Opioid therapy for chronic non cancer pain: how to make the right choice

Short review
Pathos 2020, 27; 1. Online 2020, Jan 28.
https://www.pathos-journal.com/2020_1_204-html

***Filomena Puntillo*,[1] *Mariateresa Giglio*,[2] *Angela Preziosa*,[2]**
Nicola Brienza [3]
[1]*Assistant Professor of Pain Therapy and Palliative Care,*
Interdisciplinary Department of Medicine, Bari University
[2]*MD, Anesthesia and Intensive Care,*
Policlinico Hospital of Bari
[3]*Associate Professor of Anesthesia and Intensive Care,*
Department of Emergency and Organ Transplantation, Bari University

Summary The WHO analgesic ladder provides an approach for managing patients with malignant pain. In clinical practice, this ladder is often applied to nonmalignant chronic pain, although its application in this setting is limited by its original design for a malignant pain model and omission of pain etiology and biological mechanism in symptom assessment. The WHO analgesic ladder directs therapy based on pain severity and persistence, with drug therapy recommendations which extends from nonopioids (e.g., NSAIDs and paracetamol) for mild pain followed by *weak* (e.g., codeine) and *strong* opioids (e.g., morphine) for moderate to severe pain, and adjuvant therapies if appropriate. However, a Cochrane analysis found long-term opioid therapy was either ineffective or poorly tolerated by a third of patients with nonmalignant chronic pain.[1] This lack of evidence for long-term therapy is also problematic for nonopioid therapy. Short-term opioid therapy has been associated with adverse effects (e.g., nausea, constipation, somnolence, dizziness and pruritus) in 50-80 percent of patients.[2,3] Additional concern are tolerance and addiction to opioids during long-term opioid therapy. This short review will highlight the issues of chronic opioid therapy and propose how to optimize it.

Riassunto La scala analgesica dell'Organizzazione Mondiale della Sanità fornisce un approccio per la gestione dei pazienti con dolore cronico oncologico. Nella pratica clinica, questa scala viene spesso applicata anche al dolore cronico non oncologico, sebbene la sua applicazione in questo contesto sia limitata dal suo progetto originale designato per un modello di dolore oncologico e per l'assenza di valutazione del meccanismo patogenetico dei sintomi. La scala analgesica dell'OMS indirizza la terapia in base alla gravità e alla persistenza del dolore, con raccomandazioni di terapia farmacologica che vanno dai farmaci non oppiacei (per esempio FANS e paracetamolo) per il dolore lieve seguito da oppiacei *deboli* (per esempio codeina) e *forti* (per esempio morfina) per dolore da moderato a grave ed eventuali terapie adiuvanti. Un'analisi della Cochrane ha tuttavia rilevato che la terapia con oppiacei a lungo termine era inefficace o scarsamente tollerata da un terzo dei pazienti con dolore cronico non oncologico.[1] Questa mancanza di efficacia per la terapia a lungo termine riguarda anche la terapia con farmaci non oppiacei. La terapia a breve termine con oppiacei è stata associata a effetti avversi (nausea, costipazione, sonnolenza, vertigini e prurito) in una percentuale variabile nel 50-80 per cento dei pazienti.[2,3] Un'ulteriore preoccupazione della terapia cronica con oppiacei a lungo termine è la possibile insorgenza di tolleranza e dipendenza da essi.
Questa breve revisione della letteratura metterà in evidenza le problematiche della terapia cronica con oppiacei e proporrà come ottimizzarla.

Key words Chronic non cancer pain, opioids, long term treatment, efficacy, side effects

Parole chiave Dolore cronico non oncologico, oppiacei, trattamento a lungo termine, efficacia, effetti collaterali.

