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REVIEW ARTICLE

Opioids in cancer-related pain: current situation and outlook

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Abstract

Purpose Despite progress in treatments, cancer pain remains underestimated, poorly assessed and under-treated. Prescribing strong opioids, because of their specificities, requires precision in management considering their pharmacology but also a clear understanding of recommendations. Some clinicians highlight the risk of addiction, excessive sedation and respiratory depression and their need for information. Our objective in this review is to suggest some clinical guidance for the positioning and daily use of opioids within cancer pain management.

Methods Critical reflection based on literature analysis and clinical practice.

Results Strong opioids may be initiated as soon as pain diagnosis is defined. Factors to consider are pain aetiology, opioid pharmacokinetics and pharmacodynamics, genetic polymorphism, physiology (age, gender, weight and pregnancy), comorbidities (especially renal, hepatic, cardiovascular diseases), chronobiology, environmental factors, medication interference and treatment adherence. Achieving the best-balanced opioid treatment for background pain is complex, mainly due to the variable benefit/risk ratio between individuals and the experience of breakthrough cancer pain. Opioid initiation alongside a dynamic reassessment of pain should be fully integrated into the patient's management to optimise analgesia. The efficacy and safety of a strong opioid treatment need to be re-evaluated and adapted to individuals constantly as it varies over time.

Conclusions Cancer pain is multimorphic and permanently changing due to disease evolution, curative treatments and disruptive events (concomitant treatments, pain from associated disease, comorbidities and complications, modifications of the environment). Well-managed opioids are the cornerstone of a complex environment requiring multidisciplinary dynamic assessments integrated into the patient's care pathway.

Keywords Opioids · Pain management · Personalised medicine · Pharmacokinetics · Multimorphic pain · Cancer pain

Introduction

A literature review carried out between 2005 and 2014 on cancer-related pain prevalence revealed that half of all patients are concerned and that 38% have moderate to severe pain [1]. Despite progress in treatments, unexpectedly, these recent results are comparable with those of another review of studies carried out during the last 40 years [2]. Cancer pain remains underestimated, poorly assessed and undertreated [3–12], particularly in the most severe cases [13]. In 2006–2007, a European study revealed that 72% of cancer patients suffered from pain, with a mean intensity of 6.4 (0–10 numerical rating scale) and that 11% of patients with moderate to severe pain intensity (excluding skin cancer) did not receive any pain reliever [3]. Of treated patients, 84% received quite effective or very effective pain relief, but 6 to 28% of patients were

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undertreated. The inadequacy between pain intensity and the WHO pain ladder was corroborated by a literature review between 1987 and 2007, with 43% of undertreated patients [13]. In parallel, potentially positive effects of pain treatment on patient overall survival have been reported in several cancers [14–17].

Initial studies on cancer pain management strategies revealed that compliance with the reference WHO, three-step pain ladder allowed relieving pain in 75 to 90% of patients [18–22]. European and local guidelines recommend the use of strong opioids for moderate to severe cancer pain [23–26]. Cancer pain is essentially managed by general practitioners and oncologists [5] who sometimes fear the risk of addiction, excessive sedation and respiratory depression and have a need for information [7, 27]. These fears are unfounded if the guidelines are respected [28]. Patients may also present cultural and religious beliefs that need to be contradicted in genuinely balanced communication [29, 30]. Cancer pain is multimorphic, with frequent changes possibly related to cancer progression from diagnosis and/or to its treatments. It can also be affected by other disruptive events such as changes in concomitant treatments, associated disease pains, comorbidities and complications or modifications of the environment (Fig. 1). Cancer pain management imposes regular multimodal assessment that is interdisciplinary and integrated into the patient's care pathway (Fig. 2) [25, 31, 32].

This article highlights the role of strong opioids in cancer pain management strategies to help better treat patients with as few side effects as possible. Facing cancer patients often suffering from undertreated pain, at their consultations, the authors have carried out a critical reflection based on a literature analysis and their clinical practice. For each domain, the literature search was set up on recent reviews and the latest English and French publications on Medline.

Opioids in multimorphic cancer pain

When to prescribe strong opioids in cancerology

All pain should be treated quickly, as it affects the quality of life, decreases the patient's life expectancy and, if it persists, can become chronic. Step 3 analgesics (i.e. strong opioids) are used when step 1 or 2 analgesics are ineffective at a good dose, despite being combined with co-analgesics and possibly complementary alternative therapies [13, 24, 26, 33, 34]. They can be prescribed from the outset if the intensity of nociceptive cancer pain is moderate, without increased risk of side effects [23, 35]. Furthermore, they can be envisaged as first-line analgesics, regardless of the pain intensity, as long as multidisciplinary assessments highlight their utility and the dose is adapted [36, 37]. Finally, in cases of complex tumoural pain (nociceptive plus neuropathic), a similar approach should be considered [22, 36, 37].

