Pain Mechanism Classification Clinical Pearl
Part 2: Nociceptive pain

Introduction

Chimenti et al.[1] divide the biological mechanisms of pain into three classes – nociceptive, neuropathic, and nociplastic – and state that they are the biological drivers of the varied pain presentations observed in the clinic. Nociceptive pain is defined as "pain that arises from actual or threatened damage to non-neural tissue."[2] This Clinical Pearl discusses nociceptive pain, a pain state driven by activation of the nociceptive pathway. Subtypes of nociceptive pain, clinical features for diagnosis, and strategies for treatment will all be discussed. This Clinical Pearl is part of a series on pain mechanisms. Future installments will discuss other components of the framework.

Subtypes of Nociceptive Pain and Their Stimuli

Three types of nociceptive pain have been proposed[3,4] and are named according to their underlying noxious stimulus – mechanical, inflammatory, and ischemic. The foundation of nociceptive mechanical pain is accordingly a noxious mechanical stimulus. For example, joint capsule stretch or bony impingement at intensities sufficient to cause tissue damage may underlie nociceptive mechanical pain. Nociceptive inflammatory or ischemic pain are different – they are chemically, rather than mechanically, mediated. Inflammatory mediators such as cytokines[5-7] or products of anaerobic metabolism such as hydrogen ions[8-10] are stimuli that underlie nociceptive inflammatory or ischemic pain, respectively. This is just a glimpse into the machinery of nociceptive processing. The author of this Clinical Pearl refers readers to work done by Sluka[11] and Cohen and Raja[12] for a more comprehensive review.

Diagnosis

To use the mechanism-based approach most effectively, it is important to recognize its limitations. The author of this Clinical Pearl encourages readers to review past discussion of those limitations.[1,3,4,7]

Nociceptive pain can be classified across several dimensions. Location is one such dimension. Nociceptive pain is typically well-localized,[1,4,7] and when referred, it is distributed in a manner consistent with non-neural tissue involvement.[3,12] In nociceptive pain, symptom onset is generally linked to a noxious mechanical stimulus[7] and symptoms correspond to the timing and magnitude of that stimulus.[4,13]

Nociceptive pain is often described as “sharp” and “intermittent” or “dull” and “aching.”[3,14-16] A background ache may reflect nociceptive inflammatory pain with subsequent sensitization of nociceptors.[13] Symptom descriptors can help one distinguish from competing diagnoses such as neuropathic pain, in which symptoms are often described as “burning,” “electric shock-like,” and “shooting.”[3,12]

Nociceptive pain should be clearly linked to aggravating and alleviating factors.[3,4,13] Alleviating factors include rest and removal of load from the involved tissue.[3,13] Aggravating factors include activity, movement, or postures sufficiently noxious to activate nociceptors.[3,12,13] Nociceptive inflammatory pain may be aggravated by any of these factors, however provocation may occur at a lower stimulus intensity.[13] Anti-inflammatory agents can be particularly effective in alleviating nociceptive inflammatory pain,[4,12,13] and inflammatory pain should improve as inflammation subsides.[17] Tissue ischemia, particularly that which develops as a result of sustained postures, may produce nociceptive ischemic pain.[8]

Limited evidence exists to explain the 24-hour pain patterns associated with each type of nociceptive pain. However, several authors do suggest that morning pain and stiffness are associated with nociceptive inflammatory pain, particularly when these symptoms persist for greater than 30 minutes.[13,18,19]

Clinical signs should reflect nociceptive symptoms. Observation is the first step in examination in which one can correlate signs with symptoms. Though postural dysfunction is not specific to any one nociceptive subtype, it may offer insight into the positional drivers of nociceptive ischemic pain. Observably antalgic gait may result from nociceptive mechanical knee pain. It is correlating observations like these with subjective and other objective data that helps implicate suspected pain mechanisms. In the case of nociceptive inflammatory pain, signs of inflammation – swelling, redness, heat – may also be observable.[4,7] Nociceptive pain symptoms should be localized to the area of actual or potential tissue injury or referred in a pattern consistent with such injury.[1,3,4,7,12] Symptoms present in a dermatomal pattern may reflect neuropathic pain.[3] If negative, the straight leg raise test can rule-down neuropathic pain,[20] especially when pinprick sensation is intact.[21] Generalized or vague symptoms may represent altered pain processing[1] and further investigation is required.

