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REVIEW

Fixed-dose combinations at the front line of multimodal pain management: perspective of the nurse-prescriber

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Abstract: Pain should be treated promptly and effectively to restore the patient to full function, avoid pain chronification, and preserve quality of life. A recent pain specialists' meeting discussed the use of different pharmacological treatment options, such as topical analgesics, nonopioid agents (such as paracetamol and nonsteroidal anti-inflammatory drugs), weak and strong opioids, and fixed-dose combination products in the management of moderate to severe pain from different etiologies. One of the topics discussed in, and subsequent to, this meeting was the role of fixed-dose combination products for nurse-prescribers who are in many ways at the front line of managing both acute and chronic pain syndromes. The panel agreed that proper product selection should take into account the patient's age, condition, type of pain, and comorbidities, as well as balance safety with effectiveness. Although nurse-prescribers need to be aware of cumulative paracetamol dosing, fixed-dose combination products, such as tramadol-paracetamol, may offer important advantages, eg, by providing opioid-sparing without sacrificing efficacy.

Keywords: tramadol, paracetamol, fixed-dose combination analgesics, pain management

Background

Pain is a common health problem imposing a substantial burden on the afflicted individual and society.[1] In the US, more individuals suffer from chronic pain than from diabetes, heart disease, and cancer combined,[2] and one in five Europeans is afflicted by moderate-to-severe chronic pain lasting 6 months or more.[3] Pain prevalence in the elderly is high;[4] indeed, the aging population in the developed nations strongly suggests that chronic pain will become increasingly prevalent, problematic, and expensive.

Acute pain is the normal and expected adaptive response to noxious stimuli and diminishes as the body heals, whereas chronic pain is more complex and maladaptive, and involves altered pain perception. Acute pain may transition to chronic pain in a process known as chronification, which involves sensitization of the central nervous system. Chronic pain is often defined simplistically as pain that persists for more than 3 or 6 months, but this definition may be outmoded and cause us to view pain incorrectly, ie, to treat chronic pain as a form of prolonged pain, when it actually involves different mechanisms.[5] Chronic pain may be entirely nociceptive, neuropathic (ie, as a direct consequence of a lesion or disease affecting the somatosensory system),[6] or nociceptive with a neuropathic component (Figure 1). A well known example of this so-called mixed-pain is low back pain.[7]

Pain is one of the main reasons patients seek health care services.[8] Common pain syndromes in general health care are acute or chronic musculoskeletal pain, headache,

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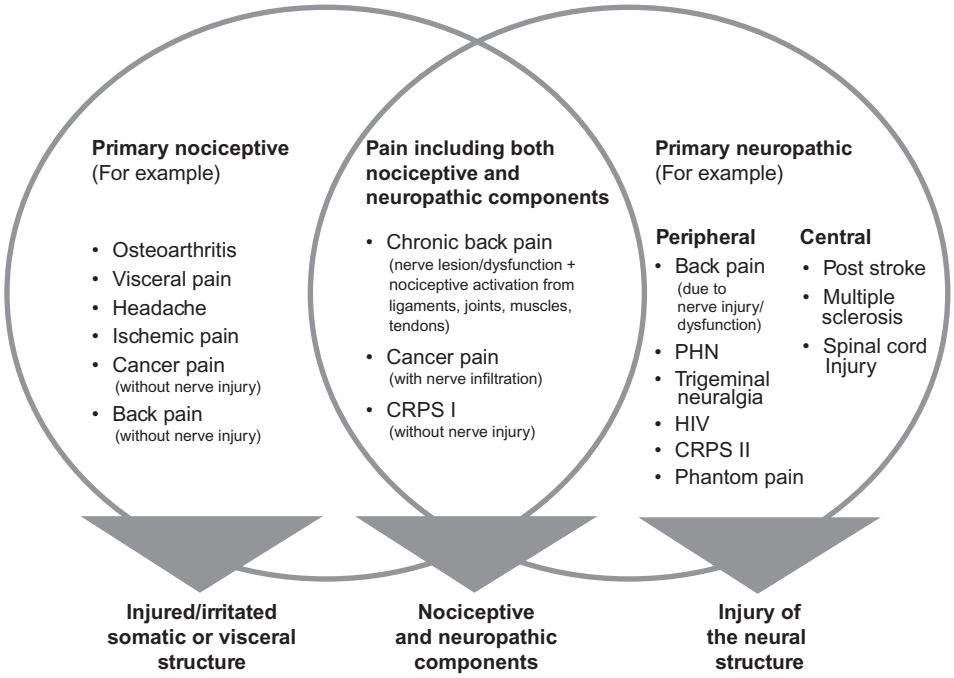