The most common strong opioids

Morphine, methadone, oxycodone, hydromorphone, fentanyl, buprenorphine and levorphanol are among the most commonly prescribed strong opioids in Europe, with significant differences between countries [38, 39]. In Scandinavia, tapentadol is only available in Norway and Sweden, and there are specific guidelines for cancer pain management only in Norway and Finland [40, 41]. Similarly, depending on the country, certain pharmaceutical forms or doses are not available [38], or indications are restricted [38]. The use of these drugs is evolving. For example, for more than 5 years, the use of oxycodone, fentanyl and transdermal buprenorphine has been increasing in certain countries, such as Italy [42].

Oral administration is the first-line treatment, to be preferred to the transdermal approach, provided that appropriate doses and pharmaceutical forms are available for titration [24]. The characteristics of the main strong opioids are presented in Table 1. Their analgesic action comes from their binding to the medullary and supramedullary mu opioid receptors, but they can also bind to delta and/or kappa opioid receptors. Depending on their action on receptors, opioids are classified as pure or partial agonists or agonist-antagonists. Through their physical and chemical characteristics, these opioids have different pharmacokinetic and pharmacodynamic properties. The different pharmaceutical forms available (immediate (IR) or extended (ER) release oral, transdermal (TD), transmucosal, parenteral intravenous (IV) or subcutaneous forms) increase the opportunities to personalise pain management. Theoretically, agonist-antagonists, pure opioids or partial agonists should not be combined [27].

Nowadays, the genetics of pain is the subject to considerable research, and more than 400 genes are currently seen as pain modulators [71]. Genetic polymorphism must be considered, as it interferes with opioid metabolism, and possibly elicits interactions with cytochrome p450 (CYP) inductors or inhibitors, or some of their subtypes [43] (Table 1). The induction/inhibition of CYP3A4 cytochromes has a significant impact on the pharmacokinetics of oxycodone, and the lowest serum concentrations of oxycodone in women, confirming their high sensitivity to opioids [72]. For opioid receptor mu 1 gene (OPRM1), β-endorphins binding at the 118A>G variant receptors triggered a 3 times more potent agonist-induced activation of G protein-coupled potassium channels than wild type [73, 74]. Patients carrying 118A>G allele thus have a pain threshold lower than A118 homozygous patients, with a greater need for morphine to achieve pain relief, but without increased side effects [75].