In nociceptive pain, there should be clear stimulus-response relationships during examination.[4] For example, if a patient with low back pain reports that forward bending aggravates his symptoms, one would expect to see that lumbar flexion reproduces such symptoms in an appropriate distribution at an appropriate intensity. One would also expect a consistent stimulus-response relationship with palpation and joint play – patients with nociceptive pain should respond to the applied force in a manner consistent with that force’s intensity and duration.[3,4,15]

Basic examination skills such as resisted isometric movement testing (e.g., manual muscle testing) should also assist with pain differential diagnosis. Pain with resisted isometric movement testing may implicate contractile tissue or its associated structures, which can generators of nociceptive pain.[22] To further implicate nociceptive pain, weakness (if present) with such testing should present in a non-myotomal pattern.[22]

Treatment

Despite a new emphasis on identifying – and subsequently treating – a single process driving a patient's presentation, physical therapy interventions influence multiple processes.[1,11] Many manual therapy techniques are available to influence many pain pathways. Massage techniques may address nociceptive pain by improving descending inhibition, a function that attenuates the flow of incoming nociceptive signals.[11] Neurotransmitters such as oxytocin and serotonin have been implicated in the mechanisms of massage.[11,23] Massage also influences expression of inflammatory mediators and may therefore be particularly effective for patients with nociceptive inflammatory pain.[11,24]

Joint mobilization and manipulation can be particularly powerful tools in addressing pain processing – both local and widespread changes in pain processing following mobilization or manipulation have been documented.[25-31] For example, joint mobilization in individuals with knee osteoarthritis was shown to improve pressure pain thresholds at the affected knee, unaffected knee, and the hand.[27] In another example, both manipulation of the spine *and* the upper extremity conferred benefits for those with lateral epicondylalgia.[32] Spinal manipulation may also be useful for those with pain generated by muscle spasm and driven by tissue ischemia (i.e., nociceptive ischemic processes) – evidence suggests that manipulation reduces electromyography activity of the paraspinal muscles.[33]

Like manual therapy, exercise is a pillar of physical therapy practice and essential in addressing nociceptive pain. Strengthening, in addition to neuromuscular re-education, can improve movement and tissue loading in a variety of clinical populations.[34-40] This may subsequently attenuate or eliminate noxious peripheral stimuli. Promoting movement variability may be particularly important for those with nociceptive mechanical pain.

Besides restoring movement, exercise can also upregulate the body's own pain management system and promote exercise-induced hypoalgesia.[11] Both opioidergic and nonopioidergic pathways have been implicated in the positive effects of exercise on pain processing.[41-43] Interestingly, even low-intensity exercise like passive or active movement can improve symptoms in those with nociceptive inflammatory pain.[13] Researchers propose that these symptoms improve, in part, as a result of decreased pressure from swelling.[13] Exercise also influences the inflammatory pathway by promoting anti-inflammatory cytokines.[44-46]

In treating nociceptive ischemic pain, the primary intent is to decrease tissue ischemia and increase perfusion. Exercise is accordingly a primary intervention because it increases blood flow.[8,12] One recent meta-analysis of exercise for patients with intermittent claudication found that exercise improves pain-free walking distance and maximum walking distance.[47]

A more indirect – but important – strategy for addressing ischemic pain is education. Patients should be counseled on co-morbidities (e.g., of diabetes), smoking cessation, and exercise.[8] Such counseling may serve to influence the physiological environment in which nociceptive processing occurs. Patient education for other forms of nociceptive pain may focus on active (versus passive) treatment, optimal training load, weight management, and the biopsychosocial nature of pain itself.[48,49]

Clinical Pearls

Nociceptive pain is defined as “pain that arises from actual or threatened damage to non-neural tissue.”[2] Three types of nociceptive pain have been proposed.[3,4] They are named according to their underlying noxious stimuli – mechanical, inflammatory, and ischemic.