Figure 1 Although chronic pain is often defined as pain that persists for 3 or 6 months, it is actually clinically and biologically distinct from acute pain. Some examples of the different pain types are given in the chart.

Abbreviations: CRPS, complex regional pain syndrome; PHN, postherpetic neuralgia.

post surgical pain, and scar pain. As a result of an aging population, nurse-prescribers often have an elderly clientele, therefore "wear and tear" indications, such as low back pain and osteoarthritis, and the pain associated with these conditions, is frequently encountered. Table 1 lists the most common indications encountered by nurse-prescribers.

As shown in Figure 1, pain syndromes belong to different pain types and might thus require different treatment approaches. Pharmacological options include topical pain relievers, nonopioid agents (such as aspirin, paracetamol [acetaminophen], and nonsteroidal anti-inflammatory drugs [NSAIDs]), and opioids acting on the ascending or descending pain pathways (Figure 2). It should be noted that, depending on the country, not all nurse-prescribers have prescribing rights for strong opioids (eg, in Ireland, palliative care nurses are able to prescribe strong opioids, such as morphine or fentanyl, but pain management nurses are only able to prescribe morphine for pain due to trauma or myocardial infarction).

Fixed-dose analgesic combinations combine two or more analgesic agents in a single tablet. Ideally, the two agents have complementary mechanisms of action, and may interact with each other in an additive (agent + agent) or synergistic way (where the results are greater than the sum of the parts).[9] Possible advantages of fixed-dose combination products are dosing convenience, reduction of pill burden, the potential for greater patient adherence and, in the case of fixed-dose combination products involving an opioid and a nonopioid agent, opioid-sparing effects and fewer side effects due to the reduced doses of each single substance. The possible role of the fixed-dose tramadol-paracetamol combination for pain relief in patients seen by nurse-prescribers is discussed here.

Meeting details

A consensus meeting attended by all authors of this publication was held on November 20, 2010 in Paris, France, to discuss the management of moderate to severe pain from different etiologies using different pharmacological treatment options, including the fixed-dose tramadol-paracetamol analgesic combination (Ixprim®, Zaldiar® or Ultracet®). Presentations by four of the authors were followed by a

Table 1 Pain syndromes frequently encountered by nurse-prescribers

- Musculoskeletal pain
  - Back pain of unknown origin
  - Osteoarthritis
  - Rheumatoid arthritis
  - Disc herniation
- Headache/migraine
- Postsurgical pain/scar pain
- Wound pain
- Cancer pain
- Neuropathic pain
- Visceral pain