Introduction

Chronic non-cancer pain (CNCP) is common worldwide, with an estimated prevalence of 8-60 percent.[4] It impacts dramatically on the quality of life and the mental health of affected individuals. Moreover, CNCP is a significant economic burden for patients, health services and societies.[5] Opioids have been considered the cornerstone of moderate-severe cancer pain treatment according to WHO analgesic ladder but, in the last decade, opioids have also been widely used for chronic non cancer pain (CNCP). However, the effectiveness of opioids for long-term use in CNCP has not been established and the risk of opioid-related abuse or overdose is a real concern. A Cochrane analysis found that long-term opioid therapy was either ineffective or poorly tolerated by a third of patients with non-malignant chronic pain.[6]

Accordingly, recent guidelines from the US Centers for Disease Control and Prevention (CDC) recognize that non-opioid therapy is preferred for the treatment of CNCP.4 Other evidence in the literature support that opioids should be used only when the benefits for pain and function outweigh risks[7-9] and should be used for CNCP, with specific recommendations about patient selection, treatment tailoring, dose titration, maintenance therapy, and tapering doses during discontinuation.[10]

Opioids therapy

Opioids exert their analgesic effects in humans via agonist, partial agonist or antagonist activity on opioid receptors, δ (DOP), κ (KOP) and μ (MOP). The classical G-protein coupled opioid receptors, known as DOP, KOP and MOP are widely distributed in the CNS and to a lesser extent in the periphery.[11, 12] Various endogenous ligands derived from pro-hormone precursors act at these receptors.

The different degree of receptors' affinity of the opioids can impact on its analgesic effects but also on its side effects. Weak opioid like tramadol and codeine, but also tapentadol and buprenorphine because of their lower activity for MOP receptor than morphine, have less potential for respiratory depression and gastrointestinal side effects. Even methadone has improved safety and tolerability compared with morphine because of its lower affinity for MOP receptor.

Prolonged opioid therapy can lead to cellular and intracellular changes, including activation of N-methyl-D-aspartate receptors. Such changes may contribute to pharmacologic opioid tolerance, increased sensitivity to pain (manifested as "apparent" opioid tolerance), or both and the need for dose escalation. Prolonged opioid treatment may also result in hormonal changes and may alter immune function.[13] The opioid-induced androgen deficiency (OPIAD) can, in turn, cause a lot of other side effects like reducing libido, erectile dysfunction, oligomenorrhea or amenorrhea, infertility, bone loss, sarcopenia, obesity, cardiovascular risk and depression.[14] Once again, opioids with high affinity with MOR receptor like morphine, fentanyl and oxycodone are more liable for these side effects. About opioid induced hyperprolactinaemia, oral opioids for chronic pain increase prolactin (PRL) level;[15] on the other hand, morphine administrated intrathecally for chronic non-cancer pain had no effect on PRL.16 Finally, buprenorphine or methadone maintenance therapy for opioid dependence did not lead to high PRL level.[17,18] The presence of comorbidities, particularly diabetes, hypertension and dyslipidaemia, further increases the risk of OPIAD.[19] This risk can also be correlated with the daily doses of opioids; according to the literature and expert opinion, patients who use opioids at doses higher than 100 mg of morphine equivalents per day (MED) should be monitored for the development of hypogonadism.

Morphine increases the susceptibility to infection, accelerates the rate of progression of infection, and increases animal mortality.[20] Opioids cause a decreased recruitment of neutrophils to the area of infection or injury and impair phagocytosis and superoxide production (thus bacterial killing).[21] Recent evidence suggests that morphine alters the gut microbiome and reduces pathogen clearance thus facilitating bacterial translocation across the gut barrier.[22] The use of opioids in a group of

