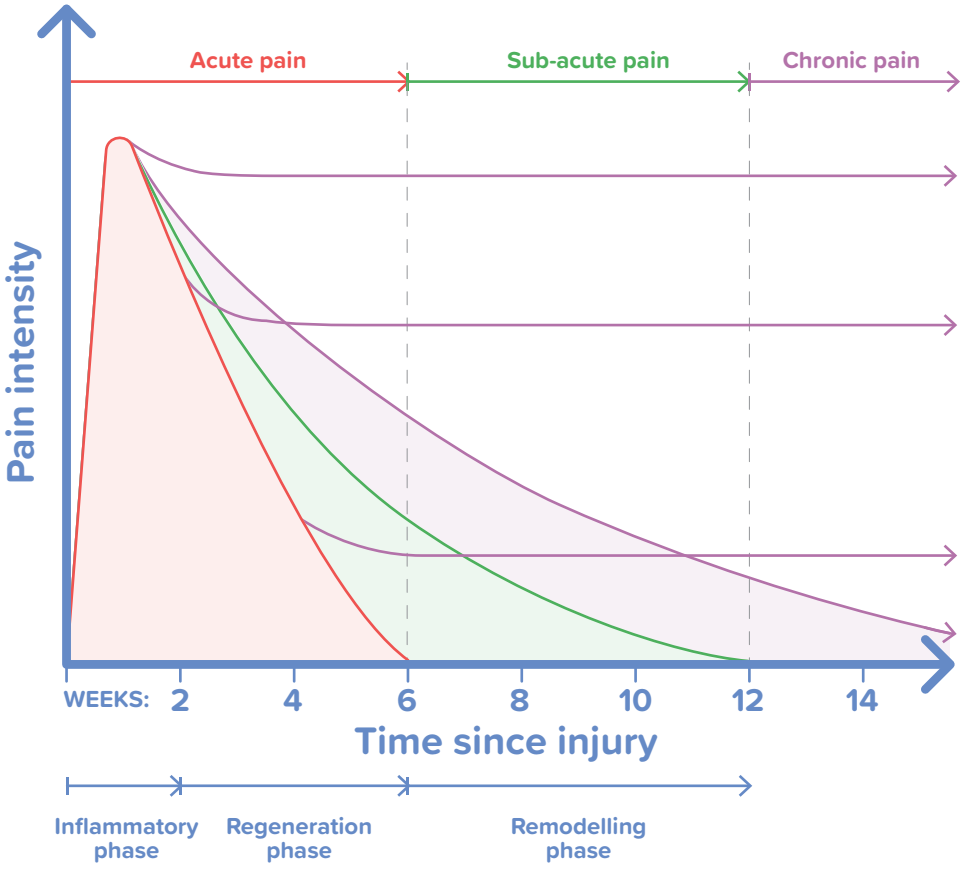
As you read through this chapter, you can keep referring back here for the definitions of the terms.

- Pain: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (1).

If we have used a term in the book and not explained what we mean, please let us know so that we can add it to this list!

- **Time-based definitions of pain** – it is useful here to think about these times in the context of tissue healing times as in Figure 1.2.
  - Acute pain: Pain lasting up to 6-weeks. As you can see in the diagram, this 6-week time reminds us that acute pain is usually associated with normal tissue healing processes in the inflammatory and regeneration phases of healing.
  - Sub-acute pain: Pain between 6 weeks and 3 months after an injury. As you can see in the diagram, this pain may be associated with tissue healing processes during the remodelling phase of healing.
  - Chronic pain: Chronic pain is defined as pain on most days for more than 3 months. Why 3 months? Because, after 3 months, most tissues have healed, so this pain has persisted beyond normal tissue healing processes.

Figure 1.2: Graph illustrating tissue healing and pain over time.



- **Mechanism-based definitions of pain**
  - Nociceptive: “Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors (2).
  - Neuropathic: “Pain arising from lesion or disease of the somatosensory nervous system” (2).
  - Nociplastic: “Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” (3) .

- **Nociception:** The process of encoding and transmitting a potentially noxious stimulus.
- **Allodynia:** Experiencing pain from a normally non-painful stimulus.
- **Hyperalgesia:** Experiencing excessive pain from a normally painful stimulus.
  - Primary hyperalgesia: Primary refers to the hyperalgesia being in the direct area of tissue damage.
  - Secondary hyperalgesia: Secondary refers to the hyperalgesia being in the surrounding tissues.
- **Function:** In the International Classification of Functioning (ICF) function relates to functioning of body structures e.g., if I have a knee injury, function of the knee may refer to having full range of motion in the knee (4).
- **Activity:** In the International Classification of Functioning (ICF), activity refers to the functioning of the individual e.g., if I have a knee injury, activity may refer to my being able to walk.
- **Participation:** In the International Classification of Functioning (ICF), participation refers to the individual’s ability to participate in all areas of life e.g., if I have a knee injury, participation may refer to my ability to do my job or play with my children or do my sport and hobbies. Participation links to meaningful life roles – the actions and behaviours that we engage in within our own context, and which contribute purpose or meaning to our lives (5).
- **Sensitisation:** “Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.” (2) When this occurs in the peripheral nervous system it is referred to as peripheral sensitisation and when in the central nervous system, central sensitisation.
- **Dysautonomia:** Dysfunction of the sympathetic and parasympathetic nervous systems i.e., autonomic nervous system, and is associated with a spectrum of symptoms including shortness of breath, tachycardia, hypotension, fainting, fatigue, excessive sweating, dizziness, nausea, and cognitive impairment or “brain fog”.

Remember that one person may present with acute and chronic nociceptive, neuoropathic and nociplastic pain at the same time. These can all overlap!

DEEP DIVE

Outcome measures in health care

An outcome measure in health care is a measurement tool used to determine the baseline and follow up information about a person's health status (6, 7).

Outcome measures are used to determine any change in the status of the person's health condition. It can measure whether there has been any progress or deterioration. The results of outcome measures can be used to guide care, and it enables a common language for communicating outcomes between interdisciplinary team members. Outcome measures can provide information on progress and can have a positive influence on motivation of the individual with the health condition.

An outcome measure needs to be valid, reliable, responsive to change, and fit-for-purpose. Therefore, an outcome measure needs to be applicable to the person and context in which it is being used.

Outcome measures have different purposes. Some outcome measures can be used for diagnostic purposes, or to determine risk category, others are used to monitor symptoms and abilities, to ascertain beliefs, or used for research purposes.

Some outcome measures are used to classify disease (e.g., the ICD – International Classification of Disease) or disability (e.g., the ICF – International Classification of Function). Outcome measures can be used to measure impairments, functional abilities, and participation according to the ICF. For example:

- **Impairment:** To measure the severity of pain,
- **Functional ability:** To measure your ability to perform an activity (such as walking a specific distance or climbing a number of stairs),
- **Participation:** To ascertain how the health condition influences your life roles, such as your ability to do your job.

There are many ways to complete outcome measures. Some outcome measures are completed by the person with the health condition themselves (self-administered), some are completed by the clinician based on information received, or by the caregiver. Other outcome measures are scored by the clinician when observing the person with the health condition performing an activity. Outcome measures that rely on patient reports of their health, are called patient-reported outcomes (PRO).

Pain teams - interdisciplinary vs multidisciplinary

As healthcare professionals, we know that we deliver better care when we work in teams. These teams can be interdisciplinary or multidisciplinary. We like to describe it like this:

> *"A multidisciplinary team can be likened to an orchestra, where all musicians are following the same song sheet, but each has a clearly delineated role, the conductor is never challenged, and the person with pain is a passive listener. An interdisciplinary team can be likened to a jazz band, where the musicians follow the same song-sheet, but roles are flexible, while each has a preferred instrument (i.e., remains in their scope of practice). In the interdisciplinary team, there is a blurring of roles and a fluidity in leadership with the leadership role passing from one to another, with active participation of the person with pain contributing to the form of the music. In this interdisciplinary jazz band model of healthcare, the physiotherapist will often take a leadership role but will also mentor people with pain to enable them to ultimately take the lead. The pain sciences have increased our awareness of how we work in teams and emphasised the value of paying attention to inter-professional communication in order to foster person-centred care" (6).*

Sometimes we must work in a transdisciplinary way if we are working in a setting where other healthcare professionals are not available. In these situations, we might become a “one-man band” and have to learn skills from other disciplines to be able to offer people with pain the care they need and deserve. This does not mean that we step out of our scope of practice, it means we upskill ourselves to benefit the people who come to us for help.

Who is in the team?

An interdisciplinary team comprises professionals from various disciplines, as well as the person with pain and their family or people who provide support. The team collaborates and coordinates their expertise to provide comprehensive and person-centred care. This team-based approach allows for a more holistic and integrated management of pain, addressing the psychological, social, and cultural dimensions of pain, as well as the biological contributors.

The team would consist of various professionals working together to provide comprehensive and coordinated care. Potential members of the interdisciplinary team include:

Nurses provide direct patient care, including administering medications, monitoring vital signs, and educating people with pain and their families on self-care and management strategies.

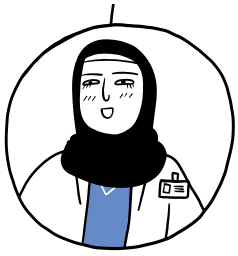
Physiotherapists/Occupational Therapists focus on physical and vocational rehabilitation, helping people with pain improve their physical function, mobility, and independence through therapeutic exercises, pain management techniques, and assistive devices.

Physicians play a central role in diagnosing and managing medical conditions, prescribing medications, and coordinating overall care.

The person with pain and their family: providing guidance on the goals of treatment.

Community Health Workers play a crucial role in resource-constrained settings, acting as liaisons between the healthcare team and the community. They provide education, outreach, and support to people with pain and their families, helping to bridge gaps in access to healthcare and addressing cultural and community-specific needs.

Social Workers assist people with pain and their families with psychosocial and practical challenges, such as accessing community resources, addressing social determinants of health, and providing support during the recovery process.



Psychologists/Counsellors contribute expertise in addressing the psychological and emotional aspects of pain management, providing counselling, therapy, and psychological support to people with pain and their families.

Optimising teamwork

In resource-constrained settings where healthcare resources may be limited, the advantages of an interdisciplinary team in pain management become even more pronounced. By pooling together everyone's expertise, the person with pain, physicians, nurses, psychologists, physiotherapists, occupational therapists, and social workers can optimise the use of the available resources. This allows for a more comprehensive assessment and management of pain, leading to improved outcomes.

However, there are also challenges associated with implementing and sustaining an interdisciplinary team in resource-constrained settings. One challenge is the need for effective communication and collaboration among team members, as it requires time, effort, and clear channels of communication. Limited resources, including staffing and financial constraints, may also impact the feasibility of establishing and maintaining a fully functional interdisciplinary team. Additionally, the availability and accessibility of specialists from different disciplines may be limited in certain areas, posing a barrier to interdisciplinary collaboration.

Despite these challenges, the advantages of an interdisciplinary team in pain management outweigh the disadvantages. The team-based approach allows for a more comprehensive understanding of pain and its impact on the individual, leading to tailored interventions that address the multifaceted nature of pain. It promotes shared decision-making, reduces fragmentation in care, and enhances the overall quality and efficiency of pain management services.

To maximise the effectiveness of the team, clear roles, responsibilities, and communication channels should be established. Regular team meetings, case discussions, and shared documentation systems are essential for effective coordination and collaboration. In resource-constrained settings, the team should prioritise efficient use of available resources, considering the feasibility and cost-effectiveness of interventions.

The team-based approach allows for a more comprehensive understanding of pain and its impact on the individual, leading to tailored interventions that address the multifaceted nature of pain.

2 What's going on inside?

Gill Bedwell
Luyanduthando Mqadi
Murray McDonald
Brett Mason
Tory Madden
Romy Parker

Introduction

There is a LOT of information in this chapter; it is content heavy! Because of that, we give you some key learning outcomes to clarify what we hope you will take away from this chapter. For each section, we will give you a list of our learning outcome goals, so that you can look out for that information as you read.

The physiology of the multiple mechanisms which contribute to pain can be complicated to understand. A model is a way for us to break down complex ideas or systems, so as to learn and understand complex events or processes. To help us understand pain, we have used a four-part model consisting of:

1. The peripheral nervous system
2. The spinal cord
3. The brain
4. The synergistic systems which impact on the peripheral and central nervous systems

Please note: Although we use this four-part model to explain pain, it's important to understand that these four systems do *not* work independently nor sequentially. **Instead, they work together, simultaneously influencing each other.** It is like fireworks all going off at once!

We think it is much easier to learn about pain if you can relate it to your own experiences. In this chapter, we are going to explain pain based on this story...

Imagine you reach over the stove and accidently your hand touches a hot plate that you didn't realise was on. "OUCH!" you shout, and rapidly pull your hand away from the stove. You feel a sharp, burning pain in the skin on your thumb as you rush over to the sink to run cold water over your hand and relieve the pain. You feel a wave of irritation wash over you. You are already running late for work and now this! You start to feel a bit anxious as you remember you needed to meet your boss first thing this morning. After a few minutes under the cold water, you dry your hand and inspect the skin. You notice the skin is bright red where your hand touched the stove.

For the rest of the day, you are very aware of this burn. Even the skin that wasn't burnt seems sensitive. You notice that stimuli that are not usually painful are now painful, such as warm water from the shower and rubbing your hand on a towel. While at work later that day, you accidently knock your same hand on the corner of your desk (you are clearly having a clumsy day). "OOOOUCH!" you yelp. You realise that hitting your hand on the desk is much more painful now than it would usually be. You inspect the injured area again and notice that the area of redness has spread slightly beyond the area that you burnt. You found this interesting, so you poked the area around the burn with the tip of your pen – "Eina!". You realise that poking the area next to the burn is more painful than it would usually be. By the end of the day, it's not just your hand that is aching, the pain has spread past your wrist. It's all feeling sensitive - and so are you!

Let's look at the physiology of what exactly happened in your body when you burnt your hand and how these physiological processes related to what you felt, how your skin looked, and what thoughts and feelings you had.

What is happening in the peripheral nervous system when we feel pain?

By the end of this section, we hope you will have a clear understanding of:

1. The signs and symptoms indicative of peripheral upregulation.
   - **a.** Primary hyperalgesia.
   - **b.** Pain which behaves in a predictable pattern or in a way that is clearly associated with particular tissue damage.
   - **c.** How the onset and timing of pain is associated with tissue damage and the phases of tissue healing.
   - **d.** The signs associated with inflammation (hot, red, swollen).
2. The basic physiological mechanisms, including peripheral sensitisation, which underlie these signs and symptoms of peripheral upregulation.

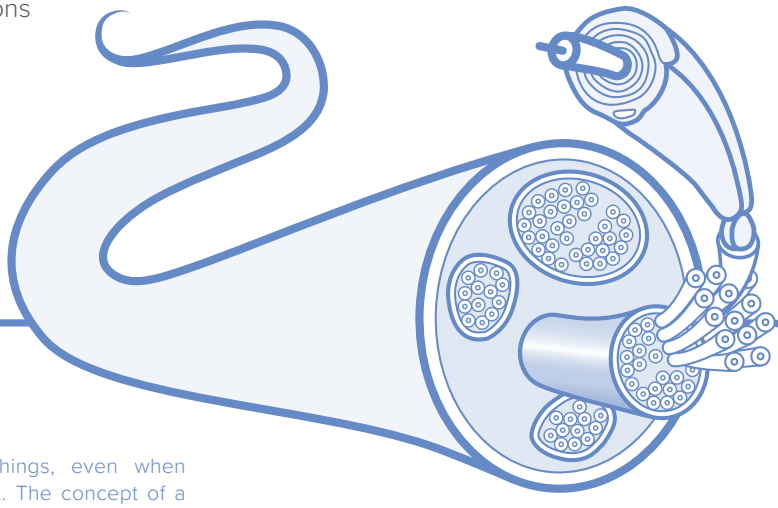
DON'T MISS THIS

Primary hyperalgesia is normal

Primary hyperalgesia is NORMAL and helpful when there is acute tissue damage. It is helpful and important to protect damaged tissue to help it heal! But primary hyperalgesia which outlives the normal phases of tissue healing is problematic and suggests chronic nociplastic changes.

We are focusing here on the neurons of the peripheral somatosensory nervous system, namely the:

- A-beta fibres (Aβ fibres)
- A-delta fibres (Aδ fibres)
- C-fibres



DEEP DIVE

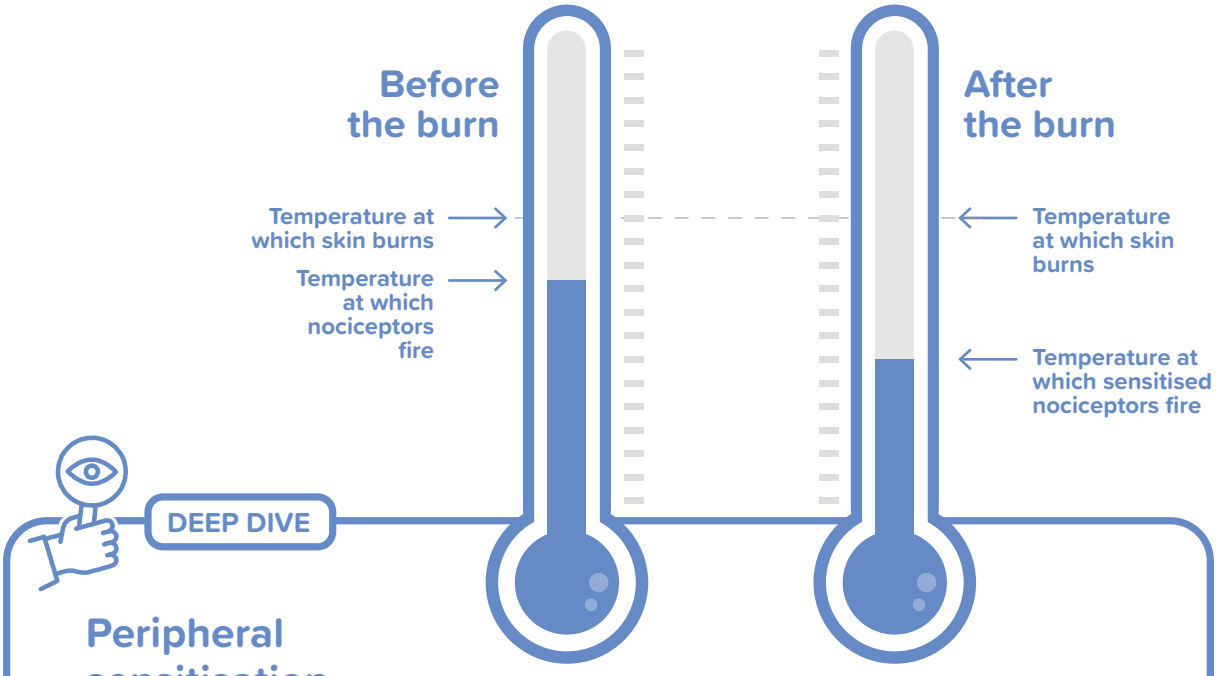
Nociceptors

We humans like to simplify things, even when they are actually rather complex. The concept of a nociceptor is useful, but defining a nociceptor is tricky. When scientists first looked at neurons with a microscope and described what they were seeing, they used the diameter of the neuron to create a naming system: A, B, C, etc. Later, they divided each diameter into subcategories, and that's how we arrived at the names of A-beta, A-delta, and C-fibres. There is some consistency in the behaviour of neurons that fall within these subcategories, but also plenty of variation within each subcategory, and a few exceptions! For example, C-fibres can respond to mechanical, heat, and cold input, but not all C-fibres respond to cold input. Also, while we think of a nociceptor as responding to high-intensity input only, some nociceptors lower their response threshold to respond to low-intensity input after they have received a 'sensitising' barrage of input. Should they still be considered nociceptors if they are capable of responding to low-intensity input under certain conditions? Probably the most important thing is to remember two things: (1) that nociceptors are specially adapted to respond to events that could be harmful, and (2) that some nociceptors can adjust their response range when the tissue is more vulnerable, such that they now respond to events that are usually non-harmful, but that could now be harmful (to vulnerable tissue). Isn't that a remarkably versatile system? Also remember to hold lightly to this terminology – as science progresses and we learn more, the language could change!

What happened when we touched this hot stove?

The heat from the stove is a high threshold stimulus that threatens tissue integrity. There are two important classes of nerve fibres that respond to high threshold stimuli: Aδ and C fibres. These fibres are termed *nociceptors;* they respond to (potentially) threatening stimuli (what we mean here is that their firing threshold is just below the point of tissue damage – they fire before we are injured. After all, pain is protective; the point of pain is to get us to change our behaviour to prevent or reduce tissue damage or protect ourselves if tissue damage has occurred). In response to the tissue damage, there will be vasodilation and an increase in proinflammatory cytokines at the injury site. These proinflammatory cytokines, together with increased local tissue acidity and temperature contribute to upregulation of the nociceptors (i.e., Aδ and C fibres). Upregulated nociceptors are sensitised and have:

1. A lowered firing threshold,
2. An increased responsiveness to stimulation,
3. Activation of silent nociceptors.



DEEP DIVE

Peripheral sensitisation

When we refer to upregulation of nociceptors, we are referring to the plasticity of the nervous system. Neurons are not "hard wired" for messages. They are plastic; they have the ability to become more or less sensitive to stimuli. You have probably noticed this plasticity yourself. Have you ever tried to fall asleep at night when you can hear a tap dripping? You try not to listen to the drip, drip, drip. But the more you try not to listen to it, the louder it gets! It's like you "tune into it". You know the drip is not actually getting louder; your system has 'upregulated' its sensitivity to the sound. Whenever we are thinking about pain, we are fundamentally engaging with the plasticity of the nervous system, which is its amazing ability to learn and change.

Upregulation in the peripheral nervous system is also often referred to as peripheral sensitisation – the peripheral nerves have become sensitive. You know what it feels like when you are feeling a bit sensitive, right?

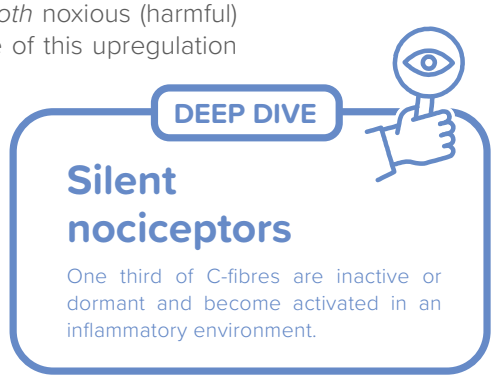
1. Your firing threshold is low – it doesn't take much to set you off!
2. You have an increased responsiveness to stimulation – when you "go off at someone" you really do it loudly and noticeably.
3. You have more of your nervous system on alert. You know that feeling of being super aware and noticing everything going on?