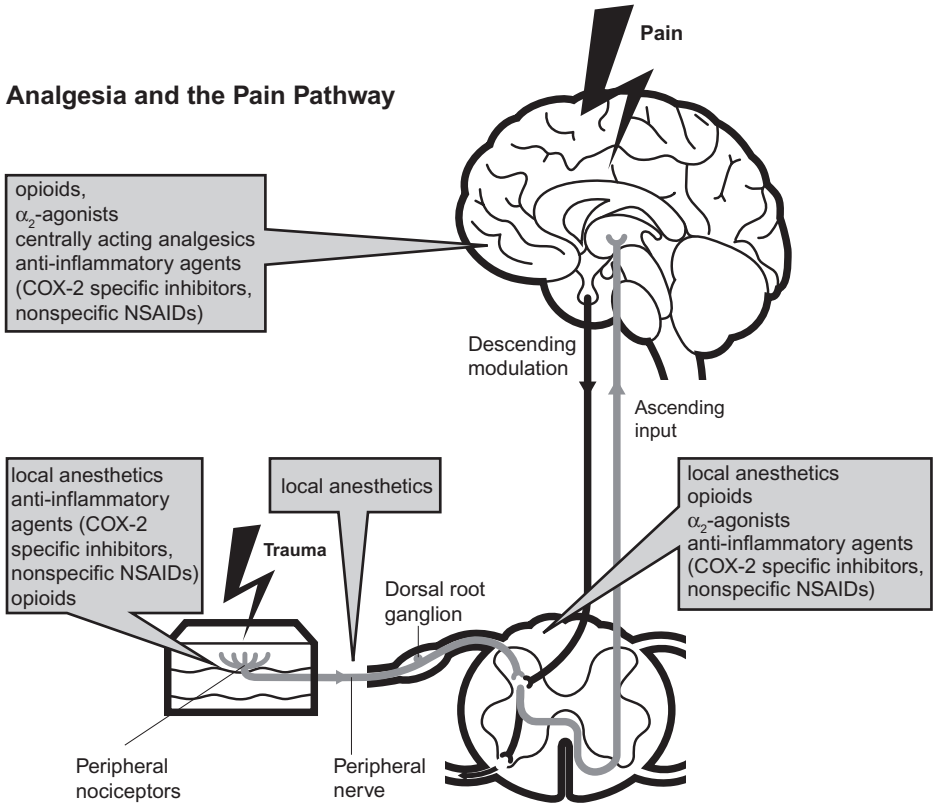

Figure 2 Analgesia and the pain pathway.
Copyright © 2012. John Wiley and Sons. Reprinted with permission from Pergolizzi J, Alegre C, Blake D, et al. Current considerations for the treatment of severe chronic pain: the potential for tapentadol. *Pain Pract.* 2012;12:290–306.[129]
Abbreviations: COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs.

group discussion and review of pain management issues and available guidelines/recommendations based on the clinical experiences of the participants. Subsequent to the meeting, the panelists discussed specific clinical issues in pain, including the role of fixed-dose combination products for nurse-prescribers, who in many ways are at the front line of managing both acute and chronic pain syndromes. Their final consensus is summarized in this publication.

Pain and quality of life

Chronic pain has a devastating effect on the lives of patients. Among chronic pain patients who suffered from pain ≥ 5 (on a 10-point numeric rating scale of 1 to 10 with 10 the worst pain imaginable) for 6 months or more, 21% had been diagnosed with pain-related depression, 61% were unable or less able to work outside the home, and about one-third were not receiving any pain treatment.[3] Pain-related depression has been correlated with decreased quality of life in chronic pain patients,[10] and the severity of chronic pain was shown to correlate significantly with reduced health-related quality of life in adults[11] and adolescents.[12] However, multiple regression analysis of data from a recent study of heterogeneous chronic pain patients found pain catastrophizing to be a more important predictor of low quality of life than pain severity.[13] Among migraine sufferers, the frequency of migraine episodes also correlated inversely with poor health-related quality of life scores.[14] A review of 52 quality-of-life studies conducted among patients with six different types of neuropathic pain syndromes found that the presence and severity of neuropathic pain was associated with impaired quality of life.[15] Effective pain management can improve a pain patient's quality of life. In a study of 106 chronic non-malignant pain patients who agreed to participate in a medically supervised pain management program, quality of life significantly improved after one month of pain management over baseline scores.[16] Recent studies investigating patient perceptions of the 5% lidocaine medicated plaster[17] and the 7-day low-dose buprenorphine patch[18] also found marked improvement in quality of life after 12 weeks of pain treatment.