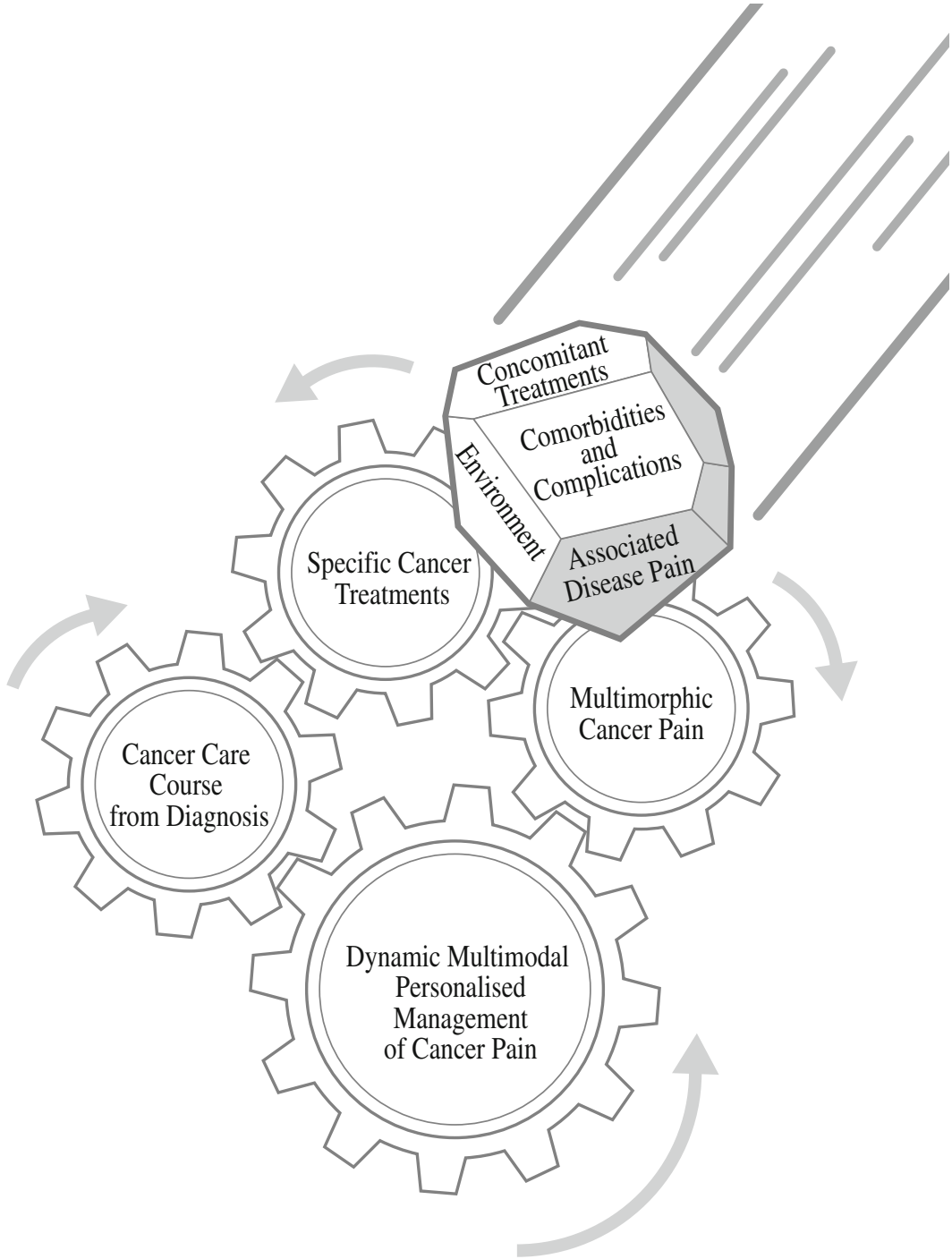

Fig. 1 Disruption key elements in the dynamic, multimodal, targeted, personalised management of multimorphic cancer pain

Which first-line opioid?

No overall recommendation on the choice of strong opioid can be made as the analgesia is guided by local considerations. For instance, in Europe, recommended first-line treatments for moderate and severe pain are oral morphine [23, 24] and oxycodone [24, 76–79]. Oral hydromorphone should be privileged in cases of resistance to, or intolerance of, morphine in France [24, 26]. Transdermal forms (fentanyl, buprenorphine) are unsuitable for titration because they are too inert. The choice of strong opioid must focus on the patient, taking into account [24–26, 43, 80]:

- Age, comorbidities (particularly renal and hepatic) and past history (including addiction and misuse)
- Concomitant treatments and risk of potential drug interactions

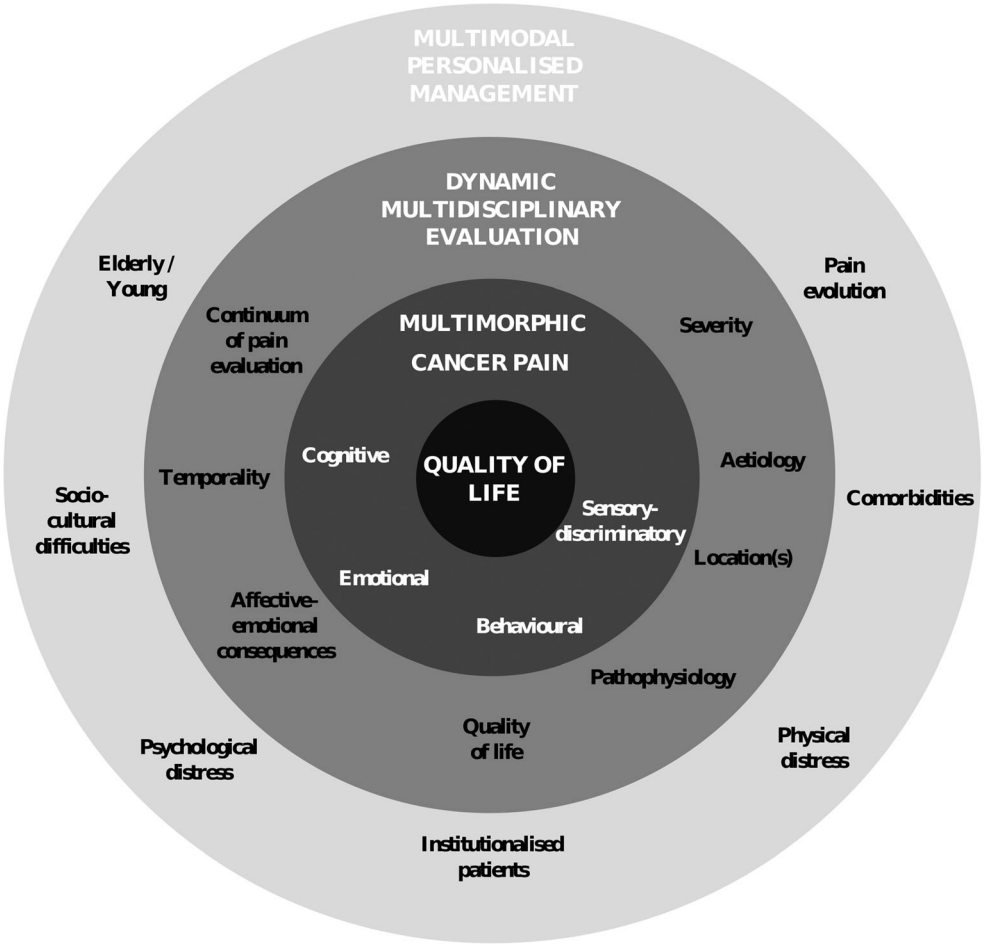

Fig. 2 Model of the multimodal, targeted, personalised management of multimorphic cancer-related pain

