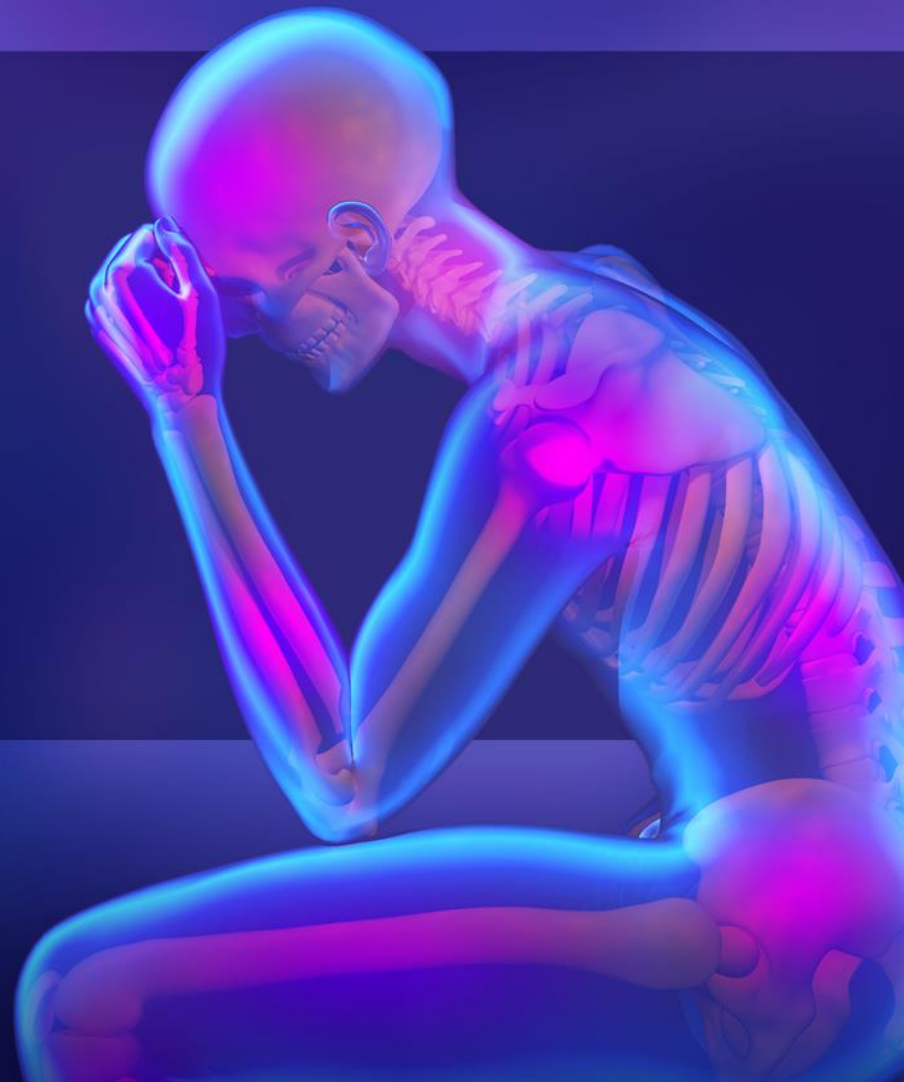
MultipleMyelomaHub

Holistic pain management in multiple myeloma

November 10, 2022

Chair: Mohamad Mohty

Speakers: Heinz Ludwig, Barry Quinn, Flaminia Coluzzi



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Welcome and introductions

Disclosures

Mohamad Mohty

- The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):
  - Research grant(s)/in kind support: Celgene, Janssen, Sanofi, Jazz Pharmaceuticals
  - Participation in accredited CME/CPD: None
  - Consultant/strategic advisor: None
  - Holder of patents/shares or stocks related or unrelated to this presentation: No
  - Non-financial interests: None

Agenda

Time (CET)	Item	Presenter
17:00–17:10	Welcome and introductions	Mohamad Mohty
17:10–17:25	Understanding pain in early multiple myeloma	Heinz Ludwig
17:25–17:40	Implementing a holistic pain treatment plan in advanced disease	Barry Quinn
17:40–17:55	Dos and don’ts in pain management	Flaminia Coluzzi
17:55–18:05	Q&A session and evaluation	All
18:05–18:10	Closing remarks	Mohamad Mohty

Learning objectives

Following this symposium, participants will be able to:

- Identify and use appropriate tools for **collecting patient-reported outcomes** and **assessing quality of life** in patients with multiple myeloma
- Accurately **assess pain** and identify the key components of **an individualized holistic pain management plan** for patients with multiple myeloma
- Select **appropriate pharmacological analgesics** for patients based on **individual needs**
- Describe **key side effects** and **contraindications for analgesics**
- Implement **adequate risk assessments** when **prescribing analgesics** and state practices that **minimize or prevent adverse consequences**

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Faculty

Our expert panel

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Chair

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Heinz Ludwig

Wilhelminen Cancer Research Institute, Vienna, AT

Barry Quinn

Queen's University Belfast, Belfast, UK, and Mohammed Bin Rashid University, Dubai, AE

Flaminia Coluzzi

Sapienza University of Rome, Rome, IT

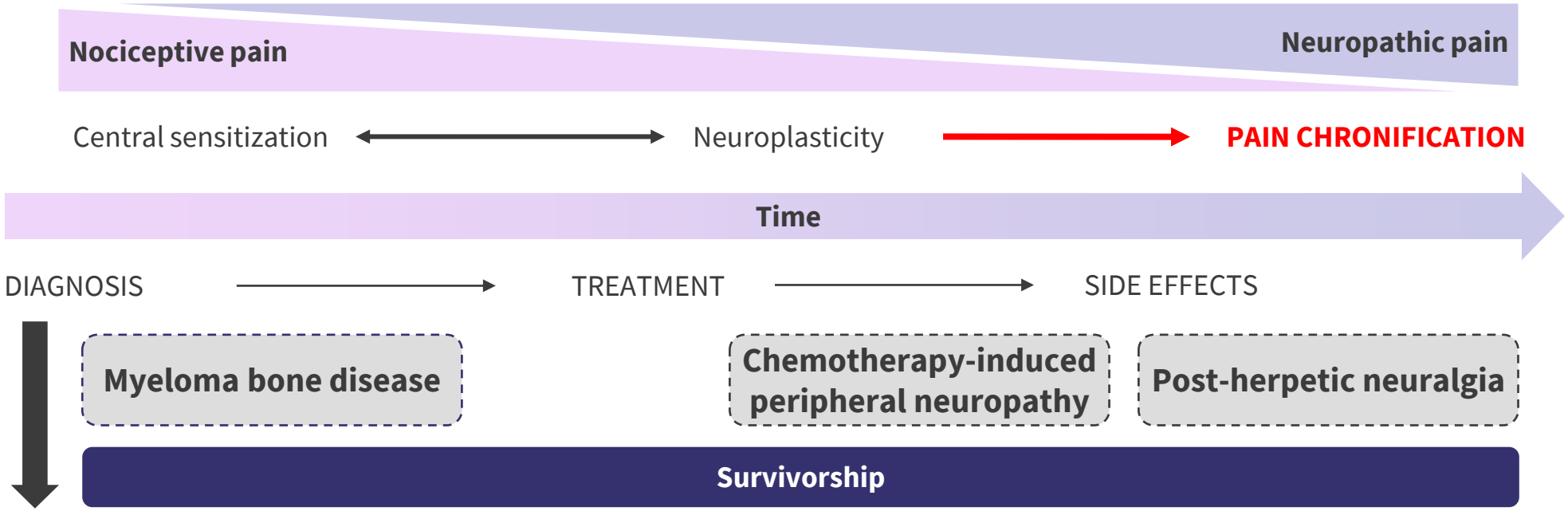
Why is pain important in multiple myeloma?[1–3]

- Pain can have a profound adverse effect on the **HRQoL and treatment outcomes** of patients with multiple myeloma.
- Despite both pharmacological and non-pharmacological treatments, **pain is often ineffectively managed** in multiple myeloma.
- Poorly managed pain can lead to **psychological distress and anxiety** for both patients with multiple myeloma and their carers.
- Pain can contribute to **increased multiple myeloma-related morbidity** and disability.
- Patients are often averse to raising pain as a problem, with different perceptions of the **priority of care** to clinicians.

HRQoL, health-related quality of life.

1. Coluzzi F, et al. *Cancers.* 2019;11(12):2037. **2.** Fischer J, et al. *BMC Cancer.* 2022;22(1):1032. **3.** Quinn B, et al. *Pain Manag.* 2022:12(1):59-74.

Pain and pain management evolve over the course of the disease



Adapted from Coluzzi F, et al. *Cancers (Basel)*. 2019;11(12):2037.

APAP, acetaminophen (paracetamol); BP, bisphosphonate.

Understanding pain in early multiple myeloma

Dr Heinz Ludwig
Wilhelminen Cancer Research Institute, Vienna, AT

Disclosures

Heinz Ludwig

The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):

- Research grant(s)/in kind support: Amgen, Takeda, Sanofi
- Consultant/strategic advisor: Amgen, Takeda, Celgene-BMS, Janssen, Pfizer, Sanofi

Participation in accredited CME/CPD, patents/shares or stocks related or unrelated to this presentation, non-financial interests: nothing to declare.

Objectives

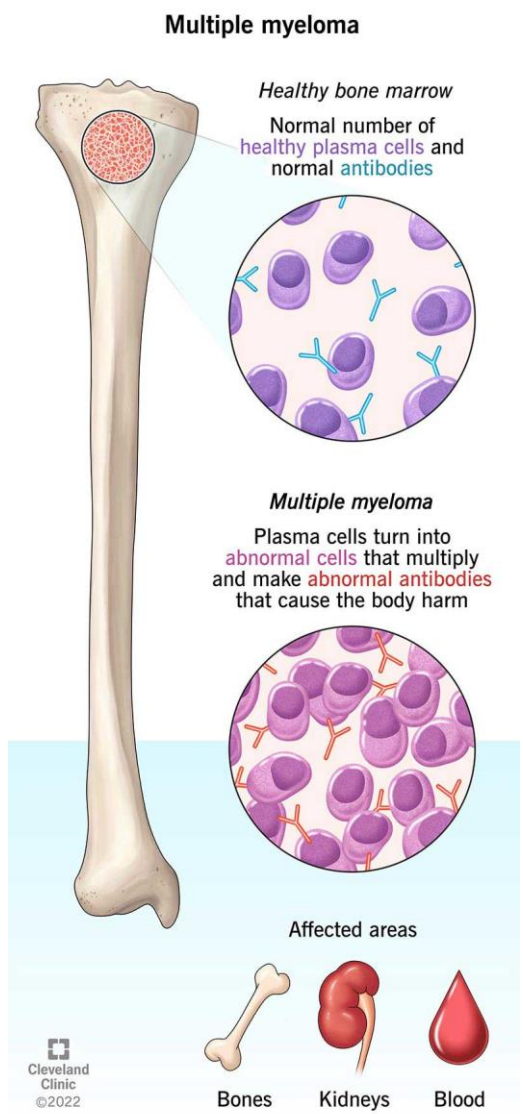
- Consider pain symptoms experienced by patients with multiple myeloma
- Provide an overview of how pain can change with disease progression
- Review common causes of pain at presentation, diagnosis, and early lines of multiple myeloma treatment
- Explore the importance of patient-reported outcomes, patient-reported outcome measures, and quality-of-life questionnaires in pain assessment
- Understand the impact of pain on patients with multiple myeloma
- Consider the pharmacological and non-pharmacological approaches to pain, including bone disease

Symptoms in patients with early multiple myeloma

- 16X times greater risk of fracture in 12 months before diagnosis[1]
- **70% of patients with multiple myeloma experience bone pain**[2]
- **Osteolytic bone lesions occur in 80–90% of patients (mostly spinal)**[3]

Symptoms[4]:

- **Bone fractures, spinal cord compression**
- Fatigue, weakness
- Increased rate of infections
- Decrease in kidney function
- Weight loss, night sweats
- Symptoms from surplus proteins, e.g., cryoglobulinemia



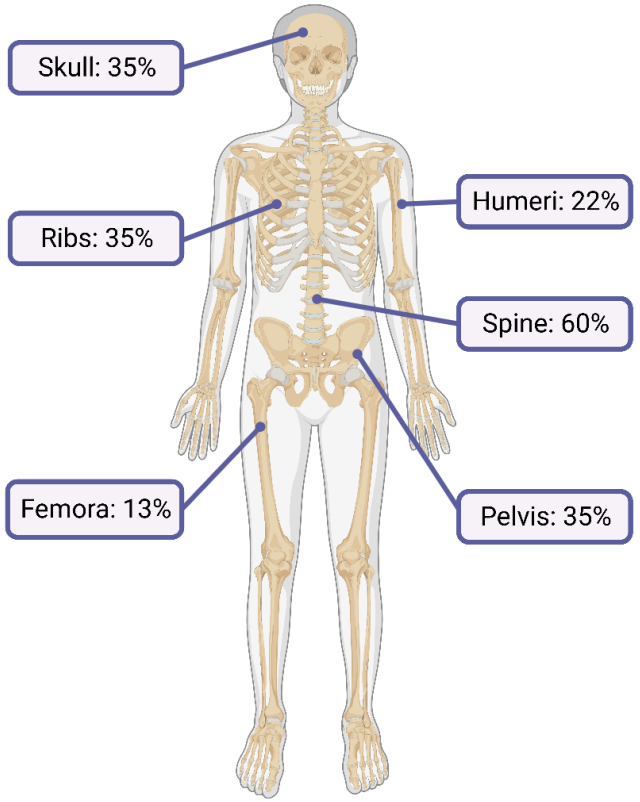
Cleveland Clinic. Multiple myeloma. https://my.clevelandclinic.org/health/articles/6178-multiple-myeloma. Accessed Oct 31, 2022.

1. Melton LJ, et al. *J Bone Miner Res*. 2005;20(3):487-93. **2.** Diaz-delCastillo M, et al. *Cancers (Basel)* 2021;13(7):1596. **3.** Coluzzi F, et al. *Cancers (Basel)* 2019;11(12):2037.
4. Cleveland Clinic. Multiple myeloma. https://my.clevelandclinic.org/health/articles/6178-multiple-myeloma. Accessed Oct 31, 2022.

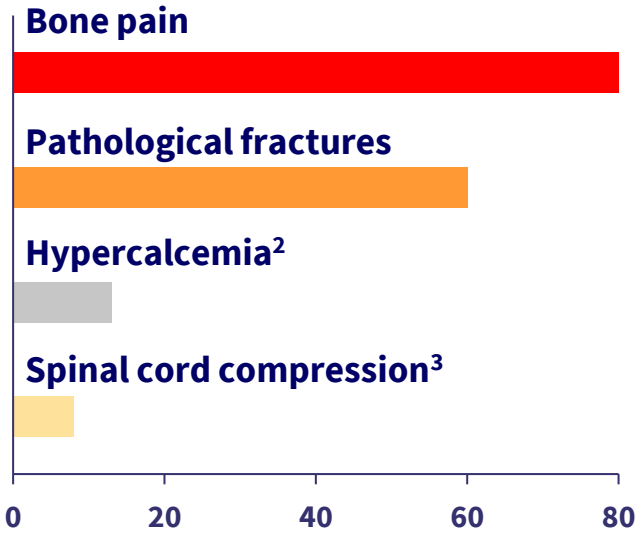
Common causes of pain in multiple myeloma

Bone lesions: osteoclastic lesions, fractures, microfractures[1]

Position of the bone lesions



Clinical manifestations



Neurological[1,4]
- Neuropathy
- Compression
- Tension pain

Therapy
- Mucositis[5]
- Surgery[6]
- Bone marrow biopsy

Infections[4]

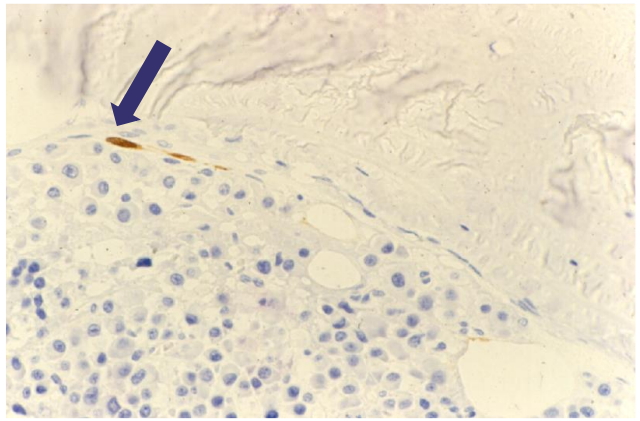
Organ manifestations[7]
- Visceral pain
- Joint/capsular pain
- Soft tissue infiltration

Adapted from Delforge M. Educational session. 15th Congress of EHA. Jun 10, 2010; Barcelona, ES.
Created using BioRender.com.

1. Coluzzi F, et al. *Cancers (Basel)* 2019;11(12):2037. **2.** Blimark CV, et al. *Haematologica.* 2018;103(3):506-513. **3.** Chen B, et al. *Crit Rev Oncol Hematol.* 2021;160:103205. **4.** NORD. Multiple myeloma. https://rarediseases.org/rare-diseases/multiple-myeloma/. Accessed Oct 31, 2022. **5.** Fleming S, et al. *Clin Lymphoma Myeloma Leuk.* 2014;14(4):291-296. **6.** Myeloma UK. Surgical intervention in myeloma. https://www.myeloma.org.uk/wp-content/uploads/2018/03/Myeloma-UK-Surgical-intervention-Infoguide-1.pdf. Accessed Oct 31, 2022. **7.** Myeloma UK. Pain and myeloma. https://www.myeloma.org.uk/wp-content/uploads/2018/03/Myeloma-UK-Pain-and-myeloma-Infoguide.pdf. Accessed Oct 31, 2022.

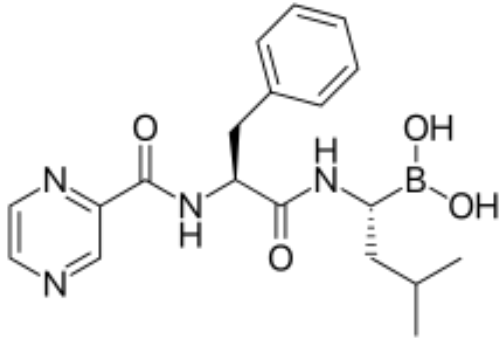
Causes of neuropathic pain in multiple myeloma

Bone marrow biopsy specimen



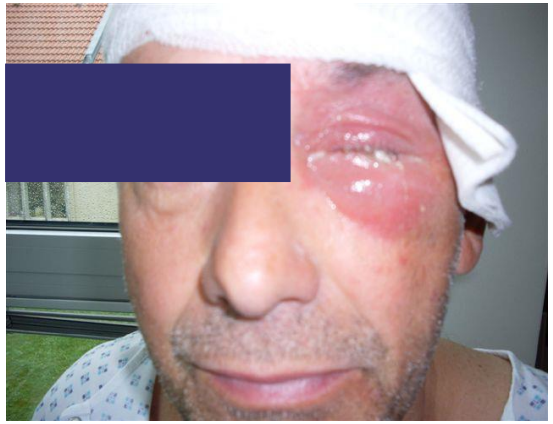
Pecherstorfer M. wie entstehen knochenmetastasen. https://slideplayer.org/slide/867519/. Accessed Oct 31, 2022.