Pain management in clinical practice

Pain is prevalent and widely under-treated.[19,20] The World Health Organization (WHO) has advocated strongly for more liberal use of analgesic medicines[21,22] and encourages national

programs for relief of the most extreme forms of pain.[23] Pain impairs a patient's quality of life,[24] which improves when pain is effectively managed.[25] Long-term pain is associated with cognitive impairment[26,27] and depression.[3] The effect of pain on patients is devastating, and the socioeconomic impact of chronic pain is overwhelming.[24,28] In a study of chronic low back pain, patients had a significantly greater comorbidity burden than control patients including higher rates of depression and sleep disorders.[29] These patients spent significantly more on drug therapy and had significantly higher total medical costs; annual medical costs were US$ 8386 ± 17,507 compared with US$ 3607 ± 10,845 for control patients.

Chronic pain negatively affects productivity, resulting in absenteeism from work, premature retirement, reduced ability to perform activities of everyday living, and presenteeism (a condition in which the pain patient reports to work but may not be able to fulfill his/her job duties completely).[30] A recent study quantifying the costs of headaches in Europe (including health care expenses plus lost productivity) estimated costs of approximately 112 billion Euro annually.[31] There are thus important personal, clinical, and social reasons to manage pain more effectively.

While acute and chronic pain syndromes must both be managed effectively, it is clear that chronic painful syndromes represent the greater individual and social burden. Acute pain does not always transition to chronic pain, but unmanaged, it can set the stage. Moreover, chronic pain can worsen when not managed promptly and effectively. Acute postsurgical pain may transition into long-term pain; a study of patients undergoing urologic surgery found that 51.2% reported pain 3 months after surgery.[32] To prevent chronification or worsening of chronic pain, pain should be rapidly and accurately diagnosed and managed effectively.[33] While most nurse-prescribers would agree with this statement, implementing it in daily practice can be challenging.

One important barrier to better pain management is the reticence of some patients to disclose pain. Some patients wait a considerable amount of time, even a year or more, before seeking medical care to help with pain.[34] A patient's attitude toward pain and pain perceptions may be influenced by his or her culture,[35] gender,[36,37] socioeconomic factors,[38,39] ethnic and religious attitudes,[40] age,[41] and the beliefs held by the patient or their family.[42,43] Not all patients in pain will seek treatment, and factors such as culture and ethnicity can influence if and how much a patient will discuss painful symptoms.[44,45] Thus, nurse-prescribers must be sensitive to patients who may be reticent to discuss their pain and encourage them to report all symptoms. In addition, further patient education is needed to assure patients that there are safe and effective ways to control or at least manage painful symptoms and that pain is not something they must simply endure.

Once a patient reports pain, it is important to assess that pain and its impact on the patient in an accurate manner. The most commonly used pain assessment tools include questionnaires (for both pain intensity and quality of life), patient interviews, a visual analog scale, and a numerical scale that allow the patient to quantify pain. Such tools are inherently subjective, but they are easy to use, inexpensive, and widely accepted.[46] Using pictures (smiley faces) or observing behaviors associated with pain are often used for patients who cannot verbalize their pain, eg, the very young and those with cognitive impairment.[47] Not only should the intensity of the pain be assessed, but also the quality of the pain, which can be important in identifying neuropathic pain or pain with a neuropathic component.[48] For example, back pain with a neuropathic component has been shown to be associated with greater health care resource utilization and related costs than back pain without a neuropathic component.[49]

Overview of pain management therapies

Nonpharmacological options

Nonpharmacological options for pain management include massage, exercise, weight loss, diet, and relaxation techniques.[50] Cognitive and behavioral therapies, as well as psychotherapy, biofeedback, and hypnotherapy may sometimes be effective.[51–53] It is beyond the scope of this article to discuss nonpharmacological pain management in detail, but the authors agree that these can be very important as the foundation of a pain management plan. In some cases, a multidisciplinary approach to pain may be undertaken, involving a nurse, physician, physical therapist, occupational therapist, nutritionist, massage therapist, and other health care professionals. Complementary and alternative medical techniques, such as acupuncture, may be helpful for selected patients.[54] Growing evidence supports the use of some complementary and alternative medical approaches in pain management, and a recent study found that 70% of arthritis patients were using some sort of complementary and alternative medical technique, although most did not disclose this in their medical history.[55]