- Characteristics of the multimorphic pain, associated with cancer, identified during the initial interdisciplinary assessment
- Pharmacologic properties of the envisaged drug(s)
- Patient's representations and preferences.

When possible, pharmacogenomics must be analysed, due to therapeutic involvement of fast and low metabolisers [81, 82].

The hepatic metabolism of oral morphine and oxycodone produces active metabolites responsible for adverse events. In patients with severe liver failure, or in case of drug interactions, low doses of hydromorphone and oxymorphone should be privileged [82]. Buprenorphine should be used with precaution, and fentanyl and oxycodone are not recommended [83].

Regardless of the stage of chronic kidney disease (CKD), there is no evidence for preferring any opioid [84]. Morphine, oxycodone and hydromorphone must be used with caution [85]. For safety reasons, the lowest effective dose should be used with the appropriate dose spacing. In patients with CKD stages 3–5, morphine and oxycodone should be avoided [65, 84, 86–88]. Buprenorphine is the best-suited strong analgesic. Methadone and fentanyl are also recommended, as they have no active metabolites [89, 90].

For the elderly (> 75 years) or fragile patients (Eastern Cooperative Oncology Group Performance Status (ECOG-PS) > 2 [91]), opioids should be used at lower doses [92]. The renal function being common in the elderly, thus buprenorphine is the recommended opioid treatment [92].

For severe pain requiring rapid relief, first-line parenteral approaches should be privileged, with a preference for continuous intravenous administration (IV) and titration, using an electric syringe pump, preferably with patient-controlled analgesia (PCA) [24]. Average equianalgesia between oral, subcutaneous and intravenous routes, corresponds to a ratio of 1 to 0.5 or 0.3 for morphine [24] and to 1 to 0.5 for oxycodone [50].

Finally, after preliminary interdisciplinary assessments including patient-reported outcome (PROs) measures, multimodal, personalised management should make it possible to choose the optimal strong opioid(s) for a rapid, adapted response, followed by frequent and regular reassessments [24, 26, 93].

Table 1 Characteristics of the most common strong opioids (oral, transmucosal transdermal and sublingual forms)

	Morphine (oral) [43–49]	Oxycodone (oral) [50–54]	Hydromorphone (oral) [43, 45, 55–59]	Fentanyl (transmucosal, transdermal) [43, 45, 60–62]	Methadone (oral) [43, 45, 49, 63, 64]	Buprenorphine (sublingual, transdermal) [65–70]
Mode of action	MOR, KOR and DOR agonist	MOR, KOR and DOR agonist	MOR and DOR agonist	MOR agonist	MOR, DOR and NMDA agonist, SNRI	MOR partial agonist and KOR antagonist
Class	Pure agonist	Pure agonist	Pure agonist	Pure agonist	Pure agonist	Partial agonist
Bioavailability	30%	60–87%	50–60%	Transmucosal 50–90% Transdermal 92%	80%	Sublingual 30–70% Transdermal 60%
Analgesic potency vs. oral morphine	1	1.5	5–7.5	100	5/1–10/1	Sublingual 30–50 Transdermal 100–115
Binding to proteins	35%	40%	8%	90%	60–90%	30%
Liver metabolism	Hepatic metabolism by the enzyme UGT	Major substrate of CYP3A4 Bioactivation by CYP2D6	Hepatic metabolism by the enzyme UGT	Major substrate of CYP3A4	Major substrate of CYP3A-4, CYP2B6 Minor substrate of CYP1A2, CYP2C19, CYP2D6	Substrate of CYP3A-4 and 2C8
Active metabolites	Morphine-6-glucuronide	Oxymorphone	HG3 neuroexcitatory (no analgesic activity)	No active metabolite	No active metabolite	Norbuprenorphine poorly active
Renal excretion	Yes	Yes	Yes	Yes	Low renal excretion	Low renal excretion
Peak of action	IR 1 h ER 3 h	IR 1 h ER 1 h	IR 1 h ER 3 h	Transmucosal 5–10 mins Transdermal 12 h	2 h	Sublingual 15–45 mins Transdermal 12–24 h
Duration of action	IR 4 h ER 12 h	IR 4 h ER 12 h	IR 4 h ER 12 h	Transmucosal 1–3.5 h Transdermal 72 h	6–8 h (half-life 12–120 h)	Sublingual 6–8 h Transdermal 72 h

CYP, cytochromes P; *DOR*, δ-opioid receptor; *KOR*, κ-opioid receptor; *IR*, immediate release; *ER*, extended release; *MOR*, μ-opioid receptors; *NMDA*, N-methyl-D-aspartate receptors; *SNRI*, serotonin-norepinephrine reuptake inhibitor

Which dose to start a first-line strong opioid?