This is sensitisation!

Primary Hyperalgesia - a sign of peripheral upregulation

Remember in the story hitting your hand on the desk was now *more* painful than it usually would be? This is explained by the phenomenon of hyperalgesia – increased pain to a normally painful stimulus. Primary hyperalgesia – increased pain *in the area of tissue damage* – is a clinical sign that could indicate upregulated peripheral nociceptors.

In response to the release of proinflammatory cytokines at the site of tissue injury, the nociceptors have become upregulated. First, nociceptors develop a lowered firing threshold. This means that they are now respond to *both* noxious (harmful) and innocuous (not harmful) stimuli, whereas in the absence of this upregulation (i.e., at 'resting' state) they would respond to noxious stimuli only. Second, nociceptors develop an increased responsiveness to stimuli. This means they respond more quickly to stimulation by depolarising and repolarising more quickly. Finally, a sub-class of C-fibres (silent nociceptors) become activated.



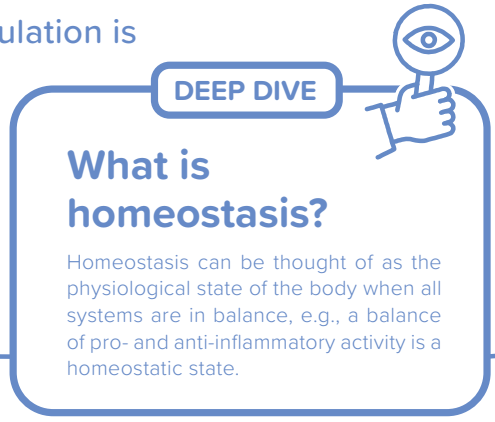
These three mechanisms all contribute to the peripheral nociceptive system's being more sensitive, meaning we experience more pain than usual when the site of tissue damage is exposed to stimuli that are normally painful. Remember: peripheral upregulation (or sensitisation) is normal when there is acute tissue damage. In the story about burning your hand, you can recognise that this is a normal response. The timing of injury, inflammation, and evidence of tissue damage tell us that the primary hyperalgesia you experienced – increased pain when you hit your burnt hand on your desk – is normal; it is form of nociceptive pain, and it is protective.

Symptoms that indicate the peripheral upregulation is associated with acute tissue damage (nociceptive mechanisms)

Primary hyperalgesia is usually associated with inflammatory processes. This means that, if primary hyperalgesia is present during the acute phases of healing (72hrs to 14 days), it is considered normal, because it is temporally associated with the inflammatory response. In addition to considering tissue healing times, the clinician can also assess for signs of inflammation such as redness or changes in colour, increased local tissue temperature, and swelling – further indicators that the primary hyperalgesia is underpinned by normal peripheral upregulation in response to the inflammatory process. Finally, pain arising from peripheral upregulation tends to be predictable. What we mean here is that there will be clear stimuli (mechanical, thermal or chemical) which aggravate and ease the pain. Think of burning yourself on the stove, it feels better when you keep it still, but movements which stretch the burnt skin are painful.

Symptoms that indicate the peripheral upregulation is associated with neuropathic or nociplastic mechanisms

As tissue heals, inflammation decreases and so should pain. Your burn will be painful for a few days but as tissue healing progresses and inflammation resolves, the pain should ease over time. This is the normal process of restoring homeostasis.



However, if there is lesion or disease of the peripheral nerves (pathology of the nerves i.e., a *neuropathic* problem) then the nerves can start to fire spontaneously. This is known as spontaneous, ectopic, pacemaker-like activity. This spontaneous firing of the nerves can result in continued peripheral upregulation, even when the tissues that the nerves innervate have healed. The symptoms that suggest that the primary upregulation may be associated with neuropathic mechanisms include:

1. The nature of the pain being spontaneous, electrical, shooting or pins and needles
2. The person has comorbidities associated with neuropathies e.g., uncontrolled diabetes mellitus.
3. There is evidence of lesion or disease of the somatosensory nervous system, such as loss of sensation or loss of motor control confirmed by a neurological examination.

With chronic nociplastic pain, it is possible that primary hyperalgesia may be maintained even after the initial tissue damage has healed. This is a situation where homeostasis has not been restored. The symptoms that suggest that the peripheral upregulation may be associated with nociplastic mechanisms include:

1. Pain remaining (or increasing) despite tissue healing times having been surpassed, e.g., it's more than 6 weeks since your burn but you still have pain.

2. Pain remaining (or increasing) despite there being evidence of the inflammation resolving. The heat may have gone or reduced, the colour is normalising, and the swelling is steadily reducing or gone.

DON'T MISS THIS

Describing neuropathic pain

The sensation we describe here as "pins and needles" is a cultural description. In some cultures, this altered sensation is described as "tingling" or "feels like ants or insects are crawling along my skin" or "itching" or "pricking" (8). Useful clinical tools to help you diagnose neuropathic pain which we will discuss in the next chapter are the DN4 – Douleur Neuropathique-4 (9), and the LANSS – the Leeds Assessment of Neuropathic Symptoms and Signs (10).

What is happening in the spinal cord when we feel pain?

By the end of this section, we hope you will have a clear understanding of:

1. The signs and symptoms indicative of spinal cord upregulation.
   a. Allodynia.
   b. Secondary hyperalgesia.
   c. Pain referred into the neighbouring spinal segment.

2. The basic physiological mechanisms which underlie these signs and symptoms of spinal cord upregulation.

Before we begin to understand the mechanisms behind spinal cord upregulation, we need to explain how nociceptive action potentials from the periphery are transmitted to second-order neurons in the spinal cord. We also need to understand how nociception can be modulated in the spinal cord. Have you ever heard of Melzack and Wall's "Gate Control Theory"? The "Gate Control Theory" is a really useful model for us to understand how nociception is modulated at the level of the spinal cord. (11) Let's take a look!

Have you ever banged your shin against a sharp corner? Painful, isn't it?! What is the first thing that you do? I usually quickly rub the shin and it starts to feel better. Why?

When you bang your shin, your nociceptors in the peripheral nervous system will fire; they are responding to a noxious (potentially damaging) stimulus. That action potential will be delivered to the second-order neuron in the dorsal horn of the spinal cord. The second-order neuron will "hear" that action potential and generate an action potential to transmit nociception up to the brain. In the brain, the nociceptive information is transmitted across multiple areas of the cortex. One of the areas that will receive the information is the hippocampus – the memory area. You may remember that, when you were a child, a caring adult once taught you to rub the skin if you hurt yourself because it makes you feel better. And so, you rub your shin. Rubbing your shin stimulates the faster sensory neurons in the peripheral nervous system (like Aβ fibres, which respond to light touch) which transmit action potentials to the same second-order neuron that was receiving information from the nociceptors (and remember the nociceptors propagate action potentials relatively slowly compared to the Aβ fibres).

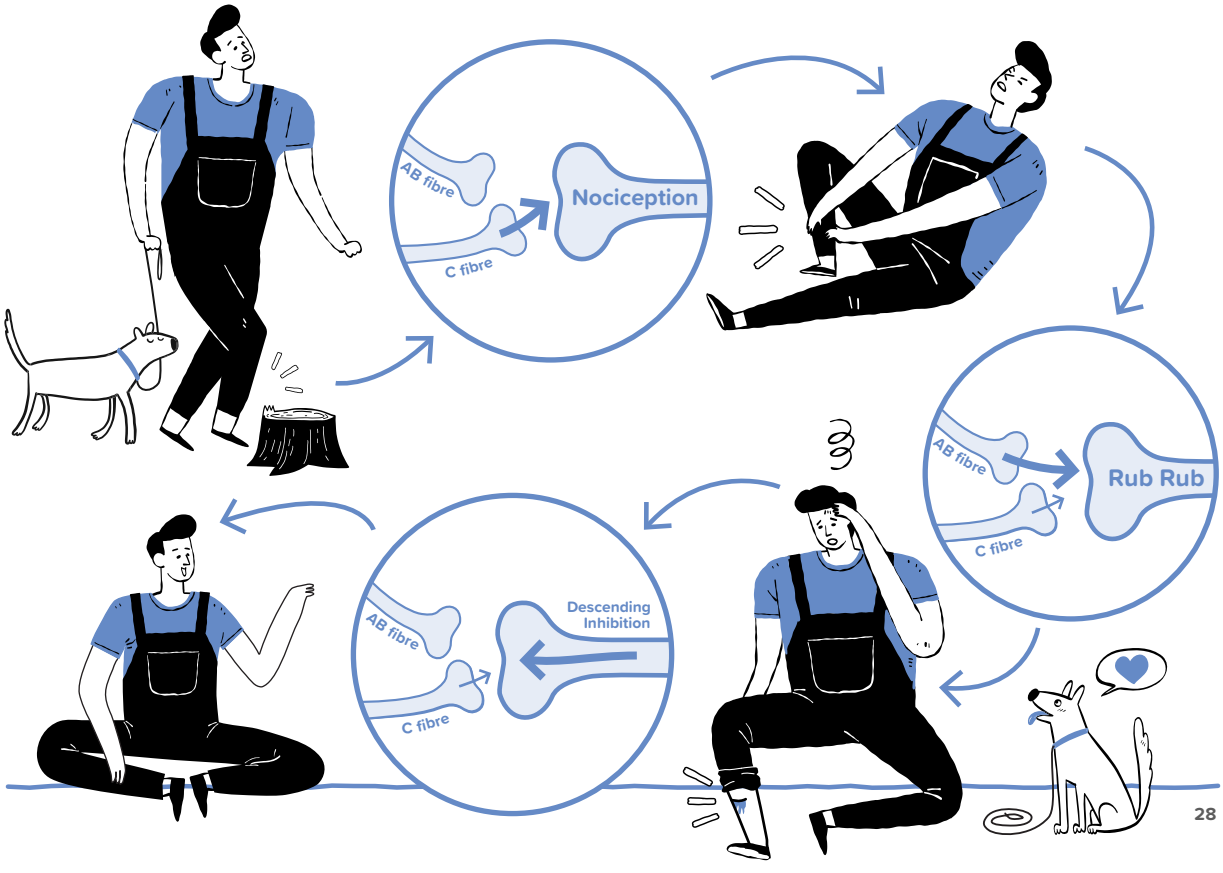
DEEP DIVE

Memory and pain

In the above scenario, using the word "remembering" might suggest to you that you are conscious of this remembering. But it is very likely that you are not conscious of it, the remembering is unconscious, but it does stimulate a learnt behaviour from you – to rub the sore spot.

The fact that these are learnt behaviours are important to be aware of as a healthcare professional, because people who are raised in environments which are not nurturing, where there were not adults to comfort and care for them when they were hurt, might not have learnt self-soothing or self-care behaviours which we recognise. They might not rub, blow, cry, or even ask for help when they have pain.

The second-order neuron now closes the gate (stops "listening") to the slow message from the nociceptors and opens the gate wide to receive the faster messages from the sensory neuron. Thus, nociception is inhibited at the spinal cord level and *not* sent up to the brain for processing, and so the system generates less pain. But you don't stop there when you've hit your shin quite hard! I always want to have a look, don't you? Why would we want to look at it?



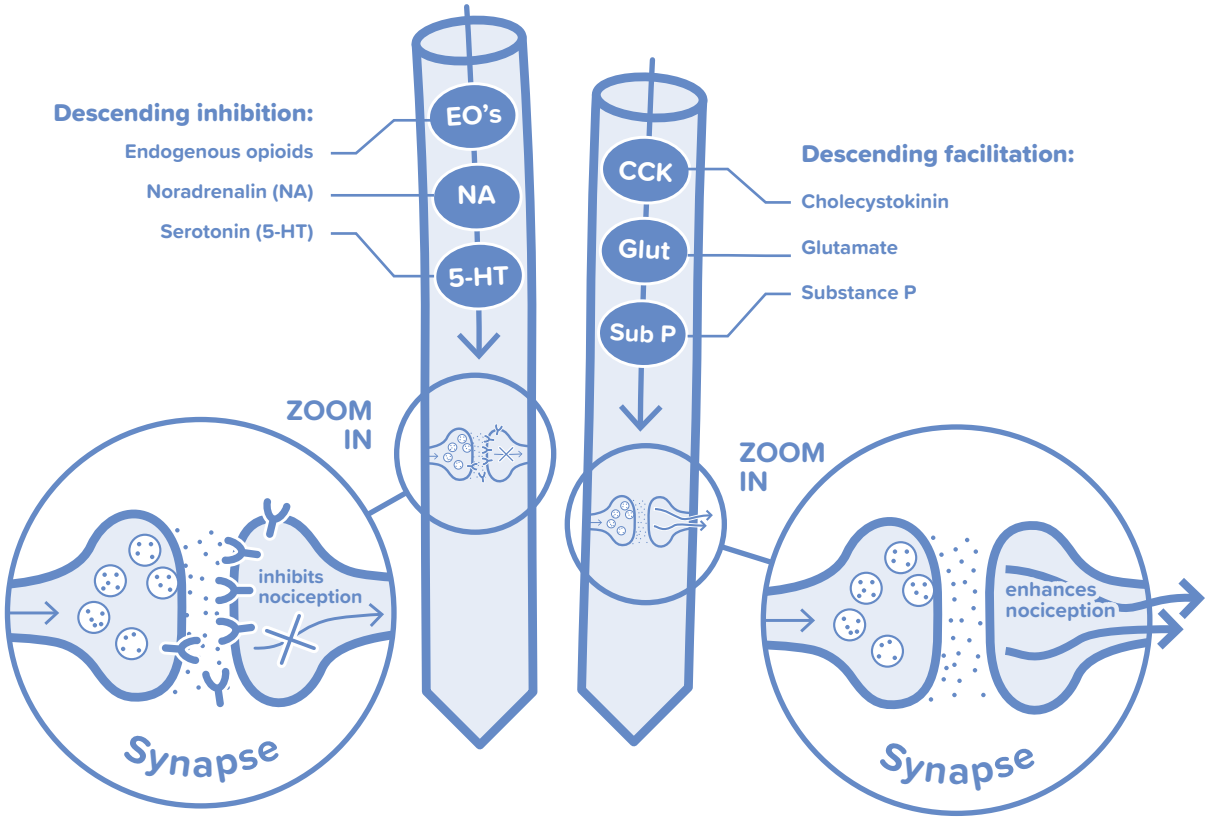
Looking at the area (or asking someone else to have a look) is a way for you to evaluate how bad it is really. Remember in Chapter 1 we talked about pain being a sensory emotion that our brain creates in response to a perception of threat? Your brain evaluates ALL the available information to conclude the danger of the situation. So, taking a look at the area is a way for your brain to get more information; your brain is trying to find out: how dangerous is this really (12)?

So, what happens if you look at your shin and it looks fine, no blood, no bruise, nothing? Well, your brain may conclude that it's not so dangerous, it's safe to carry on and your brain initiates **descending inhibitory control.** An action potential is sent in an inhibitory neuron, back down to the spinal cord, to release neurotransmitters that block the receptors at the second-order neuron (a bit like putting cotton wool in the ear so now it can't hear the nociceptive message), and so pain feels better!

But what happens if you look at your shin and there is evidence of damage (maybe there is blood or swelling or a bruise!) – your brain may conclude that this is really dangerous, it's not safe to carry on, you need to change your behaviour and get help now! Your brain can initiate **descending facilitatory control.** An action potential will be sent back down an excitatory neuron to the spinal cord, to release neurotransmitters that sensitise the second-order neuron to the nociceptive message coming in (a bit like tuning into the sound of a dripping tap!), and so the pain feels worse! Have a look at Figure 1.3 where we've provided a simple diagram to help you understand these mechanisms.

Remember: all of this is happening subconsciously in microseconds and out of your control. Melzack and Wall's "Gate Control Theory" helps us to understand how nociception can be modulated at the level of the spinal cord. Now, let's discuss what happens in the spinal cord when there is enough upregulation to lead to allodynia, secondary hyperalgesia and referred pain.

Figure 1.3
Descending inhibitory and descending facilitatory control



DON'T MISS THIS

Modulating nociceptive input

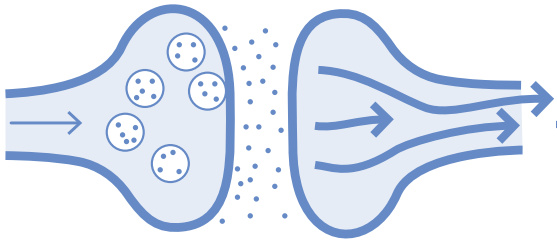
Modulating nociceptive input at the spinal cord level via competing *incoming* messages is often referred to as "bottom-up" modulation. We are "closing the gate" in the spinal cord from the bottom – by stimulating the peripheral nervous system to close the gate. Modulating nociceptive input at the spinal cord via *descending* inhibitory or facilitatory mechanisms is often referred to as "top-down" modulation of pain. We are "closing the gate" in the spinal cord from the top - our brain has the ability to turn the volume down (or turn the volume up) by decreasing (or increasing) the sensitivity of the second-order neuron in the spinal cord. We have lots of treatments that target pain from the "bottom up", including touch, movement or electrical stimulation; and we have lots of treatments that target pain from the "top down", including education, reducing fear and anxiety or centrally acting pharmacotherapy. We also have a lot of treatments which work from both the "bottom up" and "top down", like massage and exercise.

Allodynia – a sign of spinal cord upregulation

Let's go back to the burn on your hand. Picture yourself coming out of the shower and wrapping yourself in a bath towel (non-painful stimulus). OUCH! The towel brushes your burnt skin on your hand, and you immediately realise that your skin feels painful. The towel is an innocuous stimulus that activates Aβ fibres – fast and thickly myelinated fibres that carry signals in response to light touch. Now why has a stimulus that should produce a sensation of touch, generated pain?

The second-order neuron in the spinal cord can become sensitised via "bottom-up" and/or "top-down" mechanisms. The "bottom-up" mechanism of sensitisation occurs if there are a lot of incoming action potentials from the first order neuron (i.e., peripheral nociception). Lots of nociception coming in from the periphery can result in a lot of excitatory neurotransmitters, such as glutamate and substance P, being released into the synapse. The result is that the second-order neuron becomes sensitised.

DEEP DIVE



Spinal cord sensitisation

Second-order neurons in the spinal cord can become sensitised, specifically, at the synapse between the first-order neuron from the periphery and the second-order neuron in the dorsal horn of the spinal cord. When there is a lot of activity at this synapse there is an increase in the release of excitatory neurotransmitters, such as glutamate and substance P, and proinflammatory mediators, such as nitric oxide and calcitonin gene-related protein (CGRP). This increase in excitatory neurotransmitters contributes to an increase in the expression of α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and activation of N-methyl-D-aspartate (NMDA) receptors on the post-synaptic membrane. Further, CGRP and substance P, which are released from the C-fibre presynaptic membrane, are thought to disinhibit NMDA receptors. This increase in excitatory neurotransmission and upregulation of receptors enhances nociception from the dorsal horn of the spinal cord to the brain. This increased synaptic activity within the dorsal horn of the spinal cord is referred to as spinal long-term potentiation.

But remember the "Gate Control Theory" has "bottom-up" and "top-down" modulation. Once nociception is transmitted through the dorsal horn and up to the brain, the brain integrates and evaluates all the information it has (e.g., is the environment safe/dangerous, is/isn't there evidence of tissue damage, have I experienced this before, etc). The brain may conclude that the situation is dangerous and generate an experience of pain, and at the same time activate the "top-down" descending facilitatory mechanisms. These descending facilitatory mechanisms will contribute to spinal cord upregulation. In order words, the system 'turns the volume up' at the spinal cord.

Allodynia is an indicator of sensitised second order neurons.

Next, let's imagine you are concerned about the pain from the burn. You are worried that you aren't going to be able to use your hand, you are worried it might not heal, you are worried about not being able to do your work properly with this injured had. Together, those worries could activate further descending facilitation. The "top-down" mechanism releases more neurotransmitters like substance P and brain-derived neurotrophic factor (BDNF) into the synapse in the spinal cord, sensitising the second-order neuron and contributing to spinal cord upregulation.

A sensitised second-order neuron has (i) decreased firing thresholds, (ii) increased firing rates and (iii) increased receptor field sizes. These three mechanisms contribute to allodynia – pain from a stimulus that is normally non-painful.

Secondary hyperalgesia and referred pain – signs of spinal cord upregulation

Remember, in the story, the redness or flare response spread beyond the area of the burn, and there was exaggerated pain in this area adjacent to the burn when it was poked with a pen? In the section on the peripheral nervous system, we learnt that increased pain to a normally painful stimulus *in the area of tissue damage* is termed **primary hyperalgesia** and occurs due to peripheral sensitisation. Now, we are introducing you to a similar term with a subtle but important difference: **secondary hyperalgesia.** Secondary hyperalgesia refers to increased pain to a normally painful stimulus *adjacent to the area of tissue*. Secondary hyperalgesia occurs due to sensitisation within the spinal cord.

Secondary hyperalgesia indicates that the second-order neuron has not only reduced its firing threshold (making it more sensitive to stimulus) but has also increased the size of its receptive field, and there is activation of adjacent neurons. We can refer to this activation of adjacent neurons as a 'spill over' of nociceptive activity. This 'spill over' or spread of nociceptive activity, together with the lowered firing threshold, contributes to the spreading of hyperalgesia beyond the area of tissue damage. Therefore, as a clinical sign, secondary hyperalgesia indicates that there is upregulation in the spinal cord.

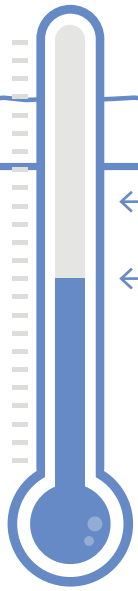
And remember, in the story, not only were the hyperalgesia and redness spreading, but the pain spread too. By the end of the day the pain had spread to your wrist which was aching uncomfortably. The referral of pain into neighbouring spinal segments is another indicator of spinal cord upregulation. The second-order neuron increases its receptive field size and so the pain spreads. From the second-order neuron in the spinal cord, the nociceptive message is transmitted up the spinothalamic and the spinomesencephalic tracts to the brain.

DEEP DIVE

Secondary hyperalgesia and allodynia

Generally, secondary hyperalgesia (SH) is a long-lasting clinical feature of various pain types, usually occurring in the absence of visible tissue injury, as seen in people with neuropathic pain. SH is pain to a usually painful stimulus, that extends beyond the injured skin area. In a laboratory setting, SH can be induced using a wide range of cutaneous injuries, including burns, electrical stimulation, freeze injuries, etc.