Topical analgesics

Topical analgesics are available in gel, cream, or patch form, and are applied to the affected area. Many are available over-the-counter. Some examples are the 5% lidocaine

medicated plaster,[56] the NSAIDs patches, such as the diclofenac epolamine patch,[57] menthol,[58] and essential oxygen oil.[59,60] The advantages of topical products include localized delivery of medication, good evidence for efficacy, better tolerability due to less or no systemic action, and possible benefits in terms of patient adherence.[61] The capsaicin patch, containing an 8% concentration of capsaicin,[62] acts locally but not as an analgesic: a 30–60-minute application provides an improvement for several weeks/months by local nerve defunctionalization.

Paracetamol and NSAIDs

Paracetamol (also called acetaminophen in some geographical areas) is an aniline analgesic, with a well established presence in the pain armamentarium. Despite its familiarity, the exact mechanism of action of paracetamol remains to be thoroughly described.[63] Paracetamol at supratherapeutic doses has been associated with hepatic toxicity[64] and is, in fact, a leading cause of serious liver injury.[65,66] Weak evidence also reports hypertension as a possible side effect of paracetamol use,[67–69] and a decrease in hemoglobin,[70] and gastrointestinal side effects have been reported.[71] Maximum daily doses of oral paracetamol should not exceed 4 g; however, in particular risk groups, such as patients with a history of alcohol abuse or existing liver disease, the use of paracetamol should be avoided.[71,72]

Although often discussed together with paracetamol, NSAIDs are a separate and diverse group of agents reducing prostaglandins and other chemical mediators which induce nociceptive activity and an inflammatory response. NSAIDs interrupt the biotransformation of prostaglandins and mediators in the arachidonic cascade by inhibiting cyclooxygenase (COX) isoenzymes.[73] Nonselective NSAIDs block both COX-1 and COX-2, whereas selective NSAIDs (coxibs) inhibit COX-2. NSAIDs have dose-dependent toxicity, which may result in gastrointestinal symptoms and cardiorenal symptoms.[74,75] Although NSAIDs can be effective pain relievers, a recent study associating NSAID use with increased risk of death from myocardial infarction[76] indicates that they should be used cautiously in patients at risk for cardiovascular disease. These safety issues prompted recommendations to limit the exposure to NSAIDs to the "shortest possible duration at the lowest effective dose."[77] In the elderly, nonselective NSAIDs and selective COX-2 inhibitors should be used "rarely and with extreme caution in highly selected individuals," and elderly patients "with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain, should be considered for opioid therapy."[78]

Opioids

According to the WHO cancer pain ladder, opioids are grouped into step 2 (weak) and step 3 (strong) medications. Frequently prescribed weak opioids include codeine, dihydrocodeine, and tramadol, and frequently prescribed strong opioids are buprenorphine, fentanyl, hydromorphone, methadone, morphine, and oxycodone. Although being effective analgesics, opioid agents in general have been associated with certain dose-dependent adverse events, including nausea, vomiting, constipation, and somnolence. These side effects may occur in the majority of patients and can be treatment-limiting.[79–81] In addition, opioids may be associated with tolerance, dependence, and addiction, and may lead to mood changes, hormonal changes, and an increased risk of fractures.[81,82] Fractures likely result from an increased risk of falls and an effect of opioids on bone metabolism.[81] Opioid-induced hyperalgesia has also been reported, a condition in which prolonged use of opioids lowers the pain threshold, paradoxically increasing the patient's pain, but this is not well understood.[83,84] However, opioids differ in their risk profile; for instance, compared with hydrocodone, tramadol is associated with a reduced risk of fracture,[81] addiction, and dependence.[85] In isolated cases, there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicinal products, such as selective serotonin reuptake inhibitors, or with monoamine oxidase inhibitors.[86] Signs of serotonin syndrome include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus, and diarrhoea. Withdrawal of the serotoninergic medicinal product usually brings about a rapid improvement. Treatment depends on the nature and severity of symptoms.[86]

Combination products

There is a need for treatment options which provide the analgesic efficacy of opioids but are better tolerated. Approaches are either to develop drugs with more than one mechanism of action, eg, tapentadol, which combines two analgesic principles, ie, μ-opioid receptor agonism and noradrenalin reuptake inhibition, in one molecule, or to develop fixed combinations of analgesics with different mechanisms of action.