immunocompetent geriatric patients was associated with an increased risk of pneumonia (OR 1.38; 95 % CI 1.08–1.76); the risk of infection was observed with more potent opioids such as morphine, fentanyl, methadone, and codeine (which is metabolized to morphine) (OR 1.88; 95 % CI 1.26–1.79).[23] However, the immune system is complex and is influenced by a lot of other system like Central Nervous System (CNS) therefore it is difficult, in the clinical setting, to understand how opioids really act on it. Depression too can cause immunosuppression and if opioid therapy resolves the reactive depression in painful patients it effect on their immune system can be variable.
Another issue about long term opioids therapy is the large interpersonal variability of analgesic/side effects of opioids. This can partly be explained with genetics. Genetically determined pharmacodynamic variability can be mediated at several stages of drug action. Genes encoding primary drug targets, for example, ion channels or receptors and intracellular secondary targets, such as components of second messenger pathways can be the source of pharmacodynamic variation. Many pharmacokinetic processes are also subject to genetic variability although the more studied are genetic variants of opioids-metabolizing enzymes.[24] Polymorphisms of the cytochrome P450 enzymes (CYP2D6) can explain interpersonal variability when using opioids like codeine, tramadol and oxycodone. Besides genetic variants, further variables, for example, age, disease, comorbidity, concomitant medication, organ function as well as patients' compliance, may have an impact on pharmacotherapy and need to be addressed when pain therapists prescribe medications.

How to optimize opioids therapy

The first step to optimize chronic opioid therapy (COT), is to decide *when* to start it and *whom*. A lot of guidelines suggest starting opioids in patients with moderate to severe pain associated with pain-related functional impairment or diminished quality of life, as part of a multimodal strategy.[25,26] According to the last CDC guidelines, nonpharmacologic therapy and nonopioid pharmacologic therapy should be preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient.
The patients had to be properly selected and monitored in order to avoid abuses or misuses ant to check the effects of the therapy. For patient selection and risk stratification, clinicians should conduct history, physical examination and appropriate testing. The factor most strongly predictive of opioid abuse, misuse, or other aberrant drug-related behaviors is a personal or family history of alcohol or drug abuse. Younger age and presence of psychiatric conditions may also predict aberrant drug-related behaviors.25 Screening tools for predicting the likelihood of aberrant drug-related behaviors include the Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1,[27] the revised SOAPP,[28] and the Opioid Risk Tool.[29] All are patient self-report questionnaires.
Another important issue is the need of an informed consent. Clinicians should always inform patients about the risks and benefits associated with COT before initiating a trial of therapy. Patients should be counseled on common opioid-related adverse effects (e.g., constipation, nausea, sedation), other serious risks (e.g., abuse, addiction, overdose) and emerging evidence on potential long-term harms (e.g., hyperalgesia and endocrinologic or sexual dysfunction). In addition to informed consent, a COT management plan is necessary to define goals for pain and function, to explain how opioids will be prescribed and taken, expectations for clinical follow?up and monitoring regarding use of concomitant therapies. To avoid unrealistic expectations regarding likely benefits, patients should be counseled that total pain relief with opioids is rare while trials suggest that improvement averages less than 2-3 points on a 0 to 10 scale.
Finally, it is important how to give the opioid. The right way is to start low and to go slow with dose escalation. In opioid-*naive* patients, opioids should be started at a low dose and titrated slowly to decrease the risk of opioid?related adverse effects. An initial dosage of no more than a 5 to 10 mg of MED 4 times daily is suggested, with dose increases of no more than a 5 to 10 mg of MED per week. Frail older persons or those with co?morbidities may benefit from particularly cautious initiation and titration of therapy. According to the last CDC guideline, if opioids are used for chronic non cancer pain, they should be combined with nonpharmacologic therapy and nonopioid

pharmacologic therapy, as appropriate, in order to improve the quality of analgesia and reduce the risk of a COT.

About the maximum daily dose of opioid, CDC guideline suggests that clinicians should use caution when prescribing opioids at any dosage; they should prescribe the lowest effective dosage and should carefully reassess evidence of individual benefits and risks when considering increasing dosage to 50 mg of MED or more, and should avoid increasing dosage to 90 mg of MED or more.6 For Canadian guideline, the optimal dose is one which improves function or decreases pain ratings by at least 30 percent. For by far most patients, this dose will be well below a 200 mg of MED.[30]

