International Guidelines for Pain Treatment

Subjects: Neurosciences

Contributor: Gianmarco Marcianò, Cristina Vocca, Maurizio Evangelista, Caterina Palleria, Lucia Muraca, Cecilia Galati, Francesco Monea, Liberata Sportiello, Giovambattista De Sarro, Annalisa Capuano, Luca Gallelli

The International Association for the Study of Pain (IASP) describes chronic pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Chronic pain lasting for at least 3 months may impair the social, psychological, and physical sphere of a subject, leading to serious impairment of both their autonomy and mood.

Keywords: nociceptive pain ; neuropathic pain ; nociplastic pain ; drug treatment

1. Introduction

The International Association for the Study of Pain (IASP) describes chronic pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. Chronic pain lasting for at least 3 months may impair the social, psychological, and physical sphere of a subject, leading to serious impairment of both their autonomy and mood [2]. Social factors (e.g., job, lifestyle, and economic and religious status), self-perception, mood alterations, and physical illness are risk factors for chronic pain [3]. According to IASP recommendations, chronic pain is classified as nociceptive (involving tissue or potential tissue damage), neuropathic (involving disease or injury affecting the nervous system), and nociplastic (with no evidence of tissue or nerve damage but persistent overregulation of the nociceptive system) [3][4].

Concerning the types (mechanisms) of pain, the choices of drugs for chronic pain include non-steroidal anti-inflammatory drugs (NSAIDs) (for cyclic short-course treatment), opioids, and central nervous system (CNS)-acting drugs.

2. International Guidelines

The first guidelines for pain treatment are presented in the World Health Organization (WHO) guidelines that, published in 1986, do not separate between both types (acute or chronic) and the different mechanisms (nociceptive, neuropathic, or nociplastic) of pain and suggest a 3-step treatment: NSAIDs (acetaminophen and other NSAIDs; Step I), weak opioids (5 mg of codeine, tramadol, and oxycodone; Step II), or strong opioids (Step III) [5].

Other international guidelines separate the types of pain, and in the presence of chronic pain, suggest a multimodal step-by-step approach, also considering the mechanisms of the pain.

The Centers for Disease Control and Prevention (CDC) guidelines report that chronic pain should primarily be managed with non-opioid drugs [6]. When utilized for pain management, opioids should be started at the lowest effective dosage and titrated slowly [6] (**Table 1**).

Table 1. International guidelines for chronic pain. SIGN: Scottish Intercollegiate Guidelines Network; CDW: Colorado Division of Workers; AGS: American Geriatric Society; COX: cyclooxygenase; DHHS: Department of Health and Human Services; NeuPSIG: Neuropathic Pain Special Interest Group; NICE: National Institute for Health and Care Excellence; NMDA: N-methyl-D-aspartate; NSAIDs: non-steroidal anti-inflammatory drugs; OTC: over the counter; SNRI: noradrenaline–serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

	STEP I	STEP II	STEP III	STEP IV	STEP V	STEP VI
			Nociceptive pain			
SIGN [7]	**Paracetamol or NSAIDs**	**Weak opioids or topical NSAIDs**	**Strong opioids**			

	STEP I	STEP II	STEP III	STEP IV	STEP V	STEP VI
CDW [8]	NSAIDs or COX-2 inhibitors					
AGS [9]	Paracetamol (up to 4 g/day)	NSAIDs	Opioids			
DHHS [10]	Ia: paracetamol Ib: ibuprofen or naproxen Ic: paracetamol plus ibuprofen or naproxen	IIa: codeine IIb: tramadol	IIIa: low-dose morphine or buprenorphine patch (if morphine is ineffective) IIIb: high-dose morphine or 5–30 mg of oxycodone twice a day or fentanyl/buprenorphine patch if morphine is ineffective IIIc: 50 mg of tapentadol twice daily			
ESCEO [11]	Chondroitin sulfate or glucosamine sulfate	Paracetamol or topical NSAIDs	NSAIDs	Intra-articular injection of hyaluronic acid or corticosteroids	Duloxetine	Surgery
			Neuropathic pain			
SIGN [7]	Amitriptyline or gabapentin	Pregabalin	SNRIs	5% lidocaine	Opioids	9% capsaicin
CDW [8]	Tricyclic antidepressants	Gabapentin/pregabalin or SNRIs (duloxetine)	Other anticonvulsants	Low-dose opioids		
AGS [9]	Duloxetine or pregabalin					
DHHS [10]	Amitriptyline/imipramine	Gabapentin (1st line) or pregabalin (2nd line) or 0.075% capsaicin cream	Duloxetine or lidocaine plasters (5%-700 mg/plaster) or capsaicin patch (8%-179 mg/plaster)			
Practice [12]	Duloxetine or TCA	Lidocaine or ketamine				
NICE [2].	Antidepressants	Gabapentin or pregabalin				
NeuPSIG [13]	TCA, SNRI, or gabapentin/pregabalin	Tramadol, lidocaine, and capsaicin patches	Opioids or botulin toxin-A			