In selecting an analgesic agent, the WHO ladder may be helpful, but it is validated only in cancer pain. The WHO ladder recommends starting with nonopioid pain relievers, then progressing to weak and finally to strong opioids, based on pain intensity. The WHO paradigm conceives of analgesia as monotherapy. Combining two analgesic agents may provide an additive or synergistic effect of the two components.

This can positively affect the analgesic efficacy of the drug; however, in some cases, it may amplify the side effect profile.[87,88] A combination analgesic regimen may be considered especially effective when the individual agents have different analgesic mechanisms and act synergistically.[9] There are a number of analgesics available combining two agents in one fixed-dose product. These fixed-dose combinations are convenient, reduce the pill burden, and may require lower dosages of the individual compounds. However, they are inflexible and may not provide ideal doses for particular patients. Many combination products use paracetamol. In order to avoid potential paracetamol overdose, patients must be aware of their daily cumulative paracetamol intake. Because paracetamol is found in over-the-counter combination products, as well as prescription combinations, and is available over-the-counter as a monotherapeutic agent, patients may exceed recommended cumulative doses (4 g/day or less[72]) whilst unaware of doing so, or may even be unaware of recommended doses.[89] Nurse prescribers may play an important role in avoiding potentially fatal hepatotoxicity by informing and counseling patients on this point. Patients should be encouraged to inform their nurse prescribers about all additional over-the-counter medications, including paracetamol-containing cold remedies, which are frequently perceived as being harmless.

Examples of fixed-dose combinations containing an opioid include codeine-paracetamol, tramadol-paracetamol, and oxycodone-paracetamol. Synergistic analgesic benefits have been demonstrated for the fixed dose combination tramadol-paracetamol.[90,91] Management with a fixed-dose opioid-nonopioid combination might require less opioid to achieve effective analgesia compared with opioid monotherapy. Opioid-sparing effects may reduce opioid-related side effects and limit the amount of narcotic drug required. Opioid-sparing was demonstrated in two studies comparing tramadol-paracetamol with tramadol monotherapy in the management of subacute low back pain[92] and pain following ambulatory hand surgery with intravenous regional anesthesia.[93] Treatment with the fixed-dose combination reduced tramadol consumption by 24% in both studies, and resulted in significantly fewer side effects than with tramadol monotherapy.

Fixed-dose combination products have shown good efficacy and tolerability in the treatment of a number of acute and chronic pain syndromes. Table 2 summarizes the study results for pain syndromes relevant to the nurse-prescriber. The efficacy of fixed-dose tramadol-paracetamol for example was observed in a large noninterventional study in elderly patients (≥65 years) attending general practices in France.[94] More than half of the patients (65%) experienced significant pain relief of their (mainly musculoskeletal) pain, the incidence of adverse events was low (4.5%), and most patients (91%) were satisfied with their treatment. In the elderly population, in whom conventional analgesics such as NSAIDs should be used with caution,[78] a fixed-dose combination such as tramadol-paracetamol might be a useful treatment option for the nurse-prescriber.

Therapeutic guidelines

There is a wealth of literature about pain management, including guidelines addressing specific pain syndromes,[72,78,111–124] but nurse-prescribers must put these guidelines into the context of a clinical practice at the front line of pain. Guidelines often address the large issues in pain, but may fail to consider matters crucial to nurse-prescribers, such as under-reporting of pain, mixed pain, and chronification. The authors note that, overall, guidelines tend to favor safety over pain relief. For example, the American Heart Association Scientific Statement recommends that patients with elevated cardiovascular risk factors suffering from musculoskeletal pain should avoid using certain pharmacological agents, even if it means that pain is undertreated.[112] Because patient safety must always be paramount, analgesic options should be found which can safely yet effectively address pain. Not treating pain is not an option.