Bortezomib neurotoxicity[1]



U.S. FDA. Bortezomib prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021602s010lbl.pdf

Inflammatory cytokines and prostaglandins irritate sensory nerves



Various causes

- Neurotoxic substances (e.g., bortezomib)[2]
- Nerve compression[2]
- Herpes reactivation[2]
- Trigeminal neuralgia[3]
- Joint pain[4]
- Paraproteinemic neuropathy[4]

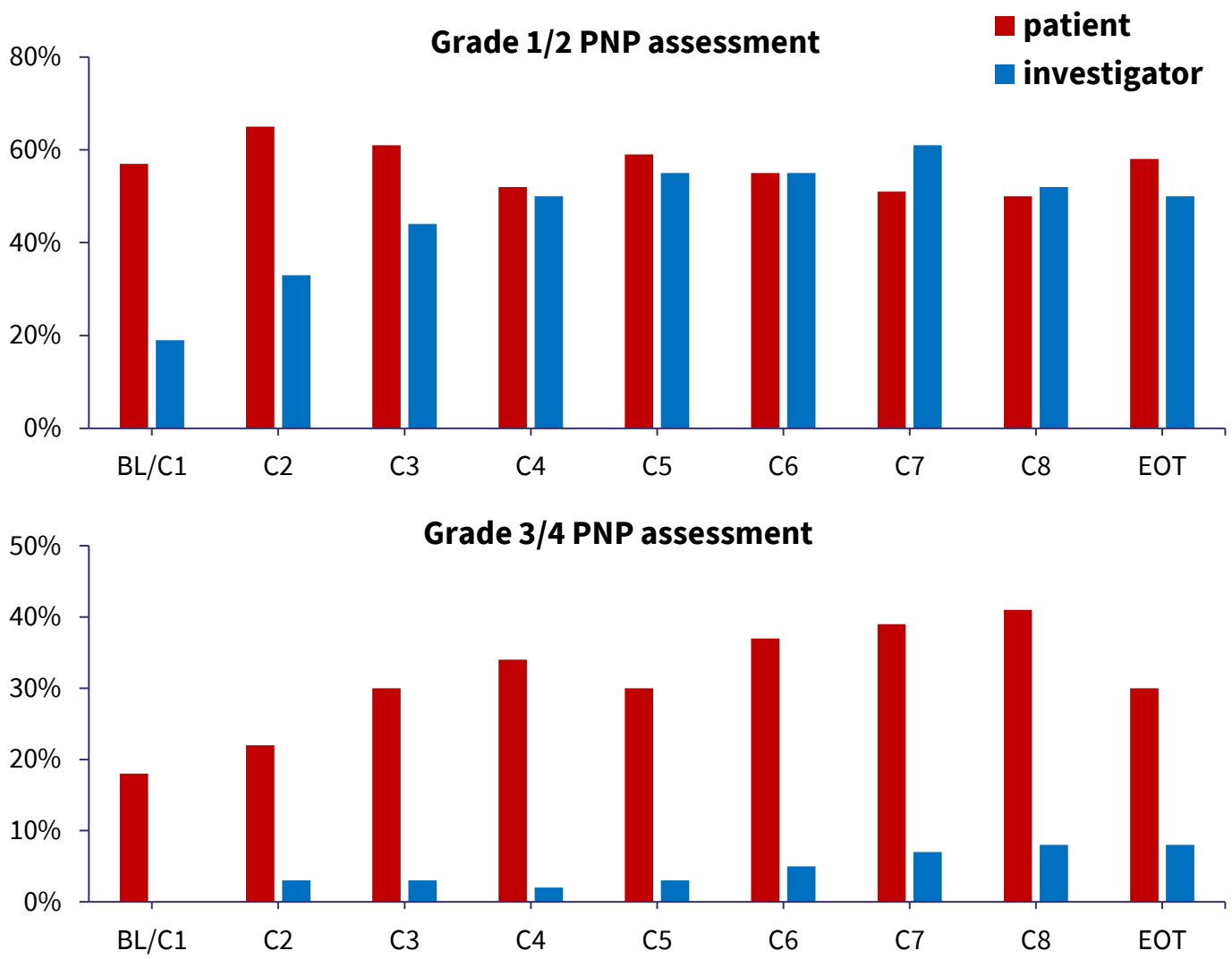
1. Boyette-Davis JA, et al., *J Pain.* 2011;12(9):1017-1024. **2.** Coluzzi F, et al. *Cancers (Basel)* 2019;11(12):2037. **3.** Cureus. Uncommon presentations of multiple myeloma. https://www.cureus.com/articles/28770-uncommon-presentations-of-multiple-myeloma. Accessed Oct 31, 2022. **4.** Myeloma UK. Pain and myeloma. https://www.myeloma.org.uk/wp-content/uploads/2018/03/Myeloma-UK-Pain-and-myeloma-Infoguide.pdf. Accessed Oct 31, 2022. **5.** Zivković SA, et al. *Leuk Lymphoma.* 2009;50(9):1422-1433.

Challenges in caregiver–patient communication on pain

- **Patients may be reluctant to admit pain**.[1]
- Less than 75% of clinical records match the level of pain reported by patients (71.5%).[1]
- In approximately 20% of patients with MM-related bone pain, there is **no record of pain** in their medical notes.[1]
- Approximately 50% of **physicians managing multiple myeloma underestimate** the severity of bone pain experienced by their patients.[1]
- Approximately one third of patients with cancer do not receive pain medication **adequate for the intensity of pain present**.[2]
- Time constraints in the clinical setting can be overcome by using self-report assessments to help patients quantify pain.[3]

1. Quinn B, et al. *Pain Manag*. 2022:12(1):59-74. **2.** Greco MT, et al. *J Clin Oncol.* 2014;32(36):4149-4154. **3.** Ludwig, et al. *Cancer Rep (Hoboken)*. 2022;5(1):e1429.

Peripheral neuropathy: Differences in patient and caregiver reporting



BL, baseline; C, Cycle; EOT, end of treatment; PNP, peripheral neuropathy.
Ludwig, et al. *Blood.* 2012;120(21):943.

Patient-reported outcomes: Measuring pain and its impact on QoL

- Patient-reported outcomes allow direct patient report on function and health.
- They give the patient the opportunity to provide structured and guided feedback on their disease and treatment.
- Patient-reported outcomes allow data to be captured **outside of routine clinical outcomes**, such as efficacy and safety.
- Relative to clinician assessments, a direct patient report can:
  - **improve the detection of symptoms**, including the presence and quantification;
  - be more sensitive to change; and
  - provide a greater degree of association with the patient's overall health status.

QoL, quality of life.
LeBlanc MR, et al. *Qual Life Res.* 2021;29(6):1419-1431.

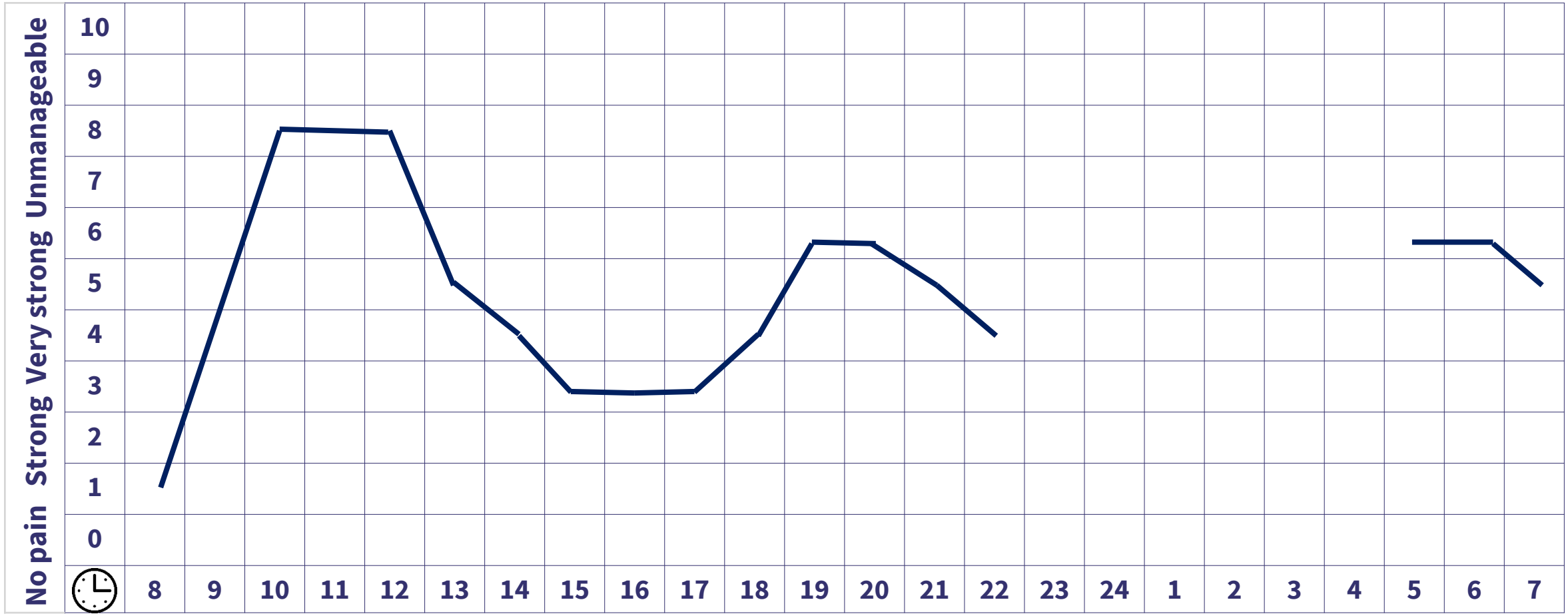
Measuring pain with the EORTC QLQ-MY20

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4

Engelhardt M, et al. *Clin Lymphoma Myeloma Leuk.* 2021;21(2):e160-e175.

EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Multiple Myeloma Module.

Patient: XY **Date: November 2022**



	Morning	Noon	Evening	Night
Pain medication	Hydromorphone 2.6 mg	Hydromorphone 2.6 mg	Hydromorphone 6 mg	Zolpidem 10 mg
	Diclofenac 75 mg			
	Olanzapine 10 mg		Olanzapine 10 mg	

Heinz Ludwig. Personal communication; Nov 10, 2022.

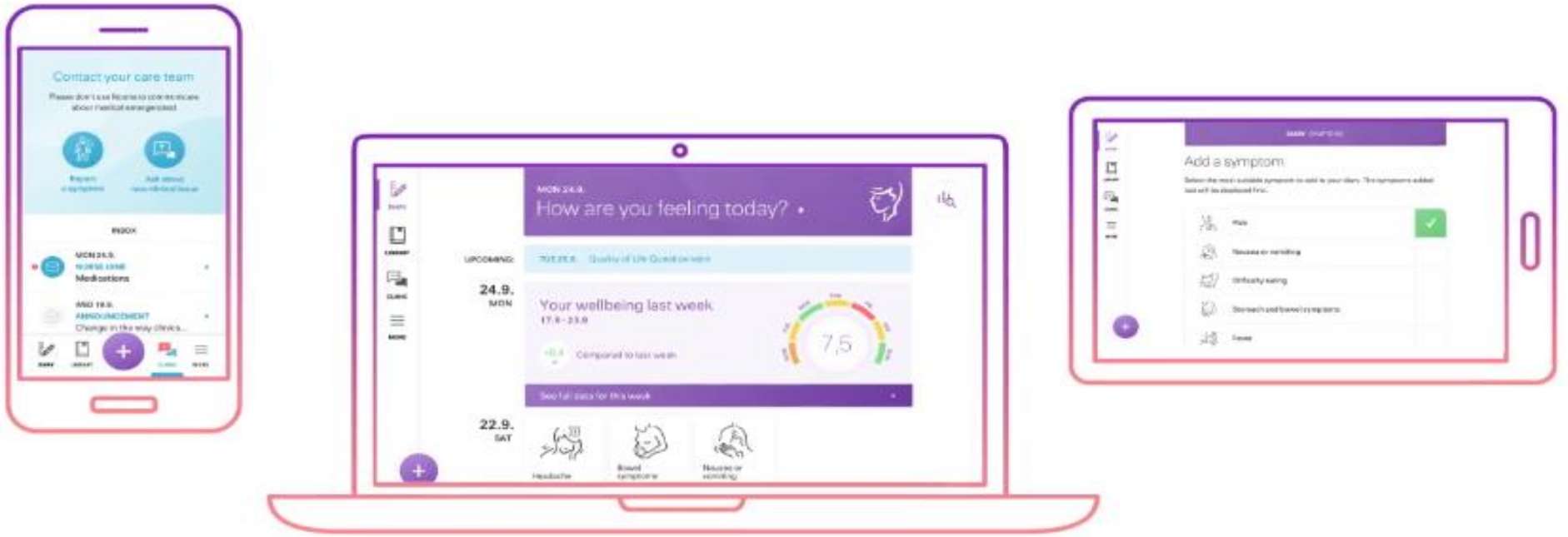
Patient-reported outcome measure tools and item banks

- **PROMIS** (Patient Reported Outcomes Measurement Information System)[1]
  - HCPs and researchers can tailor the constructs they wish to measure using PROMIS items, thus creating an adapted measure suitable for the construct they wish to measure
- **MyPOS** (Myeloma-specific QoL questionnaire)[2]
  - Myeloma UK supported tool, 30 items
- **Importa Project**[3]
  - Defined a set of outcome measures that should be monitored in patients with NDMM
- **National Cancer Institute's (NCI) PROM-CTCAE Toolbox**[4]
  - Online library comprising 124 items that assess different attributes (e.g., presence, frequency, severity, or interference with usual or daily activities)
- **Noona**[5]
  - Hematologic malignancies-specific commercial online tool
- **eSMART**[6]
  - Real-time remote symptom monitoring device using the advanced symptom management system (ASyMS) remote technology (eSMART)

HCPs, healthcare professionals; NDMM, newly diagnosed multiple myeloma; QoL, quality of life.

1. Bevans M, et al. *Nurs Outlook.* 2014;62(5):339-345. **2.** Osbourne TM, et al. *BMC Cancer.* 2105;15:280. **3.** Blade J, et al. *BMJ Open.* 2018;8)2):e018850. **4.** Basch E, et al. *J Natl Cancer Inst.* 2014l106(9):dju244.
5. Noona. www.Noona.com. **6.** Maguire R, et al. *BMJ Open.* 2017;7)5):e015016.

Noona® electronic tool for assessment of symptoms and complications

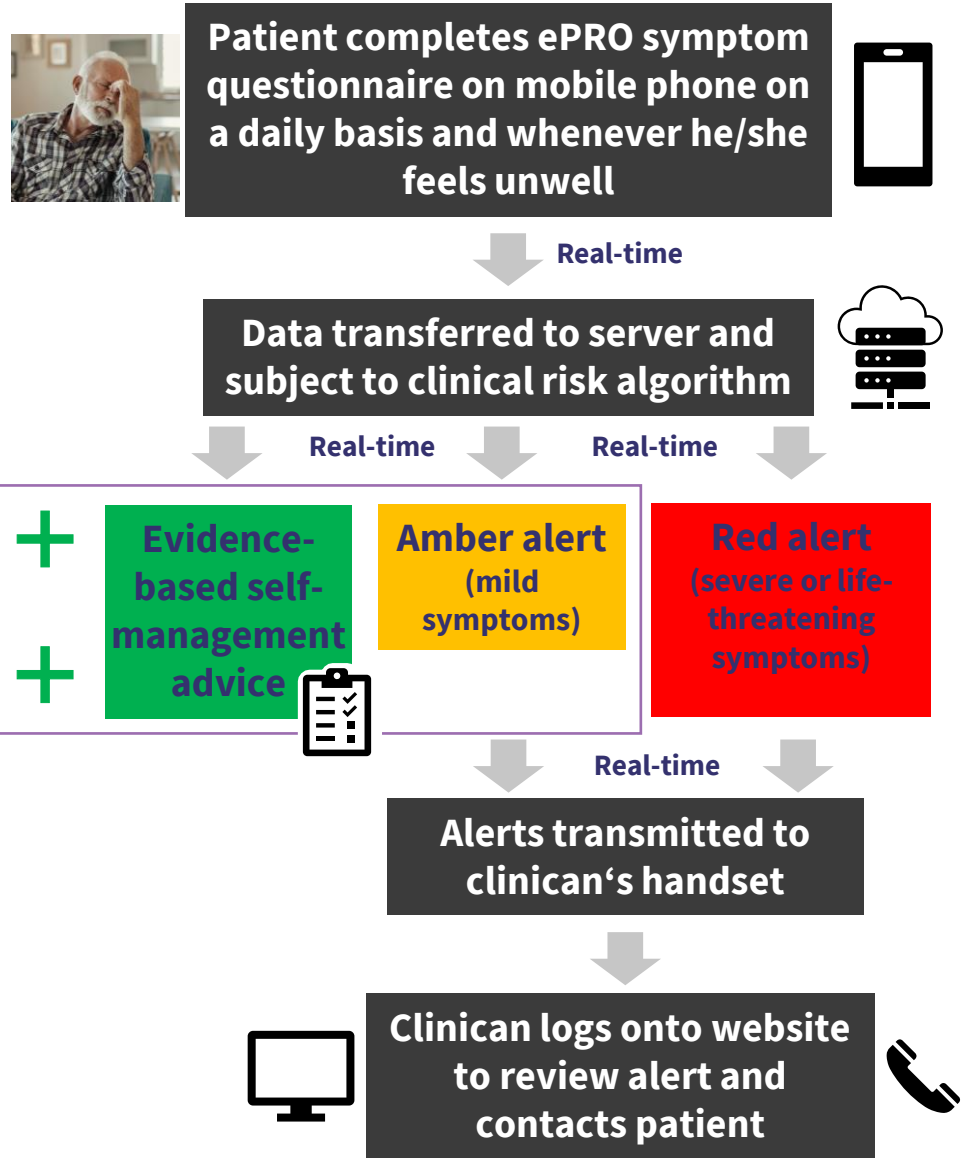


Patient reports online regularly, and at the ocurrance of acute symptoms or complications, to the care provider

Created with BioRender.com.

Electronic symptom management system remote technology (eSMART)[1]

- Mobile phone-based
- Utilizes an electronic patient-reported outcomes (ePRO) measure, creating ePRO system



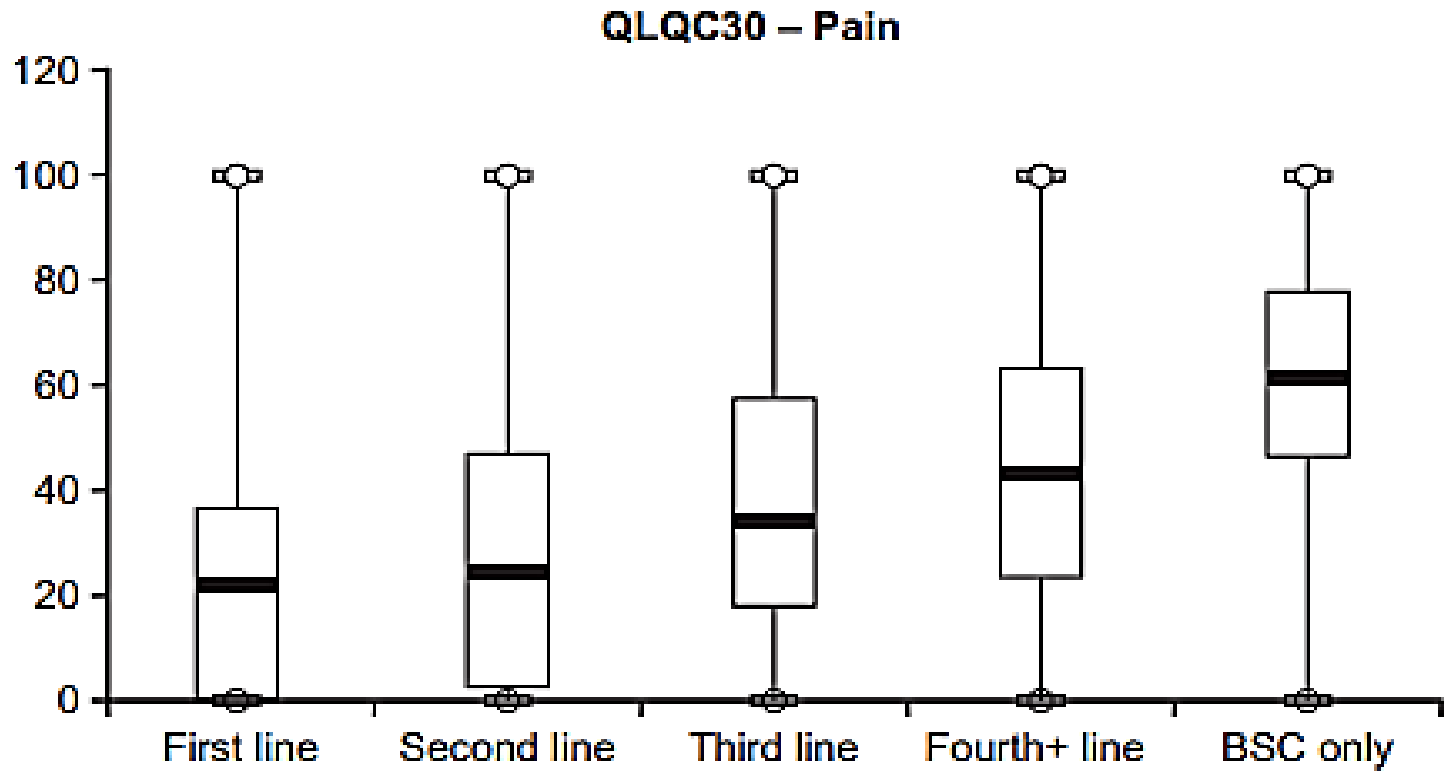
1. Maguire R, et al. BMJ Open. 2017;7(5):e015016.