Key features of nociceptive pain include: 1) result of a noxious stimulus or noxious stimuli, 2) localized symptoms, 3) symptoms correspond to suspected underlying pathology 4) described as “sharp” and “intermittent” or “dull” and “aching,” 5) aggravated by activity, movement, or posture, 6) alleviated by rest or removal of abnormal loads, and 7) clear stimulus-response relationship during clinical examination.[1,3,4,7,12-16]

Nociceptive mechanical pain, a product of noxious mechanical stimuli, may exhibit any of the above clinical features. Nociceptive inflammatory pain may present with additional features, such as swelling, redness, and heat.[4,7] Nociceptive ischemic pain may notably be aggravated with sustained postures[4] or occur in the presence of specific medical comorbidities.[8] It may respond best to strategies that improve tissue perfusion (e.g., exercise).[47]

Manual therapy, exercise, and education are three pillars of physical therapy care and can address each of the of the nociceptive pain subtypes. Manual therapy, exercise, and education are effective via many pain pathways.[1,11]

Summary

A mechanism-based approach provides a framework for diagnosis and treatment of painful conditions. The framework is grounded in the concept that certain pathobiologic mechanisms can initiate and maintain pain. One pathobiologic mechanism of pain is nociceptive. This mechanism is subdivided into mechanical, inflammatory, and ischemic classes. Despite overlap in signs and symptoms, these three classes may present with distinct features and respond to treatment in their own distinct ways.

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References

1. Chimenti RL, Frey-Law LA, Sluka KA. A Mechanism-Based Approach to Physical Therapist Management of Pain. Phys Ther 2018;98(5):302-314. (In eng). DOI: 10.1093/ptj/pzy030.
2. (IASP) IAftSoP. Terminology. (https://www.iasp-pain.org/resources/terminology/).
3. Shraim MA, Massé-Alarie H, Hall LM, Hodges PW. Systematic Review and Synthesis of Mechanism-based Classification Systems for Pain Experienced in the Musculoskeletal System. Clin J Pain 2020;36(10):793-812. (In eng). DOI: 10.1097/ajp.0000000000000860.
4. Smart KM, Blake C, Staines A, Doody C. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Man Ther 2010;15(1):80-7. (In eng). DOI: 10.1016/j.math.2009.07.005.
5. Woolf CJ, Decosterd I. Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. Pain 1999;Suppl 6:S141-s147. (In eng). DOI: 10.1016/s0304-3959(99)00148-7.
6. Goode AP, Carey TS, Jordan JM. Low back pain and lumbar spine osteoarthritis: how are they related? Curr Rheumatol Rep 2013;15(2):305. (In eng). DOI: 10.1007/s11926-012-0305-z.
7. Vardeh D, Mannion RJ, Woolf CJ. Toward a Mechanism-Based Approach to Pain Diagnosis. J Pain 2016;17(9 Suppl):T50-69. (In eng). DOI: 10.1016/j.jpain.2016.03.001.
8. Romanelli MR, Thayer JA, Neumeister MW. Ischemic Pain. Clin Plast Surg 2020;47(2):261-265. (In eng). DOI: 10.1016/j.cps.2019.11.002.
9. Issberner U, Reeh PW, Steen KH. Pain due to tissue acidosis: a mechanism for inflammatory and ischemic myalgia? Neurosci Lett 1996;208(3):191-4. (In eng). DOI: 10.1016/0304-3940(96)12576-3.
10. Waldmann R, Champigny G, Bassilana F, Heurteaux C, Lazdunski M. A proton-gated cation channel involved in acid-sensing. Nature 1997;386(6621):173-7. (In eng). DOI: 10.1038/386173a0.
11. Sluka KA. Mechanisms and Management of Pain for the Physical Therapist. 2 ed: IASP Press, 2016.
12. Cohen S, Raja S. Pain. Goldman-Cecil Medicine. 26 ed. Philadelphia, PA: Elsevier; 2020:128-137.
13. Gifford LS, Butler DS. The integration of pain sciences into clinical practice. J Hand Ther 1997;10(2):86-95. (In eng). DOI: 10.1016/s0894-1130(97)80063-4.
14. Vrooman B, Youngren K. Chronic Pain Management. Morgan & Mikhail's Clinical Anesthesiology. 7 ed: McGraw Hill; 2022.
15. Förster M, Mahn F, Gockel U, et al. Axial low back pain: one painful area--many perceptions and mechanisms. PLoS One 2013;8(7):e68273. (In eng). DOI: 10.1371/journal.pone.0068273.
16. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet 1997;350(9072):178-81. (In eng). DOI: 10.1016/s0140-6736(97)02135-1.
17. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140(6):441-51. (In eng). DOI: 10.7326/0003-4819-140-8-200404200-00010.