2.1. Neuropathic and Nociceptive Chronic Pain Treatment

The Scottish Intercollegiate Guidelines Network (SIGN) guidelines [7] suggest a seven-step treatment (**Table 1**) from history (Step I) to drug treatment (Step IV). To improve drug safety, researchers were invited to evaluate the mechanism of the pain (nociceptive and/or neuropathic pain) and the comorbidity. Step VII suggests an accurate follow-up for exacerbation management [7].

The American Pain Society suggests a multi-modal approach without a differentiation concerning the mechanisms of pain [14]. The authors suggest that opioids (mainly taken via the oral route and with caution in opioid-naïve patients), gabapentin and pregabalin, NSAIDs, and paracetamol are possible options [14].

The Colorado Division of Workers Compensation guidelines [8] suggest a drug reconciliation to avoid interaction or prescription errors. In patients with nociceptive pain, the authors suggest a cyclic treatment with NSAIDs for up to 7 days with non-selective NSAIDs and up to 10 days with COX-2 inhibitors. In patients with neuropathic pain, the authors suggest a four-step process (**Table 1**), supporting the combination of two drugs from different categories to reduce dosage and side effects (e.g., duloxetine plus pregabalin).

Concerning opioids, no evidence of the superiority of one opioid compared with other drugs has been reported. Long-acting opioids have been found to not be superior to short-acting opioids. Among these compounds, oxycodone seems to be the most abused drug.

Buprenorphine has similar efficacy in comparison with tramadol in patients with moderate–severe musculoskeletal pain and with fentanyl (regarding analgesia and sleep quality) for severe pain.

Muscle relaxants are not suggested for patients with chronic pain due to the habit-forming risk, respiratory depression, and seizure occurrence after sudden withdrawal.

Topical agents including 8% capsaicin (for postherpetic neuralgia), 5% lidocaine plasters, or 8% pump sprays (for diabetic neuropathy and post-herpetic neuralgia), and 0.1% clonidine (for diabetic peripheral neuropathy) can also be used. Among the new compounds, alpha-lipoic acid (600 mg/die for 3–5 weeks) may be used to manage neuropathic pain.

Trigger point injections (of local anesthetics with or without corticosteroids or needling alone) are a possible option for myofascial pain.

In elderly patients, the management of pain is detailed in the American Geriatric Society guidelines [9]. For chronic nociceptive pain, paracetamol (up to 4 g daily) should be the first-line medication. NSAIDs can be used in patients that have experienced failure of efficacy or the development of side effects during paracetamol treatment. Opioids can be used in patients with moderate–severe pain and functional impairment, unresponsiveness to NSAIDs, or contraindications to their use (gastritis, severe liver or renal diseases, or allergy to NSAIDs). Patients should also be assessed for the presence of drug toxicity and drug–drug interaction risks [9].

In patients with neuropathic pain or fibromyalgia, duloxetine pregabalin or gabapentin can be used even if they must be evaluated for the development of side effects; in contrast, tricyclic antidepressants should be avoided due to their high potential for side effects. Combination therapy seems to increase efficacy and reduce toxicity [9].