Benefits of patient-reported outcome measures for patients

- Improve and facilitate communication with caregivers[1,2]
  - Independent of clinic visits (great benefit for those living far away)
  - More often and much more detailed
- Reduce visits to emergency departments[1]
- Reduce hospital admissions[1]
- Result in better care[1]
- Empower patients[1]
- Demonstrated improved clinical outcomes in other cancer types, e.g., lung cancer[3]
- And……

1. Mian H, et al. *Blood Cancer J*. 2022;12(17). **2.** Lavalle DC, et al. *Health Affairs.* 2016;35(4):575-582. **3.** Voong KR, Feliciano JL. *Transl Lung Cancer Res.* 2020;9(1):4-7.

Pain control becomes more difficult with increasing numbers of relapse

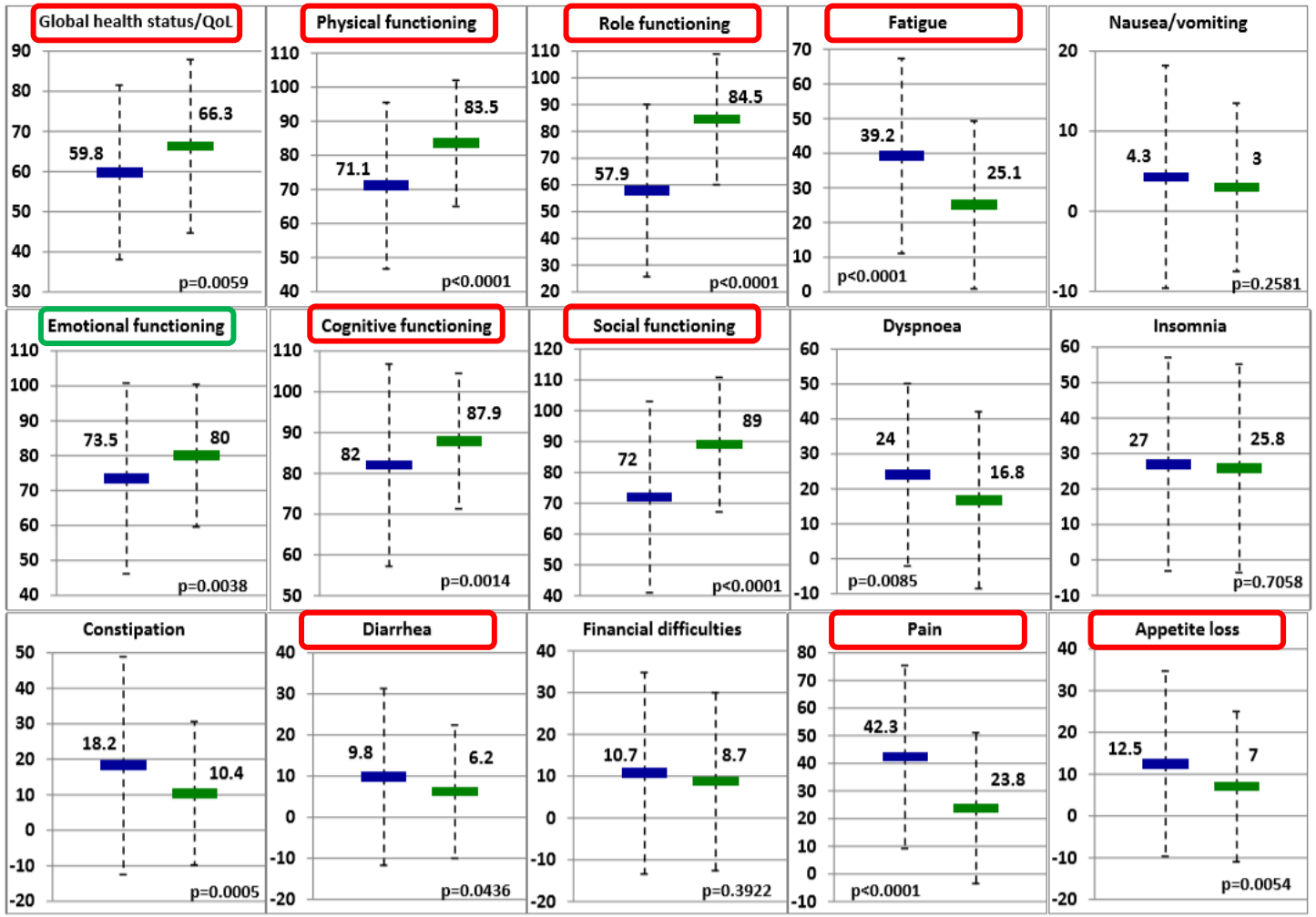


Engelhardt M, et al. *Clin Lymphoma Myeloma Leuk.* 2021;21(2):e160-e175.

BSC, best supportive care; QLQC30, Quality-of-Life Questionnaire Core 30.

QoL is significantly impaired in patients with RRMM compared with the general population

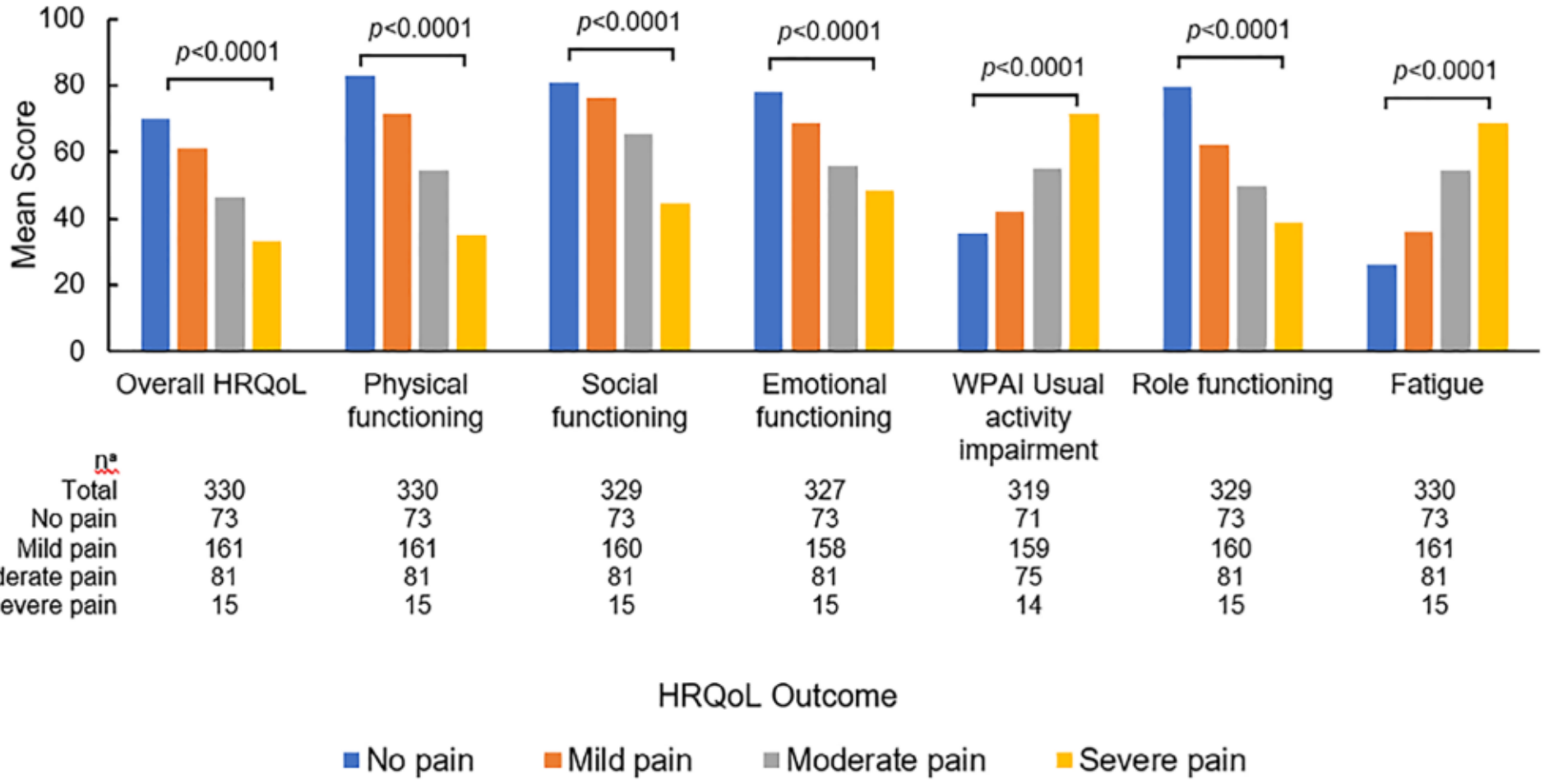
Comparison of several dimensions of QoL between patients (blue) and the general population (green).



Ludwig H, et al. *Leuk Lymphoma.* 2020;61(2):337-386.

QoL, quality of life; RRMM, relapsed/refractory multiple myeloma.

Pain intensity shows a negative correlation with QoL



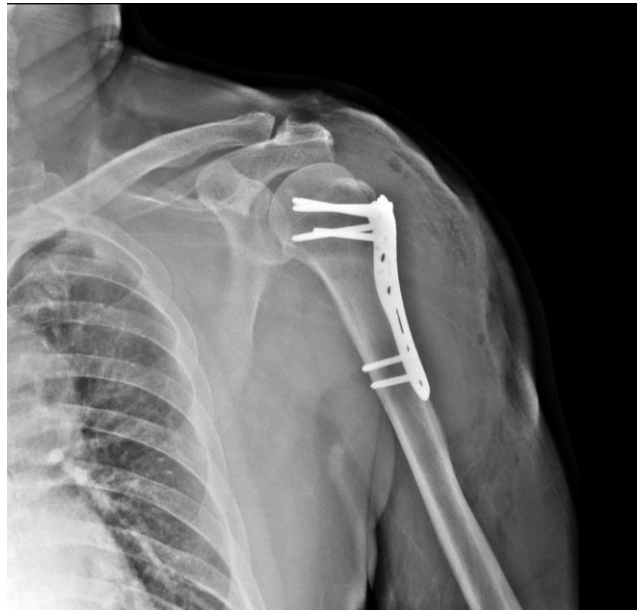
n[a]						
Total	330	330	329	327	319	329	330
No pain	73	73	73	73	71	73	73
Mild pain	161	161	160	158	159	160	161
Moderate pain	81	81	81	81	75	81	81
Severe pain	15	15	15	15	14	15	15

Ludwig H, et al. *Cancer Rep (Hoboken).* 2022;5(1):e1429.

HRQoL, health-related quality of life; QoL, quality of life; WPAI, work productivity and activity impairment.

Local pain therapy

Fractures: Surgical fixation[1]



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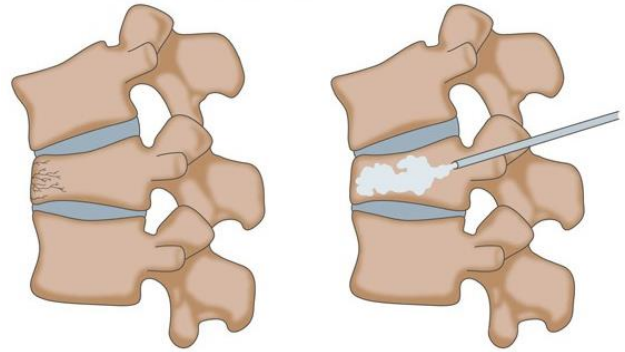
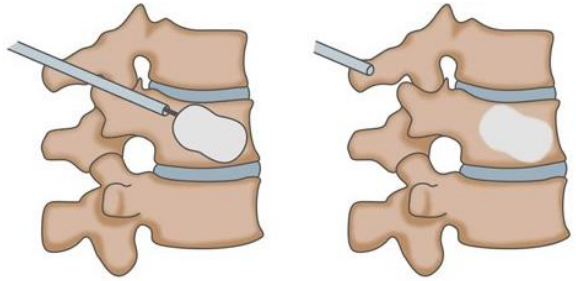
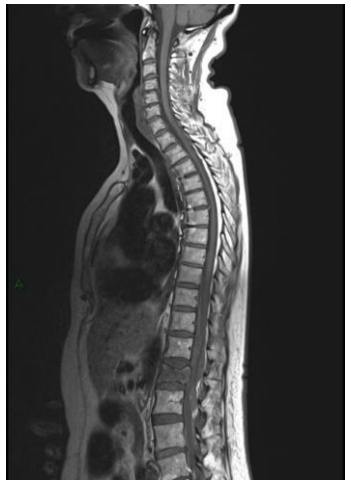
Solitary bone lesions: Vertebroplasty or kyphoplasty[2]





CIRSE. Vertebral augmentation. https://www.cirse.org/patients/ir-procedures/vertebral-augmentation/. Accessed Oct 31, 2022.

Plasmacytoma, pain: Radiotherapy[2]



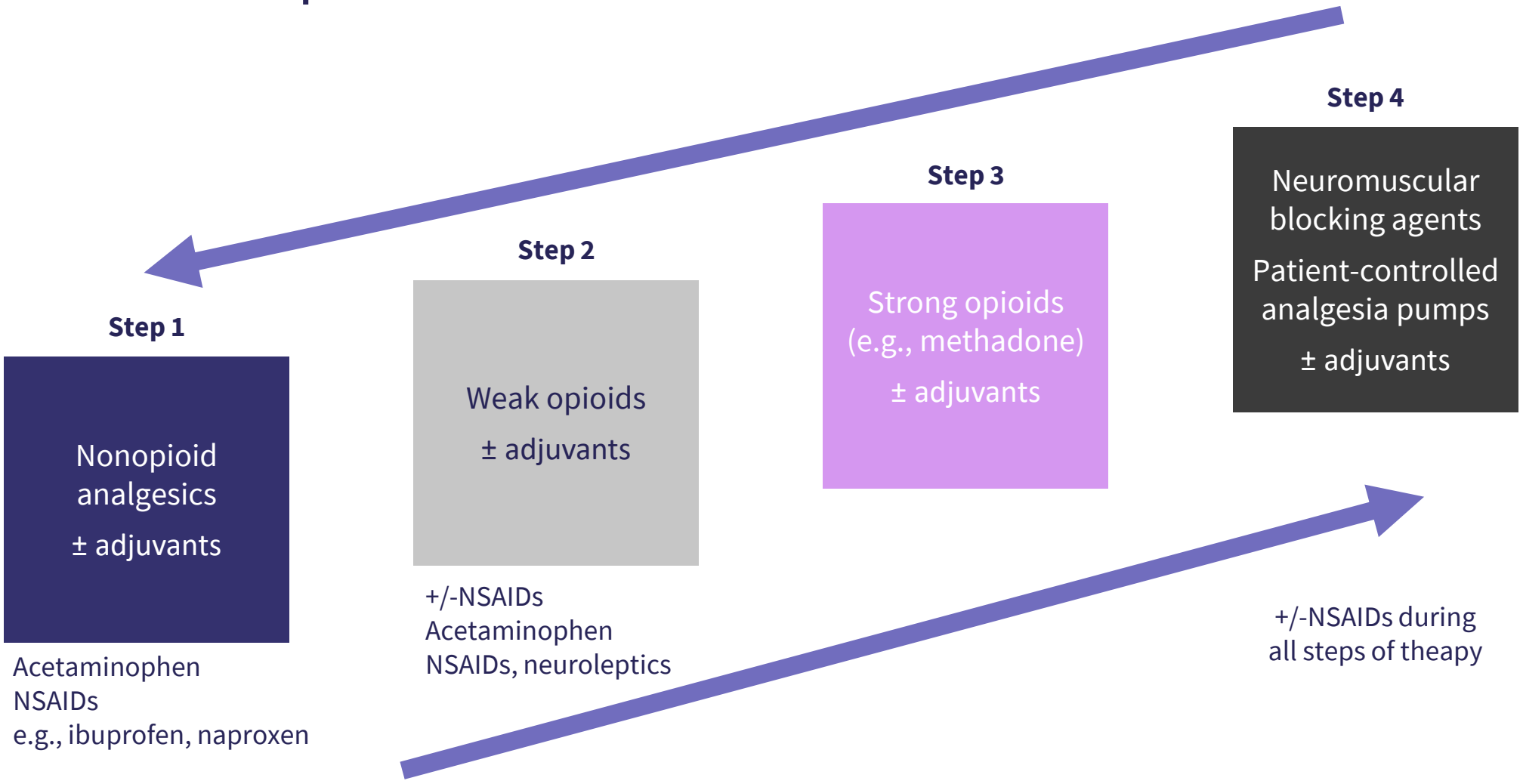
Eseonu KC, et al. *Int J Spine Surg*. 2020;14(4):559-562.

Orion Production. Shutterstock.com.

Consider bisphosphonates in all steps of therapy

1. Vaishya R, et al. *BMC Case Reports.* 2017:bcr2016218672**. 2.** Coluzzi F, et al. *Cancers (Basel)* 2019;11(12):2037.

Modified WHO pain ladder



Adapted from Pharmacy Times. Breaking through breakthrough cancer pain. https://www.pharmacytimes.com/view/breaking-through-breakthrough-cancer-pain. Published Oct 20, 2017. Accessed Oct 31, 2022.

NSAID, non-steroidal anti-inflammatory drug; WHO, World Health Organization.

Key practice points: Steps 1–3

General points[1]

- Review patient's underlying medical illnesses
- "Ceiling" effect
- Start at lowest effective dose, and practice dose titration

Adjuvant therapies[1-4]

- Choose adjuvant carefully (risk/benefit)
- Avoid initiating several adjuvants concurrently

Opioids[1-2]

- If pain is constant/chronic – use long-acting opioids with short-acting for breakthrough
- Breakthrough medication – oral or nasal fentanyl
- If intractable, switch to continuous infusion

1. Heinz Ludwig. Personal communication; Nov 10, 2022. **2.** MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf. **3.** Wickham RJ. *J Adv Pract Oncl.* 2017;8(5):475-490.
4. Murakami H. *Anticancer Res.* 2013;33(12):5557-5560.

Treatment of neuropathic pain

Anticonvulsive drugs

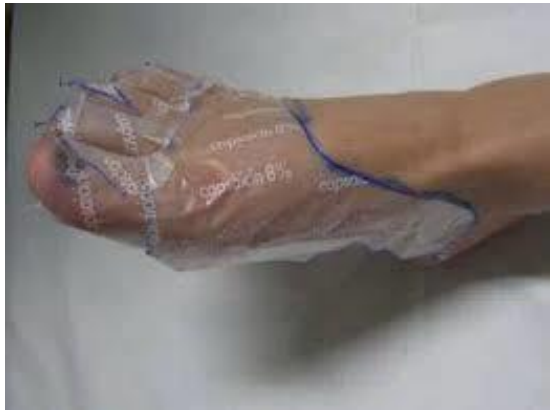
- Gabapentin/pregabalin
- Carbamazepine

Antidepressants

- Tricyclic SSRI (e.g., amitriptyline)
- Paroxetine
- Tetracyclic SSRI (e.g., maprotiline)
- Bupropion

Topical treatments

- Lidocaine 5%/prilocaine mix
- Lidocaine 5%
- Capsaicin 0.075–8%



© Health Products Regulatory Authority 2014.
HPRA. Introduction to neuropathic pain.
https://www.hpra.ie/docs/default-source/3rd-party-documents/educational-materials/qutenza_hcp_-presciber-39-s-guide_v1-08-15.pdf?sfvrsn=2.