About formulations, there is insufficient evidence and even contrary evidence to suggest that long-acting opioids (LAOs) are comparatively more effective in managing chronic pain than short-acting opioids (SAOs). There is no evidence that LAOs have less adverse effects than SAOs but the last are probably safer for initial therapy since they have a shorter half-life and may be associated with a lower risk of inadvertent overdose. Proposed benefits of transitioning to long-acting opioids with around-the-clock dosing include more consistent control of pain, improved adherence, and lower risk of addiction or abuse, but well-conducted studies have not proven these benefits. There is no evidence that LAOs have less adverse effects than SAOs. A transition to LAOs is a reasonable goal in most patients, but there is no compelling reason to require low?risk patients on stable doses of short-acting as-needed opioids to switch regimens. Combinations of long-acting opioids with short opioids are more likely to lead to opioid abuse and increase the risk of serious adverse effects and events in chronic non-cancer pain patients.[31] Some authors suggest that in equivalent doses, LAOs are significantly more likely than SAOs to cause androgen deficiency in men[32] and that the risk of pneumonia was greatest for patients on long-acting opioids (OR 3.43; 95 % CI 1.44-8.21) relative to those using short-acting opioids (OR 1.27; 95 % CI 0.98–1.64).[23]

Patients who have not responded to or who have had side effects with one opioid will sometimes benefit from switching to a different opioid.[33] Because of unpredictable and incomplete cross-tolerance, the initial opioid dose of the new opioid should be no more than 50 percent of the previous dose if the latter is higher (i.e. above a 75-mg of MED), or 60 to 75% of the previous dose if the dose of the previous opioid was moderate (i.e. below a 75-mg of MED).[30]

Regular monitoring is recommended for all patients on COT. In patients at low risk for adverse outcomes and on stable doses of opioids, monitoring at least once every 3 to 6 months may be sufficient. Monitoring should routinely include the assessment of *the four A*: Analgesia, Activity of daily living, Adverse effect and Aberrant drugs-related behavior.[2]

Patients whose pain has not responded to an adequate trial of several different opioids should have their doses tapered and discontinued. Observational studies have demonstrated that patients in severe pain despite high opioid doses experience reduced pain and improved mood with opioid tapering.[34] Tapering might work by relieving hyperalgesia and withdrawal symptoms (withdrawal at the end of a dosing interval is more severe with high doses than low doses). Tapering might also improve mood by reducing opioid-induced sedation and dysphoria.[35] When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal should be used. A decrease of 10 percent of the original dose per week is a reasonable starting point; tapering plans may be individualized and slower tapers (e.i.10% per month) may be appropriate an better tolerated when patients have been taking opioids for years.[6]

Conclusion

Chronic pain requires a multidisciplinary approach encompassing various pharmacological and non-pharmacological treatment strategies, but every option must be optimized to the individual patient. This is particularly true when considering chronic opioid therapy since proper opioid, regimen, and patient selection are paramount. When we choose an opioid for a single patient, an appropriate balance between its benefits and its risks must be done before and during the treatment. Appropriate initiation and titration of COT, regular and comprehensive monitoring while on COT, and anticipation and management of opioid-related adverse effects should result in improved

outcomes and opioid optimization. The choice of the right daily dose together with the right formulation can avoid high doses and aberrant drugs-related behaviors and abuses. *The three T's* of Titration, Tailoring, and Tapering are useful concepts and guides for rational, safe, and appropriate opioid prescribing in chronic non cancer pain

Conflict of interest
The authors certify the study was conducted without conflicts of interest
Published
28th January 2020