More recently, the Department of Health and Human Services' best practices give further information [10], recommending non-opioid or non-pharmacologic therapeutic options in order to avoid chronic treatment with these compounds. For neuropathic pain, the first-line therapy should be chosen among anticonvulsants, SNRIs, amitriptyline, and topical analgesics (capsaicin and lidocaine). For non-neuropathic, non-cancer pain, NSAIDs and paracetamol are the first-line options. Based on patients' responses, other medication classes include muscle relaxants [10]. Trigger point injection (dry needling injection of local anesthesia) may be useful for the management of headache-associated pain, myofascial pain, and low back pain.

2.2. Neuropathic Chronic Pain

The NeuPSIG guidelines' last recommendations were published in 2015 [13]. A literature revision was conducted (of 229 studies), performing a meta-analysis that evaluated the number needed to treat (NNT) for 50% patient pain relief. The trial outcomes were poor or modest even for first-line drugs, which was possibly due to overestimations of the placebo effect, scarce patient profiling, and inadequate diagnostic criteria. The new recommendations are summarized in **Table 1**. The data for the other drugs including other antiepileptics, antidepressants, cannabinoids, tapentadol, and other topical drugs were considered inconclusive. Drugs such as levetiracetam and mexiletine are contraindicated.

The NICE guidelines provide recommendations on chronic neuropathic primary pain (including fibromyalgia). They suggest the use of antidepressants in people ≥ 18 years after the careful evaluation of risk–benefit. Pregabalin or gabapentin and local anesthetics are not suggested, except for in trials for complex regional syndrome. The contraindicated drugs are benzodiazepines, antiepileptics, corticosteroids, trigger point injections, ketamine, NSAIDs, opioids, and paracetamol [2].

The PRACTICE guidelines [12] suggest the use of anticonvulsants, SNRIs, or TCAs in patients with neuropathic pain, with low evidence for the use of SSRIs, NMDA receptor antagonists (e.g., memantine or dextromethorphan), opioids, and muscle relaxants. Topical agents such as capsaicin, lidocaine, and ketamine are also possible options for neuropathic pain. Concerning trigger point injection, it may be considered a multi-modal approach option in patients with myofascial pain (**Table 1**).

2.3. Nociceptive Chronic Pain

In patients with knee osteoarthrosis (nociceptive pain), the *ESCEO* group suggests a six-step treatment: chondroitin sulfate and glucosamine sulfate (first step) with or without topical NSAIDs or paracetamol (second step), oral NSAIDs (third step), intra-articular injection of hyaluronic acid or corticosteroids (fourth step), oral SNRI (fifth step), and, finally, surgery (final step) [11].

2.4. Nociplastic Pain

To date, there are no definitive guidelines for nociplastic pain; however, considering its pathogenetic mechanism, antidepressants and pregabalin or gabapentin can be used. NSAIDs can be indicated only in the presence of clinical evidence of inflammation, while opioids are not indicated. In fact, in these patients, it has been suggested that higher concentrations of endogenous opiates and opioid use can worsen hyperalgesia and modify sleep architecture [15][16]. For nociplastic pain (e.g., fibromyalgia, chronic back pain, and complex regional pain) a low dose of naltrexone, an opioid antagonist, by increasing the density of opioid receptors, improved the response to endogenous opiates with an improvement in clinical symptoms [17]. A similar activity could be obtained using methadone, a potent MOPR agonist and weak NMDA receptor antagonist, which seems able to reduce opioid-induced hyperalgesia [18].