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SSRI, selective serotonin reuptake inhibitor.

Summary

- Pain is the most frequent symptom of myeloma at diagnosis and even more so at relapse.
- Bone lesions are the major cause of pain.
  - Other frequent causes are polyneuropathy and reactivation of herpes, as well as pain resulting from adverse events of therapy.
- Pain is associated with health-related quality of life; therefore, pain therapy is a priority of supportive care.

Summary

- Pain should be assessed by patients using established instruments, as caregivers tend to underestimate the severity of pain.
- Patient-reported outcome measures help improve symptom assessment, patient–caregiver interaction, and patient quality of life.
- Pain treatment depends on the cause of pain and includes a broad spectrum of interventions, such as local therapy, pain medication, and adjuvants for pain therapy.

Thank you for your attention!

Implementing a holistic pain treatment plan in advanced disease

Dr Barry Quinn
Queen’s University Belfast, Belfast, UK

Disclosures

Barry Quinn

The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):

- Research grant(s)/in kind support: Educational grants from Ipsen, Colgate, VasoDynamics
- Participation in accredited CME/CPD: None
- Consultant/strategic advisor: None
- Patents/shares or stocks related or unrelated to this presentation: None
- Non-financial interests: None

Objectives

- To explore the concept of pain
- To review our approach to assessing pain in patients with multiple myeloma
- To recognize barriers to pain management
- To apply a more holistic approach to pain management

Background

- Pain continues to be one of the symptoms most associated with cancer and one of the symptoms that many people fear
- Pain management remains a challenge, resulting in pain being underreported, misunderstood, and often undertreated
- Pain is personal

Assessment: Classification

Pain classifications

Pathophysiology	
Nociceptive	Pain resulting from tissue damage, often described as sharp, an ache, or a throbbing sensation
Neuropathic	Pain resulting from nerve damage or a tumor putting pressure on a nerve, often described as burning, a heavy sensation, or numbness
Duration	
Acute	Sudden onset, may last for days, hours, minutes, e.g., post-operative
Chronic	More than 3 months' duration, e.g., bone metastases
Onset	
Refractory and intractable	Cannot be adequately controlled despite interventions (not always physical in nature)
Breakthrough	Exacerbation of pain despite adequately controlled baseline pain
Incident	Pain that arises as a result of activity

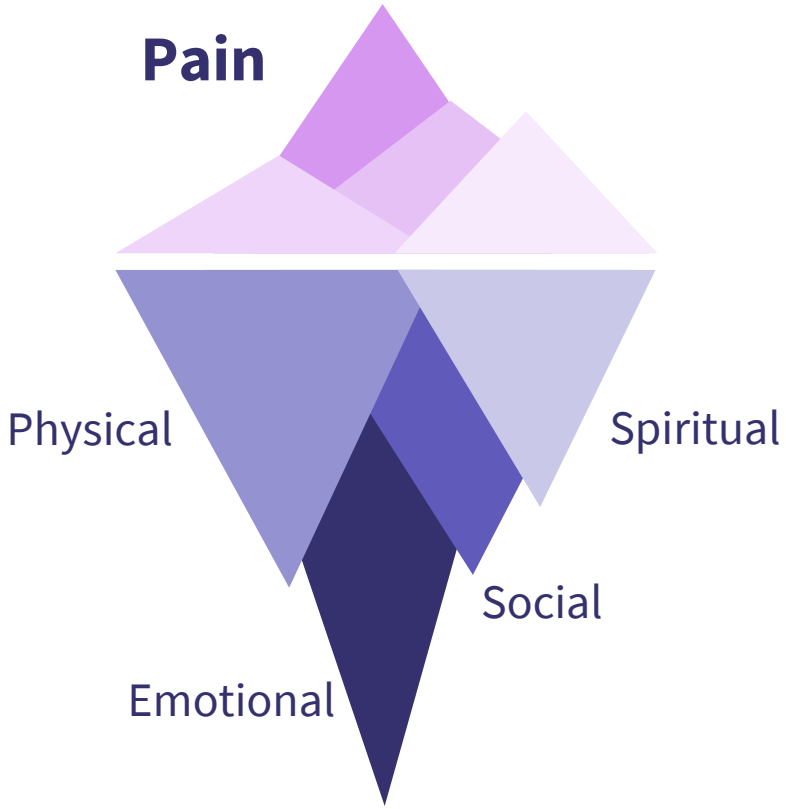
Caraceni A, Shkodra M. *Cancers (Basel).* 2019;11(4):510.
MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Hidden pain

- Pain is not easily visible to others
- The suffering and pain that arises in patients is therefore subject to interpretation
- Patients feel that many people do not understand what they are going through
- Ultimately patients can feel alone and isolated in their pain and suffering

Quinn B. *Int J Palliat Nurs*. 2020;26(6):278-283.

Assessment: Hidden elements of pain



Many of the more challenging aspects of a person's pain, including the social, emotional, and spiritual elements, exist below the surface, hidden from the view of others.

MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Obstacles

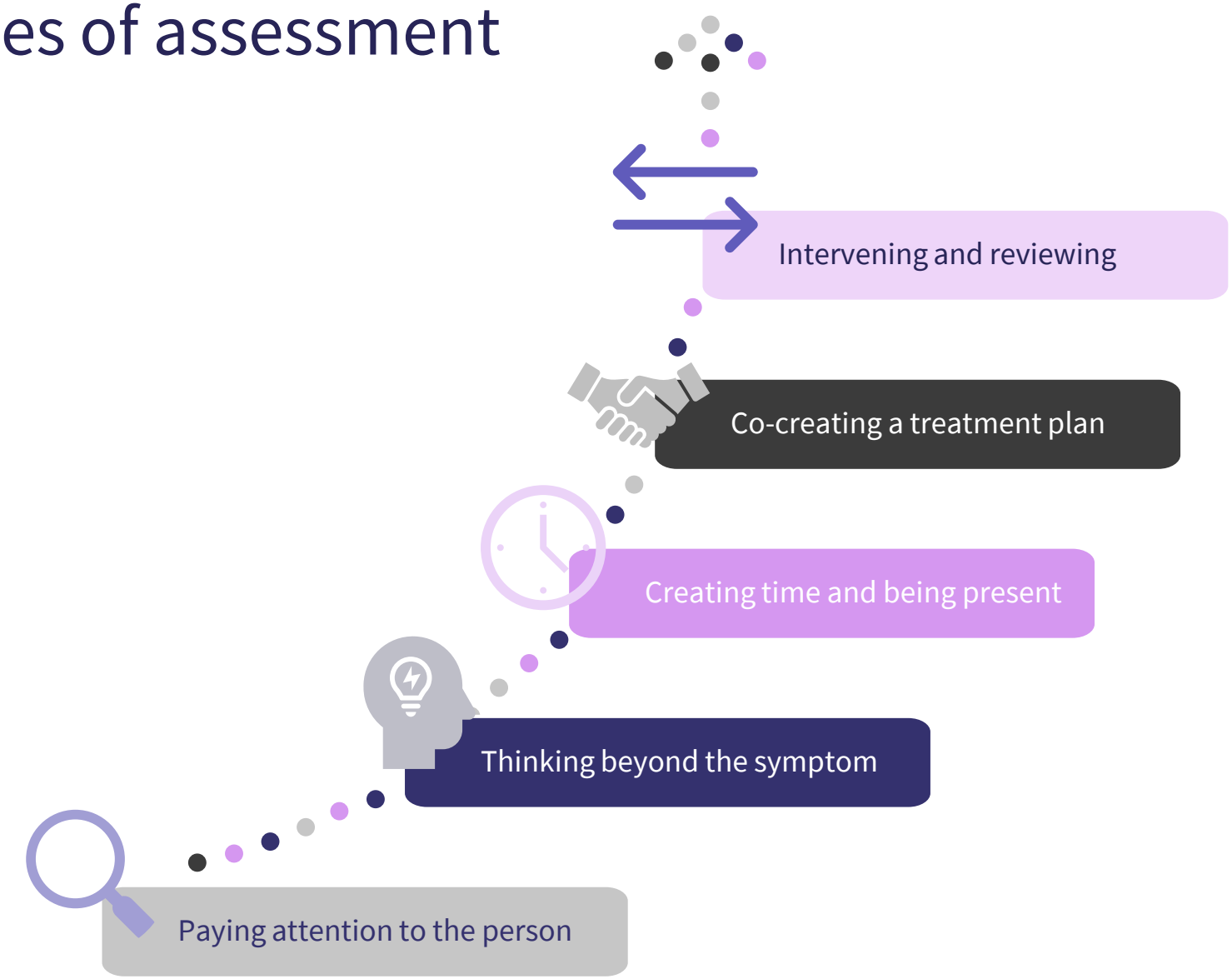
Reasons for undertreatment of pain

- Lack of knowledge (HCPs and person with cancer)
- Acceptance of suboptimal pain control
- Fear of drugs, including side effects
- Reluctance to admit pain
- Failing to understand the impact of pain on the person with cancer
- Reluctance of HCPs to ask about pain or offer treatments
- HCP fear of overprescribing
- Looking at pain in isolation from other symptoms/factors

HCP, healthcare professional.

MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.
Quinn B, et al. *Pain Manag*. 2022:12(1):59-74.

The principles of assessment



MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Assessment: Questions

Some question prompts you may wish to use

Character and site of pain

- When did your pain start? What was happening at the time?
- Where do you feel the pain?
- Does it spread to any other places?
- What pain sensation do you experience?
- How strong is you pain now/at rest/when you move/during the last week?

Expectations

- What are you hoping for from your pain treatment?
- What do you think the causes of your pain are?
- What does your family understand about your pain?
- How much better would your pain need to get for you to resume activities that are important to you?
- How do you normally cope with pain?
- Tell me what options you are aware about for managing pain. What thoughts do you have as to what might work best for you?

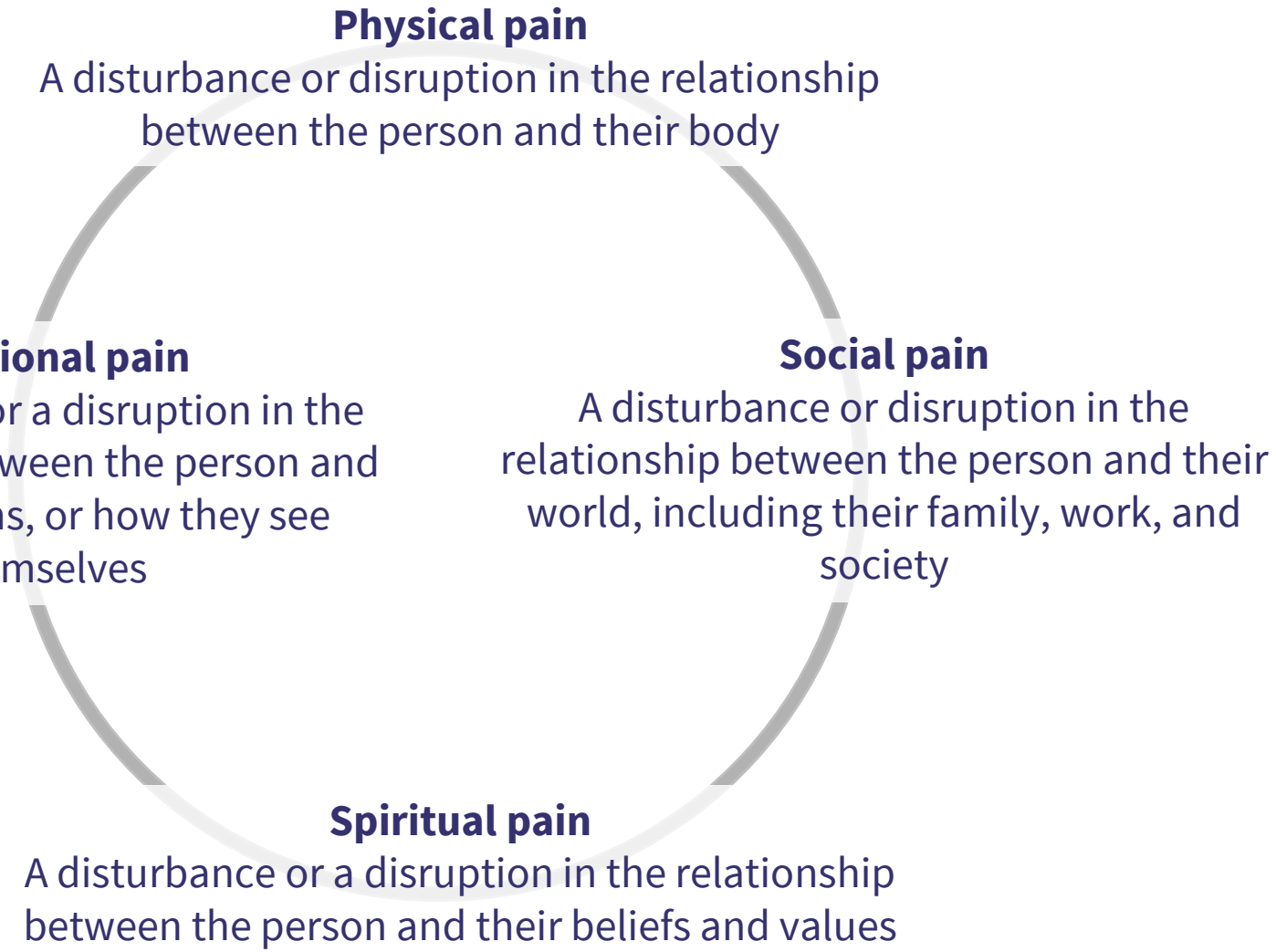
Associated factors

- What makes your pain feel better or worse?
- What other symptoms does your pain cause?
- How does your pain affect your sleep?
- How does your pain affect your social/recreational activities?
- How does your pain influence how you think about things? Your mood?

MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Assessment: Pain as disturbed relations

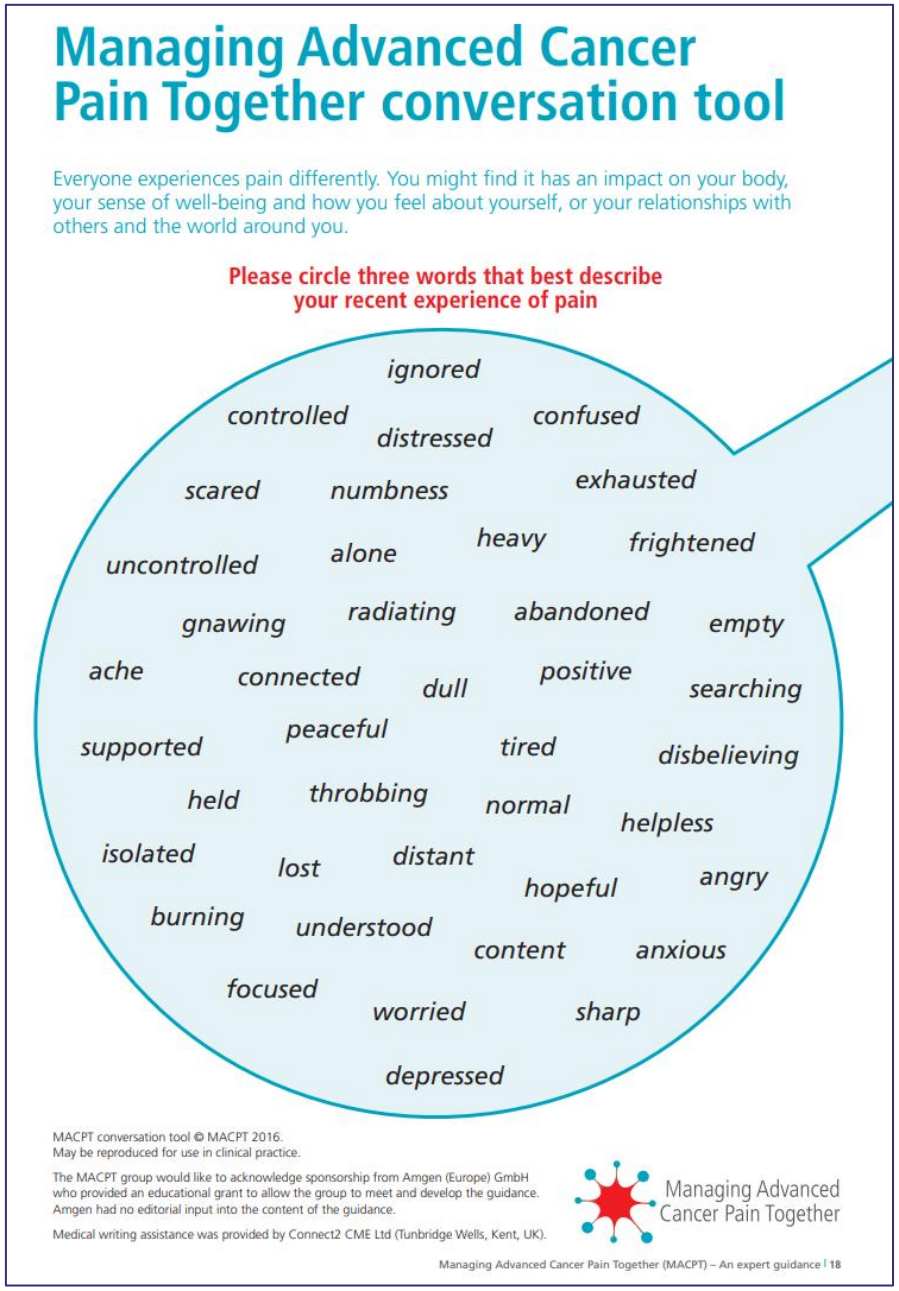
The human dimension of pain



MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.
Quinn B, et al. *Pain Manag.* 2022;12(1):59-74.

Pain conversation tool

Looking beyond the obvious symptoms to address the more hidden aspects of pain



Managing Advanced Cancer Pain Together conversation tool

Everyone experiences pain differently. You might find it has an impact on your body, your sense of well-being and how you feel about yourself, or your relationships with others and the world around you.

Please circle three words that best describe your recent experience of pain

ignored
controlled
confused
distressed
scared
numbness
exhausted
uncontrolled
alone
heavy
frightened
gnawing
radiating
abandoned
empty
ache
connected
dull
positive
searching
supported
peaceful
tired
disbelieving
held
throbbing
normal
helpless
isolated
lost
distant
hopeful
angry
burning
understood
content
anxious
focused
worried
sharp
depressed

The MACPT group would like to acknowledge sponsorship from Amgen (Europe) GmbH who provided an educational grant to allow the group to meet and develop the guidance. Amgen had no editorial input into the content of the guidance.

Medical writing assistance was provided by Connect2 CME Ltd (Tunbridge Wells, Kent, UK).

Managing Advanced Cancer Pain Together

MACPT conversation tool © MACPT 2016.
MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Approaches to reducing pain

Preventative measures

Physical pain

- Coping strategies
- Attention-diversion strategies
- Physical therapies
- Complementary therapies
- Pharmacological intervention
- Cancer treatments

Emotional pain

- Support to continue things the person enjoys doing
- Provide guidance on supporting self-esteem and self-worth
- Encouragement to share their thoughts and feelings
- Keeping a diary about feelings and emotions

Social pain

- Addressing a possible need for increased family/social support
- Support to engage with family and social groups and to continue working, if that is important
- Provide guidance on family and/or peer support

Spiritual pain

- Acknowledging the person's values and beliefs
- Seeking religious or non-religious pastoral support
- Talking to a trusted friend or a member of the oncology team
- Talking with a psychologist, counsellor, or a member of the pastoral care team

MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Pain management

Systemic

- Chemotherapy
- Hormones
- Targeted therapy
- Immunotherapy

Local

- Radiotherapy
- Surgery

- *Pharmacological interventions*
- *Non-pharmacological interventions*

Pharmacological treatments for pain

Increasing pain

	Medication	Examples
Nociceptive pain		
Mild pain (WHO step 1; NRS 1–3)	**Non-opioids** e.g., paracetamol, NSAIDs, COX-2 inhibitors ± adjuvant therapy	Paracetamol, ibuprofen, diclofenac, metamizole
Mild-to-moderate pain (WHO step 2; NRS 4–6)	**Weak opioids** ± non-opioid analgesic ± adjuvant therapy	Codeine, tramadol, dihydrocodeine
Moderate-to-severe pain (WHO step 3; NRS 7–10)	**Strong opioids** ± non-opioid analgesic ± adjuvant therapy	Morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine, levorphanol, oxymorphone, tapentadol
Neuropathic pain		
	Anticonvulsants	Pregabalin, gabapentin
Adjuvant therapy		
	Corticosteroids (for swelling/inflammation)	Dexamethasone
	Antidepressants	Amitriptyline Clomipramine
	Benzodiazepines	Diazepam

NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; WHO, World Health Organization.
MACPT. An expert guidance. http://macpt.info/download/J009950_CME1029_Pain_Guidence_Doc.pdf.