An example of a technique used to induce SH is to heat the skin at 47°C for 5 minutes to produce a burn injury. Secondary hyperalgesia peaks approximately 75 minutes after the burn injury. A mechanical stimulus such as a poke with a blunt-ended pin is often used to assess the presence of SH. A more common version of skin hypersensitivity is 'allodynia' - pain to a stimulus that is normally non-painful. To give you a real-life example of secondary allodynia (i.e., allodynia in skin adjacent to a site of injury), imagine you are chopping vegetables and accidentally cut the skin of your index finger. You immediately wash off the blood and continue chopping vegetables.



The pain may or may not disappear in the area where you cut yourself. However, a few minutes later, you realise that the area around your injury is painful every time you carry or hold objects that are in contact with your injured finger. This pain to stimuli around the injury is secondary allodynia.

This hypersensitivity of undamaged skin is thought to be characterised by several automatic responses in the dorsal horn, which include frequent afferent signalling, strengthening of synapses, 'spill-over' of neural activity to adjacent neural pathways, and increased neural activity reaching the brain to produce a broadened distribution of neural activity that extends beyond the areas of the central nervous system that are usually allocated to processing input from the site of your injury. Evidence suggests that this broad distribution of neural activity is a consequence of central sensitisation in the spinal cord's dorsal horn, and accounts for the characteristics of the hypersensitivity.

What is happening in the brain when we feel pain?

By the end of this section, we hope you will have a clear understanding of:

1. What activity occurs in the brain to generate the sensory emotional experience that is pain.

2. The signs and symptoms of brain upregulation contributing to pain.
   a. Pain referral patterns.
   b. Sensitivity to physical activity.
   c. Pain aggravated and eased by psychosocial factors.
   d. Central sensitisation.

3. The basic physiological mechanisms which underlie these signs and symptoms of brain upregulation.

Let's go back to your burnt hand and how it made you feel that day. Remember: by the end of the day, it wasn't just your hand that was feeling sensitive; you were feeling sensitive too! Pain affects our emotional state and mood. Every time you use the hand it can be a reminder of how stupid it was to touch the hot stove, or maybe even give you just a hint of fear every time you touch the stove again. Your mind keeps flitting back to the pain and the stove, so now you're finding it difficult to concentrate. You're finding it difficult to pay attention to what your boss is saying, and you keep forgetting what you just read in an email. Maybe you become hypervigilant and keep poking the area to see if it's feeling better. The pain might interrupt your sleep, and oh great, now you're tired as well as being sore, grumpy, and unfocused.

What parts of the brain might be involved in generating all this complexity? fMRI scans have allowed us to identify hundreds (yes, hundreds!) of discrete areas of the brain involved in pain. The parts of the brain generating the immediate sensory symptoms of pain might be fairly obvious: the thalamus distributes nociception, and the somatosensory cortices register the location and sensation of the stimulus (hot stove on hand). The premotor and motor cortices (along with the cerebellum) respond to make you move your hand away. Your frontal cortex determines your reaction and brings your attention to the stimulus – perhaps you shout/swear/cry and then you put the burn under cold water. The anterior and mid-cingulate cortices and the insula are involved with the simultaneous emotional components of pain, the "unpleasantness" of the sensation. All of this activity happens in microseconds, simultaneously and outside of our conscious control, and all we are aware of is the end product...pain!

DEEP DIVE

Mapping your body in your brain

The primary and secondary somatosensory cortices, and the pre-motor and the motor cortices, all have homuncular representations of the body. Do you remember the upside-down "mapping" of the body in the brain? Representation on the homunculus is use-dependent. This means that the more you use a limb, the better the map for that limb. fMRI studies have shown that these maps change based on the amount we use limbs, and the amount of attention we pay to them. Within two weeks of having your dominant hand and arm immobilised in plaster of Paris, fMRI scans show that the map for that hand and arm shrinks, and the map for your non-dominant hand and arm gets larger as you have now been using it more (13). We all know that if someone goes blind, their hands become more sensitive, and they can tell the difference between small coins and even feel and interpret Braille! We all tend to think that their hands have become more sensitive; actually, it is the map of their hands in the brain that has become more detailed, more sensitive. Perhaps if you think about your own experience of learning how to palpate (pulses or tissues) you will also notice that your brain-held maps of your hands have also become more sensitive with practice and training.

Pain is complex right?! As we said, pain is not only a sensation. It is also an emotion, so the brain activity doesn't end there. Several other areas, such as the amygdala, ventral tegmental area (VTA), hippocampus and nucleus accumbens (NA), help us make sense of nociception in terms of emotional (e.g., anger, fear, general grumpiness) and motivational responses (e.g., run, fight, crawl up in a ball, seek help) - they help us know how to feel, and what to do about the pain. Remember, pain is always contextual. Context incorporates past memories, current environment, and expectations of the future. Our brain accesses memories (hippocampus), current senses (e.g., visual, auditory) and future expectations (prefrontal cortex) to make sense of nociception and evaluate how threatening or safe the situation is.

And the activity doesn't stop there: remember the spinal cord and the Gate Control Theory's explanations of the "top-down" modulation of the spinal cord? These areas of the brain which generate the emotional and motivational aspects of pain link directly to the periaqueductal grey (PAG) area and the rostroventromedial medulla (RVM) in the midbrain. This is where the descending inhibitory or descending facilitatory messages originate. These are the areas of the brain that can turn the volume of the nociception at the second-order neuron up or down, just like on a radio.

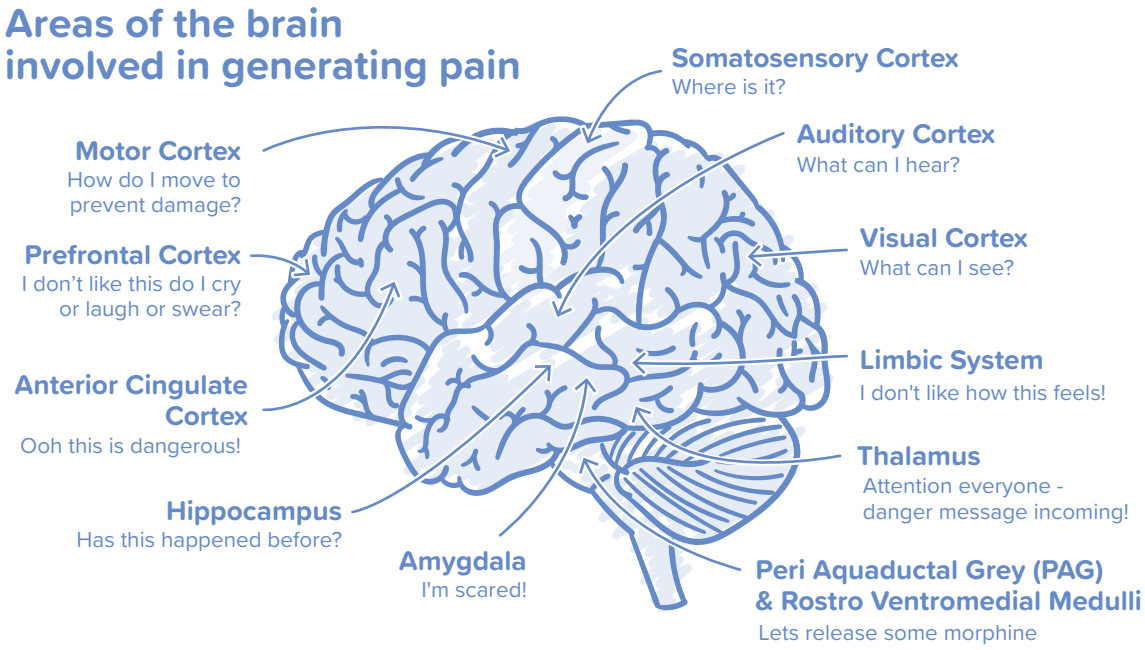


Figure 1.4: Areas of the brain involved in generating pain

By now you might be wondering, "But where is the pain centre of the brain?" to which we might reply, "We'd also love to know!". However, it is unlikely that any one of these areas is the "pain centre". Pain is a complex, emergent phenomenon - more than the sum of its parts. Your brain receives information from several different spinal tracts (and cranial nerves), processes the information based on what you know about the past, present, and expect from the future, and does its best to protect you from danger by stimulating various responses. No single area is sufficient for the experience of pain - it's a matrix, an orchestra of various pitches and rhythms that make up the rich and layered experience of pain. It is a complex and beautiful lifesaving system, but its complexity might also lead us into problems.

What happens in the brain when we suffer from neuropathic or nociplastic pain?

Several regions of the brain have been found to change the way that they function when pain is ongoing. The global changes in the brain are referred to as brain upregulation or sensitisation. There are alterations in the connectivity between regions of the brain; some areas become more active, and connections become more efficient, whereas other areas become less active, and connections become less efficient. Further, there are alterations in the functioning of the descending systems to the spinal cord – the "top-down" systems get out of balance with an **increase** in descending **facilitation** and **decrease** in descending **inhibition**.

A: Pain referral patterns – an indicator of possible cortical/brain upregulation

People who have chronic nociplastic pain often report that their pain spreads, and spreads in ways that don't make sense in terms of peripheral nerve innervation or dermatomes or in terms of spinal cord neuroanatomy. fMRI scans have helped us to understand that the spreading of pain to multiple areas of the body, or in referral patterns which don't make sense, actually do make sense if we think about representation of the body on the somatosensory homunculi. Remember we said representation on the homunculus was use-dependent? Perhaps pain is also "use" and the more pain we have in an area, the more attention we will pay to that area, the larger our brain will make the map of that area.

DON'T MISS THIS

Treatments to "redraw" maps!

In the section on perioperative management, we have included the story of one person's experience of phantom limb pain and the use of Graded Motor Imagery treatment which aims to "redraw" the maps.

DEEP DIVE

More about mapping your body in your brain

Have you ever squashed your thumb, or your finger, and it has been really sore and feels very swollen and stiff, but when you look at it it's not swollen, and it seems to move fine? It is possible that the swelling and stiffness are because the map in your brain has changed(16)! It's a very clever way to get your attention and get you to look after that sore thumb until it heals. Changes on these homuncular maps are not always pathological: when there is an acute injury, they can be protective and helpful. But if these changes are maintained beyond tissue healing times, they stop being helpful!

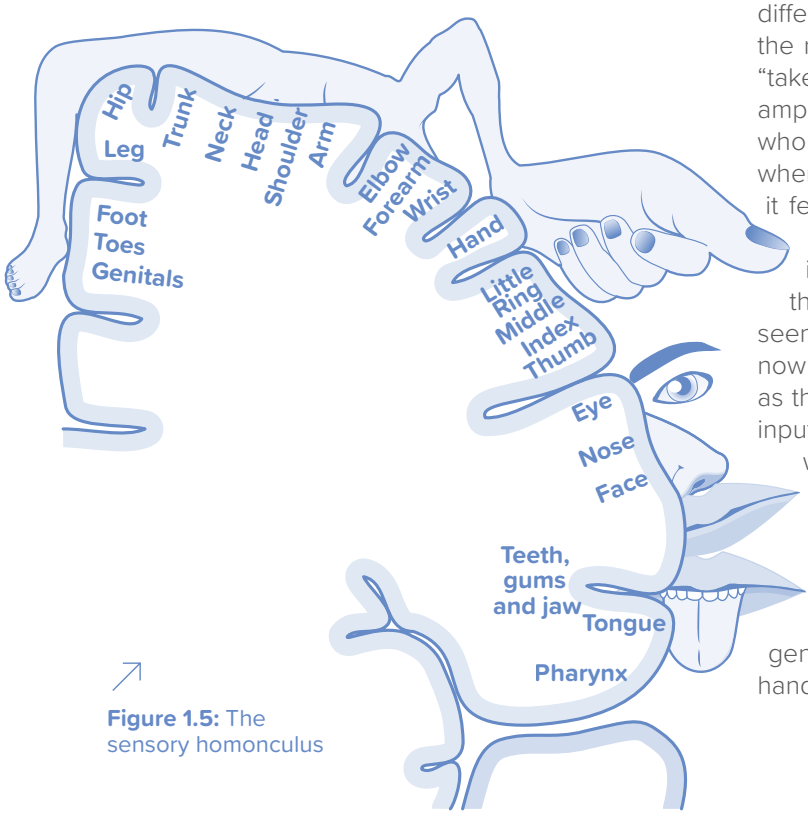


Figure 1.5: The sensory homonculus

With chronic nociplastic pain, there are alterations in the representation on the somatosensory cortices; the maps change. An early study found that, in people with chronic low back pain, the map of their lower back gets larger, they have larger representation of the anatomical area of the lower back than people who have had low back pain for a short period of time. This increase in representation correlated not only with the area of spread of their pain but also with the length of time the pain had been present (14). In people with complex regional pain syndrome (CRPS), the evidence from a systematic review is that the opposite occurs. The representation of the painful limb in the primary somatosensory cortex gets smaller compared with the non-painful limb (15). We must note that the variable quality of the evidence means it is difficult for us to be clear about whether these changes in the somatosensory cortex occur as a result of the chronic pain or are part of the cause.

Phantom limb pain is another chronic nociplastic pain condition in which fMRI changes have been recorded to help us to understand the pain. How do you have pain in a limb which is no longer there? fMRI studies of people with phantom limb pain have shown that their bodily representation in the somatosensory cortex changes, with the map for the amputated limb "moving" to a different part of the cortex. When this occurs, the remaining parts of the map also change to "take over" the space formerly occupied by the amputated limb. There are cases where people who have had a hand amputated report that, when they touch their cheek on the same side, it feels like they are touching the palm of the hand that is no longer there! How might we interpret this? The face is mapped next to the hand on the somatosensory cortices. It seems that the map for the face moves into the now vacant map of the hand. Put differently: it's as though the neurons that previously received input from the now-absent hand become bored with the lack of input, and gradually switch to receiving input from the face. However, the rest of the system has always interpreted activity in those neurons as originating from the hand, so when they are activated (by touch to the face), the percept that is generated by the system is of a touch to the hand.

B: Sensitivity to physical activity – an indicator of possible cortical/brain upregulation

When we exercise, our brain produces chemicals that makes us feel great including endogenous opioids, noradrenaline and serotonin, to name a few. These chemicals are anti-nociceptive; in other words, they are part of the descending inhibitory control system that inhibits nociception at the spinal cord. These chemicals are why most of us feel amazing after exercise! However, many people with chronic nociplastic pain will report that exercise or physical activity makes their pain worse, instead of better. This phenomenon is often referred to as sensitivity to physical activity (17) and it suggests to us that their "top-down" system, particularly the descending inhibitory system which includes endogenous opioids (which are100 times stronger than oral morphine) is no longer working effectively.

DON'T MISS THIS

Linking physiology to your assessment

In the next chapter we will discuss the principles of assessing pain. Don't miss the assessment techniques we can use to assess these different areas of the brain! Look out for two-point discrimination, left/right judgements and imagined movements to assess brain-held body maps, for sensitivity to physical activity, and for the central sensitisation inventory – a tool we can use to assess sensitivity to multiple stimuli described above.

C: Pain aggravated and eased by non-mechanical and non-inflammatory factors – an indicator of possible cortical/brain upregulation

People who suffer from chronic nociplastic pain often tell us that stress makes their pain worse. Instead of telling us that movement, or heat makes it worse, they will say things like "on Mondays my pain is worse!". Pain affects all aspects of the person, and when the central nervous system is sensitised, innocuous stimuli can generate a response of pain. After all, stress is a threat to me as a human being, right? So why not generate pain in response to that threat? Not only will they notice their pain responding to stress, but central sensitisation might result in them noticing that they are sensitive to multiple stimuli, such as light, sound, strong smelling chemicals and more (18). They may also notice that they struggle to sleep and are fatigued, have sensitive gastrointestinal tracts, sensitive skin and find that their mood is disturbed too – everything, all their systems are centrally sensitised.

Do you notice how these responses overlap with the synergistic systems? Stress will also affect the autonomic nervous system, which will contribute to cortical upregulation. Similarly, gut function is closely linked to the immune and autonomic systems, and all these players can be tough to untangle. The main thing is that you should be alert to these features and equipped to interpret them, alongside the other features of the person's pain, to inform your clinical reasoning.

What do the synergistic systems have to do with pain?

The synergistic systems interact with each other and the somatosensory nervous system (which we have focused on so far) to maintain homeostasis. The synergistic systems are important in restoring homeostasis after an injury, but they can also upregulate nociception and pain resulting in increased severity and/or duration of pain. None of these systems acts in isolation and they should all be kept in mind when assessing and collaboratively planning the treatment of a person with pain.

The synergistic systems are interconnected, and each system influences the others, and nociception and pain. This means that all of these systems have the potential to increase (or decrease) acute pain that is associated with tissue damage (i.e., nociceptive pain), as well as increase (or decrease) pain that is *not* associated with tissue damage (i.e., nociplastic and neuropathic pain). The synergistic systems that we are referring to here are the somatosensory nervous, endocrine, autonomic nervous, and immune systems.

We have discussed the somatosensory nervous system at great length in the sections above, so now we are going to focus on the endocrine, autonomic (i.e., the sympathetic and parasympathetic nervous system), and immune systems. These three systems work synergistically, influencing each other. Given that they are so interconnected, we are going to look at them all together and not as separate parts.

By the end of this section, we hope you will have a clear understanding of:

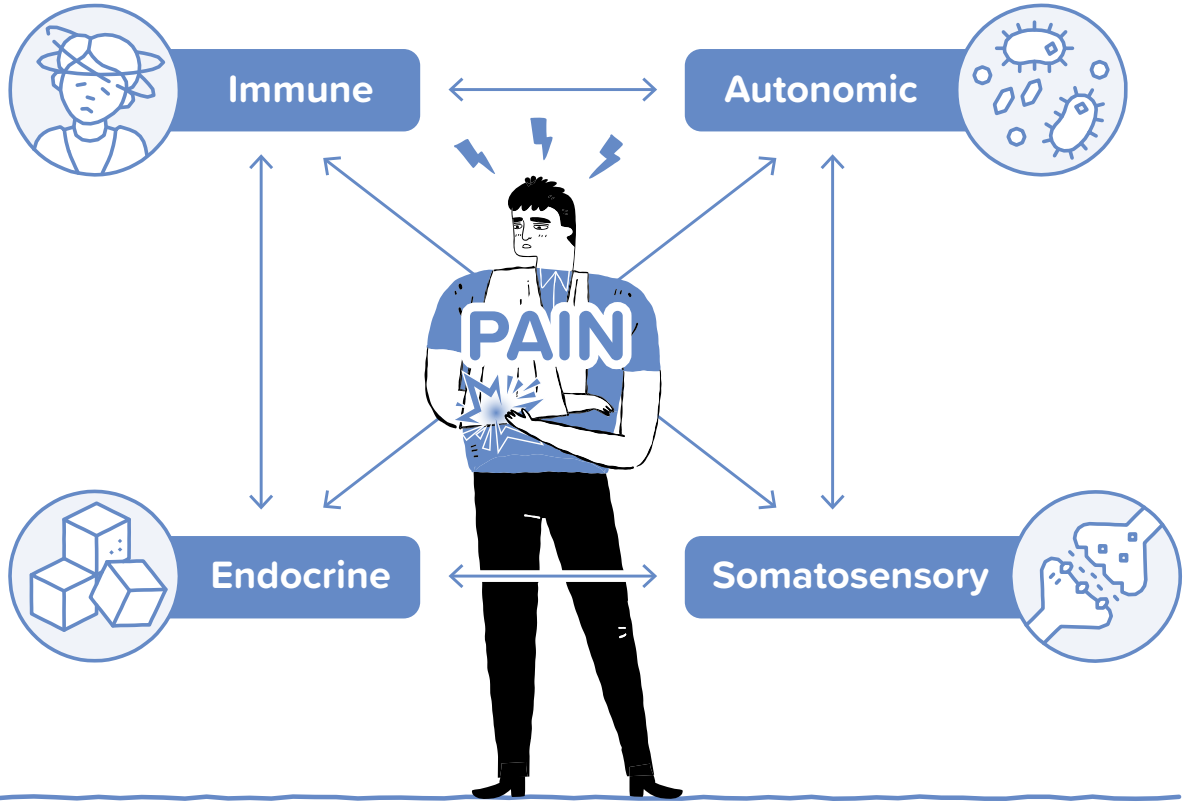
1. How the synergistic systems contribute to the experience of pain.
2. The signs and symptoms suggesting that the synergistic systems might be influencing pain.
3. The basic physiological mechanisms which underlie these signs and symptoms of synergistic system involvement.

What is happening in the endocrine, autonomic nervous, and immune systems when we feel pain?

Acute stress can increase OR decrease your pain. Let's imagine that, when you burnt your hand on the stove, it was the morning of an important job interview. You were already tense and anxious about the interview and now you burnt your hand. How much will that burn hurt now? Probably a lot more than if you had burnt your hand on a lazy, casual Sunday!

Figure 1.6: Multidirectional relationships among the synergistic systems influence nociception and pain.

Let's unpack how acute stress can make pain worse. The stress of the job interview likely activated your sympathetic nervous system – the fight or flight system. Specifically, stress leads to activation of the hypothalamic-pituitary-adrenal axis (HPA axis). The HPA axis regulates the release of stress hormones such as cortisol. These stress hormones are pro-nociceptive. In other words, they upregulate nociception at the periphery and spinal cord.



On the other hand, if the acute stress is life threatening, we may not feel pain until after the life-threatening situation is over. Remember, our brain is always evaluating and prioritising all the available information and using this information to make the best decision to protect us and to avoid harm. So, if you burnt your hand while escaping a life-threatening situation, your brain is more likely to direct your attention to escaping the life-threatening situation than to the relatively minor threat of tissue damage in the hand.

Now, imagine the past few months have been incredibly stressful. Maybe you recently moved house or have continuously been behind on deadlines. How might these months of stress affect how much that burn will hurt? It probably has a bigger effect than you think!