References

1. Raja, S.N.; Carr, D.B.; Cohen, M.; Finnerup, N.B.; Flor, H.; Gibson, S.; Keefe, F.J.; Mogil, J.S.; Ringkamp, M.; Sluka, K.A.; et al. The Revised IASP definition of pain: Concepts, challenges, and compromises. Pain 2020, 161, 1976–1982.
2. National Institute for Health and Care Excellence (NICE). Chronic Pain (Primary and Secondary) in over 16s: Assessment of All Chronic Pain and Management of Chronic Primary Pain; National Institute for Health and Care Excellence (NICE): London, UK, 2021.
3. Cohen, S.P.; Vase, L.; Hooten, W.M. Series Chronic Pain 1 Chronic pain: An update on burden, best practices, and new advances. Lancet 2021, 397, 2082–2097.
4. Fitzcharles, M.-A.; Cohen, S.P.; Clauw, D.J.; Littlejohn, G.; Usui, C.; Häuser, W. Nociplastic pain: Towards an understanding of prevalent pain conditions. Lancet 2021, 397, 2098–2110.
5. Yang, J.; Bauer, B.A.; Wahner-Roedler, D.L.; Chon, T.Y.; Xiao, L. The modified WHO analgesic ladder: Is it appropriate for chronic non-cancer pain? J. Pain Res. 2020, 13, 411–417.
6. Dowell, D.; Haegerich, T.M.; Chou, R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. MMWR Recomm. Rep. 2016, 65, 1–49.
7. SIGN Scottish Intercollegiate Guidelines Network. Management of Chronic Pain. Available online: http://www.sign.ac.uk/pdf/SIGN136.pdf (accessed on 17 July 2022).
8. Colorado Division of Workers' Compensation. Chronic Pain Disorder Medical Treatment Guideline; Colorado Division of Workers' Compensation: Denver, CO, USA, 2017; pp. 1–178.
9. American Geriatric Society. Pharmacological Management of Persistent Pain in Older Persons. J. Am. Geriatr. Soc. 2009, 57, 1331–1346.
10. U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations; U.S. Department of Health & Human Services: Washington, DC, USA, 2019; p. 116.
11. Kucharz, E.J.; Szántó, S.; Ivanova Goycheva, M.; Petronijević, M.; Šimnovec, K.; Domżalski, M.; Gallelli, L.; Kamenov, Z.; Konstantynowicz, J.; Radunović, G.; et al. Endorsement by Central European experts of the revised ESCEO algorithm for the management of knee osteoarthritis. Rheumatol. Int. 2019, 39, 1117–1123.
12. Rosenquist, R.W.; Benzon, H.T.; Connis, R.T.; De Leon-Casasola, O.A.; Glass, D.D.; Korevaar, W.C.; Mekhail, N.A.; Merrill, D.G.; Nickinovich, D.G.; Rathmell, J.P.; et al. American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine Practice guidelines for chronic pain management. Anesthesiology 2010, 112, 995–1004.
13. Finnerup, N.B.; Attal, N.; Haroutounian, S.; McNicol, E.; Baron, R.; Dworkin, R.H.; Gilron, I.; Haanpaa, M.; Hansson, P.; Jensen, T.S.; et al. Pharmacotherapy for neuropathic pain in adults: Systematic review, meta-analysis and updated NeuPSig recommendations. Lancet Neurol. 2015, 14, 162–173.
14. Chou, R.; Gordon, D.B.; De Leon-Casasola, O.A.; Rosenberg, J.M.; Bickler, S.; Brennan, T.; Carter, T.; Cassidy, C.L.; Chittenden, E.H.; Degenhardt, E.; et al. Management of postoperative pain: A clinical practice guideline from the American pain society, the American society of regional anesthesia and pain medicine, and the American society of anesthesiologists' committee on regional anesthesia, executive commi. J. Pain 2016, 17, 131–157.
15. Xia, W.S.; Peng, Y.N.; Tang, L.H.; Jiang, L.S.; Yu, L.N.; Zhou, X.L.; Zhang, F.J.; Yan, M. Spinal ephrinB/EphB signalling contributed to remifentanil-induced hyperalgesia via NMDA receptor. Eur. J. Pain 2014, 18, 1231–1239.
16. Rosen, I.M.; Aurora, R.N.; Kirsch, D.B.; Carden, K.A.; Malhotra, R.K.; Ramar, K.; Abbasi-Feinberg, F.; Kristo, D.A.; Martin, J.L.; Olson, E.J.; et al. Chronic opioid therapy and sleep: An American academy of sleep medicine position

statement. J. Clin. Sleep Med. 2019, 15, 1671–1673.

17. Palareti, G.; Legnani, C.; Cosmi, B.; Antonucci, E.; Erba, N.; Poli, D.; Testa, S.; Tosetto, A. Comparison between different D-Dimer cutoff values to assess the individual risk of recurrent venous thromboembolism: Analysis of results obtained in the DULCIS study. Int. J. Lab. Hematol. 2016, 38, 42–49.
18. Axelrod, D.J.; Reville, B. Using methadone to treat opioid-induced hyperalgesia and refractory pain. J. Opioid Manag. 2007, 3, 113–114.