Approaches to treatment

Barry Quinn, personal communication, Nov 10, 2022.

“Amidst the uncertainty and the painful realities each person had to face, caring was perceived as occurring when another person carried out a simple act of kindness with a caring attitude, which required the other to be attentive to them”

EONS. EONS Magazine – Autumn 2014. https://issuu.com/eons/docs/eonsmagazine2014autumn. Published Nov 29, 2014.
Quinn B. *Int J Palliat Nurs.* 2020;26(6):278-283.

Summary

- Pain is frequently underreported and undertreated
- The physical, social, emotional, and spiritual dimensions of pain need to be considered
- Open, honest, and sensitive communication is essential
- Prevention is an often overlooked component of pain management and should be considered
- Aim to co-create a pain management plan with the person living with advanced disease

Dos and dont’s in pain management

Flaminia Coluzzi
Sapienza University of Rome, Rome, IT

Disclosures

Flaminia Coluzzi

- The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):
  - Research grant(s)/in kind support: Epitech Group SpA, Molteni, Sandoz, Grunenthal
  - Participation in accredited CME/CPD: Epitech Group SpA, Molteni, Grunenthal
  - Consultant/strategic advisor: Epitech Group SpA, Molteni, Grunenthal
  - Patents/shares or stocks related or unrelated to this presentation: None
  - Non-financial interests: None

Objectives

- Consider the principles of a mechanism-based approach to pain management in multiple myeloma
- Review the intensive and active approaches to pain management
- Review the approaches to tailoring pain control to symptoms and patients' needs
- Consider the approaches to preventing myeloma pain from becoming chronic
- Address the management of breakthrough cancer pain and neuropathic pain
- Consider the monitoring of opioid-related adverse events and their management

DO

USE A MECHANISM-BASED APPROACH TO PAIN

cancers

MDPI

Review

Pain Management in Patients with Multiple Myeloma: An Update

Flaminia Coluzzi [1,*], Roman Rolke [2] and Sebastiano Mercadante [3]

[1] Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, 04100 Latina, Italy

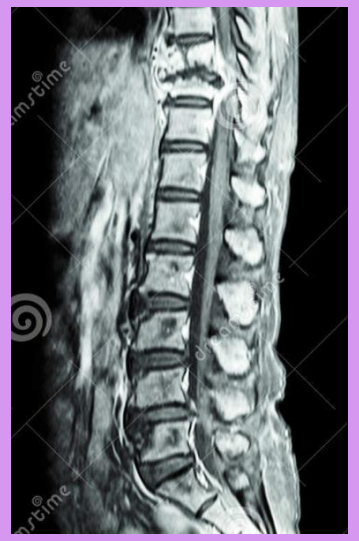
Management of bone metastases

Radiotherapy

Surgery

Chemotherapy

Analgesia



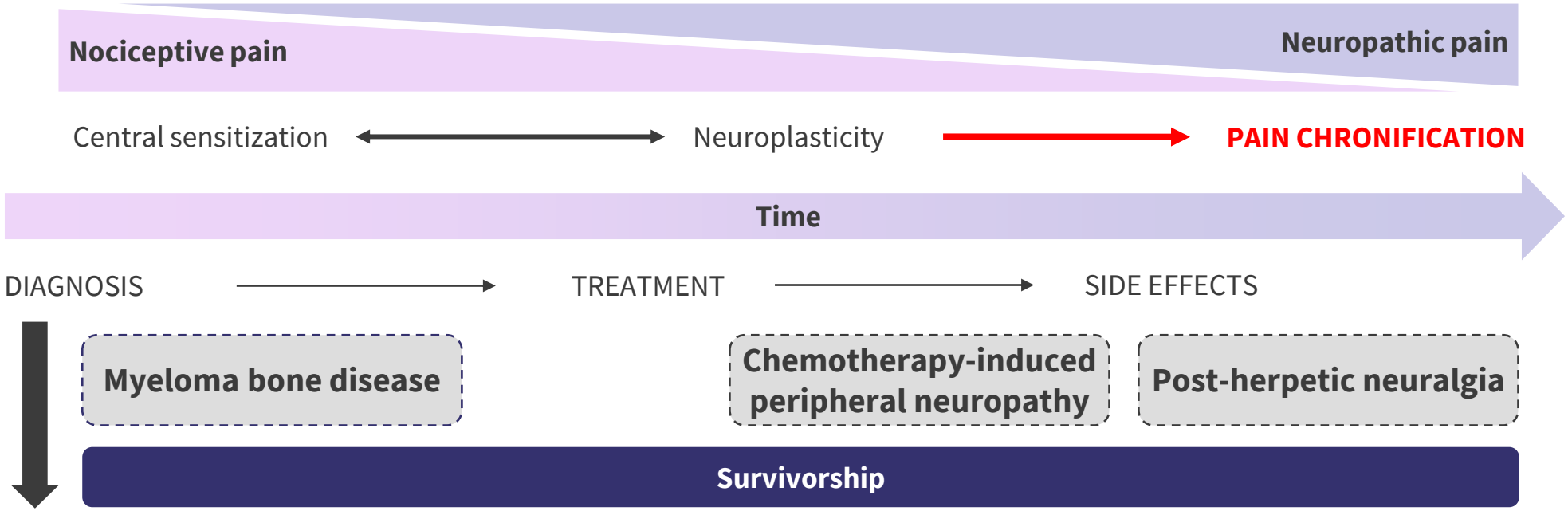
ID 65287139 © Puwadol Jaturawutthichai | Dreamstime.com

Bisphosphonates

Targeted therapy

Steroids

Bonneau A. *Can Fam Physician.* 2008;54(4):524-527.



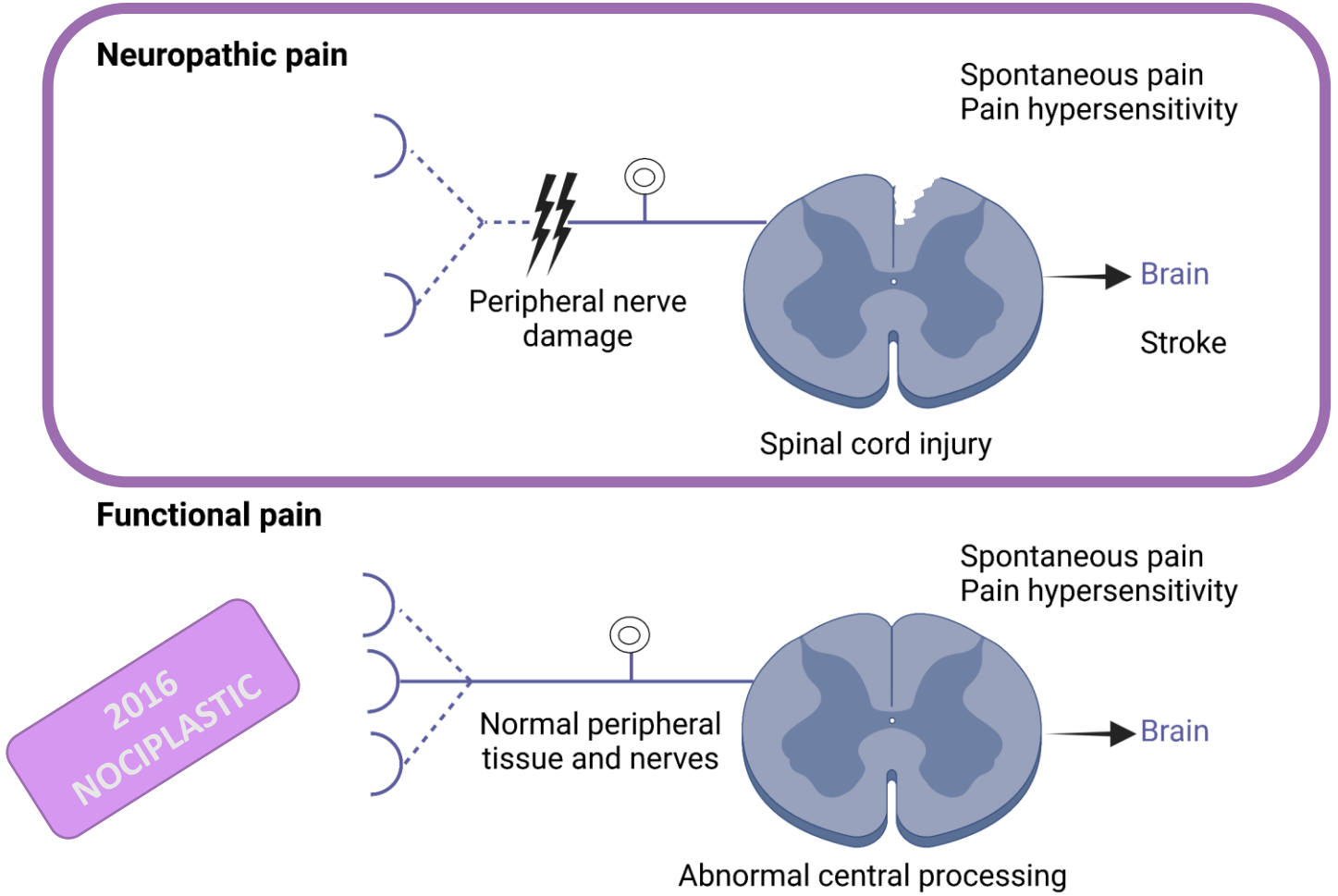
Adapted from Coluzzi, et al. *Cancers (Basel)*. 2019;11(12):2037.

APAP, acetaminophen (paracetamol); BP, bisphosphonate.

Maladaptive pain

Absence of external potentially noxious inputs

- Maladaptive pain
- Neuropathic
- Nociplastic

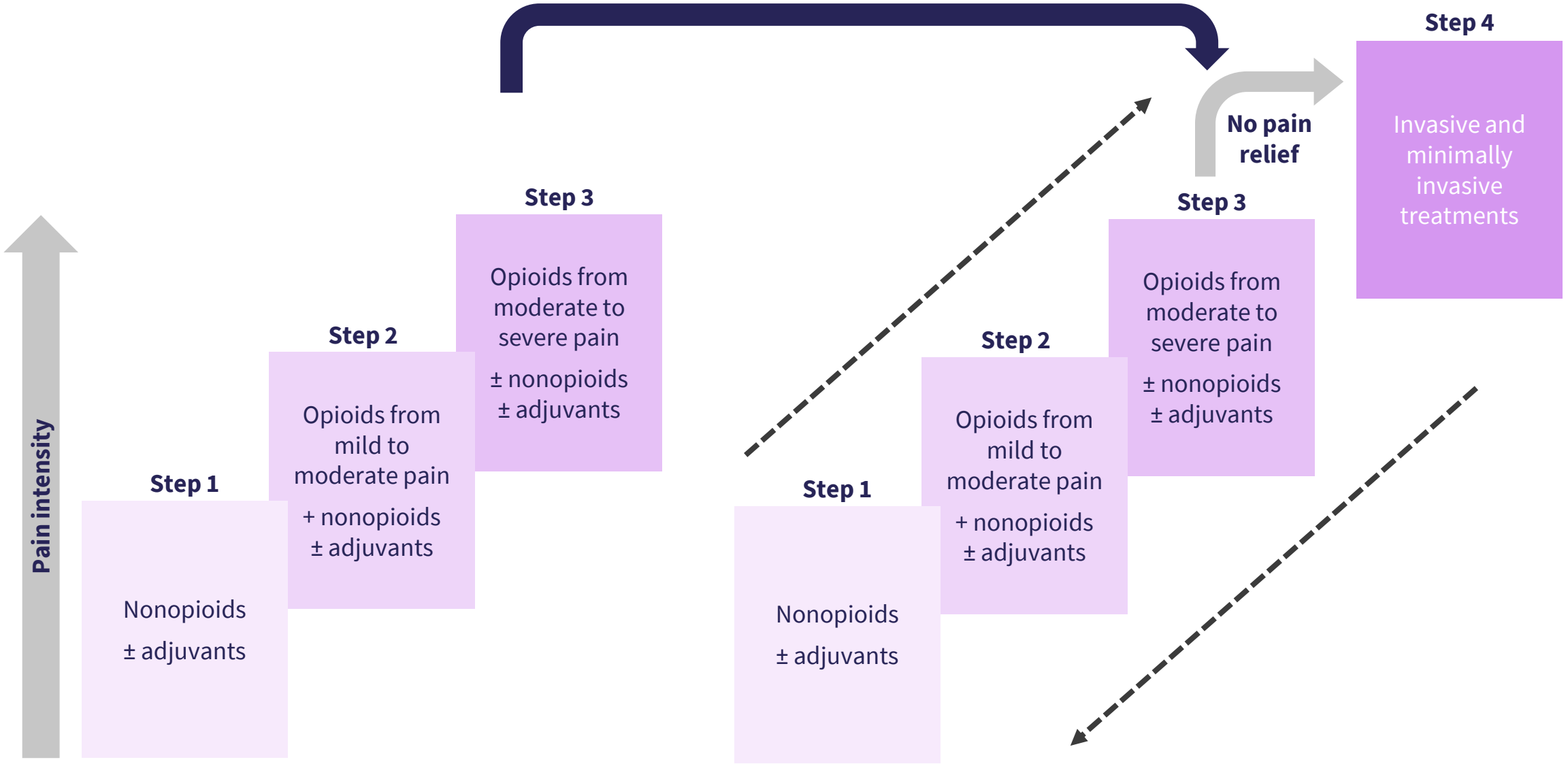


Adapted from Woolf CJ, et al. *Ann Intern Med.* 2004;140(6):441-451.
Created using BioRender.com

DO

TREAT PAIN AGGRESSIVELY

Is the WHO analgesic ladder appropriate in myeloma bone disease?



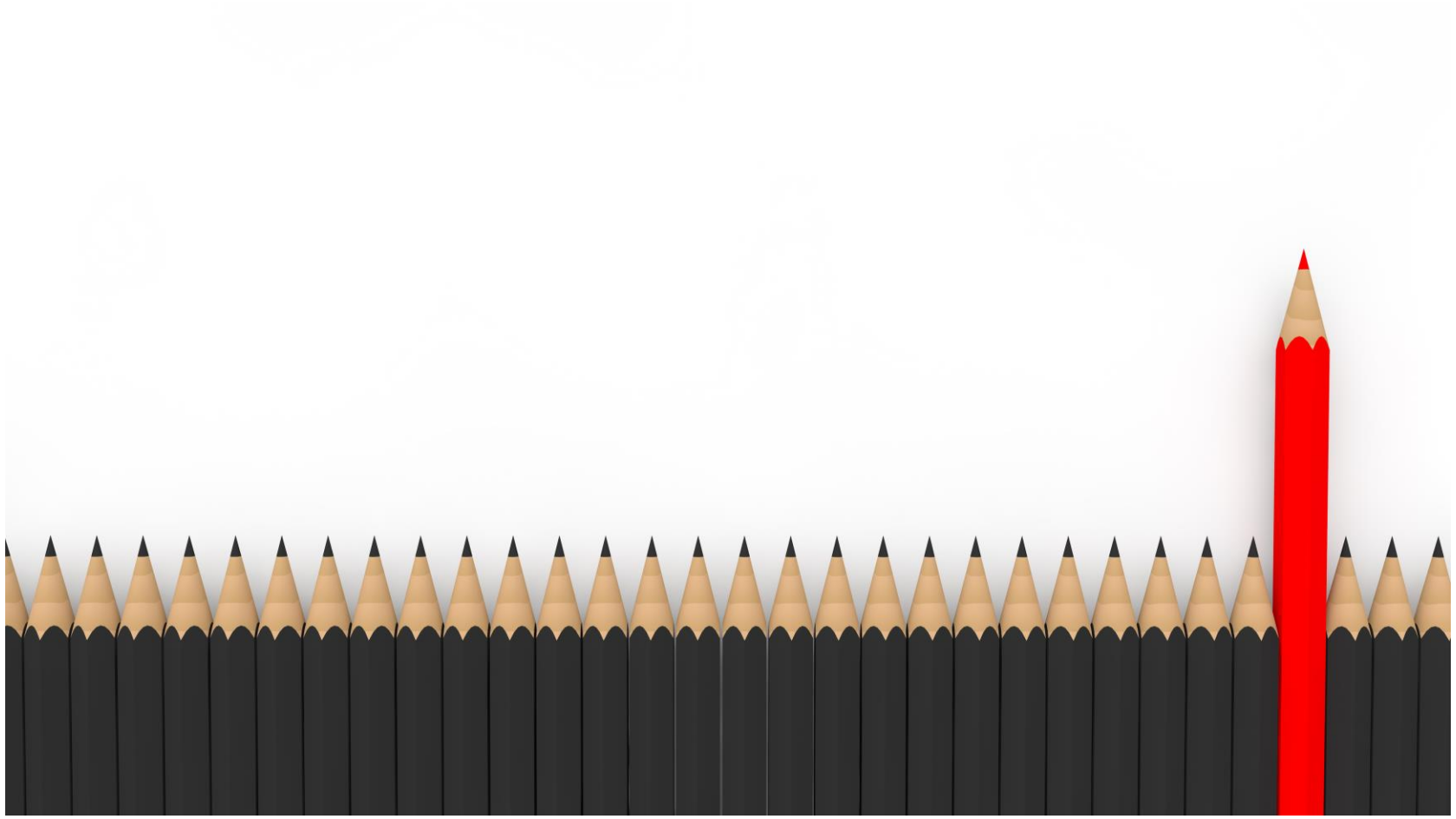
WHO, World Health Organization.

Adapted from Pharmacy Times. Breaking through breakthrough cancer pain. https://www.pharmacytimes.com/view/breaking-through-breakthrough-cancer-pain. Published Oct 20, 2017. Accessed Nov 3, 2022.

DO

PREFER A TAILORED THERAPY

How to choose…



Opioid classification in cancer pain[1–3]

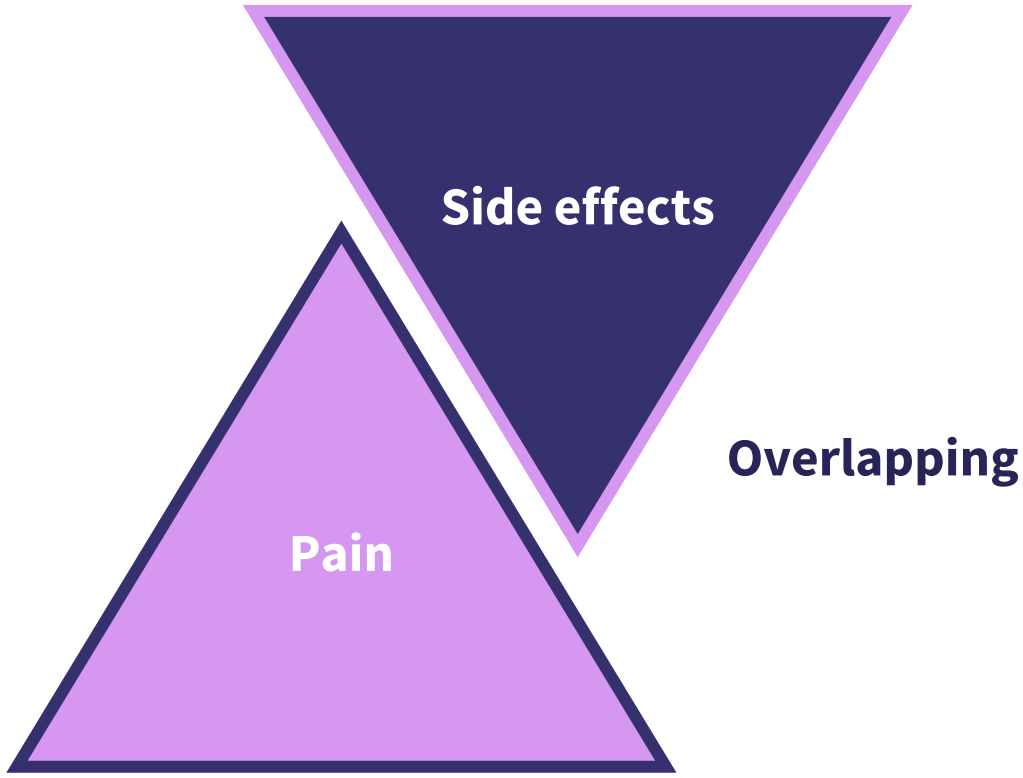
	LAO	SAO	ROO
ANALGESIA	**Long acting**	**Short acting**	**Rapid onset**
Onset	1–2 hours	30–40 min	15 min
Duration	8–12+ hours	4 hours	1–2 hours

LAO, long-acting opioid; RAO, rapid-acting opioid; SAO, short-acting opioid.