18. Chauhan K, Jandu JS, Goyal A, Al-Dhahir MA. Rheumatoid Arthritis. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2022, StatPearls Publishing LLC.; 2022.
19. Wenker KJ, Quint JM. Ankylosing Spondylitis. StatPearls. Treasure Island (FL): StatPearls Publishing
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20. Camino Willhuber GO, Piuzzi NS. Straight Leg Raise Test. StatPearls. Treasure Island (FL): StatPearls Publishing
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21. Scholz J, Mannion RJ, Hord DE, et al. A novel tool for the assessment of pain: validation in low back pain. PLoS Med 2009;6(4):e1000047. (In eng). DOI: 10.1371/journal.pmed.1000047.
22. Magee D. Orthopedic Physical Assessment. 6 ed. St. Louis, MO: Saunders, 2014.
23. Agren G, Lundeberg T, Uvnäs-Moberg K, Sato A. The oxytocin antagonist 1-deamino-2-D-Tyr-(Oet)-4-Thr-8-Orn-oxytocin reverses the increase in the withdrawal response latency to thermal, but not mechanical nociceptive stimuli following oxytocin administration or massage-like stroking in rats. Neurosci Lett 1995;187(1):49-52. (In eng). DOI: 10.1016/0304-3940(95)11335-t.
24. Crane JD, Ogborn DI, Cupido C, et al. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. Sci Transl Med 2012;4(119):119ra13. (In eng). DOI: 10.1126/scitranslmed.3002882.
25. Moss P, Sluka K, Wright A. The initial effects of knee joint mobilization on osteoarthritic hyperalgesia. Man Ther 2007;12(2):109-18. (In eng). DOI: 10.1016/j.math.2006.02.009.
26. Martins DF, Bobinski F, Mazzardo-Martins L, et al. Ankle joint mobilization decreases hypersensitivity by activation of peripheral opioid receptors in a mouse model of postoperative pain. Pain Med 2012;13(8):1049-58. (In eng). DOI: 10.1111/j.1526-4637.2012.01438.x.
27. Courtney CA, Steffen AD, Fernández-de-Las-Peñas C, Kim J, Chmell SJ. Joint Mobilization Enhances Mechanisms of Conditioned Pain Modulation in Individuals With Osteoarthritis of the Knee. J Orthop Sports Phys Ther 2016;46(3):168-76. (In eng). DOI: 10.2519/jospt.2016.6259.
28. Bialosky JE, Bishop MD, Robinson ME, Barabas JA, George SZ. The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. BMC Musculoskelet Disord 2008;9:19. (In eng). DOI: 10.1186/1471-2474-9-19.
29. Bulbulian R, Burke J, Dishman JD. Spinal reflex excitability changes after lumbar spine passive flexion mobilization. J Manipulative Physiol Ther 2002;25(8):526-32. (In eng). DOI: 10.1067/mmt.2002.127073.
30. Dishman JD, Bulbulian R. Spinal reflex attenuation associated with spinal manipulation. Spine (Phila Pa 1976) 2000;25(19):2519-24;discussion 2525. (In eng). DOI: 10.1097/00007632-200010010-00015.
31. George SZ, Bishop MD, Bialosky JE, Zeppieri G, Jr., Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. BMC Musculoskelet Disord 2006;7:68. (In eng). DOI: 10.1186/1471-2474-7-68.