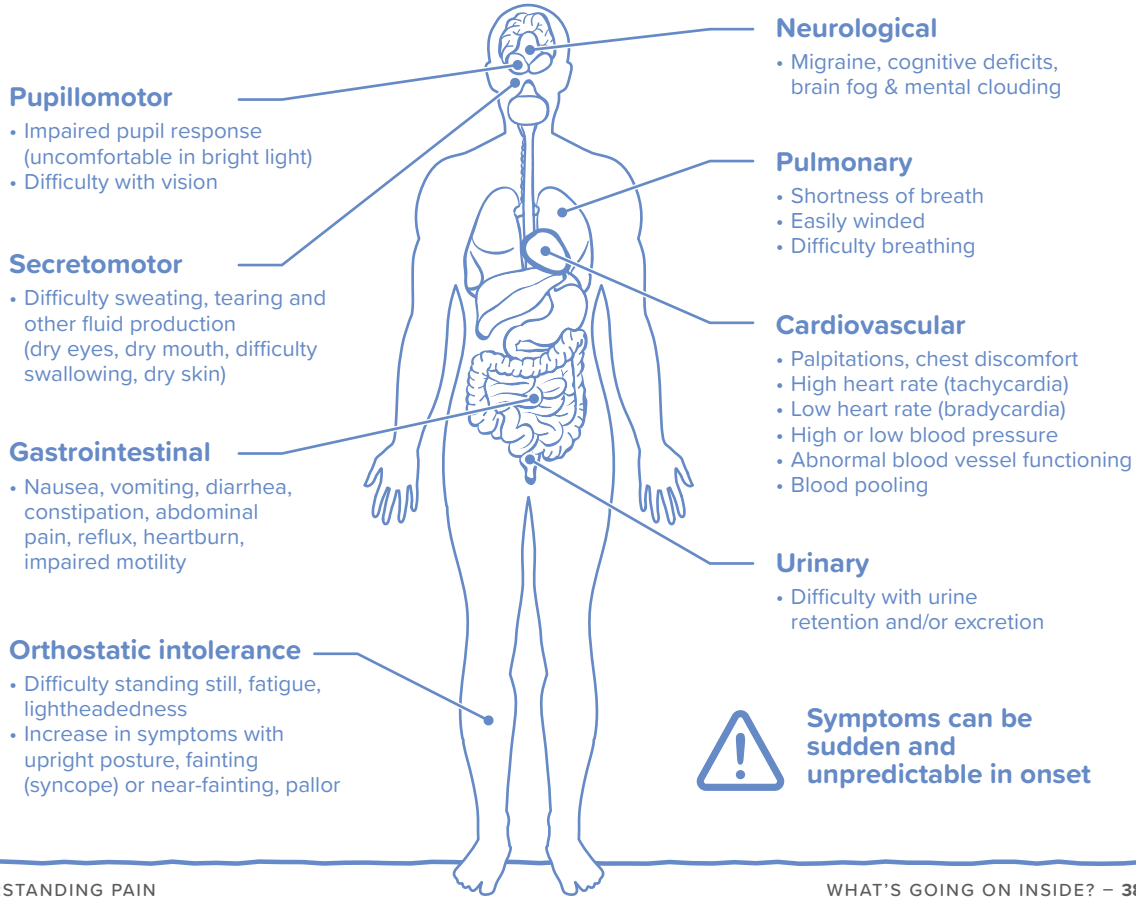
Chronic activation of the HPA axis can lead to a variety of negative health consequences such as cardiovascular disease, certain cancers, depression, anxiety, and, of course, chronic pain. The endocrine, autonomic nervous, and immune systems work together to maintain homeostasis. However, chronic stress (whether it be psychological, emotional and/or physical) can lead to dysregulation in these systems.

DEEP DIVE

The importance of glial cells

Glial cells are capable of a LOT more than we originally thought! In fact, glial cells make up 70-90% of the cells in the central nervous system. They are vital in maintaining homeostasis. There are 3 main types of glial cells that play an important role in neuroimmune functioning: astrocytes, microglia, and oligodendrocytes. Astrocytes play an important role in regulating synaptic activity; they regulate the release of neurotransmitters from the pre-synaptic membrane and clear excess neurotransmitters from the synaptic space. Microglia respond to neural damage and are responsible for the innate immunity of the central nervous system. Oligodendrocytes make up the myelin sheath around axons that facilitates the propagation of action potentials.

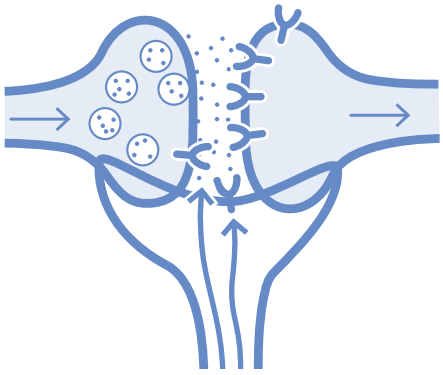
Figure 1.7: Symptoms of dysautonomia.



DEEP DIVE

Lateral signalling

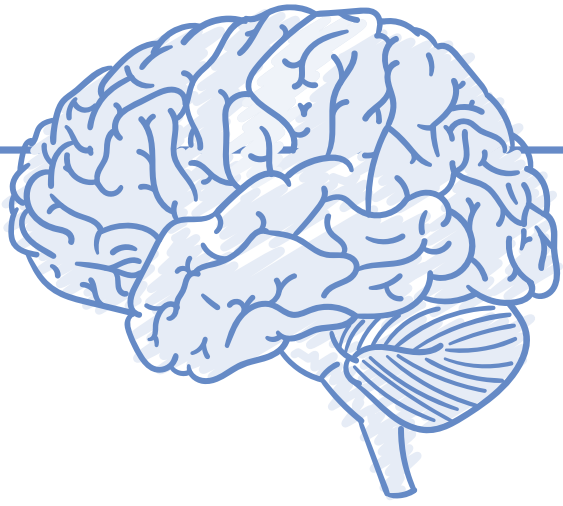
Let's go back to those all-important glial cells. When there is spinal cord and brain upregulation i.e., persistent excitatory synaptic activity, these glial cells can further sensitise the system! Specifically, astrocytes connect with thousands of synapses. Persistent excitatory synaptic activity at one synapse will activate the astrocyte that connects with that synapse, and this activation can result in calcium wave propagation which sensitises a parallel synapse. This is called **lateral signalling** and is essentially the spreading of synaptic activity to adjacent related AND unrelated synapses.



Chronic stress is associated with autonomic nervous system dysfunction. Essentially, the sympathetic nervous system is in overdrive and there is a loss of homeostasis between the sympathetic and parasympathetic nervous systems. This autonomic nervous system dysfunction is termed **dysautonomia**. People living with chronic pain often have symptoms of dysautonomia. The clinical signs and symptoms of dysautonomia are diverse but often include shortness of breath, tachycardia, hypotension, fainting, fatigue, excessive sweating, dizziness, nausea, brain fog. Chronic stress also impacts the immune system and in addition to being in a sustained "fight or flight" mode with increased sympathetic nervous system activity, the immune system increases proinflammatory activity. A group of cells critical in the change in inflammatory activity in the nervous system are the glial cells.

DEEP DIVE

A complex system that shapes neural signals



A synapse consists of far more than just two neurons (i.e., pre- and post-synaptic neurons). The term 'pentapartite synapse' was proposed in 2011, to acknowledge the contributions of astrocytes, microglia, and T-cells to synaptic activity (alongside the pre-synaptic and post-synaptic neurons) (19). Recently, the term 'active milieu' has been put forward to describe the dynamic space within and around a synapse, as we learn that oligodendrocytes, the extracellular space, the extracellular matrix, and blood vessels also influence, and are influenced by, neural signalling (20). Just consider this: the final, flat extensions (leaflets) of astrocytes that surround a synapse can create a kind of maze that neurotransmitters must travel through as they diffuse through the space towards their destination. This 'tortuosity' of the microenvironment is one example of how the non-neural components of the 'active milieu' shape the responsiveness of the neural system. Astrocytes can also carry their own kind of action potential: astrocytes signal across large areas in response to neural activity, and this signalling also influences the neural system. One astrocyte may have contact with many different synapses, so astrocyte signalling could even transfer heightened sensitivity from one synapse to another synapse quite far away!

Chronic proinflammatory processes mediated by microglial cells can lead to dysfunction of the astrocytes. In the deep dive we pointed out that the astrocytes regulate the release of neurotransmitters. Dysfunction of astrocytes is associated with chronic pain because they upregulate glutamate released into the synapse and lose the ability to effectively clear excess glutamate from the synapse. This leads to hyperexcitability (i.e., upregulation) of the synapse.

Putting the physiology together

That is a lot of physiology detail to read through – well done for getting this far. As you continue with the book, we suggest you keep coming back to this chapter to make sure that you have the information embedded in your memory. For every person with pain whom you engage with, you want to develop a hypothesis, based on their signs and symptoms, about what is going on (i) in the peripheral nervous system; (ii) in the spinal cord; (iii) in the brain; and (iv) in the synergistic systems. To be able to do this, you need to have the information we've given you here at your fingertips!

For every person with pain, develop a hypothesis about what is going on in the peripheral nervous system, the spinal cord, brain and synergistic systems.

3 Principles for the assessment of pain

Romy Parker
Gill Bedwell
Jocelyn Park-Ross
Marisa Coetzee
Tory Madden

In this chapter we will discuss the principles of assessing pain before we cover the key pillars of pain treatment. These principles and key pillars are just that: principles that need to be adapted for the person suffering from pain to ensure they are relevant and appropriate, based on the mechanisms of the person's pain and their context. As you continue working through this book, you will see how these assessment and treatment principles are adapted to each context. We encourage you to keep referring back to this chapter as you engage with each case.

Remember that, in this book, we are focusing on pain. If the person consulting you also has a cough, or any other symptoms, you MUST also assess and integrate that information into your clinical reasoning. Here, we are focusing on the *pain* component of an assessment that you need to incorporate with your other knowledge and skills.

A structured approach to assessment

A good place to start when conducting an assessment is knowing what information you need to gather to be able to clinically reason your way to, and through, a hypothesis.

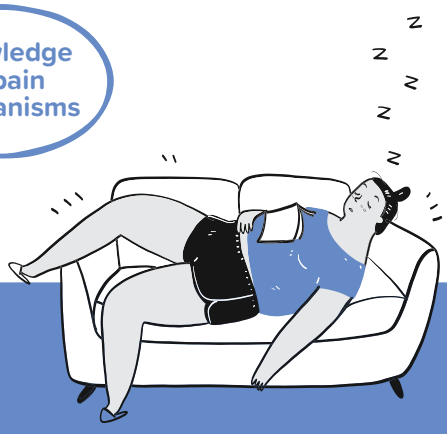
By the end of any pain assessment, you should:

1. Know what the person with pain is worried is wrong (their ideas and concerns).
2. Know what the person with pain wants to achieve from consulting you and from their treatment with you (expectations).
3. Have an idea of the timeline and the stage of healing (recent onset vs long-lasting pain).
4. Have assessed for indicators of physiological mechanisms contributing to pain in the:
   a. Peripheral nervous system (PNS)
   b. Spinal cord (SC)
   c. Brain
   d. Synergistic systems
5. Have considered all the biopsychosocial factors that might be contributing to, or maintaining, pain (the vulnerability factors).

With this information you will be able to classify the pain mechanism as nociceptive, neuropathic or nociplastic, and as acute, sub-acute or chronic. You will also be able to design a treatment plan that targets the mechanisms in the PNS, SC, brain and synergistic systems that are contributing to pain.

In Figure 3.1 we have highlighted some of the tools we need to develop as healthcare professionals to be able to conduct a full pain assessment and establish the above information.

Figure 1.8 Skills the healthcare professional needs to be able to perform an effective pain assessment.



DON'T MISS THIS

Assessing pain in people who are unresponsive or unconscious.

Someone who is unconscious is not experiencing pain – pain is a conscious construct. This means that the clinicians MUST assess for danger messages (nociceptive mechanisms) that can contribute to pain.

Because we can't easily measure nociception effectively, you need to assess for conditions under which we would expect danger messaging to be occurring. For example, a person who has been in an accident may have several fractures and be unconscious – but we would expect plenty of nociceptive signalling after a fracture. Your goal is to identify likely activity in the peripheral nervous system, the spinal cord, and the brain, that would contribute to pain when the person does become conscious. This nociceptive activity can also promote nociplastic changes while the person is unconscious, which could set them up for a greater pain problem when they regain consciousness. We don't ignore the fractures just because the person is unconscious: there will be danger messages (nociception) from those fractures which must be considered in the assessment and targeted in treatment. We will discuss this more in sections 4 and 5.

Initiating your consultation

The first step for a successful pain assessment is to initiate your consultation with clear communication to establish what concerns the person has. You need to find out what they are worried about and what they would like from you as the healthcare professional – this is known as establishing the ICEs (ideas, concerns, and expectations). You can sometimes do this very briefly with someone who is on the ward, or it may take longer in an outpatient consultation when many people have more than one concern. Sometimes people don't say straight away that they are in pain – do not assume that they are not in pain if they don't volunteer it. Always ASK whether they are in pain! When you have clearly established all the reasons for the consultation, check that you and the person who has come to you for help are on the same page in terms of priorities. Don't assume that the first issue that the person with pain has raised is the most important one. This is known as establishing an agenda that prioritises the most important issue(s).

Gathering information on pain

Once you have initiated the consultation and established an agenda, i.e., you know why the person is consulting you and what you need to achieve in this interaction, you can start to gather information. Many healthcare professionals are taught to do this information gathering under the headings of past medical history, past surgical history, history of the present condition, and sociodemographic history.

If pain is a key symptom, you need to ensure you get all the pain information outlined in Table 1.1 on the "O, P, Q, R, S, T, U, V, W" of pain.

DON'T MISS THIS

Asking for Ideas, Concerns and Expectations (ICEs)

Make sure you establish the ICEs with every person who consults you about their health. You can find out what their *Ideas* or thoughts are about what is or might be wrong with them by asking: "What do you think is wrong?". Then find out what their *Concerns* are by asking: "What worries you about this pain/condition?". Finally find out their *Expectations* by asking: "What do you want from me? What would you like to get out of this consultation?"

DEEP DIVE

Assessing pain in people who are non-verbal and the care dyad

When you are working with children, people with intellectual disabilities and older people, remember you are working with a dyad – the person and their carer. Carers can be your best source of information when assessing pain in someone who is non-verbal (e.g., a baby, a person with a disability, a person with dementia). Their carer is the person who spends the most time with them. They may have noticed increased aggression, restlessness, changes in sleep and appetite, or simply have a sense that something isn't right. In these situations, it is also important to assess not only the person with pain's understanding (U) of pain, but also their carer's understanding. This is particularly relevant when treating children.

There is more detail about this in the prehospital and emergency care, and perioperative sections which dive deeper into paediatric and geriatric patients, and assessing pain in challenging situations.

Next Page: Table 1.1: The "O, P, Q, R, S, T, U, V, W" information for a full pain assessment

Gather information on the...	Examples of questions to ask	How will you use this information?
Onset	• When and how did this start? • How long does the pain last? • How often do you get the pain?	Establish a timeline to link to stage of healing. Helps to classify pain as acute or chronic; and nociceptive, neuropathic or nociplastic
Provoking and palliating (easing) activities	• What causes the pain? • What makes it better? • What makes it worse?	Provides information for identifying mechanisms in the PNS, spinal cord, brain, and synergistic systems.
Quality of the pain	• Can you describe your pain?	Different pain types have particular qualities, e.g., neuropathic pain is typically burning, electrical, and associated with tingling or pins and needles.
Region or radiation	• Where is the pain? • Does the pain spread? • Where does it spread to?	Provides information for identifying mechanisms in the PNS (discrete area, dermatome, or nerve distribution), spinal cord (referral within a spinal segment), or brain (homuncular referral).
Severity	• How severe is your pain? • How severe is it right now/at its best/at its worst and on average? • How severe is your pain when you try to be active?	Understanding what impact, the pain is having on the person, and to guide treatment choices.
Treatment	• What treatments have you tried for your pain? • How well did that work? • Have you had any side-effects from these treatments?	Provides information for identifying mechanisms in the PNS, SC, brain, and synergistic systems.
Understanding beliefs and impact	• What do you think is causing your pain? • What do you think is wrong? • What are you worried this pain could mean? • What can you not do because of your pain? • How is this pain affecting you and your family?	Information on what might be contributing to the perception of threat and generation of pain. Informs a functional focus in the treatment plan – after all, our goal is to restore function! This information is critical for the healthcare professional to gain insight into the threat factors.
Values	• What is your goal in getting your pain treated? • What do you want me as a healthcare professional to do for your pain? • What are you not doing because of your pain that you want to be able to do? • What is your pain stopping you from doing?	Informs treatment planning and ensures that we are on the same page in terms of restoring participation in meaningful life roles. Helps the healthcare professional understand what the person in pain has lost or is afraid of losing in terms of participation in their lives e.g. "I'm not being the father I want to be".
What else?	• What else is going on in your life? • How are you generally? • What else do you think it would be useful for me to know?	Information useful to evaluate what synergistic systems might be contributing in terms of stress, sleep, immune, and endocrine systems.

DON'T MISS THIS

It is difficult to assess and treat pain in the emergency and perioperative setting

Many of the people who need emergency care, whether pre-hospital or in-hospital, have pain which requires management. Pain assessment and treatment is a vital element of caring for all people undergoing surgery. The importance of a good assessment is to ensure that we are able to treat and manage pain!

Assessing and treating pain in emergency and perioperative settings can be challenging for many reasons. The emergency care and perioperative sections are designed to help you understand and prepare for these challenges, don't miss out!

One of the most common methods to assess pain severity is to ask how severe the pain is on a scale of 0 (zero) to 10. It is important when you use this scale to give consistent descriptors for 0 and 10.

The words we find most useful are: *"How severe (or bad) is your pain on a scale from 0 to 10 where 0 is 'no pain' and 10 is the 'worst pain you can imagine'?"*

> *It is this wording that is very important: 10 = the worst pain you can* **imagine**.

Using the word "imagine" helps people to consider how severe their pain is beyond their current experience and seems to allow for more nuanced use of the scale. However, if you have ever been in pain, you will know that it can be very hard to find a number for a feeling that is deeply unpleasant and eating you up from the inside. For many people, choosing a number for their pain seems almost impossible. If the person with pain cannot give you a number, simply ask:

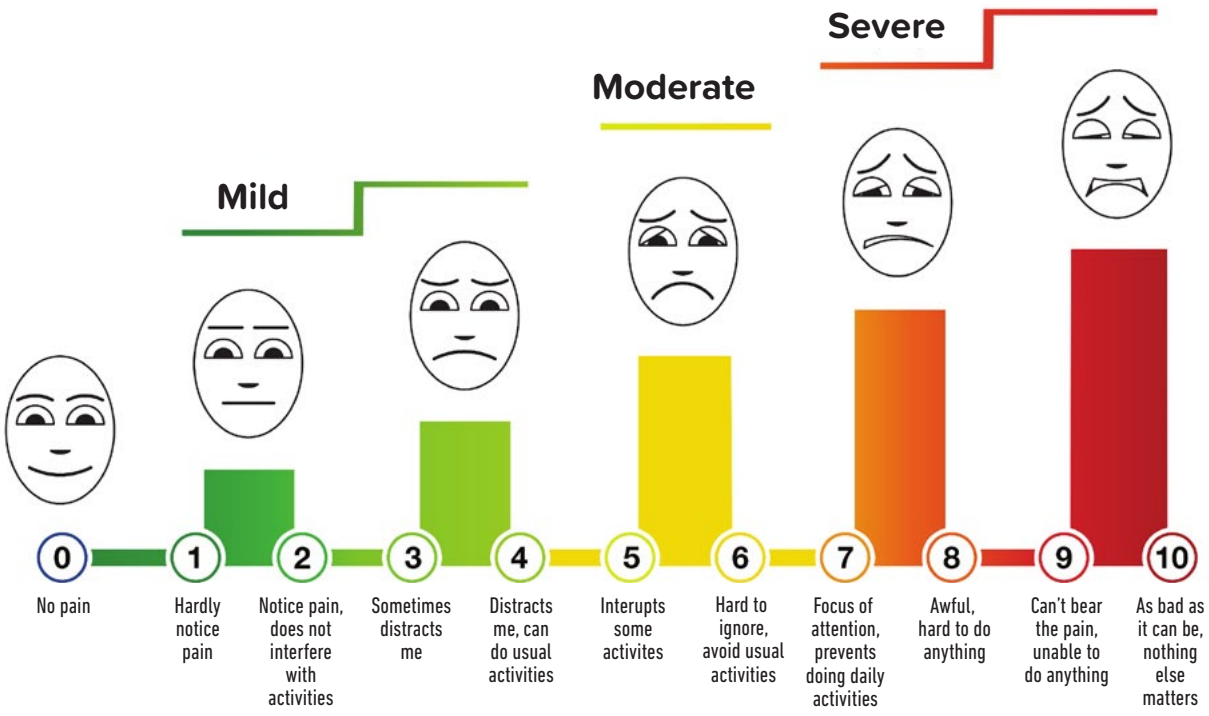
> *"How bad is your pain? Mild? Moderate? Severe?"*

This three-level classification is sufficient to inform your clinical reasoning. And most clinicians will convert the numeric score for pain into a three-step severity score with 0-3 = mild; 4-6 = moderate and 7-10 = severe. Pain that is moderate to severe really interrupts us, and interrupts our thoughts, our feelings, and our physiology. An example of an assessment tool that combines the 0 to 10, with the mild, moderate, severe classification and with faces of pain, is the Defence and Veterans Pain Rating Scale (Figure 3.2). You can clearly see how the numeric scores can be converted to the three categories. (21) This bright, colourful tool and variations on it are used in many clinics and hospitals to measure pain. In Figure 3.3 shows another version of a clinical pain assessment tool that has been developed for use in South African hospitals. People with low levels of literacy often find the vertical scale easier to understand.

DON'T MISS THIS

Special considerations for the young and the elderly

The young (paediatric) and the elderly (geriatric) require special attention while learning about the physiology, assessment and treatment of pain. You can follow brave little Leah's story of being burnt by hot water through her emergency care in section 4, and her perioperative care and recovery in section 5. Gogo Elizabeth has to leave her grandchildren and travel far to seek care for a fractured femur in section 5.