Due to high interindividual variability reported with opioids, dosing must be personalised [79]. Treatment starts with a titration phase. Usually, for adults weighing 60 kg, the common starting dosage is 1 mg/kg/day equivalent oral morphine in opioid-naive patients, 10 mg every 4 h (IR form) or 30 mg every 12 h (ER form) [24, 26]. For fragile patients (age > 75 years, poor general health (ECOG-PS > 2), with kidney or liver failure, hypoproteinaemia, etc.), the dosages must be adapted and lowered to 0.5 mg/kg/day equivalent morphine, preferring IR forms [89]. In patients with moderate pain, certain recommendations favour starting with the lowest dose of strong opioid [24].

How to titrate

Controlling background pain requires initial, fast and progressive titration, to obtain a balanced analgesic state with the minimum effective dose of opioids without any side effects [24]. First-choice background treatment is an ER strong opioid, associated with IR opioid rescue doses (1/6 to 1/10 of the total daily background dose, as required) during flares or residual pain. The rescue doses could be administered every 4 h, or even hourly without exceeding 4 consecutive administrations in 4 h. In fragile patients, certain authors recommend titration using only IR forms [26]. When patients use more than 3 or 4 rescue doses per 24 h, excluding those used to prevent procedural pain, the background treatment must be increased, adding the daily dosages of the background treatment and the rescue treatment, until a state of analgesic control is obtained [24]. The cumulated dose of IR and ER forms should be distributed throughout the day in ER form, and the dosages of the rescue doses increased in consequence. Fast-acting fentanyl citrates (rapid onset opioids, ROO) should not be introduced at this stage. In emergency situations requiring a very fast analgesic response, IV administration with PCA, continuous flow and bolus are preferred.

Titration supposes frequent pain reassessments, at least once daily, controlling treatment efficacy and tolerance. Increasing the dosages depends on the steady state of the oral opioids used. For morphine, oxycodone and hydromorphone, this may be done every 24–48 h. For TD fentanyl, dosages may be increased every 72 h [26]. In outpatient cases, there must be regular telephone contact.

When background pain is under control, there is still work to be done

Most cancer patients with pain describe controlled background pain and flares of pain with slow or fast time to peak pain intensity. Since 1990, these 'transitory flares of pain that occur on a background of relatively well-controlled baseline pain' are known as breakthrough cancer pain (BTcP) [94].

There is no consensus on a precise definition of BTcP [95–97], as shown by the results of prevalence studies (19 to 95%). For instance, depending on the recommendations, end-of-dose breakthrough pain caused by insufficient around-the-clock analgesia may or may not be considered as BTcP [24, 26, 39, 97, 98]. We thus define BTcP as episodes of moderate to severe intensity, rapid onset and short duration in a context of background pain controlled by strong opioids excluding end-of-dose flares and transient pains (exacerbations of pain with slow time to peak pain intensity) [97–99].

That said, precise titration objectives for pain exacerbations at the start of treatment prevent increasing the dosages of around-the-clock analgesia and potential overdose, and relieve all exacerbations [100]. Despite the lack of international consensus on the definition, European recommendations, and those of most European countries, consider that background pain control is reached when the pain intensity is controlled or mild and patients have 4 episodes of BTcP/day or less, based on the median number of BTcP/day observed in several studies [24, 26, 101, 102]. Otherwise, the around-the-clock treatment should be adapted following a reassessment of pain and its mechanisms [24, 95, 97, 103, 104].

How to treat breakthrough cancer pain

When background cancer pain is controlled with a minimum of 60 mg/day equivalent morphine for at least 7 days, any predictable or unpredictable possible BTcP still needs to be managed in a specific manner [105, 106]. ROOs, with delays of action of 10 to 15 mins, and durations of action of 1 to 2 h, have a full role to play [104]. ROOs come in several pharmaceutical forms [107], to be chosen according to administration method, patient preference and any possible contraindications. There is a poor correlation between the effective dosages of ROO and background opioid treatment [108] and no equianalgesic effect between the different pharmaceutical forms of ROO [107]. It is necessary to start with the smallest dosage of ROO, until satisfactory analgesia and tolerability is obtained for the BTcP [103]. If the BTcP is not relieved enough with the first ROO administration, it is usual practice to administer an identical second dose, 15 to 30 mins afterwards, depending on the ROO, with a maximum of 2 administrations per BTcP and a maximum of 4 BTcPs treated per day [24, 103]. If patients are not relieved during the BTcP, the immediately higher dose will be administered at the next episode, with a minimal delay of 4 h [103].