Prescribing considerations for patients in pain

Pain management must take into account the age, comorbidities, functional state, mental health, occupation, family status, and other aspects of the patient's life, as well as the type and anticipated duration of pain. Particular care is advised in treating pediatric and geriatric patients. A full medical history is required. In particular, the nurse-prescriber must be aware of all drugs the patient is taking, including herbal supplements and over-the-counter products. This may require specific inquiry. The more drugs a patient takes, the greater the likelihood of potentially dangerous drug-drug interactions.[125] Paracetamol is safe and effective at recommended doses, but is associated with toxicity at high doses.[126] Paracetamol poisoning can occur accidentally, in that patients may be unaware that paracetamol is contained in many prescription and over-the-counter products. Thus, while fixed-dose combination analgesic products using paracetamol may be effective, opioid-sparing, and safe, it is important to be aware of the patient's cumulative paracetamol dose. Nurse-prescribers can educate patients about the benefits and risks of paracetamol and help patients to understand cumulative paracetamol dosing.

Table 2 Acute and chronic pain syndromes managed with fixed-dose combination analgesics (selected studies are listed)

Study	Patients	Agents	Efficacy	Side effects
Musculoskeletal pain				
Hewitt et al[95] Randomized, placebo-controlled	603 Acute pain associated with ankle sprain	**Tramadol-paracetamol** 37.5 mg/325 mg or 75 mg/650 mg **Hydrocodone-paracetamol** 7.5 mg/650 mg Placebo daily for 5 days	Both combination products provided significantly greater pain relief than placebo with no significant difference between the agents.	Somnolence, nausea, dizziness, vomiting.
Mejjad et al[94] Observational, prospective, open-label, in clinical practice	2663 ≥65 years, primarily with musculoskeletal pain	**Tramadol-paracetamol** 37.5 mg/325 mg Mean daily dose 143 mg/1235 mg median treatment 30 days	Marked reduction from baseline in mean pain intensity score at final assessment. 91% of patients were satisfied or completely satisfied.	Rate of AEs was 4.5%.
Rheumatoid arthritis				
Lee et al[96] Double-blind, randomized, placebo-controlled	277 Add-on for patients with inadequate pain control by conventional NSAIDs and DMARDs	**Tramadol-paracetamol** 37.5 mg/325 mg tid Placebo	Significant improvement in pain relief, significant reduction in pain intensity, no difference in physical function.	Significantly higher rate of AEs. Discontinuation due to AEs was 19% for combination and 3% for placebo.
Raffaeli et al[97] Open-label case series	29 Chronic moderate to severe pain, not taking biological drugs	**Oxycodone-paracetamol** 5 mg/325 mg Mean daily dose at end of study 14 mg/720 mg	42% had good clinical response (EULAR) and 50% showed 20% improvement.	Mild to moderate nausea and vomiting. No serious AEs.
Osteoarthritis				
Choi et al[98] Safety study, randomization to titration and nontitration group	250 Knee OA on stable NSAID therapy	**Tramadol-paracetamol** 37.5 mg/325 mg tid Titration over 7 days for titration group	Titration was associated with equivalent analgesia and better tolerability.	Discontinuation rate was significantly lower in titration group with nausea, vomiting and dizziness the most common AEs (all significantly more frequent in the nontitration group). No SAEs reported.
Corsinovi et al[99] Randomized, single-blind, 6-week study	154 female Geriatric nursing home residents with moderate to severe OA pain	**Oxycodone-paracetamol** (average dose 16 mg/900 mg) **Codeine-paracetamol** (average dose 115 mg/1916 mg) Conventional nonopioid therapy	Fixed-dose combinations significantly reduced mean pain at 6 weeks versus conventional therapy.	AEs did not differ significantly among groups.
Pareek et al[100] Double-blind, randomized, comparative, multicenter 10-day study	220 Knee OA flare	**Etodolac-paracetamol** 300 mg/500 mg bid Etodolac 300 mg bid	Fixed-dose combination significantly reduced pain intensity and improved function Results noticeable within 30 minutes of first dose.	AEs similar in both groups.
Doherty et al[70] Double-blind, four-arm, parallel-group short-term (10 days) and long-term (13 weeks) study	892 Chronic knee pain (85% had OA)	**Ibuprofen-paracetamol** 200 mg/500 mg **Ibuprofen-paracetamol** 400 mg/1000 mg Ibuprofen 400 mg Paracetamol 1000 mg	At day 10, ibuprofen/paracetamol 400 mg/1000 mg showed significantly more pain relief than paracetamol. At 13 weeks, significantly more patients found combination therapy excellent or good compared with paracetamol monotherapy.	Decreases in hemoglobin (≥1 g/dL) occurred in all groups but was twice as frequent in patients taking ibuprofen/paracetamol 400 mg/1000 mg compared with monotherapy.