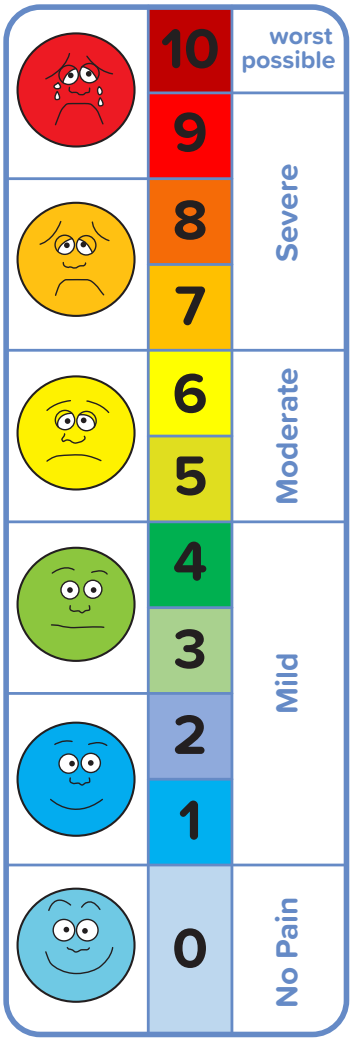


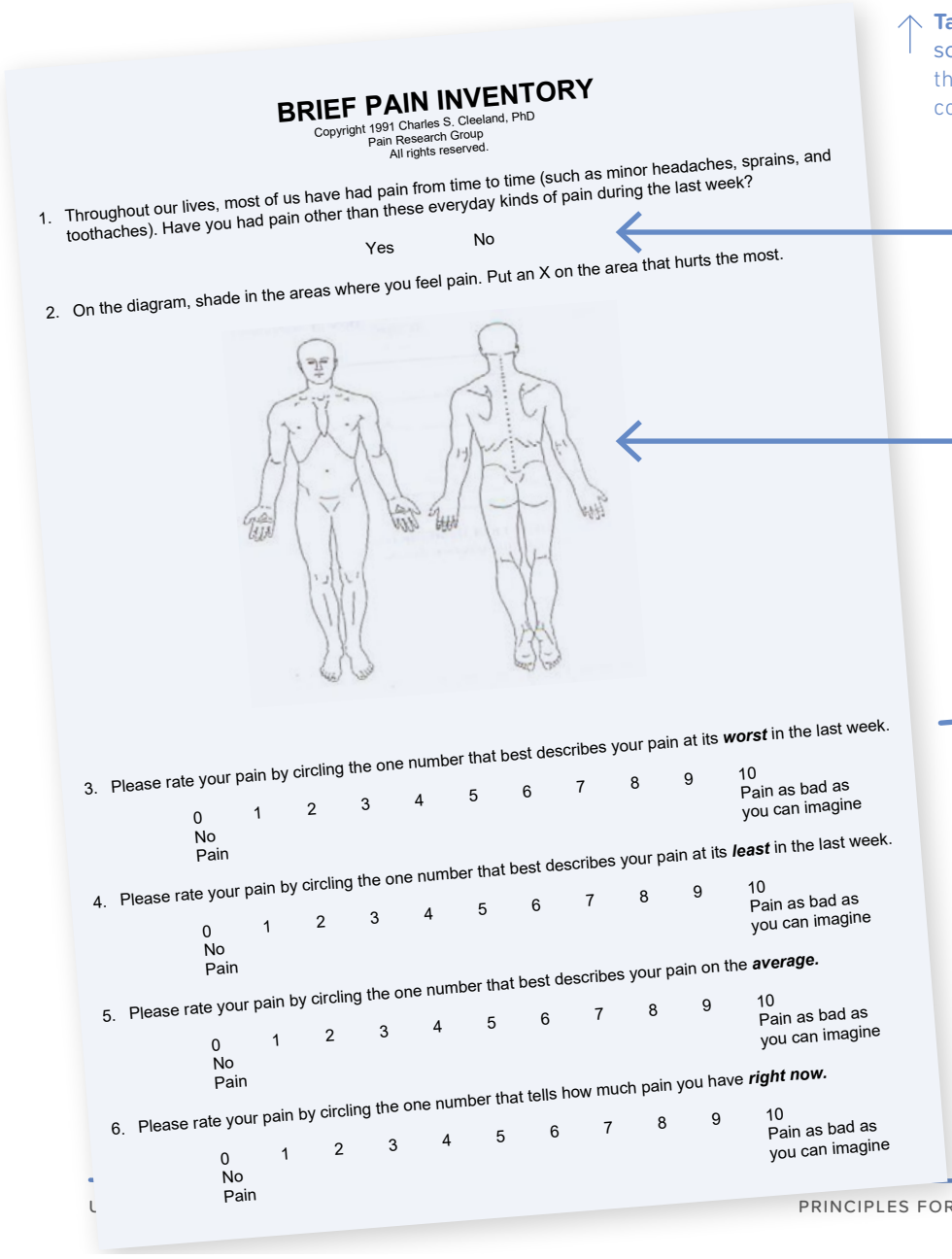
Figure 1.9: Defence and Veterans Pain Rating Scale (Source: Defence & Veterans Center for Integrative Pain Management)

Figure 1.10: Vertical pain rating scale (Source: PainOut)

When working with children, people who are non-verbal or who have communication challenges, dementia, intellectual disability or learning challenges, or people who are unconscious, you need to consider their condition, their needs, and the context more deeply. A tool such as the faces of pain scale may be useful. If the person cannot self-report on the faces of pain scale, you can use a tool to guide your observation of *behaviours associated with* pain. One of the most commonly used and well validated tools is the FLACC – face, legs, activity, cry, consolability scale (22, 23) (Table 3.1). The FLACC scale draws on scores from five categories to give a total score of 0 to 10, with pain severity interpreted as mild, moderate, or severe.

Categories	Score Zero (0)	Score one (1)	Score two (2)
Face	No particular expression or a smile	Occasional grimaces or frown, withdrawn, disinterested	Frequently to constantly quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No crying (awake or asleep)	Moans or whimpers, occasional complaints	Crying steadily, screams or sobs, frequent complaints
Consolability*	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficulty to console or comfort
Each category is scored as 0-2 and a total score of 0-10 is calculated.			

Table 1.2: The FLACC pain scale (23). *Consolability means that they can be comforted or consoled.



BRIEF PAIN INVENTORY

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved.

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain during the last week?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by circling the one number that best describes your pain at its ***worst*** in the last week.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its ***least*** in the last week.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the ***average.***

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have ***right now.***

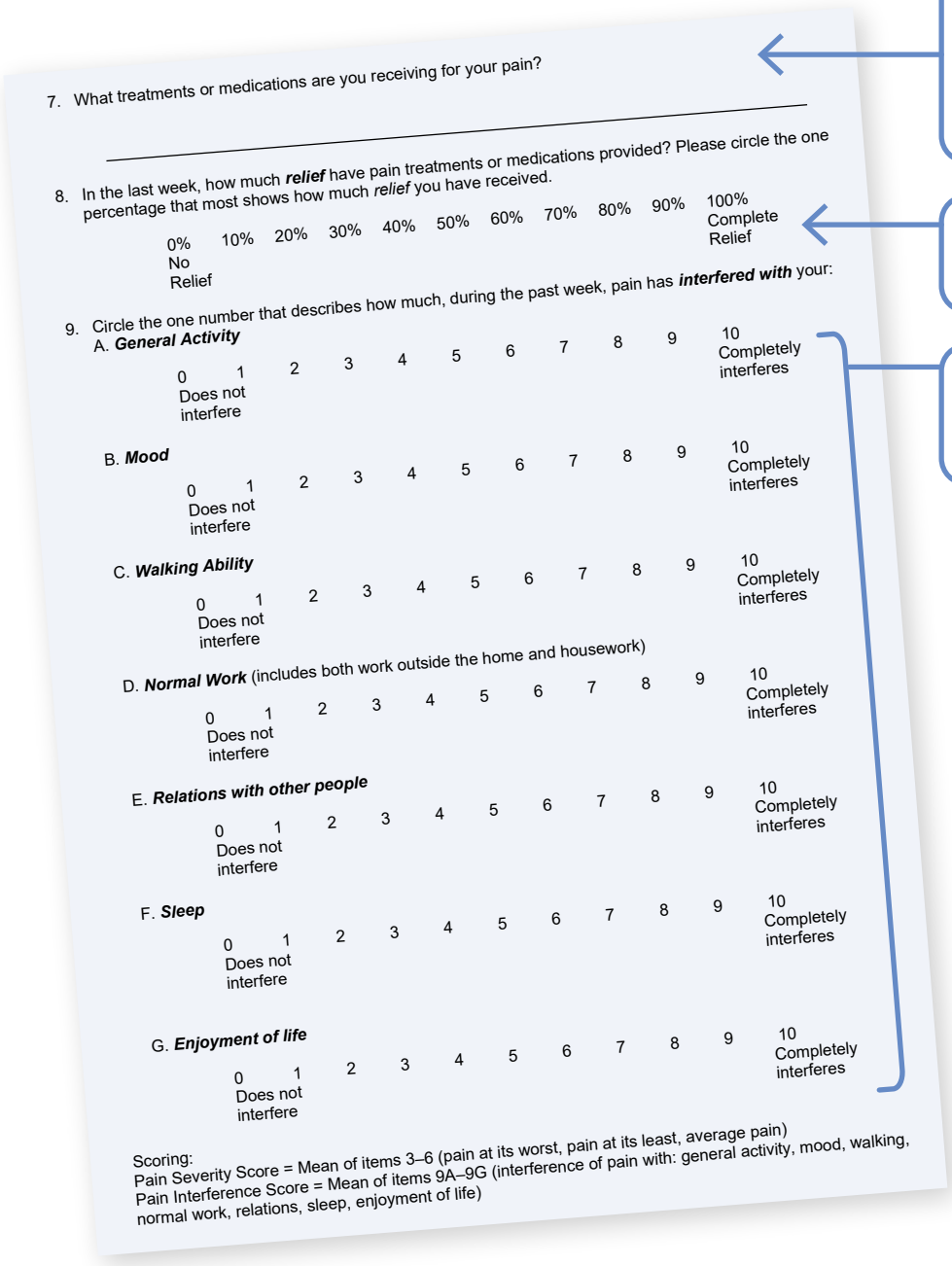
0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

This question is really useful as it reminds everyone that pain is a normal part of life, but that we are interested in new pain or pain that is worrying them.

Whenever possible let the person with pain shade in the diagram themselves. It gives us a lot of information about the pain mechanisms.

Calculate average of the scores for questions 3 to 6 – this gives the Pain Severity Score out of 10.

Figure 1.11: The Brief Pain Inventory (page 1) (Source: Pain Research Group, WHO Collaborating Centre for Symptom Evaluation in Cancer Care)



7. What treatments or medications are you receiving for your pain?

_____

8. In the last week, how much ***relief*** have pain treatments or medications provided? Please circle the one percentage that most shows how much *relief* you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how much, during the past week, pain has ***interfered with*** your:

A. ***General Activity***
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

B. ***Mood***
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

C. ***Walking Ability***
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

D. ***Normal Work*** (includes both work outside the home and housework)
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

E. ***Relations with other people***
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

F. ***Sleep***
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

G. ***Enjoyment of life***
0 Does not interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

Scoring:
Pain Severity Score = Mean of items 3–6 (pain at its worst, pain at its least, average pain)
Pain Interference Score = Mean of items 9A–9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life)

This question and the next question (about how effective these treatments are) give us information about what pain mechanisms may be present.

Useful information for thinking about the pain mechanisms.

Calculate average of these scores to get the Pain Interference with Function score out of 10.

Figure 1.12: The Brief Pain Inventory (page 1) (Source: Pain Research Group, WHO Collaborating Centre for Symptom Evaluation in Cancer Care)

One of the most robust pain assessment tools is the Brief Pain Inventory (BPI) (Figure 1.11). We recommend you use this tool for every outpatient whose primary reason for seeking healthcare is pain. In the emergency and inpatient setting, select questions from the BPI can be used. See the figure below for more about how to use and interpret the BPI. The BPI has been translated and validated for use in South African English, Afrikaans, isiXhosa, isiZulu, Setswana and Tsonga (24, 25).

DON'T MISS THIS

Questions not to miss in your assessment

We said it before, but it's worth saying again: make sure you understand the U and V components of your pain assessment. Get into the habit of making sure to ask these questions of every person with pain:

1. "What do you think is wrong?
2. "What worries you about this pain?"
3. "What are you not doing/not able to do because of your pain?"

Red flags

A red flag is a clinical indicator of potentially serious pathology that requires urgent attention. It is critical that you screen for red flags in every person who is suffering from pain. Never assume that there is nothing serious going on, screen for red flags routinely. In the primary care setting, it is strongly recommended that clinicians screen for groups of red flags rather than making decisions based on a single flag alone. In Table 3.2 we have listed common red flags individually, followed by listing groups of red flags which are stronger indicators of potentially serious pathology requiring urgent attention.

Below: Table 1.3: List of red flags and conditions

Red Flag	Potential indicator of...
Unremitting night pain (i.e., linked to clock time rather than sleeping position)	Nociceptive pain mechanism
Sudden, unexplained weight loss (≥5kgs within 3 months)	Malignancy, tuberculosis, HIV
Bladder and/or bowel incontinence	Cauda equina syndrome
Saddle anaesthesia, (i.e., loss of sensation in the perineal area and medial aspects of both thighs)	Cauda equina syndrome
Night sweats (i.e., drenching clothing/linen)	Tuberculosis
Acute onset of severe, unremitting pain	Nociceptive pain mechanism
Bilateral pins and needles or loss of sensation	Neurological compromise e.g., spinal stenosis
New onset of severe headaches	Nociceptive pain mechanism of structures of the head and neck (including the brain)
Groups of red flags	
Pain in an extremity associated with pallor, pulselessness, and paraesthesia	Vascular compromise, e.g., compartment syndrome, deep vein thrombosis
No improvement in pain over one–month; insidious (gradual) onset, person >50 years old; no relief with bed rest; systemically unwell; unexplained weight loss, fevers ,and thoracic pain **(26)**	Malignancy
Bladder and/or bowel incontinence; saddle anaesthesia, (i.e. loss of sensation in the perineal area and medial aspects of both thighs), unilateral or bilateral radicular pain and/or loss of sensation or power in a dermatome/myotome, person <50 years old, unilateral symptoms progressing to bilateral **(27)**	Cauda equina syndrome
Insidious, increasing low back pain with progressive sensory/motor loss, progressive bowel and/or bladder incontinence or dysfunction **(27)**	Lumbar spinal stenosis
Thoracolumbar spinal or referred pain which may be localised (can point to it with one finger) or diffuse, unexplained weight loss, night sweats, progressive sensory/motor loss, progressive bowel and/or bladder incontinence of dysfunction, low grade fevers, gibbus, pain on percussion of the vertebrae, paraspinal cold abscess, no mechanism of injury, gradual onset of pain, history of pulmonary tuberculosis, immunocompromised, younger than 20, or older than 50 years of age **(28, 29)**	Spinal tuberculosis (TB spine)
Significant corticosteroid use, osteoporosis, >65 years old, female, trauma or history of falls, previous fracture, thoracic pain, new onset severe pain, **(27)**	Spinal fracture

A physical examination to identify indicators of physiological mechanisms contributing to pain.

As a healthcare professional, you need to perform a physical examination of every person with pain. In addition to your normal physical examination for pathology, musculoskeletal disorders, and disease, the following examination techniques provide specific information about physiological mechanisms contributing to pain.

Assessment of Peripheral Nervous System (PNS) Mechanisms

1. Examine for inflammation – in your physical examination of the painful area, check for the classic signs of inflammation – heat, swelling, and changes in pigmentation suggesting inflammation (e.g., redness).

2. Examine for primary hyperalgesia – excessive pain from a normally painful stimulus. This is normally tested with a special, blunt ended 'pinprick' device or the end of a paperclip. First, gently poke a non-painful area of the body (the contralateral side is best) and ask the person to rate the feeling. Then, gently poke the painful area with the same amount of pressure and ask for a rating of that feeling. If the poke to the painful area is more painful, the person has primary hyperalgesia, which can indicate peripheral sensitisation.

3. Examine for sensory changes. It is important to check for loss of sensation to touch and/or pinprick in the location of pain if you suspect a neuropathic mechanism (lesion or disease of the sensory nervous system).

Assessment of Spinal cord mechanisms

1. Allodynia – pain to a stimulus that is normally non-painful - is classically assessed with a brush similar to a paintbrush. In the clinical setting you may not have an appropriate brush, in which case you can assess allodynia by brushing across the painful area with a tissue or cotton wool. Again, first do the test in an unaffected body part (ideally, the contralateral equivalent to the painful part). Pain to a normally non-painful stimulus is an indicator of central sensitisation.

2. Secondary hyperalgesia is assessed in the same way as primary hyperalgesia, but in the area surrounding the tissue damage. Secondary hyperalgesia is also an indicator of central sensitisation.

Assessment of Brain Mechanisms

1. Two-point discrimination provides information on the brain-held maps of the painful area (the site of the sensory homunculus map). Two-point discrimination can be easily assessed as demonstrated in this simple video. The assessment may show increased or decreased two-point discrimination in the painful area. An increase in the distance between two points (increased threshold) suggests a loss of precision in homuncular representation; a decrease in the distance between the two points suggests a gain in precision. Take care not to over-interpret a difference though: for example, you need to observe *at least* a 15mm difference at the back and at least 24mm at the neck before you could consider it to reflect a 'real' difference (30). Note that this assessment is only useful when the peripheral nervous system is intact. If there is loss or altered sensation, suggesting a lesion or disease of the nervous system, then this assessment is not reliable.

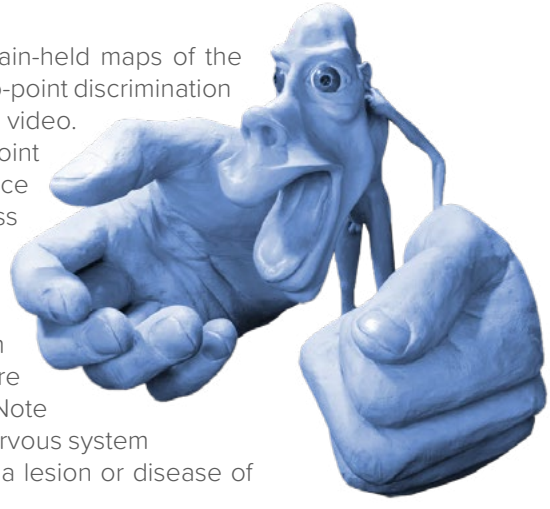


Figure 1.13: This is what you would look like if you were made in direct proportion to your homunculus.

2. Left-right judgements also reflect the brain-held maps of the painful area but, unlike two-point discrimination, this *can* be assessed when the peripheral nervous system is not intact. For this assessment, the person with pain is shown a random series of pictures of body parts matching the painful body part - e.g., if I have pain in a hand, I am shown pictures of right and left hands in random order. The person with pain is asked to judge whether the picture shows a right or a left hand. To be able to recognise whether the pictured body part as right or left, we subconsciously use our brain-held body maps. This assessment can be done with flash card pictures, a free app called Orientate or a purchasable app called Recognise. Slow performance probably reflects delayed processing of information related to that body part; inaccuracy probably reflects alterations to the map of that body part. Left-right judgements are commonly impaired in people who have pain in one limb or in the face (31). There are helpful videos and instructions here.

3. Imagined movements – this assessment technique informs us about the cortical representation of the painful area in the premotor cortex where we have a motor homunculus map. When we visualise or imagine moving, the premotor cortex prepares the movement pattern. To assess premotor representation, ask the person with pain to imagine moving the painful limb in different directions or in a particular activity. Once they have imagined the movement, ask how easy or difficult it was to imagine the movement (it may be more difficult to imagine moving the painful limb than to imagine moving the non-painful limb), and then ask what happened to their pain while they were imagining the movement. It may be painful or increase their pain if their premotor homuncular map is altered.

4. Sensitivity to physical activity – this assessment technique gives us information about the descending signals that inhibit nociceptive signalling (17). When we perform physical activity or exercise which raises our heart rate, the descending inhibitory mechanisms should be activated from the brainstem down to the spinal cord to inhibit nociception being transmitted up the spinal cord to the brain. To conduct this test, palpate a bony prominence such as the tibial tuberosity or the lateral epicondyle of the elbow (DO NOT palpate the painful limb). Press on the bony prominence to the first blanching of your thumb nail and ask, “how painful was that on a scale of 0 – no pain, to 10 – worst pain you can imagine”. Note down the response. Then ask the person with pain to do a 6-minute walk/sit-to-stand/step test. They need to raise their heart rate to around 60% of heart rate maximum or exercise at the level of ‘somewhat hard’ on the Borg Scale. Immediately after they have completed the 6-minute test, reassess pain to the same pressure on the same bony prominence. In a healthy system where the descending inhibitory mechanisms are intact, the pain will reduce after the activity. When descending inhibition is impaired, the pain will get worse.

5. The Central Sensitisation Inventory (CSI) is a useful tool to confirm the presence of central sensitisation (18, 32). The inventory is a 25-item questionnaire with a series of statements that cover a range of symptoms which, together, can indicate central sensitisation. For each statement, the person with pain selects one response from “never”, “rarely”; “sometimes”; “often” or “always”. Scores are calculated by allocating a score of 0 – 4 to each item based on the response, and then totalling all item scores. A total score >40 suggests clinically meaningful central sensitisation (18).

6. The Self-report Survey for the Assessment of Fibromyalgia is a validated, short and useful tool to confirm a diagnosis of fibromyalgia (also known as chronic widespread pain) (33). The tool includes a Widespread Pain Index where the person with pain is able use a body chart to indicate all the sites where they experience pain. The second part of the tool has a short series of questions to assess symptom severity. A score of ≥13 points is consistent with a diagnosis of fibromyalgia.

DON'T MISS THIS

Using these techniques with people with pain

In Section 2 which explores pain in the Primary Healthcare Setting, we hear from Theresa about her experiences with Fibromyalgia and we describe how the Survey for the Assessment of Fibromyalgia can be used and interpreted in the clinic.

In Section 3 which explores chronic pain, we hear from Jo about her experiences with Complex Regional Pain Syndrome (CRPS) and we describe how two-point discrimination, left/right judgements and the CSI can be used and interpreted in the clinic.

Assessment of Synergistic mechanisms

Two key areas which should be considered whenever you are assessing a person with pain are their sleep and their autonomic nervous system. Sleep problems, including difficulty initiating sleep, maintaining sleep, waking early, and non-restorative sleep not only increase pain, but increase the risk of developing nociplastic pain (34). Autonomic nervous system dysfunction (poor balance between sympathetic and parasympathetic activity disrupting homeostasis) is also commonly recorded in people with pain. While it is not known whether dysfunction of the autonomic nervous system causes, or is caused by pain, it is useful to assess it to include it in the treatment plan if present (35).

1. Assessing sleep can be accomplished with general questions about sleep. Gather information on the overall quality of the person's sleep, how many hours they sleep for, their sleep routine, how easily they fall asleep at night, and whether they are regularly sleepy during the day (36). If sleep does appear to be poor, then a more comprehensive assessment is indicated with a validated tool such as the Pittsburgh Sleep Quality Index (37).