Patients and their families must be trained to recognise, assess and treat BTcP, to obtain the best analgesia and to avoid misuse of ROOs and their associated side effects [109]. If patients experience more than four BTcP/day, the background treatment must be reassessed rapidly.

Prevention and management of the side effects of opioids

Side effects are the main reason for discontinuing analgesics and altering the quality of life. They must be systematically prevented, screened for and treated [23, 31, 32]. Patients and their relatives must be informed of potential side effects. Before relating a side effect to opioids, all differential diagnoses must be eliminated. Neuropsychiatric disorders, metabolic disorders, renal failure, tumour or brain metastases or other causes should thus be screened for [23, 31, 32].

Opioid-induced constipation (OIC) is a non-dose-dependent adverse event, belonging to a more global entity (opioid-induced bowel dysfunction), associated with opioid receptor binding in the gastrointestinal tract [110]. Systematic OIC preventive treatments based on hygiene and diet recommendations, and specific pharmaceutical treatments, must be prescribed. Three days without bowel movements, with optimal constipation treatment and no digestive obstacles, leads to using peripheral μ-opioid receptor antagonists (PAMORA, e.g. subcutaneous methylnaltrexone or naloxegol), which have no impact on the analgesia itself [110]. In certain countries, it is possible to use a strong opioid associated with low doses of naloxone or oral naloxone [111].

Nausea and vomiting are common after starting an opioid treatment [79]. Prevention is recommended with anti-emetics in the first week to avoid any discontinuation of the oral analgesia. Nausea and vomiting are rare after the 4th day of treatment. If these events start several days after opioid initiation, another aetiology should be sought. Opioids can provoke well-known neuropsychiatric disorders [23, 31, 32] which can be treated by switching opioids. The drowsiness induced by opioids must be differentiated from drowsiness induced by recuperation of sleep debt, which must not be considered as an opioid side effect. More rare side effects can be experienced, such as psychological dependency (4 cases in 12,000 patients, [112]). Opioids may also induce hyperalgesia with diffuse allodynia [113], through hyperactivity of the NMDA (N-methyl-D-aspartate) receptors. Ketamine can stop this process [114]. However, hyperalgesia must be differentiated from increased pain sensitivity and reduced pain tolerance [115]. Finally, pruritis, which generally occurs with intrathecal administration, can be treated by opioid switching and is not a matter for standard antihistaminic treatments.

What to do when analgesia fails

With ineffective or poorly tolerated analgesia, first, ensure that patients have fully understood the treatment, are fully compliant and receive symptomatic effective treatment of side effects through regular preventive assessment [24, 25, 31, 32, 93]. The multimodal approach makes possible to eliminate any other causes or comorbidities generating analgesia inefficacy or poor tolerance (Fig. 2). Following this assessment, and in the case of unidentified factors, two strategies can be proposed.

- Opioid switching

In 1995, Bruera et al. [116] presented the concept of opioid rotation, defined as systematically changing one opioid for another, to prevent opioid tolerance. Nowadays, the switch to another opioid is usually supported by a side effect refractory to any treatment, insufficient efficacy of analgesia or evolution in patient management (e.g. when facing a risk of drug interaction at treatment initiation for comorbidity) [24, 31, 44, 105, 117–120].

No choice criteria have yet been validated to favour one pure opioid over another. The choice is based on the same criteria as previously defined for opioid treatment initiation. In practice, new opioid dosages are based on equianalgesic proportions of the previous background opioid dosage, without including that of the rescue doses. Nevertheless, human clinical studies are controversial as there are significant inter- and intra-individual variations [81, 121]. Safety must be privileged over rapidity, using the lower ranges in opioid equianalgesic dose tables [31, 39, 121]. The pharmacokinetics of the different opioids must be considered in order to avoid action overlap between the two opioids or any interruption in their action.

Finally, any change in opioid requires frequent and repeated reassessments [31, 39].

- Change of administration method

Sometimes, parenteral approaches using PCA-type equipment are recommended. This is most common when the oral approach is impossible for mechanical (swallowing disorders, etc.) or pharmacokinetic (bioavailability, etc.) reasons, inappropriate galenic form, unstable pain, uncontrolled side effects or urgency of treatment. Treatment initiation follows the same principles as for opioid switching.

How to avoid inappropriate escalation in the doses of strong opioids

Regularly, repeated multidisciplinary assessments of cancer pain allow personalising its management, taking into account the multimorphic nature of pain: mechanisms and characteristics, patient's sociocultural difficulties and any comorbidities (Fig. 2). This type of personalised management will lead to the prescription of the lowest effective dosage of the best-adapted opioid (Fig. 3).