1. Bennet D, et al. *P T.* 2005;30(6):354-361. **2.** Texas Health and Human Services. Onset, peak and duration of common pain medications. https://www.hhs.texas.gov/sites/default/files/documents/doing-business-with-hhs/provider-portal/QMP/PainMedicationTable.pdf. Accessed Nov 8, 2022. **3.** Smith HS. *Ann Palliat Med.* 2012;1(1):42-52.

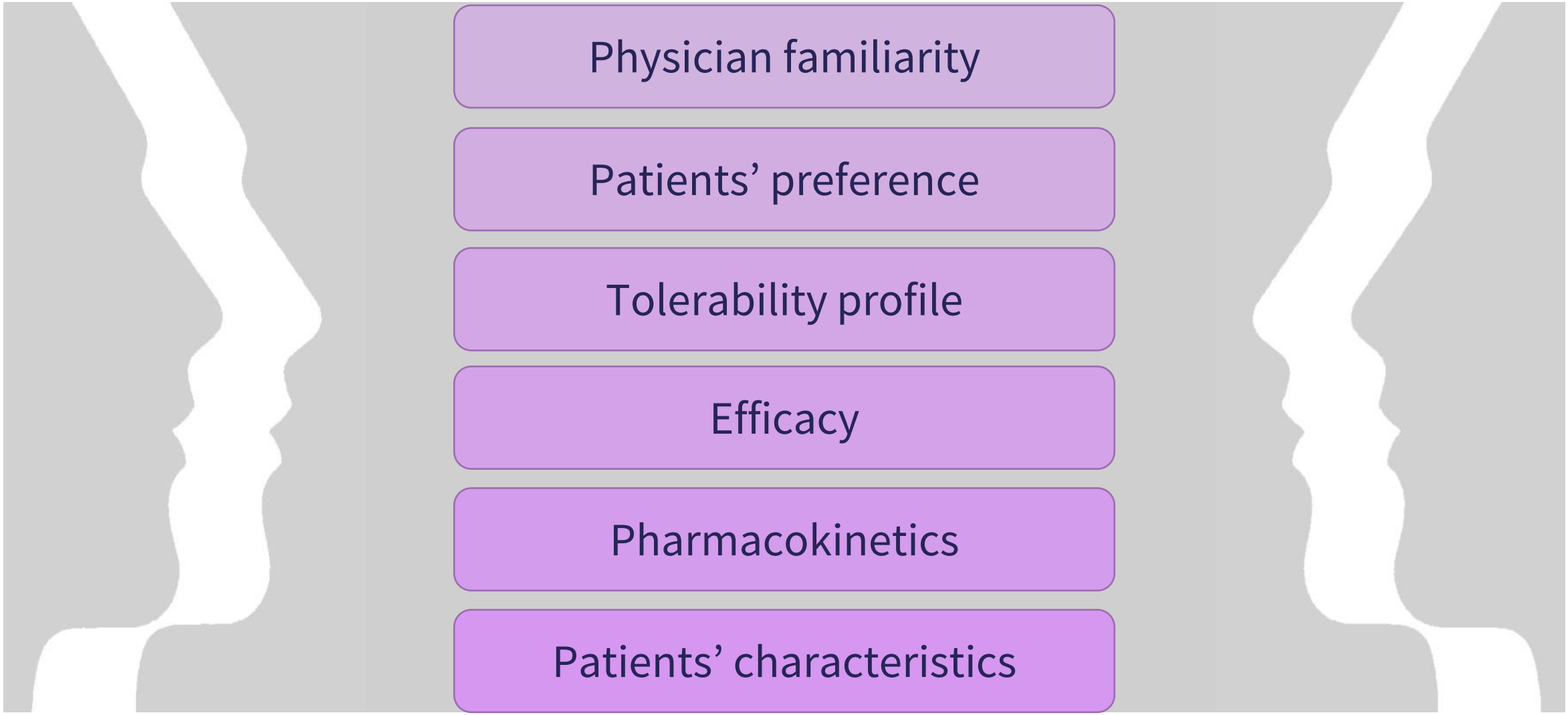
Titration is the first step

- Reach to lowest effective dose
- Minimize side effects
- Tailored therapy



Flaminia Coluzzi. Personal communication; Nov 10, 2022.

Choosing the right long-acting opioid



Flaminia Coluzzi. Personal communication; Nov 10, 2022.

Assessing and treating chronic pain in patients with end-stage renal disease

Pharmacological treatment for chronic pain management in ESRD

Opioids	Route of administration	Starting dosage	Indications	Clinical considerations
Buprenorphine patch	Transdermal	5 µg/h	Severe chronic pain	Safer profile
Fentanyl patch	Transdermal	12 µg/h	Severe chronic pain	Safer profile No clinically significant accumulation in CKD
Hydromorphone	Oral	4 mg bid	Severe chronic pain (second-line treatment)	Safe, but use with caution Dose adjustment required
Oxycodone	Oral	5 mg bid	Severe chronic pain (second-line treatment)	Safe, but use with caution Dose adjustment required
Tramadol	Oral	50 mg bid	Severe chronic pain (second-line treatment)	Safe, but use with caution Dose adjustment required
Tapentadol	Oral	25 mg bid	Severe chronic pain (second-line treatment)	No dose adjustment needed for CrCl ≥30 ml/min Data are not available in ESRD
Morphine				Not recommended due to accumulation To be avoided
Codeine				Not recommended due to accumulation To be avoided

Adapted from Coluzzi F. *Drugs*. 2018;78(14):1459-1479.

bid, twice a day; CKD, chronic kidney disease; CrCl, creatinine clearance; ESRD, end-stage renal disease.

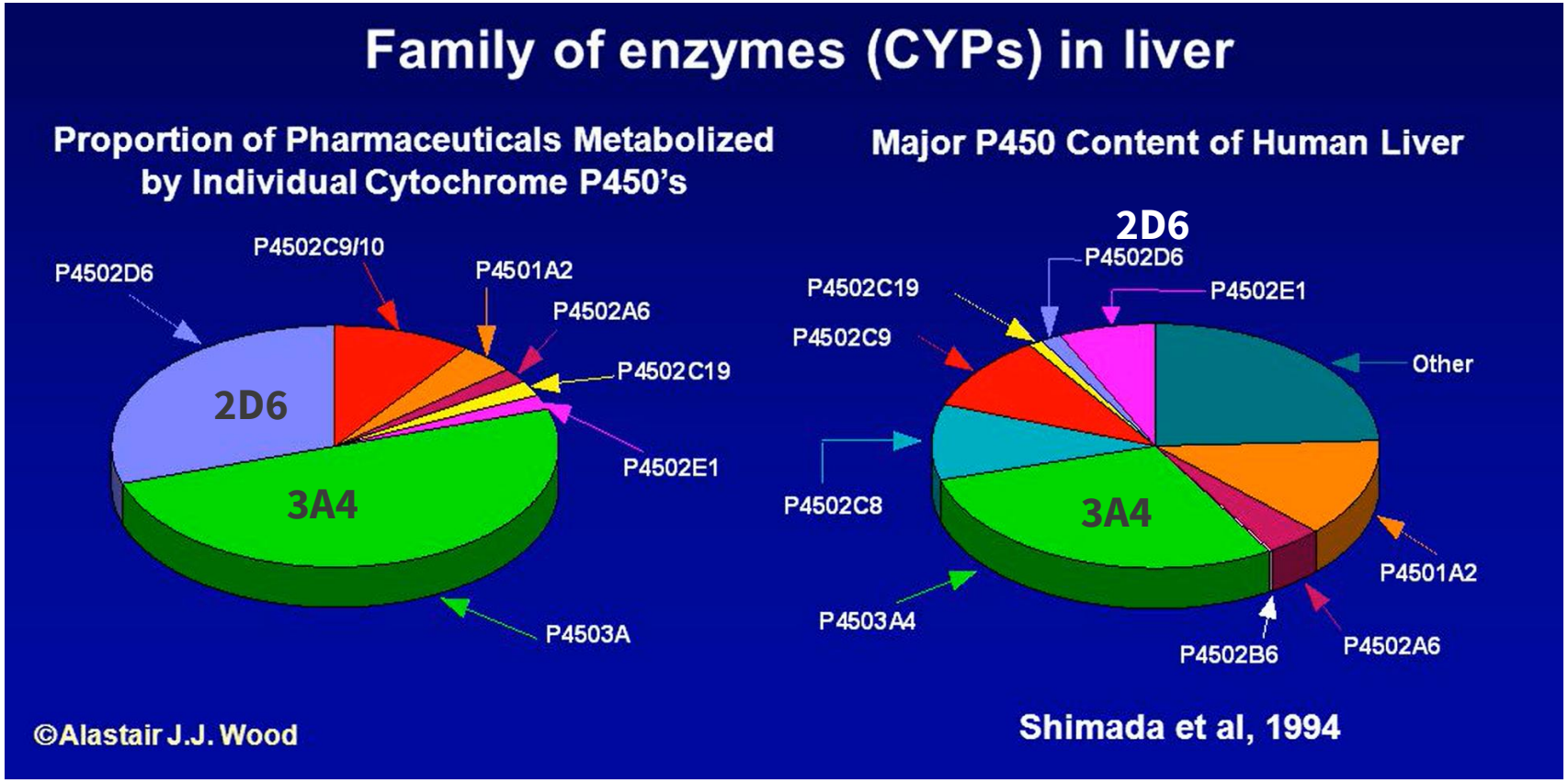
Opioids in liver failure

Recommendations for opioids in hepatic impairment

Codeine	Not recommended; in severe hepatic dysfunction codeine is not converted to morphine, lead to poor analgesia
Fentanyl	99% metabolized in liver; studies have not demonstrated PK alterations; careful monitoring is warranted
Hydrocodone	Use with caution; monitor for overdose due to parent compound not being converted to metabolites
Hydromorphone	Undergoes phase II reaction; however, use with caution due to its immediate extraction ratio
Methadone	Use with caution; risk of accumulation because of increased free drug
Meperidine	Not recommended; toxic metabolite, normeperidine, may accumulate
Morphine	Use with caution; monitor for overdose due to high extraction ratio
Oxycodone	Use with caution; dose adjustment recommended (1/2 to 1/3 of original dose)
Oxymorphone	Contraindicated in moderate-to-severe hepatic impairment
Tramadol	Not recommended; significant pharmacokinetic changes in moderate-to-severe hepatic impairment

Davis M. *Clin Pharmacokinet*. 2007;46(10):825-850.
Johnson SJ. Opioid safety in patients with renal or hepatic dysfunction. *Pain Treatment Topics*. http://paincommunity.org/blog/wp-content/uploads/Opioids-Renal-Hepatic-Dysfunction.pdf. Accessed Nov 3, 2022.

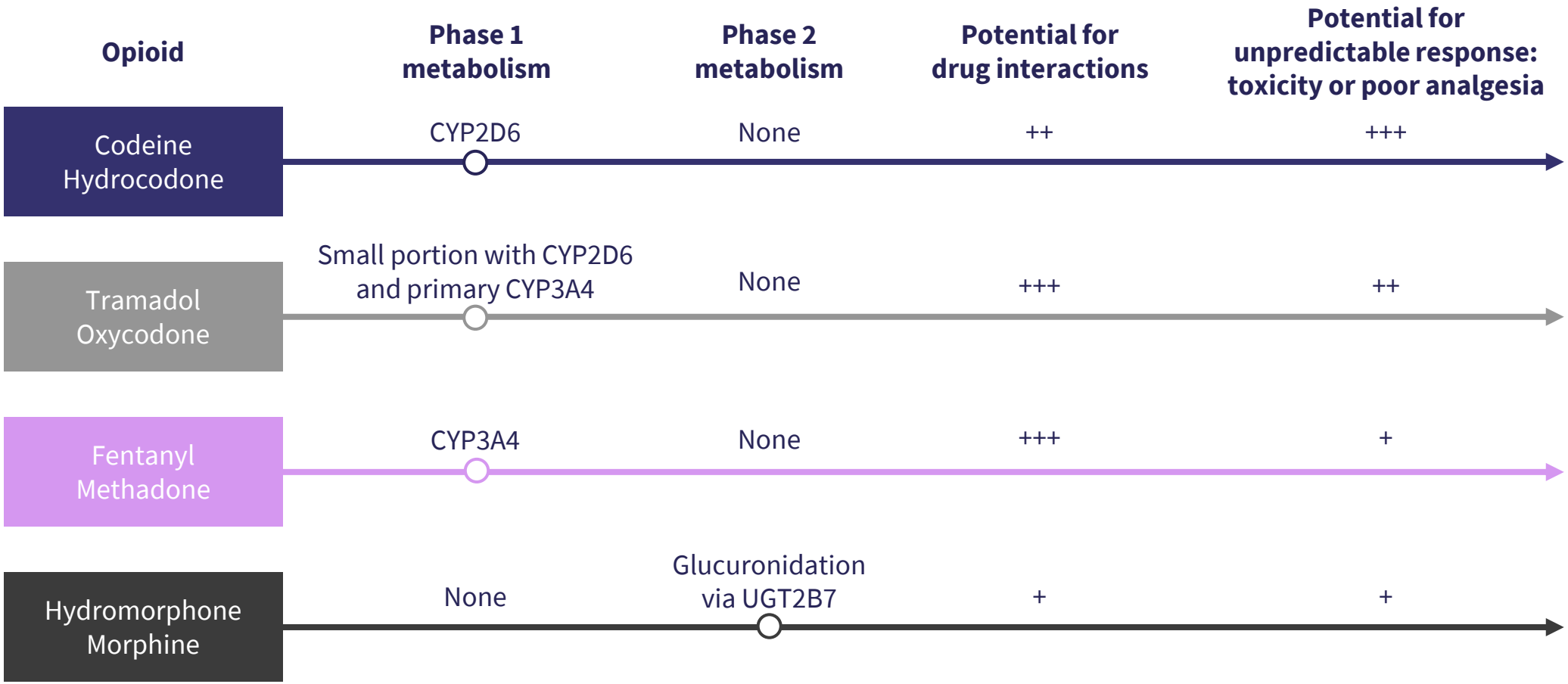
Drug-drug interactions: Role of CYP450



Pruit N. Ethnic variability in drug response. https://slideplayer.com/slide/1691484/. Accessed Nov 3, 2022.

Shamida, et al. *J Pharmacol Exp Ther*. 1994;270(1):414-423.

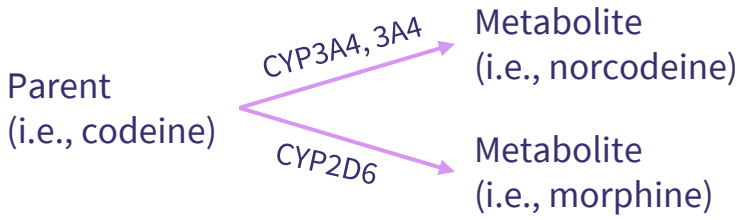
Opioid metabolism



Adapted from Davison SN. *Clin J Am Soc Nephrol*. 2019;14(6):917-931.

Opioid metabolism

CYP2D6 dependent	CYP2D6 non-dependent
• Codeine	• Hydromorphone
• Hydrocodone	• Morphine
• Methadone	• Oxymorphone
• Oxycodone	• Tapentadol
• Tramadol	

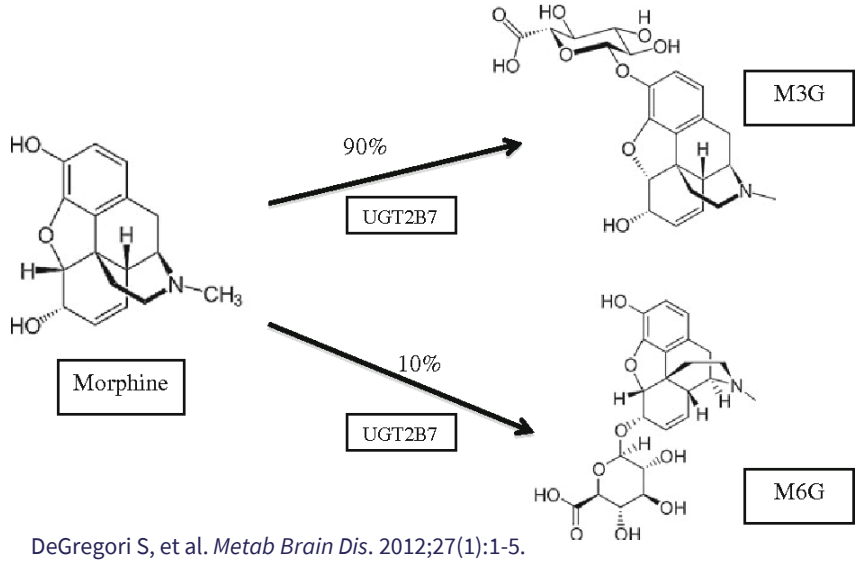


Adapted from Practical pain management. Pharmacogenetics and pain management. https://www.practicalpainmanagement.com/resources/diagnostic-tests/pharmacogenetics-pain-management. Accessed Nov 3, 2022.

- Morphine
- Hydromorphone
- Oxymorphone
- Tapentadol

Common drugs used in pain and their metabolism pathway			
CYP2D6	CYP2C9	CY3A4/5	CYP2B6
Amitriptyline	Celecoxib	Codeine	Methadone
Codeine	Flurbiprofen	Diazepam	
Desipramine	Ibuprofen	Fentanyl	
Diazepam	Meloxicam	Hydrocodone	
Hydrocodone	Piroxicam	Oxycodone	
Imipramine		Methadone	
Methadone			
Nortriptyline			
Oxycodone			
Tramadol			
Venlafaxine			

Adapted from Practical pain management. Pharmacogenetics and pain management. https://www.practicalpainmanagement.com/resources/diagnostic-tests/pharmacogenetics-pain-management. Accessed Nov 3, 2022.



DeGregori S, et al. *Metab Brain Dis*. 2012;27(1):1-5.