2. Be alerted to features that suggest problems in the autonomic nervous system (ANS) when you are gathering information with your routine questions. Indicators of possible ANS problems include sleep dysfunction, symptoms of irritable bowel syndrome, high levels of stress, postural orthostatic tachycardia (POTS), or symptoms similar to panic attacks. If autonomic nervous system dysfunction (referred to as dysautonomia) is strongly suspected, then use the COMPASS-31, which is a validated tool for the full assessment of the ANS (38). However, this is a long tool and complex to score so we suggest using it only if you have clear indication that the ANS is contributing to pain, and you have a clear plan about how the results would change your choice of treatment interventions.

Two key areas which should be considered whenever you are assessing a person with pain are their sleep and their autonomic nervous system.

Screening for contributing and vulnerability factors

By now you will probably recognise that, if pain is about a perception of threat, then a pain assessment needs to evaluate all possible sources of threat that might be contributing to pain. Screening for these contributing and vulnerability factors is important, even in people with short-lived pain, because they can increase the risk of developing pain and for that pain to be maintained as nociplastic pain.

The contributing and vulnerability factors have been described as yellow flags (as opposed to red flags). Like a traffic light, red flags are meant to get the clinician to stop and assess the risk further; yellow flags are meant to remind us to slow down, and assess more thoroughly, because these factors can contribute to poor outcomes.

DON'T MISS THIS

Sympathetic activation and "fight or flight" mode

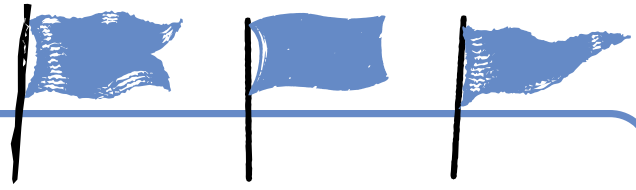
When the sympathetic nervous system is dominating activity, we are in "fight or flight" mode. Can you think of a time when you have been in "fight or flight" mode? Perhaps before an exam that you were particularly nervous about... What did you look like, and how did you feel? Were your eyes wide open and your pupils dilated? You couldn't relax or sleep? Were you pale? Perhaps you felt nauseous and shaky too? Was your stomach churning and you had to run to the bathroom several times? Was your heart pounding, your breathing shallow and were your muscles tense? All of these are automatic responses to stressful situations driven by the sympathetic nervous system. These are normal and useful responses for us to cope and survive short-term stress. After the stress is over, the parasympathetic nervous system ("rest and digest") should become more active so that we can recover. If we get stuck with sympathetic activation, it is not helpful in the long term! Make sure you are observing and asking the person with pain about how they are feeling generally.

The factors which have been clearly demonstrated to increase pain and increase vulnerability to developing nociplastic pain are depression and anxiety, pain catastrophising, and fear-avoidance beliefs.

One tool that has been developed to screen for all of these items in people with musculoskeletal pain is the Keele STarT MSK tool (40). This tool is based on the Keele STarT back tool (41) and a start has been made to translate it and validate its use in South African populations (42). The STarT tools screen for depression, anxiety, fear-avoidance beliefs and pain catastrophising with one question for each and are designed for use in the primary care setting. The tools are easily scored, and the score translates to an estimate of whether the person with pain is at low, medium or high risk of developing chronic nociplastic pain. However, testing of this final risk estimate is in its infancy, so it's best to use this tool to guide for your decision-making as you design the treatment plan, rather than as an absolute measure of risk.

You may work in a setting where a single screening tool is not appropriate, or you may like to assess these risk factors in more depth.

DEEP DIVE



The move beyond yellow flags

The flag movement was designed to assist healthcare professionals to reflect on the information they were gathering during an assessment and take appropriate action. The yellow flags were originally described as:

A: Attitudes and beliefs towards pain e.g., pain means something dangerous is happening.

B: Behaviours associated with pain e.g., when I have pain, I shouldn't move.

C: Compensation issues e.g., an ongoing legal case.

D: Diagnostic issues e.g., one doctor advised to rest and not move, now you are advising exercise.

E: Emotional issues e.g., depression and anxiety.

F: Family e.g., a family who is dismissive of the illness, or a family who is overly supportive.

G: Work issues e.g., conflict at work, lack of support from colleagues.

However, research has shown that healthcare professionals find it difficult to recognise these factors when conducting an interview (39). We also need to recognise that some of these yellow flags are not amenable to treatment. In this book we focus on the contributing and vulnerability factors which we know can be assessed using validated tools and can be targeted in treatment.

1. **Depression and anxiety** can be screened for quickly and easily with the 4-item Patient Health Questionnaire (PHQ-4) (43). This short tool has two questions to screen for depression and two screening for anxiety. The scoring is simple and gives the primary care clinician an indication of severity and whether referral to a mental health professional is indicated.

If the person with musculoskeletal pain is at high risk of developing chronic nociplastic pain, or already has chronic nociplastic pain, then the healthcare professional should go on to assess pain catastrophising and fear avoidance beliefs in full.

2. **Pain catastrophising** is described as an unhelpful way of thinking about pain (44). It has three components:

    a. Magnification: a tendency to think about the pain as a bigger problem than it is and to experience the pain as more severe e.g., my pain is terrible, no one has experienced pain like this.
    b. Rumination: difficulty disengaging one's thoughts from the pain to be able to think about or engage in other activities.
    c. Helplessness: a tendency to think and feel that there is nothing that one can do to diminish the pain.

Pain catastrophising is an unhelpful way of thinking about pain. Catastrophising includes magnification, rumination and helplessness.

Of course, aspects of catastrophising are normal in the early stages of pain; your challenge as a clinician is to work out whether the person is 'stuck' in these thought patterns to an extent that is inhibiting their function and recovery. We can also intervene early to diminish catastrophising. There is a large amount of literature clearly showing the importance of catastrophic thinking in increasing the severity of the acute nociceptive pain experience and to increase risk to develop chronic nociplastic pain. The Pain Catastrophising Scale is a 13-item tool which has been translated and validated for use in many languages and populations including South African English and Afrikaans (45). It is useful and important to assess pain catastrophising formally using a tool such as this, as most people around the world are poor at recognising pain catastrophising simply from an interview, particularly when working in cross-cultural settings. Identifying pain catastrophising supports the implementation of treatments to specifically target the components of catastrophising, thus increasing overall treatment efficacy.

3. **Pain-related fear-avoidance beliefs** can develop if your understanding or belief about pain is that it is an accurate measure of tissue damage (46). The thoughts might go something like this: "I try to move, it hurts, pain means I'm hurting myself, I'm causing damage, don't move!" Now this is a very logical and sensible fear to have if you have a fracture: keep it still to let it heal. But, as we heal, we slowly need to become brave and test our ability to move. If we don't confront our fear of moving, we may get stuck never moving, leading to more and more disability. This is why fear-avoidance beliefs are predictors of chronic, disabling nociplastic pain, because people get stuck not doing things, in order to avoid the pain. Fear-avoidance beliefs can be assessed with a range of tools including the Fear Avoidance Beliefs Questionnaire (FABQ) and the Tampa Scale of Kinesiophobia (TSK). Both of these tools have been used in South African settings (45, 47). The FABQ is particularly useful because it gives scores for fear-avoidance beliefs related to work, and fear-avoidance beliefs related to physical activity (48). The TSK is shorter, and useful to identify fear-avoidance beliefs to be able to target them in the implementation of treatment.

Putting it all together

Once you have completed your pain assessment, you need to put all the information together. What does it mean? What is it telling you? How can we collaboratively design a treatment that will target all the factors contributing to pain in this person?

One way to make sense of all of this information is to create a mind-map based on the framework shown in Figure 3.5. In the figure, we have included all of the evidence you are looking for in your assessment, divided into the three main sections of the nervous system, and the synergistic systems. To complete the mind-map for a person with pain, edit each section as you go: cross out where your assessment/testing indicates no problem, place a question mark next to things you are uncertain of or which you want to go back and check, and highlight where your assessment provides evidence indicating that something is definitely relevant to the person you're assessing. Next, include information on any vulnerability factors which might also be playing a role. When you have finished the mind-map, you should be able to identify where you need to target your treatments. You may also have a clear initial target – one thing that will give you more "bang for your buck" to make a difference to the person with pain.

Once you have completed a mind-map for the person with pain and you can see some targets for treatment, it's time to plan what treatments you are going to suggest to the person with pain and how they might best be implemented.

DON'T MISS THIS

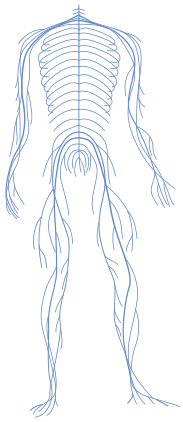
A note on ethical assessment practice

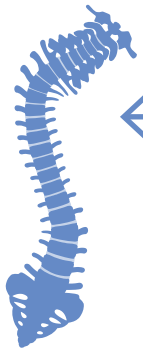
As healthcare professionals, we have an ethical responsibility to ensure that all information we gather when we conduct an assessment is relevant and will inform our treatment. If we gather information, do a clinical or laboratory test, or request imaging of some kind (X-ray, ultrasound, MRI, etc), then we must be clear about how the information, or the results of the test will influence our treatment. For example, if you order an X-ray but what you see on that X-ray will have no influence on your treatment options, then why are you ordering it? We should only be gathering information or doing tests that inform our hypothesis and which will guide your treatment planning. Every test or assessment procedure has an associated risk or cost – and costs are not just financial.

This also means that if we have gathered information indicating that someone is at risk of developing chronic nociplastic pain, we must take action based on that information i.e., design a treatment to address that risk. Do not assess and identify risk, and then fail to take action to reduce that risk.

Next page: Figure 1.14: A mechanism-based clinical reasoning mind-map to guide analysis of a pain assessment

Mind-mapping all the information gathered in the assessment to identify targets for treatment





Pain

Peripheral Nervous System

Spinal Cord

Brain

Evidence of activity

Signs of inflammation
Primary hyperalgesia
Clear aggravating and easing factors
Within tissue healing times
Good response to analgesics and NSAIDs

Evidence of activity

Allodynia
Secondary hyperalgesia
Pain referred in a spinal segment
Temporal summation
Response to medication

Evidence of activity

Where is the pain?

Cortical activity contributing to pain

Pain referred to multiple areas
Pain gets worse (Sensitivity to Physical Activity)
Central Sensitisation Inventory Score >40
Two-point discrimination altered
Altered left-right discrimination
Pain on imagining movement

Synergistic Systems

Evidence of activity

Sleep disturbances
Autonomic nervous system dysfunction
Endocrine system dysfunction
Immune system dysfunction

What vulnerability factors seem to be contributing to pain for this person?

Depression
Anxiety
Pain catastrophising
Fear-avoidance beliefs

4 Principles of treating pain

Romy Parker
Gill Bedwell
Claire Pfister
Jocelyn Park-Ross
Tory Madden
Johannes Stofberg
Johan van Der Walt

We are approaching pain as a conscious construct of the brain in response to a perception of threat. Therefore, to effectively manage pain, we must target all variables which may be contributing to a sense of threat or danger. We can all acknowledge, even as healthcare professionals, that the healthcare environment itself and the medical consultation can be threatening. We must focus on our communication skills and the environment we work in to reduce any implicitly threatening messages – verbal, non-verbal, conscious and unconscious. The first step in effectively treating pain is to build a strong therapeutic alliance with our patients.

The therapeutic alliance

The therapeutic alliance is the collaborative relationship between a person seeking health care and the healthcare provider. A strong therapeutic alliance provides psychological safety. When a person feels safe, they are more likely to give honest information on their own behaviour, and more likely to feel brave enough to try out changes. In short, a strong therapeutic alliance facilitates productive treatment and recovery – it is an essential element of good treatment! There are three elements which contribute to a strong therapeutic alliance. These are: (i) mutually agreeing on the goals of treatment; (ii) establishing consensus on the tasks, activities or processes to be followed to reach those goals, and (iii) forming a positive emotional bond (49).

To build a strong therapeutic alliance with people who are seeking our help, we must pay attention to our verbal and non-verbal communication skills. The communication skills of active listening and validation are foundational to building the alliance between ourselves, as healthcare professionals, and the person with pain. Healthcare professionals who demonstrate empathy, respect, flexibility and genuine interest in the person who has consulted them for help, lay good foundations for a strong therapeutic alliance (49). It's important to be explicitly trained in these skills – it is not a matter of simply having a "good bedside manner" or a "way with people"! If you have not received dedicated training in communication skills, it is worth obtaining this training and working at these skills, to enhance your effectiveness as a healthcare professional - regardless of the context in which you work. A trusting therapeutic alliance built using respectful communication skills allows us to establish our all-important collaborative relationship with the person in pain, so that we can begin to reduce the threat factors which may be contributing to pain and provide the supportive launchpad they will need to begin their recovery.

Empowering the person with pain through knowledge

Once we have a trusting relationship with the person with pain, we can then address threat with knowledge. This is not necessarily knowledge about the injury or potential tissue damage; in fact, sometimes knowledge of the injury or tissue damage or disease can increase threat and make pain worse. Rather, we directly address what the person brings to us by providing information on what the person thinks is wrong – treatment starts with addressing the U (understanding) in your pain assessment. Addressing the person's ideas and concerns about what might be wrong, what this pain means, and what the potential consequences are, directly addresses these threats. In an emergency situation, we may not be able to provide that information, but we can reduce threat with reassurance by carefully informing the person with pain of what is happening every step of the way. (Note that this is not false reassurance that things are better than they actually are; even if you can't honestly say that things are better than the person thinks they are, you can still reassure the person that you are with them and managing the situation alongside them.)

Understanding the three core concepts of pain is powerful medicine. Pain is not an accurate measure of tissue damage; pain is about context; and pain is produced by our brains in response to threat.

The next step in empowering the person with pain through knowledge is to teach them about pain – Pain Science Education (also known as "Explain Pain"; "Pain Neuroscience Education" and "Therapeutic Pain Neuroscience Education") (50). Understanding three core concepts have been found to help people with pain to recover, and it is our job to help them to consider these ideas - which will often conflict with the understanding of pain that they first brought to us. The three core concepts are (i) pain is not an accurate measure of tissue damage; (ii) pain is affected by biological, psychological and social factors (or pain is about context); (iii) pain is always produced by our brains when the brain concludes that there is threat or danger.

Remember that simply telling someone facts is not the best way to help someone to revise their beliefs - typically, if our beliefs are challenged head-on, we dig into our beliefs more deeply! We need to gently facilitate their process of reconsidering their ideas about pain, coming alongside them in the learning process rather than positioning ourselves as teacher lecturing to a pupil. All the concepts that you have learnt about in this section on the "Nuts and Bolts of Pain" are also helpful concepts for the person with pain to learn. Understanding that my pain is about more than my tissues helps me to understand that, to treat my pain, I need to do more than just treat those tissues. This knowledge empowers me to actively engage in pharmacological and non-pharmacological treatments for pain.

Pharmacological principles for treating pain.

A common tool for healthcare professionals to understand analgesia, is the World Health Organisation (WHO) Analgesic Ladder which indicates that mild pain (0-3 out of 10) is treated with mild analgesics or with analgesics and NSAIDs; moderate pain (4-6) is treated with weak opioids and severe pain (>7) is treated with opioids. You may even have learnt about the modified four-step ladder (51). We propose that the analgesic ladder could be updated as below to remind us that our pharmacological management of pain should take place within the therapeutic alliance and alongside the non-pharmacological treatments.

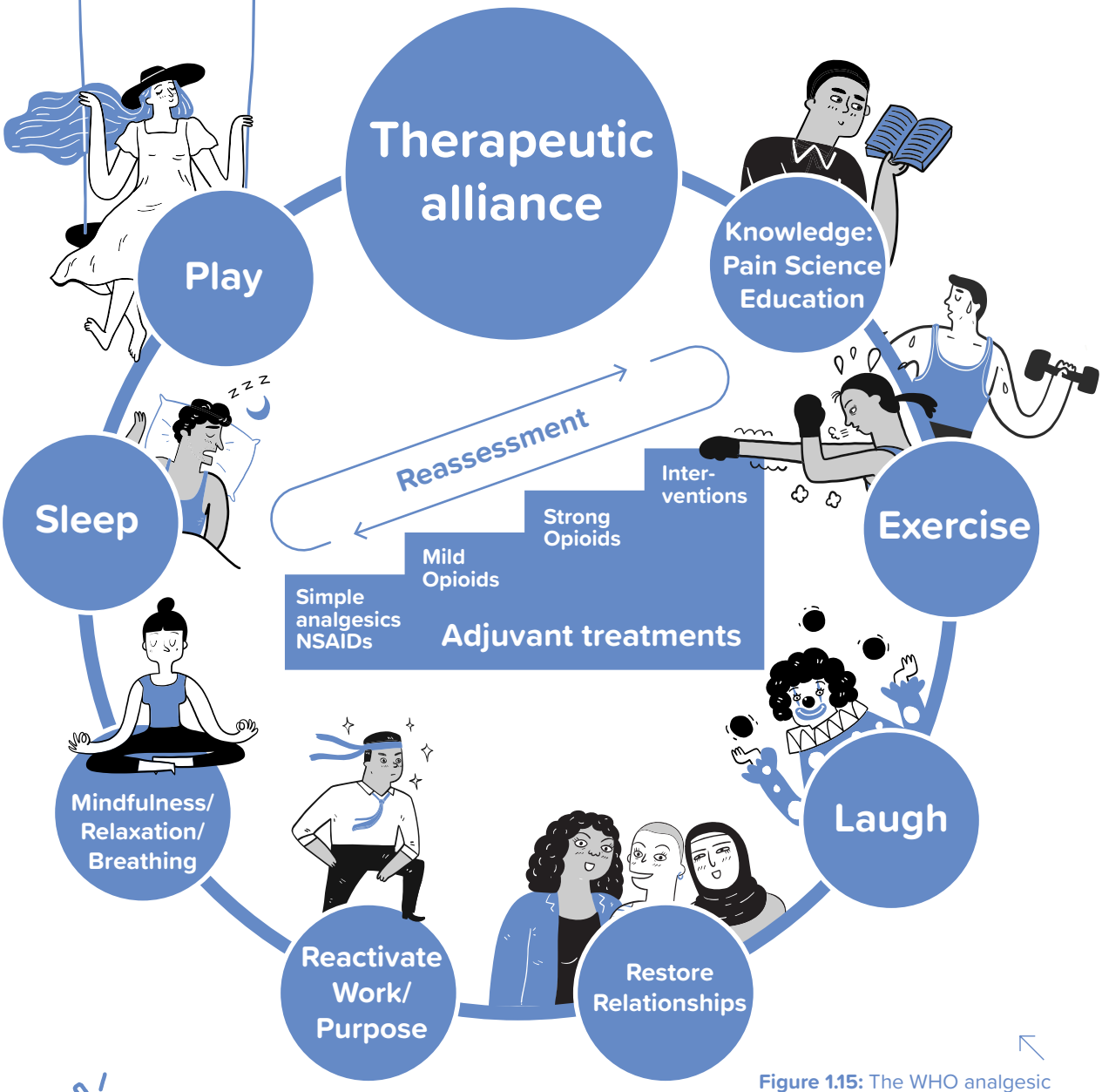


Figure 1.15: The WHO analgesic ladder in the context of holistic pain treatment strategies

DON'T MISS THIS

Mechanism-based treatments for pain

In this book, we take this approach further by encouraging you to design your treatment based on the mechanisms of pain, not merely the severity of pain. Is the person's pain nociceptive? Then the nociception should be targeted in the peripheral nervous system. Or is their pain neuropathic with lesion or disease in the periphery or centrally? Or is their pain nociplastic? If so, the plastic changes in the nervous system could be targeted pharmacologically.

In Table 1.4, we have summarised the drugs which are commonly used in the management of pain and included the site (peripheral, spinal cord, or brain) at which the drug has its primary effect.

Table 1.4: Common pharmacological treatment options for pain and their primary mechanistic target

Class of drug	Example	Mechanism of action	Target Effect site
Simple analgesia	Paracetamol (acetaminophen)	Multiple mechanisms: COX/POX inhibition, Serotonergic pathway activation, Endocannabinoid enhancement	Central and peripheral nervous system
NSAIDs (non-steroidal anti-inflammatory drugs)	Ibuprofen Celecoxib Parecoxib	Block COX-1 and COX-2 enzymes which are involved in inflammatory mechanisms that increase pain	Peripheral nervous system, at the sites of inflammation
Local anaesthetics	Lignocaine/lidocaine Bupivacaine Ropivacaine	Sodium channel blocker: blocks transmission of nociception via the nerve	Used to block peripheral nerves or for neuraxial techniques where the local anaesthetic is placed in or around the central nervous system, such as in: Spinal anaesthetics Caudal blocks Epidurals Lignocaine patches Trigger point injections Upper limb blocks Lower limb blocks Abdominal and trunk blocks
Corticosteroids *Can be used alone or as an adjuvant in nerve blocks to prolong duration of action.*	Methylprednisolone Prednisone Dexamethasone	Anti-inflammatory effect	Peripheral nervous system: enters the cell nucleus and binds to glucocorticoid receptors which results in inhibition of pro-inflammatory mediators
Weak opioids	Tramadol Codeine	Block mu-opioid receptors peripherally and centrally	Peripheral and central nervous system
Strong opioids	Morphine Fentanyl	Block mu-opioid receptors	Peripheral, spinal cord, and central nervous system
NMDA receptor antagonists	Ketamine Magnesium sulphate	Antagonise n-methyl-d-aspartate receptors. Ketamine also blocks some mu-opioid receptors	Spinal cord and central nervous system

continued...

Antidepressants	Selective Serotonin Reuptake Inhibitors (SSRIs) Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) Tricyclic antidepressant (TCA) e.g., amitriptyline	Promote an increase in levels of serotonin by preventing its re-uptake. SNRIs also prevent reuptake of noradrenaline. TCAs block reuptake of serotonin and noradrenaline, resulting in increased concentrations of these.	Central nervous system. These drugs may also promote sleep and have antidepressant effects, which may all contribute to recovery
Gabapentinoids	Pregabalin Gabapentin	Calcium channel blockers	Central nervous system Are also beneficial for sleep
Alpha-2 agonists *Can be used alone or combined with neuraxial and peripheral nerve blocks to prolong duration of action and improve the quality of analgesia*	Dexmedetomidine Clonidine	Block central and peripheral alpha-2-adrenoceptors to have an analgesic, sedative and anxiolytic effect	Spinal cord – specifically at the dorsal horn where they inhibit release of substance P. Also beneficial for sedative and anxiolytic effects

To manage pain effectively with pharmacotherapy, we need to select the correct drug to target the correct mechanism. We also need it to have minimal side effects and we must prescribe it appropriately. A key issue in prescribing analgesia is prescribing by the clock! Do not prescribe PRN (as needed) - if someone is in pain, they need to take their analgesia regularly – not only when the pain is severe, as then it has a limited effect. People with pain often make the mistake of thinking they must be brave, they must wait to take the pills because they don't want to be dependent, they don't want to risk addiction, and they don't want to risk side effects. However, this pattern of use leads to the need for higher doses, is less effective, and increases risks of side effects and addiction. Therefore, it is important for all healthcare professionals to check how people are using their medication and advise that the best approach is taking medication by the clock.