To avoid escalation in inappropriate doses of opioids, it is also necessary to consider the balancing period needed to

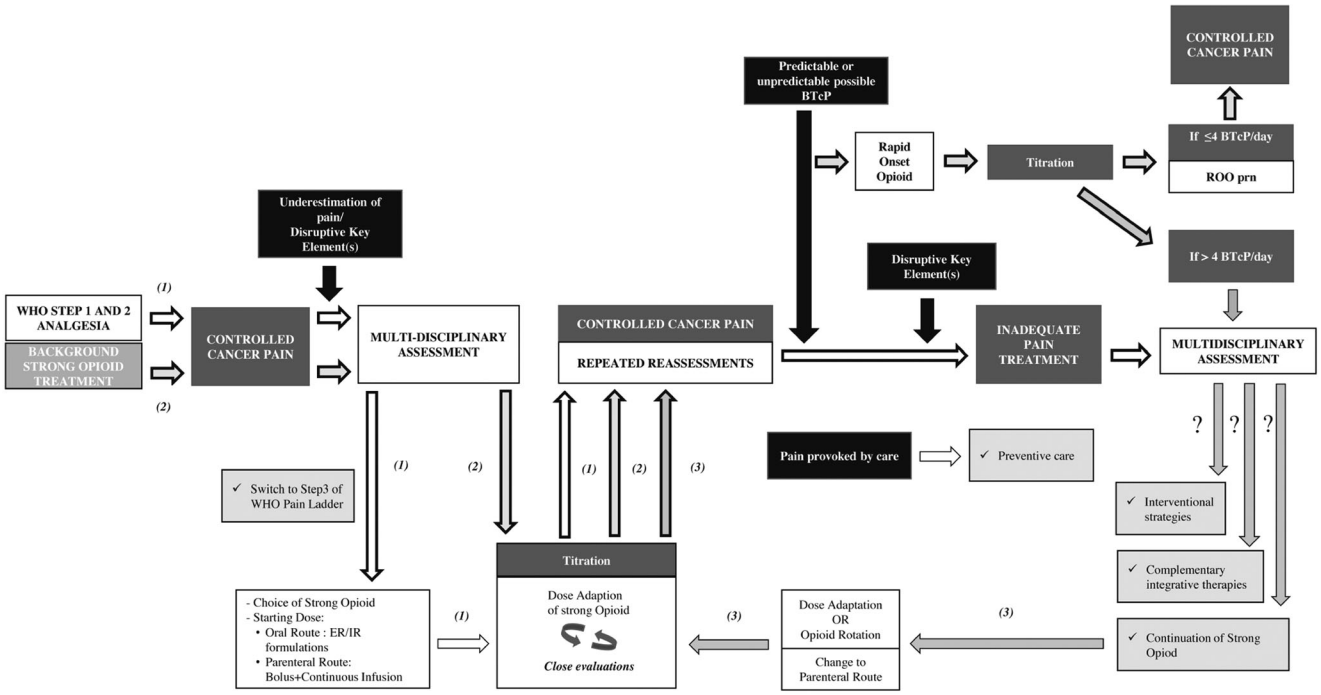

Fig. 3 Integration of strong opioids in multimodal personalised management of cancer pain BTcP, breakthrough cancer pain; prn, as needed (pro re nata)

obtain effective plasma concentrations, classically every 4–5 half-lives [122].

Knowing the pain mechanism, it is possible to act adequately by offering adapted analgesics and combining them if necessary, in non-refractory pain [123, 124]. This complementary synergy is nevertheless limited by drug interactions in patients with multiple treatments. Pharmacologic treatments can be completed with non-pharmacologic, non-invasive interventions [34].

Refractory pain

Even when the assessment and treatment strategies established above have been respected, 10 to 30% of patients present refractory pain [125, 126]. Interdisciplinary meetings allow to envisage the use of invasive interventional therapies based on the causes of pain [23, 127–129]. Despite proven efficacy on refractory pain, the interventional therapies remain underused or even avoided until the terminal phase [130]. They include interventional radiology techniques (alcoholisation, radiofrequency, cryotherapy, cementoplasty, embolisation), radiotherapy (targeted, metabolic), surgery (stabilisation, decompression, neurosurgery), peripheral nerve block techniques or peri-medullary therapies [127–134].

Stopping treatment with strong opioids

Regular multidisciplinary assessments allow detecting any signs of potential overdose that may lead to a staged decrease and/or progressive termination of opioid therapy. In all cases, with the exception of a vital emergency, opioids should not be stopped abruptly because of the risk of the onset of withdrawal syndrome, which is a real noradrenergic tornado very harmful to patients.