Cancer pain: Tapentadol in multiple myeloma

Journal of Pain Research

Dovepress
open access to scientific and medical research

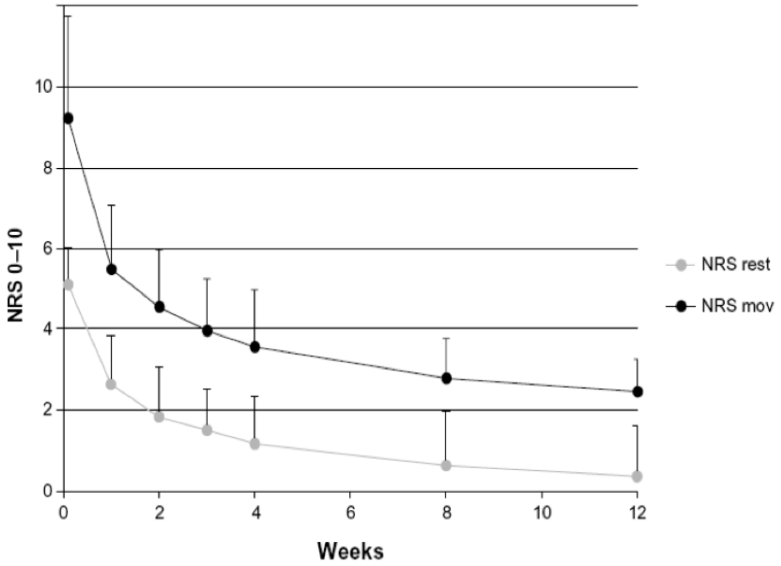
Open Access Full Text Article

ORIGINAL RESEARCH

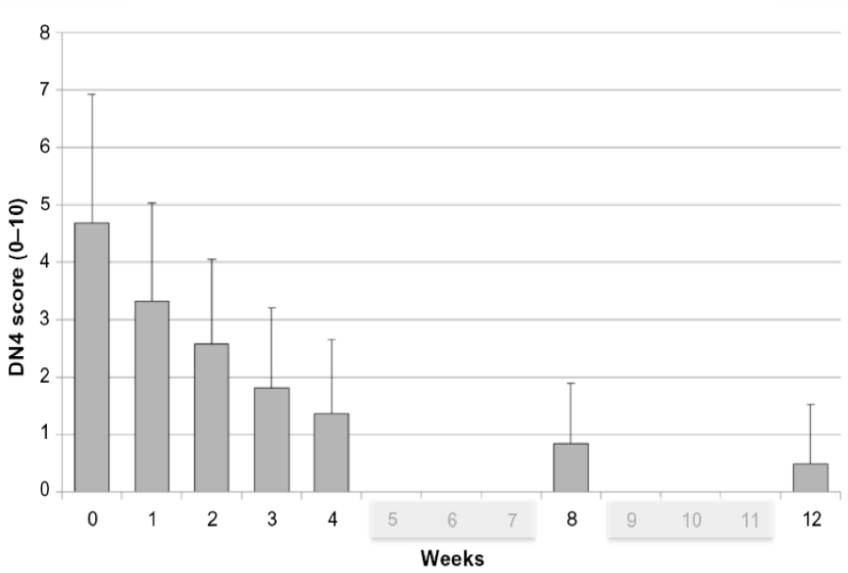
Tapentadol prolonged release for patients with multiple myeloma suffering from moderate-to-severe cancer pain due to bone disease

Flaminia Coluzzi[1,2]
Robert B Raffa[3]
Joseph Pergolizzi[4]
Alessandra Rocco[1]
Pamela Locarini[1]
Natalia Cenfra[5]
Giuseppe Cimino[5]
Consalvo Mattia[1,2]

Pain intensity (NRS)



Neuropathic component (DN4)



Coluzzi F, et al. *J Pain Res.* 2015;8:229-238.

NRS, numerical rating scale.

DO

PREVENT CHRONIFICATION

Persistent opioid use in patients with multiple myeloma post-ASCT

Frequency of opioid dose changes in active opioid users following ASCT

	Time	
Dose change	**At Day 100**	**At 1 year**
Decrease	6 (12.0%)	11 (25.0%)
Same	23 (46.0%)	23 (52.3%)
Increase	21 (42.0%)	10 (22.7%)
Total	50	44

Adapted from Danish ML, et al. *Eur J Hematol*. 2022;108(6):503-509.

ASCT, allogeneic stem cell transplantation.

DO

USE RAPID-ONSET OPIOIDS FOR BREAKTHROUGH CANCER PAIN

Opioid classification in cancer pain[1–3]

	LAO	SAO	ROO
ANALGESIA	**Long acting**	**Short acting**	**Rapid onset**
Onset	1-2 hours	30-40 min	15 min
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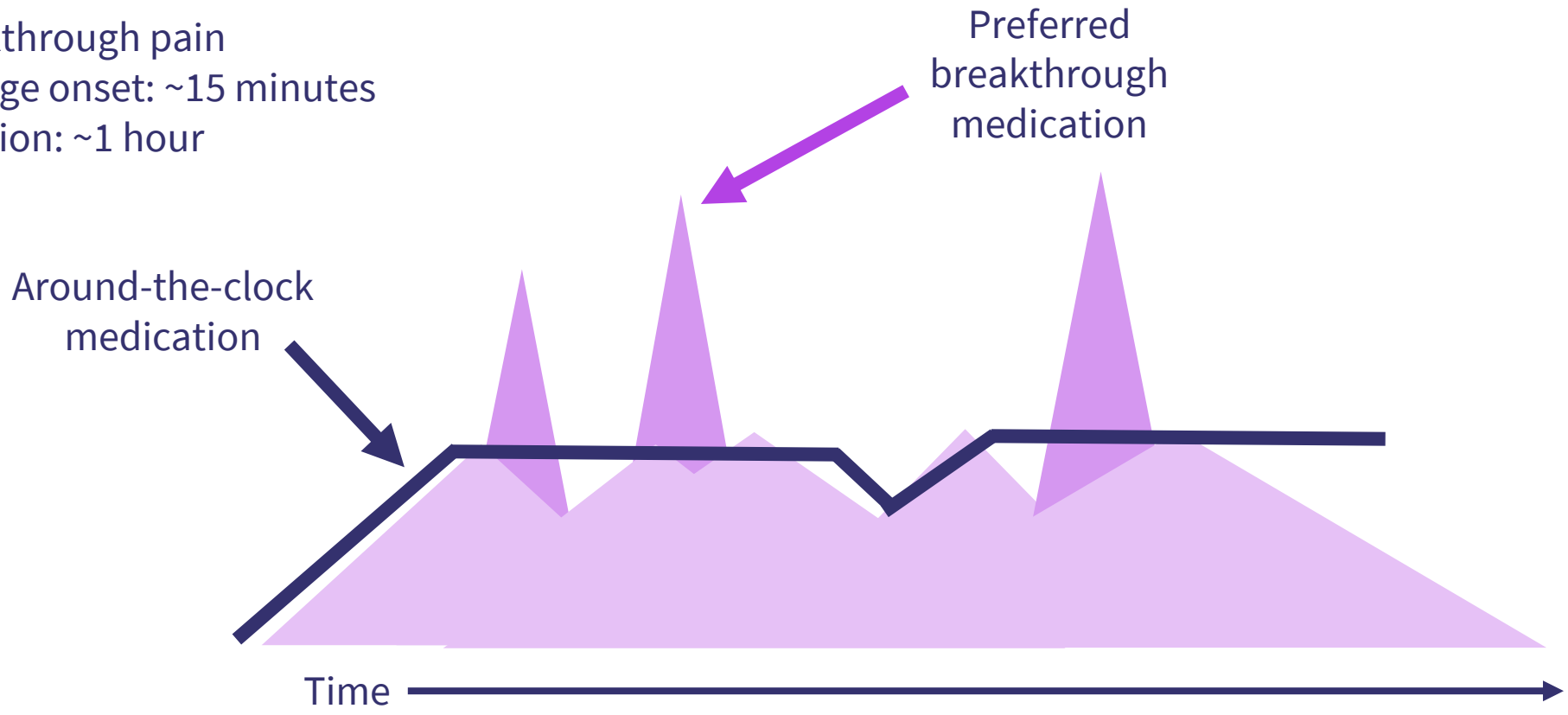
1. Bennet D, et al. *P T.* 2005;30(6):354-361. **2.** Texas Health and Human Services. Onset, peak and duration of common pain medications. https://www.hhs.texas.gov/sites/default/files/documents/doing-business-with-hhs/provider-portal/QMP/PainMedicationTable.pdf. Accessed Nov 8, 2022. **3.** Smith HS. *Ann Palliat Med.* 2012;1(1):42-52.

Rapid-onset opioids for breakthrough cancer pain

Breakthrough pain
Average onset: ~15 minutes
Duration: ~1 hour



Adapted from Alessandro Inno. Breakthrough pain: quale terapia medica? http://web2.sacrocuore.it/oncologia/Negrar_10_aprile_2019/Inno.pdf. Accessed Nov 3, 2022.

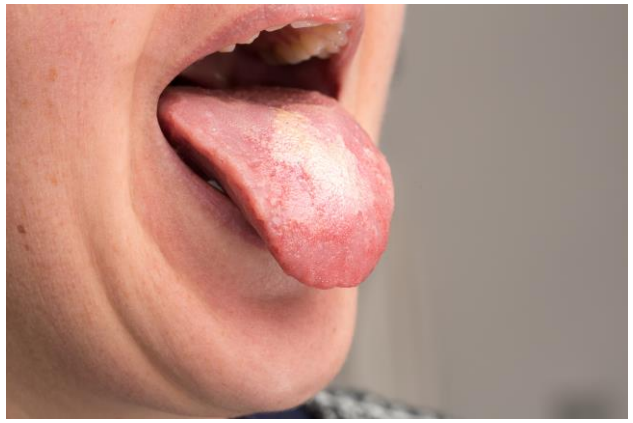
A question of time (minutes)[1–6]

	ANALGESIC ONSET (MIN)	AVAILABILITY (%)
Oral morphine	30–45	30
Oral oxycodone	30–45	40–50
Oral transmucosal fentanyl citrate	15–30	50
Fentanyl buccal tablets	15	65
Sublingual fentanyl	10–15	70
Fentanyl buccal soluble film	15	65
Intranasal fentanyl	5–10	80–90
Fentanyl pectin nasal spray	5–10	70

1. Smith H. *CNS Drugs.* 2012;26(6):509-535. **2.** Lötsch J, et al. *Clin Pharmacokinet.* 2013;52(1):23-36. **3.** Taylor DR. *Clin Pharmacol.* 2013;5:131-141. **4.** Stevens RA, Ghazi SM. *Cancer Control*. 2000;7(2):132-141.
5. Drewes AM, et al. *Br J Clin Pharmacol*. 2013;75(1):60-78. **6.** Flaminia Coluzzi. Personal communication, Nov 10, 2022.

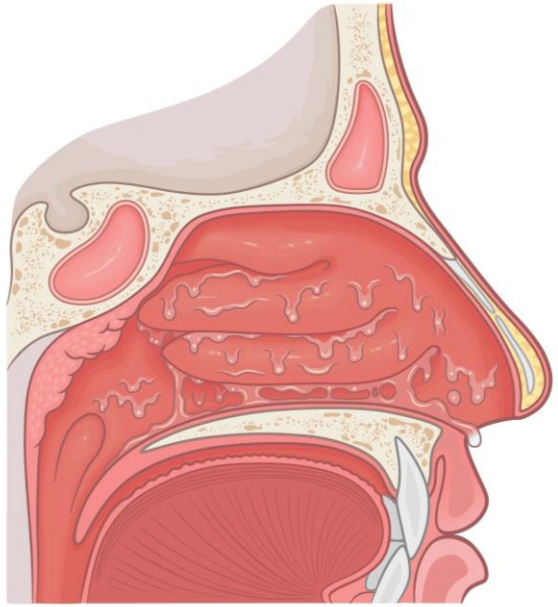
Rapid-onset opioids in special conditions

Oral transmucosal
Xerostomia
Nausea and vomiting
Oral mucositis
Impaired GI function



sruillk. Shutterstock.com.

Nasal
Nasal pathology
Vasoconstrictors for allergic rhinitis



Refluo. Shutterstock.com.

GI, gastrointestinal.

DON’T

PREFER TRADITIONAL OPIOIDS FOR NEUROPATHIC PAIN CONDITIONS

Neuropathic pain in patients with cancer

Cancer-related neuropathic pain

- Nerve infiltration
- Bone metastasis
- Nerve compression

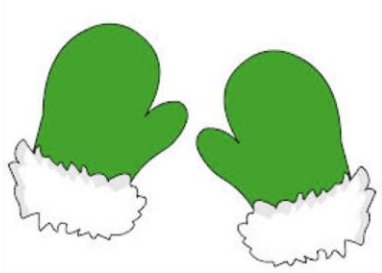
Cancer therapy-related neuropathic pain

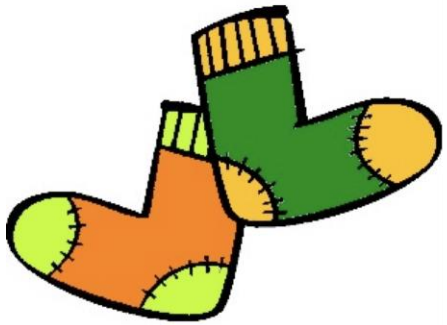
- Radiotherapy-induced neuropathic pain
- Chemotherapy-induced neuropathic pain
- Surgery

Yoon SY, Oh J. *Korean J Intern Med.* 2018;33(6):1058-1069.

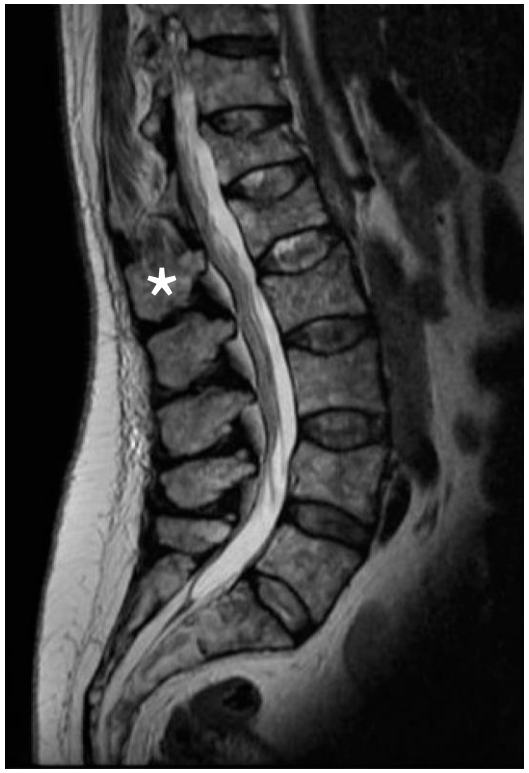
Neuropathic pain in multiple myeloma

Bortezomib



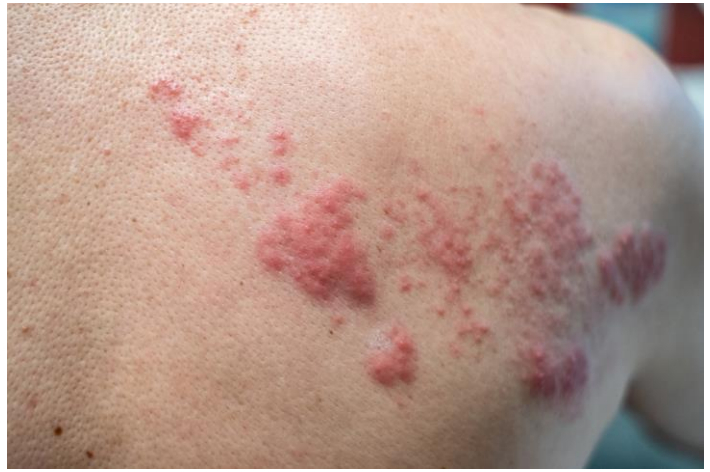


Myeloma bone disease



Rasch S, et al. *Cancers (Basel).* 2020;30;12(8):2113

Herpes zoster virus



Mumemories. Shutterstock.com

Pharmacotherapy of neuropathic pain

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis (Nanna B Finnerup, *et al.*)

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

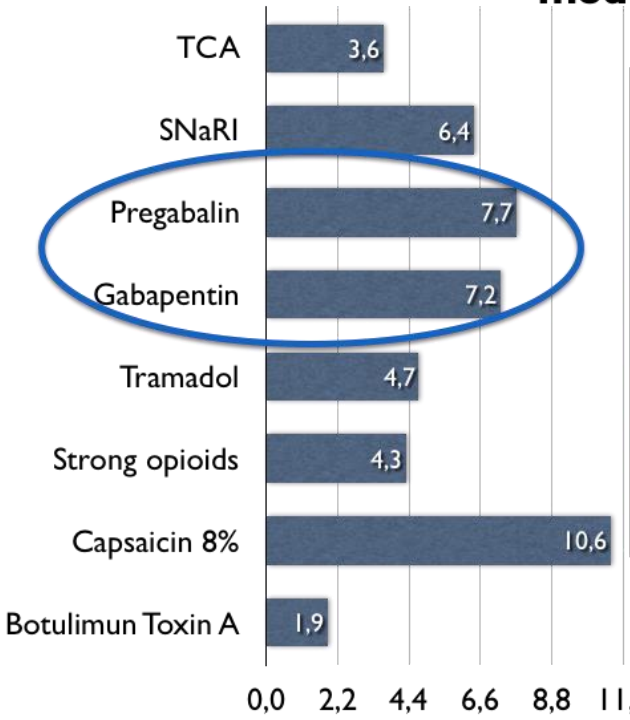
†TCAs generally have similar efficacy. Tertiary amine TCAs (amitriptyline, imipramine, clomipramine) are not recommended at dosages > 75 mg/day in older adults because of their major anticholinergic and sedative side effects and potential risk of falls. An increased risk of sudden cardiac death has been reported for doses >100 mg daily. ‡The long-term safety of repeated applications of high concentration capsaicin patches in patients has not been clearly established particularly with respect to degeneration of epidermal nerve fibres, which may be a concern in progressive neuropathy. §Sustained release oxycodone and morphine have been the most studied with maximal daily dosages of 120 mg and 240 mg, respectively, in clinical trials. Long-term opioid use may be associated with abuse particularly at high doses, cognitive impairment, and endocrine and immunologic changes.
Finnerup NB, et al. *Lancet Neurol.* 2015;14(2):162-173.