DON'T MISS THIS

Taking medication "by the clock"

Many people with severe pain tell us that paracetamol is useless – whether it is nociceptive or nociplastic pain. When we ask how they are using the medication, they invariably tell us that they wait until their pain is really bad and then take the pills, which of course then do nothing! As part of our treatment, we then discuss how the pills work for pain and ask them to take the medication every 4 to 6 hours and reassure them that this dosage is safe (4 grams paracetamol daily). Many people then report back that this approach of taking the medication "by the clock" is much more effective and keeps the pain under control and that they now need less "rescue" medication. Never prescribe analgesia "PRN" (pro re nata which is Latin for "per required need" or "as needed"); always prescribe baseline analgesia to be taken "by the clock" with clear instructions of when and how to increase dosing.

DON'T MISS THIS

Dosing

While we have done our best to ensure correct dosing, please always check a reference such as the South African Medicines Formulary for up-to-date dosing.

Paracetamol (acetaminophen)

Paracetamol is a widely used analgesic globally and the first line treatment for most pain conditions. It is the mainstay of step one in the WHO analgesia ladder and is depended upon for its synergistic effect with other pharmacological agents (51). Paracetamol's mechanism of action is still unclear; however, it appears to have anti-inflammatory effects via COX inhibition, similar to the NSAID's. In addition, paracetamol has an effect on the central nervous system, activating descending inhibitory pathways via serotonin and endocannabinoids (52, 53).

The safety profile of paracetamol is significantly better than that of NSAID's in both the acute and, particularly, in chronic use. While it has a good safety profile, paracetamol should be used with caution in people with pre-existing liver or kidney disease. Paracetamol should be started and continued at the dose of 1000mg six hourly and has its best effect when prescribed by the clock (54-56).

Many people with chronic pain conditions who have been prescribed paracetamol comment that it is not effective. The most common reason for a lack of effectiveness is not using the medication by the clock. People with chronic pain often wait until their pain is severe prior to taking their medication as opposed to taking it by the clock or when the pain is still mild. Paracetamol is classified as a mild analgesic. Instead of thinking of the term 'mild' referring to the strength of the drug, it is useful to think of the term 'mild' in terms of the severity of the pain i.e., it is a painkiller for mild pain – use it while the pain is still mild for maximum effect.

Non-steroidal anti-inflammatories (NSAIDs)

NSAIDS are widely available and inexpensive drugs used in most settings. NSAIDs exert mostly a peripheral action in modulating pain i.e., they target activity in the PNS. This group of agents has its peripheral impact by inhibition of Cyclooxygenase (COX) 1 and 2 resulting in a decrease of prostaglandin formation which decreases inflammation, thereby decreasing nociception and ultimately decreasing pain. NSAIDS also have an effect on the central nervous system (CNS) where they may result in an increase in levels of serotonin (52, 57, 58).

Optimise the efficacy of mild analgesics like paracetamol and NSAIDS by ensuring they are prescribed and taken by the clock.

NSAIDs, like all treatments, are associated with risk. They are well known to increase risk of gastrointestinal side effects and may increase a chronic user's risk of gastritis and an upper gastrointestinal bleed (57, 59, 60). NSAIDs also increase cardiovascular risk and may lead to increased risk of stroke, myocardial infarction, and kidney disease. This emphasises the principle of using NSAIDs at the lowest therapeutic dose for the shortest period of time.

Ibuprofen in the most commonly used NSAID in the South African public health context and is a non-selective COX inhibitor. The starting dose is 400mg eight hourly and may be increased to 800mg eight hourly. If NSAIDs are not effective, they should be discontinued completely, and second line treatment should be initiated.

Weak opioid (tramadol)

Tramadol hydrochloride (tramadol) is a synthetic mixed opioid which acts in the central nervous system to relieve moderate to moderately severe pain (61, 62). Tramadol is a racemic mixture of two enantiomers, each contributing to its analgesic

activity via different mechanisms. Tramadol has an effect in the spinal cord as it is (i) an agonist of the mu opioid receptor, (ii) inhibits serotonin reuptake and (iii) inhibits norepinephrine reuptake. This means it has an overall effect of inhibiting the transmission of nociception in the spinal cord (61-63).

The use of tramadol in the management of chronic nociplastic pain has become controversial. Previous systematic analyses advocated for the use of tramadol in the management of chronic pain of non-malignant origin (62, 64). Tramadol was frequently favoured in preference to morphine (which causes more nausea and constipation, and has a greater tendency for developing tolerance) and in preference to NSAIDs or selective COX-2 inhibitors (which have renal, gastrointestinal and cardiovascular side effects with long term use) (62). However, in recent years, the drug has stopped being included in many international guidelines for the management of chronic nociplastic pain. The latest NICE guidelines from the United Kingdom on the management of chronic primary pain state that the evidence of long-term harm, along with the lack of evidence on effectiveness of opioids, persuaded the committee to recommend against initiating opioid treatment for people with chronic primary pain (65).

Remain up-to-date with prescribing guidelines. For example, recent data provide evidence that tramadol has a risk for abuse, which means we now need to use more caution with its long term use.

Recent data provide evidence that tramadol has a risk for abuse, although its risk is generally lower than most of the opioids to which it is compared. Abuse, dependence or intoxication can occur, especially when tramadol is given at supra-therapeutic doses (66, 67). Epidemiological evidence of tramadol abuse appears to vary depending on how much it is regulated. Countries in which a wide variety of opioid products are available generally report low rates of tramadol abuse relative to other opioids; however, countries that impose greater restrictions on opioid products and rely more heavily on tramadol for primary pain management often report tramadol abuse (67). This has become of particular concern in some African countries, where increases in the importation of illicit and adulterated (mixed with other substances or not pure) tramadol have been recorded (67, 68).

Tramadol can be initiated at 50mg eight hourly and can be increased to a maximum dose of 100mg six hourly. However, as tramadol is not without risk, it should be used at the lowest dose for the shortest time required (69-71). In our clinical experience, one of the challenges of tramadol is that while it can be an effective analgesic, in other words it reduces pain, when the drug wears off, the pain comes back. This is why pharmacotherapy must be given as adjunctive therapy with active non-pharmacological interventions which aim to have a more long-term impact on pain and people's ability to return to their meaningful life roles.

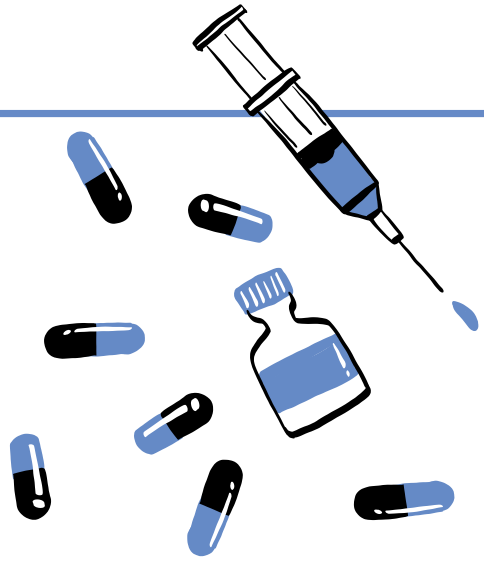
Opioids

Opioids are a class of analgesic drugs that are based on the chemical structure of the opium poppy, *Papaver somniferum* (72). Morphine is the most well-known opioid but there are many other opioids available. They can be classified based on their chemical structure as being naturally occurring (e.g. morphine, codeine), semi-synthetic (e.g. buprenorphine, diamorphine) or synthetic (e.g. fentanyl, pethidine, methadone). Opioids act at opioid receptors. These receptors are spread out throughout the central nervous system, and in peripheral neural and non-neuronal tissue (72). There is a very high concentration of opioid receptors in the periaqueductal gray (PAG) and Rostral Ventromedial Medulla (RVM), the origin of the descending inhibitory pathway down to the spinal cord. Opioid receptors also occur in the dorsal root ganglion (DRG) of the posterior column of the spinal cord.

DEEP DIVE

Classification of opioids

Opioids can be classified in other ways apart from their chemical structure. They can be classified based on how they bind to opioid receptors as opioid agonists, partial agonists, agonist-antagonists or antagonists. They can also be classified according to which opioid receptor they bind to. There are currently four different classes of opioid receptors known and each opioid receptor has a specific clinical effect when binding occurs (73). The classification of these opioid receptors has evolved over many years with the use of letters of the Greek alphabet. Currently we use the terms MOP, KOP, DOP and NOP to describe the 4 classes of opioid receptor peptides (74). The classic Mü opioid receptor (MOP) is the site of action of most analgesic drugs. The action of an opioid agonist at MOP receptors has an analgesic effect. MOP receptors also have a sedative side-effect that can be used clinically for sedation in the critical care setting. Other side effects of opioids occur due to action on MOP, KOP and DOP receptors. These side effects include respiratory depression, hypotension, bradycardia and constipation. A significant possible side effect of long-term opioid use is opioid induced hyperalgesia. This complication is believed to be the result of agonist action at the NOP receptor (73).



Opioid receptors are membrane-spanning and termed G-protein coupled receptors (73, 75). When the opioid binds the receptor, it leads to a conformational change in the receptor which causes a change in the intracellular concentration of calcium. Calcium is involved in many intracellular signalling cascades. The net effect is a change in the resting membrane potential due to hypo-polarization of the cell membrane. This causes decreased conduction of nociceptive signals and a decrease in excitatory neurotransmitter release.

The human body produces and releases its own endogenous opioids which bind to opioid receptors (72). These endogenous opioids have their own classification, but we refer to them broadly as endorphins and enkephalins and they have a significant action on the body's processing of nociception. These endorphins circulate in the body and ensure an appropriate analgesic response to tissue injury. The endorphins are also released in response to exercise contributing to exercise-induced hypoalgesia (hypoalgesia is reduced pain to a normally painful stimulus, the opposite of hyperalgesia).

Opioids are used clinically in the management of acute pain as part of a multi-modal pain management plan when non-opioid pharmacological agents have failed (76). Opioids can be administered via most routes including oral, dermal (skin) patches, intramuscular and intravenous. Opioids administered intrathecally and intravenously have more potent clinical effect than those administered orally or via dermal patches (72). This more potent clinical effect means there is a higher risk of dangerous side-effects like respiratory depression when the drug is administered via these routes. The route of administration and dosage is therefore very important to calculate before prescribing opioids to any patient.

Opioids have historically also been used for people with chronic nociplastic pain. There is however increasing evidence that the use of opioids in chronic nociplastic pain may not only be harmful but could also cause a paradoxical increase in pain (77). Opioids still form an important aspect of chronic cancer pain management. However, the use of opioids in non-cancer pain should be very carefully considered, especially in the light of the global opioid crisis (76).

DEEP DIVE

Opioid use dependence disorder

One of the risks of chronic opioid prescribing is opioid use dependence disorder (76, 78). Over the last two decades the indiscriminate use of opioids for chronic nociplastic pain, as well as illicit drug use, have escalated. Opioids are highly addictive and people who develop opioid use dependence disorder face a significant healthcare challenge. These individuals have a ten-fold higher risk of death due to opioids than the general population and other risks include overdose, HIV, Hepatitis B and C virus infection, sepsis and interpersonal violence (78). There is also major stigma associated with illicit drug use which makes it difficult to access the healthcare needed to manage this disorder. Opioid use dependence disorder, as well as other drug dependencies, should be managed as a chronic health condition. And just as we screen for diabetes and hypertension in the general population, we should screen for opioid use dependence disorder in all adults above the age of 18.

People with a family history of illicit drug use have a 50% higher risk of developing the disorder (78). Other risk factors include a history of trauma, childhood abuse and mental health conditions. A simple question may be used to screen for opioid use dependence disorder. "How many times in the past year have you used an illegal drug or prescription medication for nonmedical reasons?" An answer of "At least once" is enough to continue to assess the person with the use of the DSM-5 (the DSM-5 - The Diagnostic and Statistical Manual of Mental Disorders) (79). Like any other chronic health condition, opioid use dependence disorder has accepted management plans that should be implemented as part of an interdisciplinary team. Long term opioid substitution with Methadone, Buprenorphine or Naltrexone in conjunction with psychological and community support programs have the lowest risk of relapse.

With all the information and disinformation circulating around opioid use in pain management, healthcare providers may become hesitant to use these powerful and effective analgesic agents. The use of opioids is appropriate in the peri-operative setting and when they form part of a palliative care plan in managing end-of life pain (76, 80). Chronic non-cancer nociplastic pain represents a complex process of central and peripheral sensitisation of nociceptors (81). The use of opioids for chronic nociplastic pain may lead to opioid induced hyperalgesia and opioid use dependence order (82). More effective non-opioid analgesic agents and non-pharmacological management should be considered in people with this kind of pain.

Antidepressants - selective serotonin and noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs)

This class of drugs exerts its effect on pain by increasing noradrenaline, serotonin and endogenous opioids in the descending inhibitory pathways. (33, 83). In other words, they treat pain by targeting mechanisms in the central nervous system. This is an important message for the person with pain to understand. They are being prescribed these drugs for their pain, not because the healthcare team thinks it is "all in their heads", or that their pain is not real and that they are making it up.

SNRIs are particularly helpful in people who have comorbid features of depression or in people who are developing or have widespread pain i.e., who have nociplastic pain with central sensitisation. SNRI's are generally well tolerated with only minor or transient side-effects. These side effects can include nausea, dry mouth,

dizziness, headache, constipation, drowsiness, insomnia and agitation (52, 54, 84). Duloxetine is a SNRI which has been proven to be beneficial in the treatment of chronic musculoskeletal pain. It can be initiated at 30mg daily and increased to 60mg if required (85). Unfortunately, duloxetine may not be freely available at all clinical sites in South Africa and is relatively expensive.

Amitriptyline is a TCA which is accessible and inexpensive. It is commonly used in resource-limited health services for chronic nociplastic pain. Doses of 25 to 75mg are usually effective, with some people getting benefit from the agent at doses as low as 10mg (85). It is important to be aware of the side effect profile of TCAs and people who might be more susceptible to develop adverse outcomes. The elderly are particularly at risk of the typical side effects which might include weight gain, inattentiveness, muddled consciousness, constipation and dry mouth. TCA's can have serious cardiac adverse reactions in overdose, although the elderly are once more at higher risk, even at lower dosages. Therefore, it is advised to titrate slowly. The minimum effective dose should be continued for up to a year, when weaning can be considered. Many people might require long term or lifelong treatment (86).

Both SNRIs and TCAs have the benefit of potentially treating underlying major depressive disorder if present. While not everyone with pain will also suffer from major depressive disorder, if someone is depressed, they will also suffer with more pain. Therefore, treating the depression also has benefits for pain. Importantly, amitriptyline's antidepressant effect is only achieved at the higher doses and may need to be up-titrated (85). The other benefit of amitriptyline is that it helps with sleep. As we have discussed earlier in this section, sleep problems significantly increase pain and must be assessed and targeted in treatment (87-89).

DEEP DIVE

Evidence for anti-depressants in adults with chronic nociplastic pain

The latest Cochrane review conducted a network meta-analysis to assess the effectiveness of antidepressants for managing chronic pain in adults (86). The findings suggest that selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are more effective than placebo in reducing pain intensity. Tricyclic antidepressants (TCAs) also showed effectiveness, but they were associated with more side effects. Among the specific antidepressants analysed, duloxetine (SNRI) and amitriptyline (TCA) demonstrated the greatest pain reduction. However, it is important to consider individual patient factors and potential adverse effects when selecting an antidepressant for pain management. Further research is needed to better understand the comparative effectiveness and long-term safety of different antidepressants for chronic pain.

The review further found that both pregabalin and gabapentin were effective in reducing pain intensity in adults with chronic pain. Pregabalin was found to have a moderate effect on pain reduction compared to placebo, while gabapentin showed a small effect. However, the authors noted that the quality of evidence for gabapentin was lower compared to pregabalin. Furthermore, the review indicated that both pregabalin and gabapentin were associated with an increased risk of adverse events, such as dizziness, somnolence, and peripheral oedema. The authors highlighted the need for individualised treatment decisions considering the potential benefits and risks of gabapentinoids (86).

Gabapentinoids

The gabapentinoids include the membrane stabilising drugs Gabapentin and Pregabalin. These drugs target activity in the spinal cord, in particular by reducing the sensitivity of calcium channels in the second order neuron of the spinal cord. Pregabalin and gabapentin are α2δ-ligands with similar targets but with differing pharmacokinetics. Gabapentin, the older of the two drugs, has non-linear pharmacokinetics and dosing requires careful titration. Gabapentin is more commonly used in the paediatric population. Pregabalin has linear pharmacokinetics and can thus be titrated more rapidly to effective dosages (90).

Current guidelines recommend initiating Pregabalin at a dosage of 25mg at night to minimize initial side effects. Dose should be titrated to the lowest effective does with a maximum dose of 150mg twice daily, to minimize dose dependent side effects (91-93). Pregabalin's high symptom amelioration and effectiveness makes it a common first line drug for the treatment of neuropathic pain.

Surgery to treat pain

Although surgery causes pain in over 90% of procedures, it can also be an effective treatment for pain if the pain is occurring due to nociceptors firing because of an injury or a disease. Surgery which restores the integrity of injured tissue e.g., for a fracture, will contribute to a reduction of pain, as will surgery to remove diseased tissue e.g., a tumour -- once the surgical wound has healed, of course!

Sometimes, despite the surgery being successful, i.e., the injury or the disease has been managed, the pain carries on. This reminds us that pain is a conscious construct of the brain in response to a perception of threat: if I am still afraid that I have cancer, even though the surgeon has told me it's all gone, my pain may not go away because I'm still threatened. In these situations, we must go back to steps 1 and 2 of the principles of treating pain – build good therapeutic alliances and ensure we understand and unpack the U!

Prescribing physical activity or exercise

Exercise, being physically active for extended periods of time (typically 20 minutes), stimulates the endogenous analgesic mechanisms releasing endogenous opioids and other endogenous analgesics which reduce pain – this is called exercise-induced hypoalgesia (94). Exercise is also often social, it keeps us occupied, it distracts us, and it is rewarding – it is biopsychosocial medicine that stimulates not only the muscles, joints, and cardiovascular system, but the brain too. This is why exercise is a useful treatment strategy for pain. In people with chronic nociplastic pain, the endogenous analgesic mechanisms may be impaired (remember in Chapter 2 we talked about sensitivity to physical activity, and we discussed specifically assessing this in the principles of assessment?). This means that in people with chronic nociplastic pain, treatment with exercise may initially make the pain worse. However, the system can be retrained with graded prescription of physical activity to restore the endogenous analgesic mechanisms.

Being physically active for 20 minutes reduces pain via endogenous analgesic mechanisms

"Exercise is Medicine"® and has benefits in multiple ways: it can stimulate tissue healing when we have been ill or injured, and also (separately) reduce pain. If we regard exercise or physical activity as medicine then, like all medicine, exercise must be appropriately prescribed. If this is not your scope of practice then work with a physiotherapist or biokineticist or another healthcare professional who is an expert in exercise prescription to ensure that the person with pain is getting the correct dosage of exercise (type, intensity, frequency, quantity) to address the mechanism you think needs to be targeted.

DEEP DIVE

Prescribing exercise for chronic nociplastic pain

"What do you mean, you recommend I start exercising? Exercise makes my pain worse!"

Exercise needs to be prescribed in a structured, graded manner when someone has chronic nociplastic pain. The goal is to gradually expose the sensitised nervous system to exercise in a graded manner to desensitise the system and restore the descending inhibitory mechanisms. Note that for chronic nociplastic pain, the type of exercise doesn't matter. It can be anything the person with pain would like to do and try to make sure there is an element of fun or enjoyment in it!

The model we use is similar to that used in graded exposure therapy for a phobia. For example, if someone is afraid of clowns (a common fear), and they wish to overcome it, a psychologist would work with them using graded exposure. First, they might look at simple drawings of clowns until they could do that without feeling afraid with a pounding heart and breaking into a cold sweat. Then, they might move onto looking at photographs of clowns until they could do that without feeling afraid. They might then move onto being in the same room as a clown but keeping their distance. Finally, they might get to the point of being able to engage with the clown without having a fear response. This is graded exposure, we gradually reset a sensitised system (95).

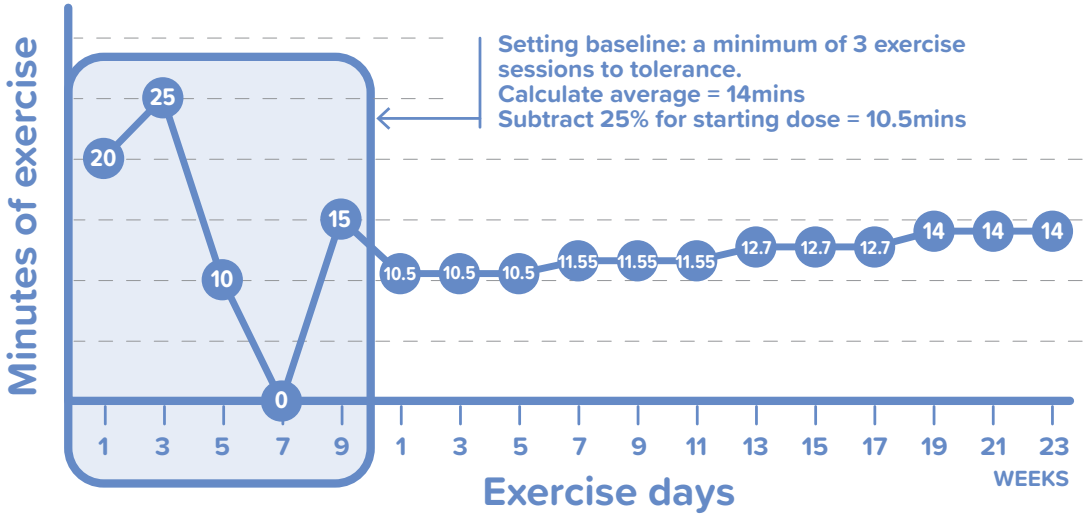
To prescribe exercise for nociplastic pain, a baseline dose of exercise needs to be set. To find the baseline, the person with pain needs to do a minimum of three separate bouts of exercise, on separate days, to their limit i.e., do what you think you can, and record how many minutes they have done. To set the baseline dose of exercise, calculate the average time of the three separate bouts of exercise and subtract 25%. Yes, subtract 25%! We want to ensure that they do not have a flare up of pain from this exercise, we aim to exercise below the alarm's threshold!