Do the opioids are at risk of cancer progression?

Some in vitro and preclinical studies, and retrospective clinical data, mainly focused on the perioperative period, have evoked that opioids could promote the metastases recurrence or the proliferation of tumours after surgery, by inhibition of the immune and endocrine systems, decrease of the cytotoxicity of NK cells and promotion of angiogenesis. [135]. However, surgical manipulations promote the release into the circulation of tumour cells. Pain, surgical neuroendocrine stress, and inflammatory response also induce immunosuppression and inhibit the killing power of NK cells. [136]. Randomised controlled clinical trials are needed to establish if a real risk exists. Today, the strong opioids remain the cornerstone of cancer pain management, as current scientific data do not question our therapeutic strategies.

Risk of opioids addiction in cancer pain management

Opioid addiction when prescribed in chronic non-cancer pain has become a public health issue, particularly in the USA where the number of overdose deaths was estimated at more than 15,000 in 2015 [137]. The risk of addiction is the meeting

of a particular substance and a patient profile. Opioid addiction for medical use in cancer pain patients is rare [112, 138, 139]. Predictive screening scales for patients at risk for addiction have been validated outside cancer [140]. Excessive prescriptions of opioids in non-cancer pain, and their consequences, should not limit the adequate prescription of opioids in evolutive cancer pain. However, dedicated patient profile screening tools and surveillance of patients on opioids are essential, since cancer, that has become a chronic disease, imposes longer treatments and causes sequelae like chronic pain.

Use of co-analgesics

Whenever possible, co-analgesics should be associated with strong opioids [141]. It is thus possible to obtain a potential opioid-saving effect. They include some antidepressant and anticonvulsant drugs in neuropathic pain, NSAIDs or corticosteroids in inflammatory pain, bisphosphonates in bone metastases pain. Anxiolytics, antispasmodic and antidepressant drugs are also relevant.

Discussion and perspectives

Personalised multimodal pain management considering the multimorphic nature of cancer pain should improve patient care (Fig. 2). Most patients can obtain satisfactory pain management through the association of anti-tumour treatments, systemic analgesia and non-invasive approaches. However, these good pain management practices are too often unknown and insufficiently applied around the world, compromising the delivery of quality care [3, 7, 142, 143]. The implementation of 6-month educational programmes for healthcare professionals to alleviate these barriers will result in improved cancer pain management [144]. It should be noted that in France in 2010, prescriptions for pain management in cancer patients were still essentially made by oncologists (91%) and general practitioners (64%), while specialised pain structures accounted for only 7% [5]. In recent years, the characteristics of cancer pain have evolved, with symptomatology changes due to the chronicisation of most cancers and the introduction of new targeted anti-cancer treatments.

In this context, and given current progress, patient cancer management as a whole (diagnosis, cure, relapse, palliative situations), especially cancer treatments impacting on pain (chemotherapy in the broadest sense of the term, surgery, radiotherapy), must form the foundation of multimodal pain management. This approach implies dynamic, multidisciplinary evaluations (Fig. 2) based on patient-reported outcomes (PRO) measures and the knowledge of the pros and cons of analgesics, to respond as fast as possible to any disturbances/disruptions with appropriate personalised multimodal management (Fig. 1).

The initiation and dynamic follow-up of analgesia by an interdisciplinary team must be integrated into patient management in order to propose optimal analgesia, using strong opioids as soon as required. The complex balance in the minimal effective background opioid treatment with the best tolerability can only be reached in this context (Fig. 3), as many sources of variability result in differences between individuals regarding active opioid concentrations and effects. These are factors related to pain aetiology, opioid pharmacokinetics and pharmacodynamics, genetic polymorphism, physiology, comorbidities (especially renal, hepatic and cardiovascular diseases), chronobiology, environmental factors and treatment adherence. Nowadays, these factors must be part of interdisciplinary pain management, except genetic polymorphism which may be part of the genomic analysis of cancer patients in the future.

Given this complexity, pain management must be multimodal to respond to the challenges set down by the emergence of new targeted anti-cancer treatments, based on real personalisation of cancer pain treatments with dynamic follow-up with appropriate information [93]. Personalised management requires that all medical and healthcare personnel, and especially the patient's general practitioners, have all the information needed. Personalised pathways must be set up to handle analgesia discontinuity, such as contacts for pain urgency.

Conclusion

Cancer pain is multimorphic and constantly evolving. It deserves particular attention from all those involved in healthcare, with patients themselves (and their family) as key players in their own management. Pain leads us to initiate multimodal, dynamic, personalised management in which strong opioids play a particular role. A good prescription of strong opioids requires good knowledge to provide the right opioid for the right patient, at the right time and the right dose, with the right follow-up. In the future, taking pharmacogenomics into account should optimise their action by further personalisation of treatments.

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Compliance with ethical standards

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