32. Vicenzino B, Cleland JA, Bisset L. Joint manipulation in the management of lateral epicondylalgia: a clinical commentary. J Man Manip Ther 2007;15(1):50-6. (In eng). DOI: 10.1179/106698107791090132.
33. Pickar JG. Neurophysiological effects of spinal manipulation. Spine J 2002;2(5):357-71. (In eng). DOI: 10.1016/s1529-9430(02)00400-x.
34. Davis HC, Luc-Harkey BA, Seeley MK, Troy Blackburn J, Pietrosimone B. Sagittal plane walking biomechanics in individuals with knee osteoarthritis after quadriceps strengthening. Osteoarthritis Cartilage 2019;27(5):771-780. (In eng). DOI: 10.1016/j.joca.2018.12.026.
35. Ferber R, Kendall KD, Farr L. Changes in knee biomechanics after a hip-abductor strengthening protocol for runners with patellofemoral pain syndrome. J Athl Train 2011;46(2):142-9. (In eng). DOI: 10.4085/1062-6050-46.2.142.
36. Turgut E, Duzgun I, Baltaci G. Effects of Scapular Stabilization Exercise Training on Scapular Kinematics, Disability, and Pain in Subacromial Impingement: A Randomized Controlled Trial. Arch Phys Med Rehabil 2017;98(10):1915-1923.e3. (In eng). DOI: 10.1016/j.apmr.2017.05.023.
37. Saad MC, Vasconcelos RA, Mancinelli LVO, Munno MSB, Liporaci RF, Grossi DB. Is hip strengthening the best treatment option for females with patellofemoral pain? A randomized controlled trial of three different types of exercises. Braz J Phys Ther 2018;22(5):408-416. (In eng). DOI: 10.1016/j.bjpt.2018.03.009.
38. Park SH, Lee MM. Effects of Lower Trapezius Strengthening Exercises on Pain, Dysfunction, Posture Alignment, Muscle Thickness and Contraction Rate in Patients with Neck Pain; Randomized Controlled Trial. Med Sci Monit 2020;26:e920208. (In eng). DOI: 10.12659/msm.920208.
39. Okamura K, Fukuda K, Oki S, Ono T, Tanaka S, Kanai S. Effects of plantar intrinsic foot muscle strengthening exercise on static and dynamic foot kinematics: A pilot randomized controlled single-blind trial in individuals with pes planus. Gait Posture 2020;75:40-45. (In eng). DOI: 10.1016/j.gaitpost.2019.09.030.
40. Nitayarak H, Charntaraviroj P. Effects of scapular stabilization exercises on posture and muscle imbalances in women with upper crossed syndrome: A randomized controlled trial. J Back Musculoskelet Rehabil 2021;34(6):1031-1040. (In eng). DOI: 10.3233/bmr-200088.
41. Li G, Rhodes JS, Girard I, Gammie SC, Garland T, Jr. Opioid-mediated pain sensitivity in mice bred for high voluntary wheel running. Physiol Behav 2004;83(3):515-24. (In eng). DOI: 10.1016/j.physbeh.2004.09.003.
42. Mazzardo-Martins L, Martins DF, Marcon R, et al. High-intensity extended swimming exercise reduces pain-related behavior in mice: involvement of endogenous opioids and the serotonergic system. J Pain 2010;11(12):1384-93. (In eng). DOI: 10.1016/j.jpain.2010.03.015.
43. Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C. Mechanisms of exercise-induced hypoalgesia. J Pain 2014;15(12):1294-1304. (In eng). DOI: 10.1016/j.jpain.2014.09.006.
44. Bobinski F, Teixeira JM, Sluka KA, Santos ARS. Interleukin-4 mediates the analgesia produced by low-intensity exercise in mice with neuropathic pain. Pain 2018;159(3):437-450. (In eng). DOI: 10.1097/j.pain.0000000000001109.
45. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985) 2005;98(4):1154-62. (In eng). DOI: 10.1152/japplphysiol.00164.2004.

46. Ortega E, Bote ME, Giraldo E, García JJ. Aquatic exercise improves the monocyte pro- and anti-inflammatory cytokine production balance in fibromyalgia patients. Scand J Med Sci Sports 2012;22(1):104-12. (In eng). DOI: 10.1111/j.1600-0838.2010.01132.x.
47. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev 2017;12(12):Cd000990. (In eng). DOI: 10.1002/14651858.CD000990.pub4.
48. George SZ, Fritz JM, Silfies SP, et al. Interventions for the Management of Acute and Chronic Low Back Pain: Revision 2021. J Orthop Sports Phys Ther 2021;51(11):Cpg1-cpg60. (In eng). DOI: 10.2519/jospt.2021.0304.
49. Willy RW, Hoglund LT, Barton CJ, et al. Patellofemoral Pain. J Orthop Sports Phys Ther 2019;49(9):Cpg1-cpg95. (In eng). DOI: 10.2519/jospt.2019.0302.