From this point on it is critical that the person with pain perform their exercises as per the time set and not stop if they have pain. This is referred to as time contingent exercise, not pain contingent exercise. If they keep stopping when they have pain, they are simply training their sensitive system to being more sensitive. The sensitive system is like a child who always demands a chocolate when you are standing in the line at the supermarket checkout. You know you can never give in because if you do, they will have a tantrum and demand a chocolate every single time you are standing at the checkout. We have to train the system that having a tantrum (causing pain) will not get it what it wants (stop the exercise). This is done slowly and carefully so that the person with pain is not suffering excessively.

The person with pain is ready to progress their exercise when they have done three sessions at that dose successfully. The amount of exercise is then increased by 10%. They do a minimum of three sessions at this new dose, and when they are able to do this without exacerbating their pain, they are ready to increase again by 10%. The graph below gives an example of what this might look like. Keep working on this pattern until the person with pain has reached a goal which you have both agreed to e.g., completing a park run (even if it's walking it!).

Resetting a sensitised nervous system can take time! You and the person with pain need to be clear that they will probably not feel better straight away using this strategy. Often, people only start to feel the benefits of exercise once they are able to tolerate 20 minutes at 60% of heart rate maximum (an intensity level of 'somewhat hard' on the Borg rating of perceived exertion scale) (96). Be prepared for setbacks and if there is a pain flare up, simply reduce the dose to the previous level and continue until the pain stabilises.

Figure 1.16: Plotting baseline dosage and exercise progressions for chronic nociplastic pain



DON'T MISS THIS

The importance of sleep hygiene

What is your sleep hygiene like? As healthcare professionals we are at risk of poor health as a consequence of the stress of our jobs. It is important that we look after ourselves and adopt all of these approaches discussed here – regular exercise, mindfulness/relaxation and making time for meaningful and rewarding activities. Plus, we need to pay attention to our own sleep. These principles of sleep hygiene are worth paying attention to:

- Make sure your bedroom is dark, cool, quiet and relaxing.
- Remove all electronic devices from your bedroom including TVs, smartphones and laptops (if you also must study in your bedroom, put these devices on the other side of the room from your bed, and NEVER use them when on your bed).

- Exercise daily.
- Get up at the same time every day, even on weekends.
- Go to bed at the same time every day, even on weekends.
- Have a bedtime routine to slowly wind-down at the end of your day – stop working or engaging on computers one to two hours before going to sleep.

Sleep

We now know that lack of sleep causes pain (97). And we can all recognise that, when we are in pain, it is hard to sleep well, so we often end up in a downward spiral of worsening sleep and pain. "Sleep hygiene" is the term used for the behaviours we can use to optimise sleep. This does not mean going to bed in clean pyjamas (although clean pyjamas are lovely). Falling asleep and staying asleep are habits we learn at a very young age, but then we often break these good habits as young adults or at other times in our lives when we have stress or trauma. This often happens to people with pain. Instituting good sleep hygiene behaviours is a foundational treatment for people with pain.

Mindfulness and relaxation approaches

Pain is a conscious sensory emotion influenced by context that we feel both in our bodies and emotionally, and can be treated with mindfulness and relaxation methods. This is not simply an issue of mind over matter: by practicing mindfulness or relaxation techniques we are modifying the activity of the brain and can therefore have a direct effect on pain (98).

Mindfulness is described as "paying attention, on purpose, in the present moment, non-judgementally" (99). There is a large body of research demonstrating that mindfulness-based stress reduction is effective in reducing a range of symptoms in people with chronic pain conditions. Engaging in a range of mindful practices can be very helpful for people with pain.

Relaxation has been shown to engage the brain in different ways to mindfulness practices. Various relaxation strategies, ranging from diaphragmatic breathing to progressive muscle relaxation strategies, can reduce pain. Studies using fMRI have shown that mindfulness, relaxation, and diaphragmatic breathing all reduce pain through different cortical pathways. Mindfulness and relaxation strategies can be used to treat acute nociceptive and chronic nociplastic pain.

DON'T MISS THIS

Prescribing exercise, sleep and mindfulness

Exercise, sleep and mindfulness/relaxation strategies need to be prescribed. Do not forget that all of these non-pharmacological treatment approaches are medicine; they change the physiological mechanisms which contribute to pain. Pay attention to using them as medicine in the same way you pay attention to treatment with pharmacotherapy – prescribe them appropriately and encourage regular use according to the prescription. These are not just "nice things to do for pain" – they are medicine.

To facilitate success, ensure that all goals are SMART (specific, measurable, achievable, realistic, and timed); that the person with pain feels confident of success (on a scale of 0-10 where 0=no confidence of succeeding at all and 10=100% confident of succeeding, we aim for them to feel at least 7); and that the person with pain has identified what reward they will give themselves for achieving each goal.

Targeting the contributing and vulnerability factors

All of the above treatment techniques target particular pain mechanisms. To ensure that your pain treatment also targets the contributing and vulnerability factors for pain, the focus shifts to *how* you implement the treatments. Table 1.5 below summarises implementation strategies which can be used to target each of the vulnerability factors.

Contributing or Vulnerability factor	Treatment strategy
Anxiety	
Negative problem orientation i.e., tendency to be pessimistic about outcomes, doubting own ability to problem-solve or cope	Pain science education, empowering the person with pain with knowledge e.g., that pain is not an accurate measure of tissue damage; set goals guaranteeing success
Rumination	Activity scheduling, purposefully staying busy with tasks/occupations
Depression	Physical activity and exercise
Pain catastrophising	
Magnification	Disclosure and validation, allowing the person with pain to express their distress and validating this experience.
Rumination	Activity scheduling, purposefully staying busy with tasks/occupations
Helplessness (low self-efficacy)	Build confidence by setting achievable goals that guarantee success
Fear-avoidance beliefs	Graded exposure to feared activities

Table 1.5: Implementation strategies to target contributing or vulnerability factors.

DEEP DIVE

How does deep breathing affect pain?

Deep breathing using the diaphragm (diaphragmatic breathing) is a breathing technique often taught by physiotherapists. However, it is also a key component of a range of different mindful practices ranging from mindful meditation to yoga and relaxation. Diaphragmatic breathing stimulates the vagus nerve – the cranial nerve which has bidirectional connectivity to the viscera, and which is the fundamental to the healthy functioning of the autonomic nervous system – in particular the parasympathetic nervous system. The vagus nerve is modulated by respiration, it is inhibited during inspiration and activated during expiration. In other words, expiration, which activates the vagus, stimulates parasympathetic activity. Diaphragmatic breathing emphasises the exhalation phase of breathing thus stimulating the vagus nerve with resulting parasympathetic activity (rest and digest) (100).

5 Conclusion

Well done, you've reached the end of Section 1! Are you now wondering how on earth you will put it all together in the clinical setting when there is a person in pain sitting in front of you desperate for your help? Good! Refer back to this section and the pain definitions whenever you need!

In the rest of the book, people who have had painful experiences or who still live with pain will share their stories from different settings and we will unpack their management.

For each story, we aim to give you information on (i) the condition; (ii) the biopsychosocial pain mechanisms; (iii) assessment of their pain; (iv) treatment of their pain. In each of the sections, we have also provided some basic information that is specific to a particular context, e.g., what to consider when working in a primary healthcare setting versus working in a perioperative setting.

DON'T MISS THIS

Key pain messages

- Pain is a sensory emotion in response to a perception of threat.
- Pain is not an accurate measure of tissue damage.
- Multiple variables can contribute to pain, including variables from the person's internal and external environments.
- To effectively manage pain we need to assess and treat these multiple variables, and empower and educate people with pain.
- Person centred and interdisciplinary care are the most effective (and we would argue most ethical) approaches to treating people with pain.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.

2. International Association for the Study of Pain IASP. IASP Taxonomy. Pain Terms.: IASP; 2017 [Available from: https://www.iasp-pain.org/resources/terminology/#pain]

3. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Hauser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397(10289):2098-110.

4. WHO. ICF : International classification of functioning, disability and health / World Health Organization. Geneva: World Health Organization; 2001.

5. Iwanaga K, Chen X, Wu JR, Lee B, Deppert B, Tansey TN, et al. Psychometric Validation of the Wisconsin Community Participation Scale in a Sample of People with Chronic Health Conditions and Disabilities Living in the Community. Rehabilitation Counseling Bulletin. 2021;66(1):58-65.

6. Kyte DG, Calvert M, van der Wees PJ, ten Hove R, Tolan S, Hill JC. An introduction to patient-reported outcome measures (PROMs) in physiotherapy. Physiotherapy. 2015;101(2):119-25.

7. Prodinger B, Cieza A, Williams DA, Mease P, Boonen A, Kerschan-Schindl K, et al. Measuring health in patients with fibromyalgia: content comparison of questionnaires based on the International Classification of Functioning, Disability and Health. Arthritis Rheum. 2008;59(5):650-8.

8. Shaikh A, Bentley A, Kamerman PR. Symptomatology of peripheral neuropathy in an African language. PLoS One. 2013;8(5):e63986.

9. Spallone V, Morganti R, D'Amato C, Greco C, Cacciotti L, Marfia GA. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. Diabetic Medicine. 2012;29(5):578-85.

10. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001;92(1-2):147-57.

11. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971-9.

12. Moseley GL, Butler DS. Expain Pain Supercharged. Adelaide City West: Noigroup Publications; 2017.

13. Langer N, Hänggi J, Müller NA, Simmen HP, Jäncke L. Effects of limb immobilization on brain plasticity. Neurology. 2012;78(3):182-8.

14. Flor H, Braun C, Elbert T, Birbaumer N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neurosci Lett. 1997;224(1):5-8.

15. Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, et al. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain. 2013;14(10):1001-18.

16. Haigh RC, McCabe CS, Halligan PW, Blake DR. Joint stiffness in a phantom limb: evidence of central nervous system involvement in rheumatoid arthritis. Rheumatol. 2003;42(7):888-92.

17. Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain. 2014;155(4):703-11.

18. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain. 2013;14(5):438-45.

19. Grace PM, Rolan PE, Hutchinson MR. Peripheral immune contributions to the maintenance of central glial activation underlying neuropathic pain. Brain Behav Immun. 2011;25(7):1322-32.

20. Semyanov A, Verkhratsky A. Astrocytic processes: from tripartite synapses to the active milieu. Trends Neurosci. 2021;44(10):781-92.

21. Polomano RC, Galloway KT, Kent ML, Brandon-Edwards H, Kwon KN, Morales C, et al. Psychometric Testing of the Defense and Veterans Pain Rating Scale (DVPRS): A New Pain Scale for Military Population. Pain Med. 2016;17(8):1505-19.

22. Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. Am J Crit Care. 2010;19(1):55-61; quiz 2.

23. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs. 1997;23(3):293-7.

24. Mphahlele N, Mitchell D, Kamerman P. Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African population. J Pain Symptom Manage. 2008;36(4):396-412.

25. Parker R, Jelsma J, Stein DJ. Managing pain in women living with HIV/AIDS: A randomized controlled trial testing the effect of a six-week peer-led exercise and education intervention. J Nerv Ment Dis. 2016;204(9):665-72.

26. Henschke N, Maher CG, Ostelo RW, de Vet HC, Macaskill P, Irwig L. Red flags to screen for malignancy in patients with low-back pain. Cochrane Database Syst Rev. 2013(2):Cd008686.

27. Finucane LM, Downie A, Mercer C, Greenhalgh SM, Boissonnault WG, Pool-Goudzwaard AL, et al. International Framework for Red Flags for Potential Serious Spinal Pathologies. J Orthop Sports Phys Ther. 2020;50(7):350-72.

28. Galloway KM, Parker R. Could an increase in vigilance for spinal tuberculosis at primary health care level, enable earlier diagnosis at district level in a tuberculosis endemic country? Afr J Prim Health Care Fam Med. 2018;10(1):e1-e9.

29. Louw QA, Tawa N, Van Niekerk SM, Conradie T, Coetzee M. Spinal tuberculosis: A systematic review of case studies and development of an evidence-based clinical guidance tool for early detection. J Eval Clin Pract. 2020;26(5):1370-82.

30. Catley MJ, Tabor A, Wand BM, Moseley GL. Assessing tactile acuity in rheumatology and musculoskeletal medicine - how reliable are two-point discrimination tests at the neck, hand, back and foot? Rheumatol. 2013;52(8):1454-61.

31. Breckenridge JD, Ginn KA, Wallwork SB, McAuley JH. Do People With Chronic Musculoskeletal Pain Have Impaired Motor Imagery? A Meta-analytical Systematic Review of the Left/Right Judgment Task. J Pain. 2019;20(2):119-32.

32. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract. 2012;12(4):276-85.

33. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311(15):1547-55.

34. Aili K, Andersson M, Bremander A, Haglund E, Larsson I, Bergman S. Sleep problems and fatigue as predictors for the onset of chronic widespread pain over a 5- and 18-year perspective. BMC Musculoskelet Disord. 2018;19(1):390.

35. Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. J Applied Biobehav Res. 2018;23(2):e12137.

36. Chaput JP, Shiau J. Routinely assessing patients' sleep health is time well spent. Prev Med Rep. 2019;14:100851.

37. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.

38. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc. 2012;87(12):1196-201.

39. Parker R. Physiotherapy students' assessment of psychosocial yellow flags in low back pain. S Afr J Physiother. 2007;63(1):6.

40. Hill JC, Garvin S, Chen Y, Cooper V, Wathall S, Saunders B, et al. Stratified primary care versus non-stratified care for musculoskeletal pain: findings from the STarT MSK feasibility and pilot cluster randomized controlled trial. BMC Fam Pract. 2020;21(1):30.

41. Hill JC, Dunn KM, Lewis M, Mullis R, Main CJ, Foster NE, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. Arthritis Rheum. 2008;59(5):632-41.

42. Schmidt PA, Naidoo V. Cross-cultural adaptation and validation of the STarT back screening tool in isiZulu. S Afr J Physiother. 2020;76(1):1402.

43. Löwe B, Wahl I, Rose M, Spitzer C, Glaesmer H, Wingenfeld K, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord. 2010;122(1-2):86-95.

44. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological Assessment. 1995;7(4):524-32.

45. Morris LD, Grimmer-Somers KA, Louw QA, Sullivan MJ. Cross-cultural adaptation and validation of the South African Pain Catastrophizing Scale (SA-PCS) among patients with fibromyalgia. Health Qual Life Outcomes. 2012;10:137.

46. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med. 2007;30(1):77-94.

47. Kahere M, Ginindza T. A cross-sectional hospital-based study of correlates of disability in patients with chronic low back pain in KwaZulu-Natal, South Africa. BMC Musculoskelet Disord. 2022;23(1):438.

48. Swinkels-Meewisse EJ, Swinkels RA, Verbeek AL, Vlaeyen JW, Oostendorp RA. Psychometric properties of the Tampa Scale for kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain. Man Ther. 2003;8(1):29-36.

49. Powell A. Therapeutic Alliance and Its Potential Application to Physical Activity Interventions for Older Adults: A Narrative Review. J Aging Phys Act. 2022;30(4):739-43.

50. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. J Pain. 2015;16(9):807-13.

51. Yang J, Bauer BA, Wahner-Roedler DL, Chon TY, Xiao L. The Modified WHO Analgesic Ladder: Is It Appropriate for Chronic Non-Cancer Pain? J Pain Res. 2020;13:411-7.

52. Majeed MH, Sherazi SAA, Bacon D, Bajwa ZH. Pharmacological treatment of pain in osteoarthritis: A descriptive review. Curr Rheumatol Rep. 2018;20(12):88.

53. Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CW, Day RO, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015;350:h1225.

54. Mao L, Wu W, Wang M, Guo J, Li H, Zhang S, et al. Targeted treatment for osteoarthritis: drugs and delivery system. Drug Deliv. 2021;28(1):1861-76.

55. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev. 2006;2006(1):CD004257.

56. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis: a meta-analysis of randomised controlled trials. Ann Rheum Dis. 2004;63(8):901-7.

57. D'Arcy Y, Mantyh P, Yaksh T, Donevan S, Hall J, Sadrarhami M, et al. Treating osteoarthritis pain: mechanisms of action of acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, and nerve growth factor antibodies. Postgrad Med. 2021;133(8):879-94.

58. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162(1):46-54.

59. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2012;9(9):CD007400.

60. Haroutiunian S, Drennan DA, Lipman AG. Topical NSAID therapy for musculoskeletal pain. Pain Med. 2010;11(4):535-49.

61. Gong L, Stamer UM, Tzvetkov MV, Altman RB, Klein TE. PharmGKB summary: tramadol pathway. Pharmacogenet Genomics. 2014;24(7):374-80.

62. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43(13):879-923.

63. Beakley BD, Kaye AM, Kaye AD. Tramadol, Pharmacology, Side Effects, and Serotonin Syndrome: A Review. Pain Physician. 2015;18(4):395-400.

64. Vijayan R, Afshan G, Bashir K, Cardosa M, Chadha M, Chaudakshetrin P, et al. Tramadol: a valuable treatment for pain in Southeast Asian countries. J Pain Res. 2018;11:2567-75.

65. Zambelli Z, Halstead EJ, Iles R, Fidalgo AR, Dimitriou D. The 2021 NICE guidelines for assessment and management of chronic pain: A cross-sectional study mapping against a sample of 1,000* in the community. Br J Pain. 2022;16(4):439-49.

66. WHO Expert Committee on Drug Dependence. World Health Organ Tech Rep Ser. 2016(998):1-34.

67. Dunn KE, Bergeria CL, Huhn AS, Strain EC. A Systematic Review of Laboratory Evidence for the Abuse Potential of Tramadol in Humans. Front Psychiatry. 2019;10:704.

68. Salm-Reifferscheidt L. Tramadol: Africa's opioid crisis. Lancet. 2018;391(10134):1982-3.

69. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. JAMA. 2018;319(9):872-82.

70. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of P, Denberg TD, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166(7):514-30.

71. Last AR, Hulbert K. Chronic low back pain: evaluation and management. Am Fam Physician. 2009;79(12):1067-74.

72. James A, Williams J. Basic Opioid Pharmacology — An Update. Br J Pain. 2020;14(2):115-21.

73. Malafoglia V, Ilari S, Vitiello L, Tenti M, Balzani E, Muscoli C, et al. The Interplay between Chronic Pain, Opioids, and the Immune System. The Neuroscientist. 2022;28(6):613-27.

74. Cox BM. A Concise Review of Concepts in Opioid Pharmacology up to the Discovery of Endogenous Opioids. Molecular Pharmacology. 2020;98(4):392.

75. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and Exogenous Opioids in Pain. Annual Review of Neuroscience. 2018;41(1):453-73.

76. Macintyre PE, Quinlan J, Levy N, Lobo DN. Current Issues in the Use of Opioids for the Management of Postoperative Pain: A Review. JAMA Surgery. 2022;157(2):158-66.

77. Koponen ME, Forget P. Pharmacological Interventions for Opioid-Induced Hyperalgesia: A Scoping Review of Preclinical Trials. J Clin Med. 2022;11(23):7060.

78. Hoffman KA, Ponce Terashima J, McCarty D. Opioid use disorder and treatment: challenges and opportunities. BMC Health Services Research. 2019;19(1):884.

79. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association; 2013.

80. Platt M. Pain Challenges at the End of Life—Pain and Palliative Care Collaboration. Reviews in Pain. 2010;4(2):18-23.

81. Eller-Smith OC, Nicol AL, Christianson JA. Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions. Frontiers in Cellular Neuroscience. 2018;12.

82. Vargas-Schaffer G, Paquet S, Neron A, Cogan J. Opioid Induced Hyperalgesia, a Research Phenomenon or a Clinical Reality? Results of a Canadian Survey. J Personalized Med. 2020;10(2):27.

83. Brown RS, Bottomley WK. Utilization and mechanism of action of tricyclic antidepressants in the treatment of chronic facial pain: a review of the literature. Anesth Prog. 1990;37(5):223-9.

84. Choopani R, Ghourchian A, Hajimehdipoor H, Kamalinejad M. Scientific Evaluation of Pharmacological Treatment of Osteoarthritis in the Canon of Medicine. J Evid Based Complementary Altern Med. 2016;21(3):228-34.

85. Rossiter D. South African Medicines Formulary. 11th ed. Rondebosch, South Africa: Health and Medical Pub. Group of the South African Medical Association Rondebosch, South Africa; 2014.

86. Birkinshaw H, Friedrich CM, Cole P, Eccleston C, Serfaty M, Stewart G, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. Cochrane Database Syst Rev. 2023;5(5):CD014682.

87. Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Arch Intern Med. 2002;162(1):19-24.

88. Staiger TO, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. Spine. 2003;28(22):2540-5.

89. Sofat N, Harrison A, Russell MD, Ayis S, Kiely PD, Baker EH, et al. The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. J Pain Res. 2017;10:2437-49.

90. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.

91. Chetty S, Baalbergen E, Bhigjee AI, Kamerman P, Ouma J, Raath R, et al. Clinical practice guidelines for management of neuropathic pain: expert panel recommendations for South Africa. S Afr Med J. 2012;102(5):312-25.

92. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain. 2013;154(11):2249-61.

93. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88.

94. Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. J Pain. 2019;20(11):1249-66.

95. Gatzounis R, Schrooten MG, Crombez G, Vlaeyen JW. Operant learning theory in pain and chronic pain rehabilitation. Curr Pain Headache Rep. 2012;16(2):117-26.

96. Scherr J, Wolfarth B, Christle JW, Pressler A, Wagenpfeil S, Halle M. Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. Eur J Appl Physiol. 2013;113(1):147-55.

97. Iacovides S, George K, Kamerman P, Baker FC. Sleep Fragmentation Hypersensitizes Healthy Young Women to Deep and Superficial Experimental Pain. J Pain. 2017;18(7):844-54.

98. Zeidan F, Vago DR. Mindfulness meditation-based pain relief: a mechanistic account. Ann N Y Acad Sci. 2016;1373(1):114-27.

99. Kabat-Zinn J. Mindfulness-based interventions in context: Past, present, and future. Clinical Psychology: Science and Practice. 2003;10(2):144-56.

100. Gerritsen RJS, Band GPH. Breath of life: the respiratory vagal stimulation model of contemplative activity. Front Hum Neurosci. 2018;12:397.


University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad
SPES BONA