Pharmacotherapy of neuropathic pain

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis (Nanna B Finnerup, *et al.*)

NNT

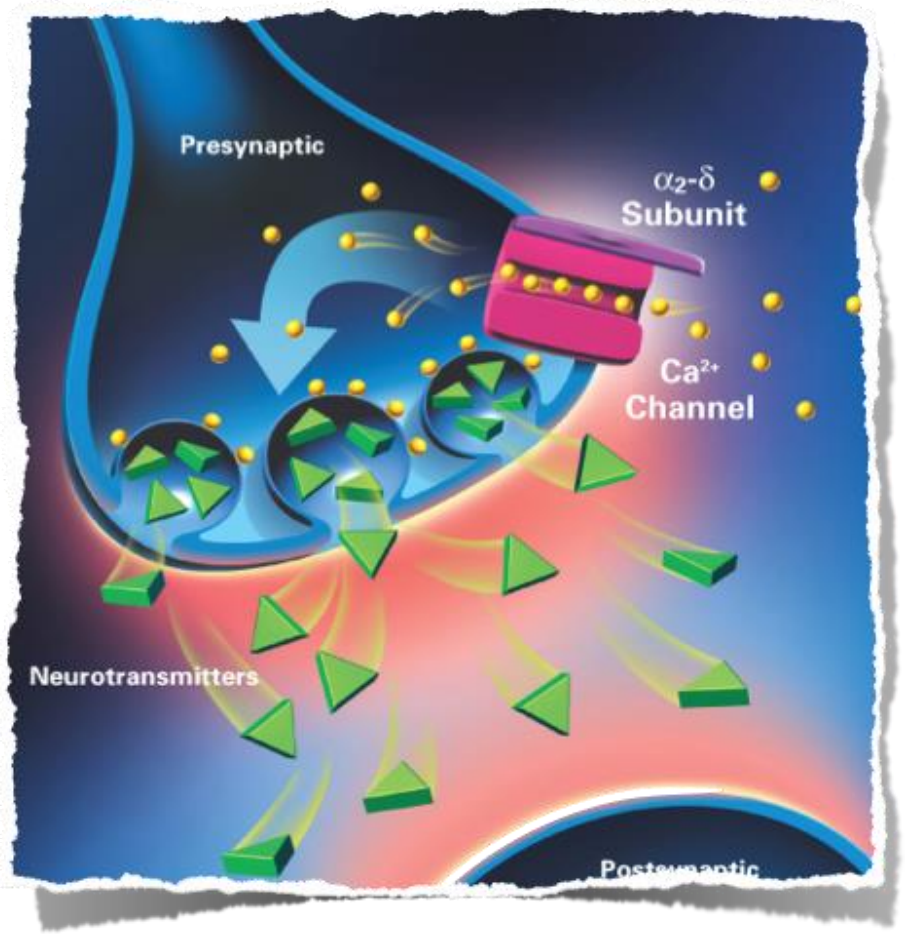
NNT for 50% pain relief range from about 4 to 10 for most positive trials; this emphasizes the **modest overall study outcomes** in NP

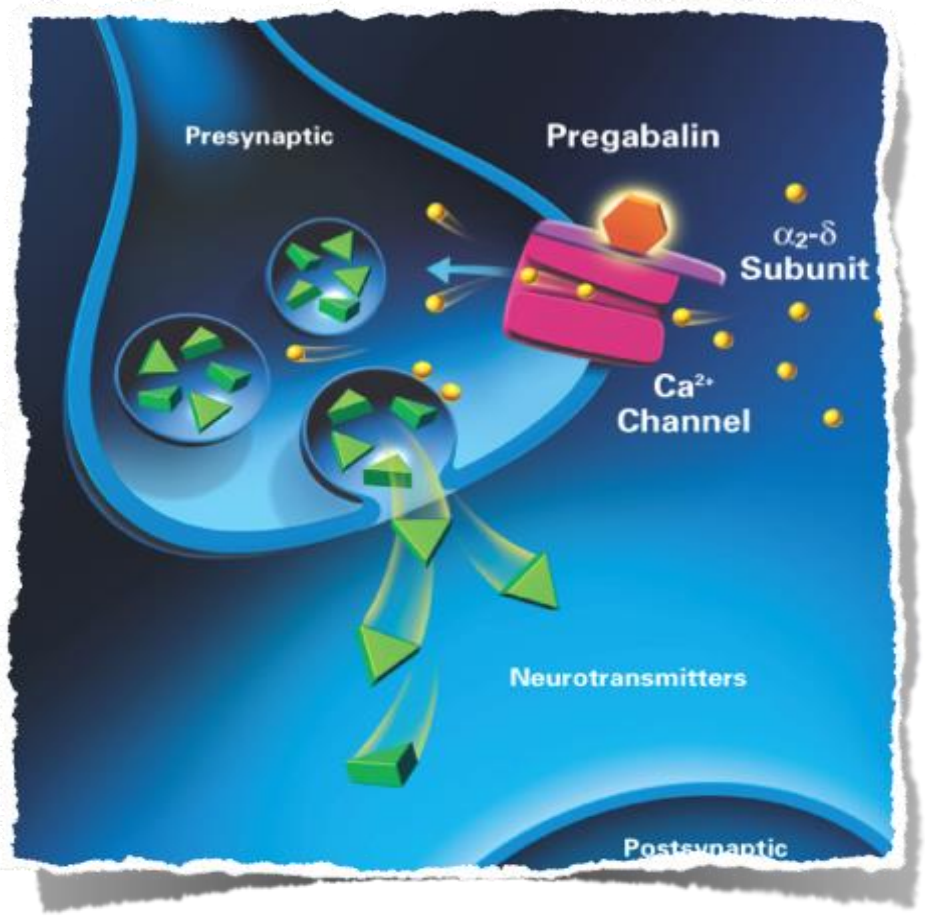


	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)	Susceptibility to bias‡
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)	1973
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)	1826
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)	2534
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)	1879
Tramadol	6	741	176/380	96/361	4·7 (3·6–6·7)	982
Strong opioids	7	838	211/426	108/412	4·3 (3·4–5·8)	1326
Capsaicin 8%	6	2073	466/1299	212/774	10·6 (7·4–18·8)	70¶
Botulinum toxin A	4	137	42/70	4/67	1·9 (1·5–2·4)	678

CI, confidence interval; NNT, number needed to treat; NP, neuropathic pain; SNaRI, selective serotonin–noradrenaline reuptake inhibitor; TCA, tricyclic antidepressants.
*Number of comparisons with placebo in included published trials and unpublished trials with results from registries are included if the report number of responders. †Total number of patients treated with active and placebo, patients count twice if cross-over study. ‡Number of patients in zero treatment effect trials that would make the NNT exceed 11, which is considered the cut-off for clinical relevance. §Including gabapentin ER and enacarbil. ¶Susceptible to publication bias, i.e., a new study with less than 400 participants with no effect could change the NNT to a level that is not clinically relevant.
Finnerup NB, et al. *Lancet Neurol.* 2015;14(2):162-173.

Gabapentinoids





van Rensburg R, Reuter H. *South African Family Practice.* 2019; 61(3):59-62.

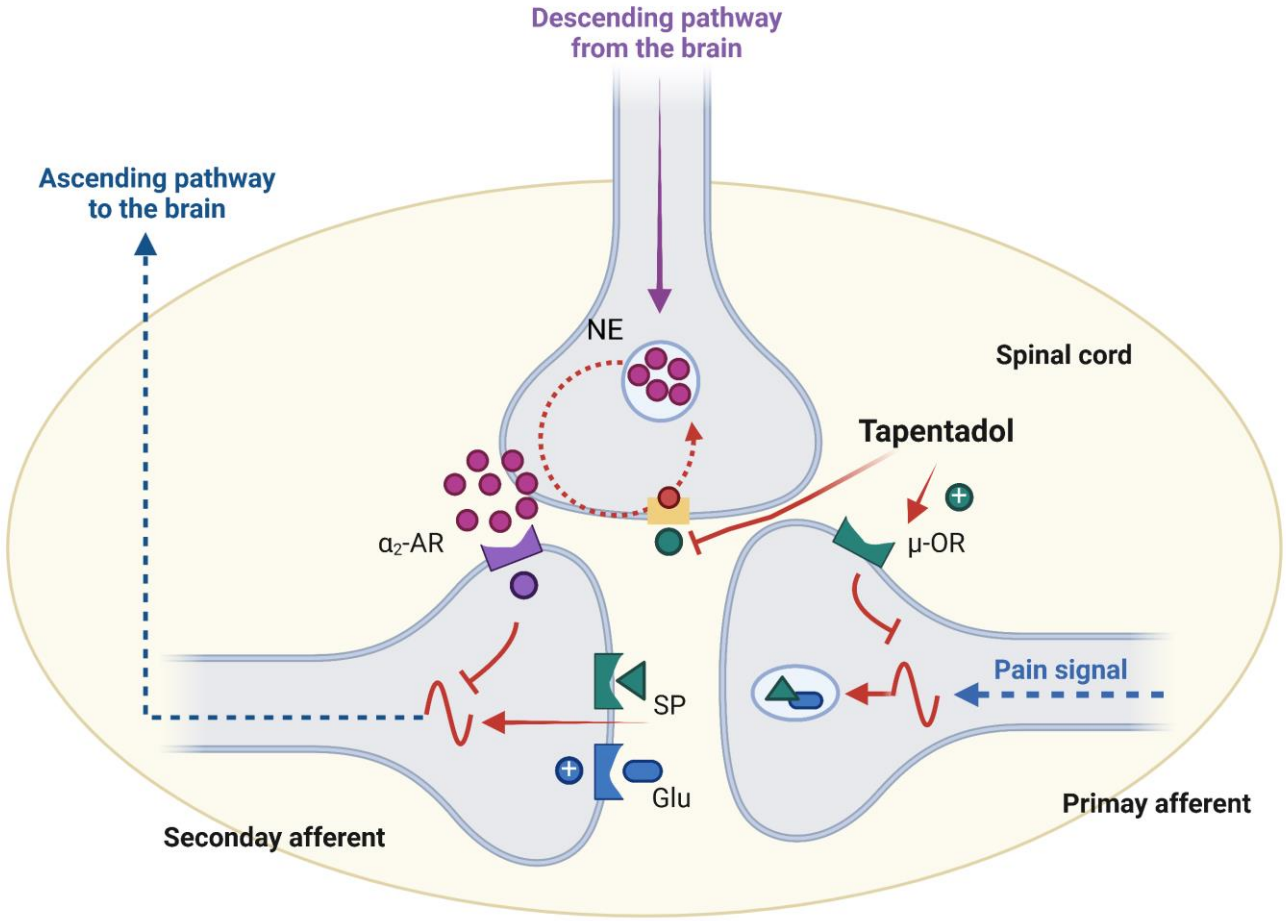
CPSP: Pharmacotherapy of neuropathic pain

- Strong opioids are now recommended as **third line**, contrasting with several previous recommendations in which they were generally thought of as first or second line.

- This stems mainly from the consideration of potential risk of abuse, particularly with high doses, and concerns about a recent increase in **prescription-opioid-associated overdose** mortality, diversion, misuse, and other opioid-related morbidity particularly in the USA, Canada, and the UK.

CPSP, chronic post-surgical pain.
Finnerup NB, et al. *Lancet Neurol.* 2015;14(2):162-173.

Tapentadol for mixed pain: **Atypical** opioid



Adapted from Seeking Alpha. A deep look at Depomed's billion-dollar bet on Nucynta. https://seekingalpha.com/article/3304835-a-deep-look-at-depomeds-billion-dollar-bet-on-Nucynta. Accessed Nov 3, 2022.
Created using BioRender.com.

α2-AR, α2-adrenergic receptor; μ-OR, μ-opioid receptor; Glu, glutamate; norepinephrine; SP, substance P.

The concept of μ-load

Adv Ther
https://doi.org/10.1007/s12325-018-0778-x

COMMENTARY

Does 'Strong Analgesic' Equal 'Strong Opioid'? Tapentadol and the Concept of 'μ-Load'

Robert B. Raffa · Christian Elling · Thomas M. Tzschentke

Table 1 Summary of the calculated estimates of the contribution of tapentadol's opioid component to its analgesic (antinociceptive) action

Pain type	Source of data	Estimate (%)
Nociceptive	Animal model: LITF-r (low-intensity tail-flick test, rat)	54
Neuropathic	Animal model: SNL-r (spinal nerve ligation test, rat)	36

54% **36%**

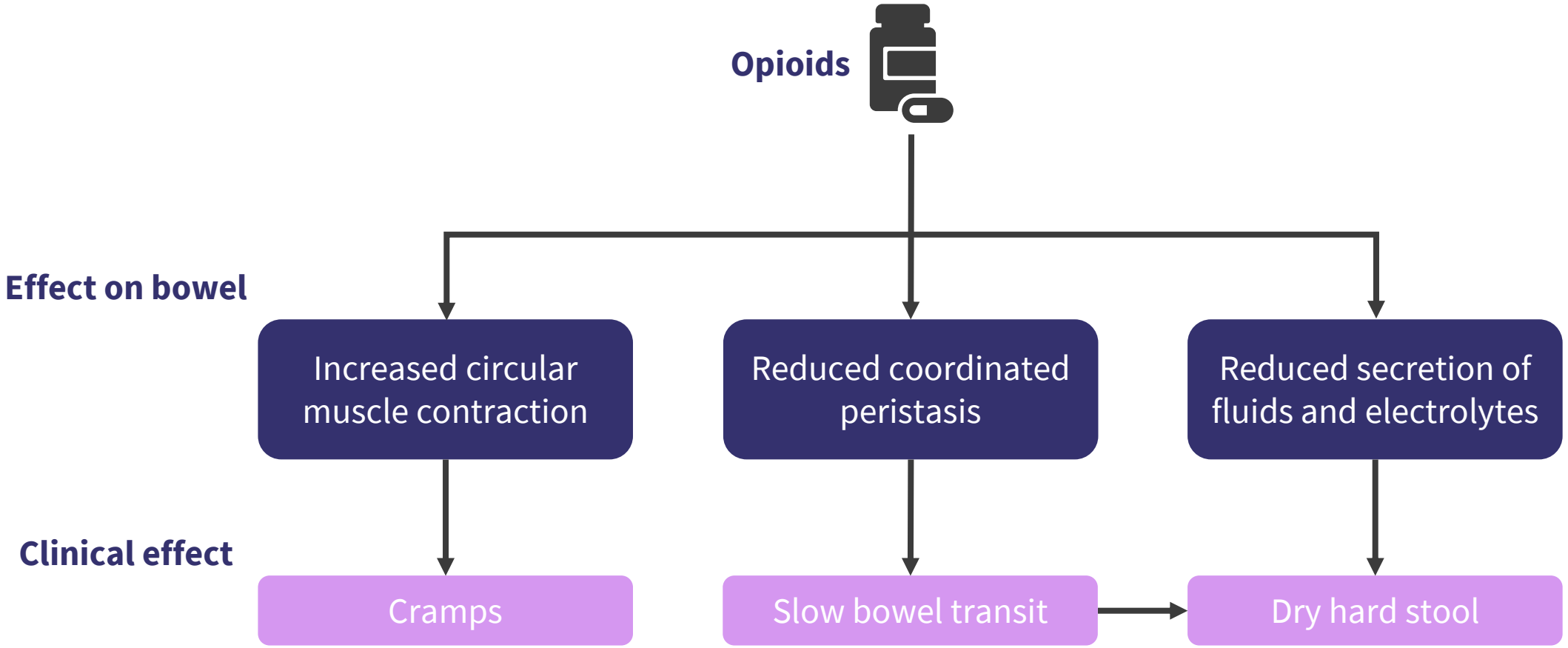
NEUROPATHIC

Raffa RB, et al. *Adv Ther.* 2018;35(10):1471-1484.

DON’T

FORGET OPIOID-INDUCED ADVERSE EVENTS

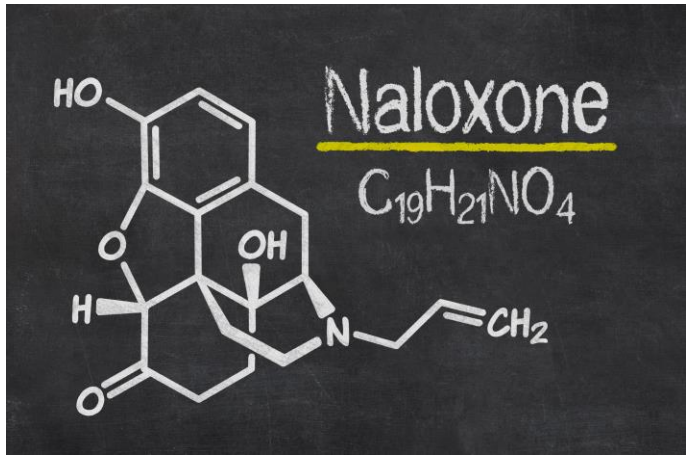
Opioid-induced constipation



Adapted from Boland JW, Boland EG. *BMJ*. 2017;358:j3313.

Oxycodone/naloxone

- Naloxone, when administered orally, has a very low systemic bioavailability of ~2% due to
- extensive first-pass hepatic metabolism.
- Naloxone exerts a local inhibitory effect, almost exclusively on opioid receptors in the GI tract.
- Co-administration of oral naloxone alongside oral opioids (oxycodone) improves bowel function without loss of analgesic effect.[1]



Zerbor. stock.adobe.com.

asnstudio. Shutterstock.com.

GI, gastrointestinal.

1.Meissner W, et al. *Eur J Pain.* 2009;13(1):56-64.

PAMORA

- **P** Peripherally
- **A** Acting
- **M** Mu
- **O** Opioid
- **R** Receptor
- **A** Antagonists

Peripheral opioid antagonists dislodge an opioid from the mu-opioid receptor in the gastrointestinal tract

PAMORA	Molecule	Route of administration	Standard dose in general population
Methylnaltrexone	Naltrexone derivative	Subcutaneous	8 mg (0.4 ml for body weight 38–61 kg) 12 mg (0.6 ml for body weight 62–114 kg)
Naloxegol	Naloxone PEGylated derivative	Oral	25 mg daily
Naldemedine	Naltrexone derivative	Oral	200 mcg daily

Data from NICE. British National Formulary (BNF). https://bnf.nice.org.uk/. Accessed Nov 10, 2022.

Pergolizzi JV, et al. *Drug Des Devel Ther.* 2020;14:1009-1025.

Naloxegol and P-glycoprotein

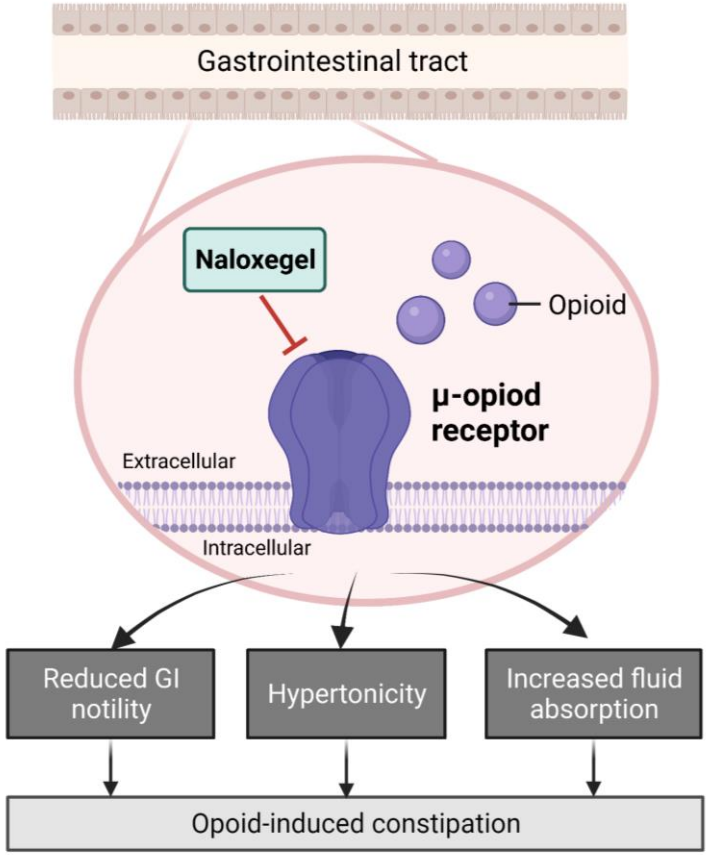
Naloxegol: polyethylene glycol derivative of naloxone

Pegylation:

- Confers oral bioavailability

Naloxegol is a substrate for the P-glycoprotein efflux transporter

Reduces transport across the blood–brain barrier



Adapted from New Drug Approvals.com. Naloxegol. https://newdrugapprovals.org/2016/08/25/naloxegol/. Accessed Nov 3, 2022.
Created with BioRender.com.

GI, gastrointestinal.

New Drug Approvals.com. Naloxegol. https://newdrugapprovals.org/2016/08/25/naloxegol/. Accessed Nov 3, 2022.

Naldemedine

Journal of Pain Research

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EXPERT OPINION

Naldemedine: A New Option for OIBD

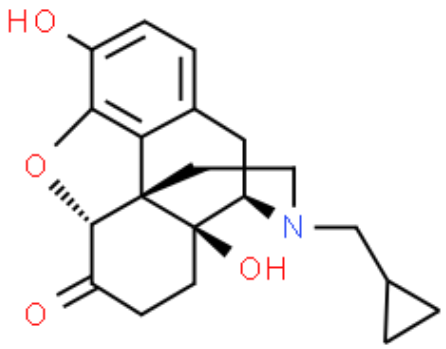
This article was published in the following Dove Press journal:
Journal of Pain Research

Flaminia Coluzzi[1]
Maria Sole Scerpa[1]
Joseph Pergolizzi[2]

[1]Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina Italy; [2]NEMA Research Inc., Naples, FL, USA

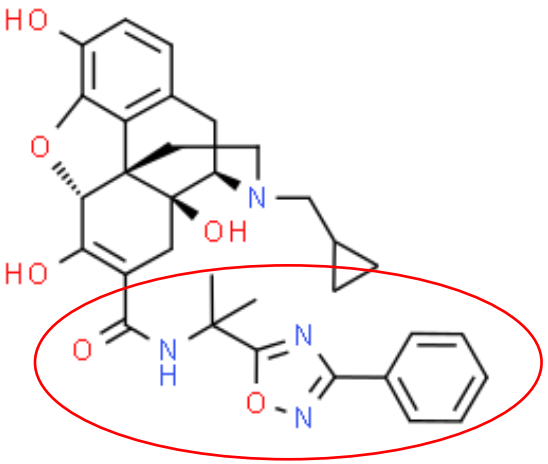
Coluzzi F, et al. *J Pain Res.* 2020;13:1209-1222.

Naltrexone



ChemSpider.com. Naltrexone. http://www.chemspider.com/Chemical-Structure.4514524.html. Accessed Nov 11, 2022.

Naldemedine



ChemSpider.com. Naldemedine. http://www.chemspider.com/Chemical-Structure.4514524.html. Accessed Nov 11, 2022.

OIBD, opioid-induced bowel dysfunction.
Coluzzi F, et al. *J Pain Res.* 2020;13:1209-1222.

Dreams…

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Thank you

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