References
1) Noble M, Treadwell JR, Tregear SJ et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010; 20(1):CD006605.
2) Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 10(2); 113-130 (2009).
3) Manchikanti L, Kaye AM, Knezevic NN et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Phys 2017; 20(2S): S3-S92.
4) Kennedy J, Roll JM, Schraudner T et al. Prevalence of persistent pain in the US adult population: new data from the 2010 national health interview survey. J Pain 2014; 15(10):979-984.
5) Phillips CJ. The cost and burden of chronic pain. Rev Pain 2009; 3(1):2-5.
6) Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain-United States. JAMA 2016;315(15):1624-1645.
7) Ambrosio F, Finco G, Mattia C et al. SIAARTI chronic non-cancer pain study group. Minerva Anestesiol 2006;72:80-859.
8) Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10(2):113-30.
9) Manchikanti L, Abdi S, Atluri S et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part 2–guidance. Pain Phys 2012;15(3 Suppl): S67–S116.
10) Coluzzi F, Taylor R Jr, Pergolizzi JV Jr et al. Good clinical practice guide for opioids in pain management: the three Ts-titration (trial), tweaking (tailoring), transition (tapering). Braz J Anesthesiol 2016; 66(3):310-317.
11) Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain 2012; 6(1):11-16.
12) Stein C, Schäfer M, Machelska H. Attacking pain at its source: new perspectives on opioids. Nat Med 2003; 9(8):1003.
13) Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003; 13;349(20):1943-53.
14) Coluzzi F, Billeci D, Maggi M, Corona G. Testosterone deficiency in non-cancer opioid-treated patients. J Endocrinol Invest 2018; 41(12):1377-1388.
15) Rhodin A, Stridsberg M & Gordh T. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. Clinical Journal of Pain 2010; 26:374-380.
16) Abs R, Verhelst J, Maeyaert J, Van Buyten JP et al. Endocrine consequences of long-term intrathecal administration of opioids. Journal of Clinical Endocrinology and Metabolism 2000; 85:2215-2222.
17) Bliesener N, Albrecht S, Schwager A, Weckbecker K et al. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. Journal of Clinical Endocrinology and Metabolism 2005;90:203-206.
18) de la Rosa RE & Hennessey JV. Hypogonadism and methadone: Hypothalamic hypogonadism after long-term use of high-ose methadone. Endocrine Practice 1996;2: 4-7.
19) Rubinstein AL, Carpenter DM (2017) Association between commonly prescribed opioids and androgen deficiency in men: a retrospective cohort analysis. Pain Med. 18(4): 637-644.

20) Wang J, Barke RA, Charboneau R, Roy S. Morphine impairs host innate immune response and increases susceptibility to Streptococcus pneumoniae lung infection. J Immunol 2005;174(1): 426-434.
21) Ninkovic J, Roy S. Role of the mu-opioid receptor in opioid modulation of immune function. Amino Acids 2013;45(1): 9-24.
22) Banerjee S, Sindberg G, Wang F, Meng J et al. Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compromise and sustained systemic inflammation. Mucosal Immunol 2016; 9(6): 1418-1428.
23) Dublin S, Walker RL, Jackson ML, Nelson JC et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. J Am Geriatr Soc 2011; 59(10):1899-1907.
24) Smith DM, Weitzel KW, Cavallari LH, Elsey AR, Schmidt SO. Clinical application of pharmacogenetics in pain management. Per Med 2018;15(2): 117-126.
25) Chou R, Fanciullo GJ, Fine PG, Miaskowski C et al. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain 2009; 10(2): 131-146.
26) Ferrel B, Argoff CE, Epplin J, Gloth FM et al. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57(8): 1331-46.
27) Butler SF, Budman SH, Fernandez K, et al. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain 2004; 112: 65-75.
28) Butler SF, Fernandez K, Benoit C, et al. Validation of the revised screener and opioid assessment for patients with pain (SOAPP-R). J Pain 2008; 9: 360-372.
29) Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med 2005; 6: 432--1342.
30) Kahan M, Mailis-Gagnon A et al. Canadian guideline for safe and effective use of opioids for chronic noncancer pain. Can Fam Physician 2011;57(11): 1257-1266, e407-18.
31) Davis MP, Mehta Z. Opioids and Chronic Pain: Where Is the Balance? Curr Oncol Rep 2016;18:7.
32) Rubinstein A, Carpenter DM () Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med 2014; 127(12):1195-1201.
33) Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev 2004;(3): CD004847.
34) Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. J Opioid Manag 2006;2(5): 277-282.
35) Braden JB, Sullivan MD, Ray GT, Saunders K et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. Gen Hosp Psychiatry 2009;31(6): 564-570.