(*Continued*)

Table 2 (*Continued*)

Study	Patients	Agents	Efficacy	Side effects
Conaghan et al[101] Open-label, randomized, parallel-group 7-day study	220 Hip and/or knee pain, ≥60 years of age	7-day buprenorphine patches (range 5–25 μg/hour) + paracetamol 1000 mg qid **Codeine-paracetamol** (either two 8 mg/500 mg or two 30 mg/500 mg daily)	Noninferiority of patch + paracetamol to codeine-paracetamol combination regarding analgesic efficacy.	Comparable incidence of AEs. High withdrawal rates in both groups.
Low back pain				
Palangio et al[102] Double-blind, randomized, parallel-group	147 Acute pain	**Hydrocodone-ibuprofen** 7.5 mg/200 mg **Oxycodone-paracetamol** 5 mg/325 mg Mean daily dose: hydrocodone-ibuprofen 13.5 mg/360 mg oxycodone-paracetamol 11 mg/715 mg	No significant differences between the groups.	No significant differences between the groups.
Ruoff et al[103] Double-blind, randomized	318 Chronic pain	**Tramadol-paracetamol** 37.5 mg/325 mg Placebo Mean daily dose 158 mg/1365 mg	Significantly improved outcome in all efficacy measures compared with placebo.	Discontinuation due to AEs was 19% for combination and 6% for placebo.
Perrot et al[92] Double-blind, randomized, parallel-group	119 Subacute pain	**Tramadol-paracetamol** 37.5 mg/325 mg Tramadol 50 mg Mean daily dose: Tramadol-paracetamol 172 mg/1495 mg Tramadol 227 mg	Comparable analgesic efficacy.	Significantly fewer AEs with the combination drug. Tramadol consumption reduced by 24% with combination tablet.
Headache				
Silberstein et al[104] Two replicate double-blind, randomized, placebo-controlled studies	576 and 535 Acute migraine	**Sumatriptan-naproxen** 85 mg/500 mg Placebo	At 2 hours, 52% and 51% of combination product patients were pain free versus 17% and 15% of placebo patients ($P < 0.001$).	Most common AEs were nausea (≤4%) and dizziness (≤2%).
Pfaffenrath et al[105] Open-label prephase Randomized, double-blind phase	1734 16–72 years of age, migraine, episodic tension headache or headache of unknown etiology, associated with moderate to very severe pain	Prephase: OTC treatment of choice Randomization: **Acetylsalicylic acid-paracetamol-caffeine** 500 mg/400 mg/100 mg **Acetylsalicylic acid-paracetamol** 500 mg/400 mg Acetylsalicylic acid 1000 mg Paracetamol 1000 mg Caffeine 100 mg Placebo	Overall greater pain reduction occurred in the triple combination group at 2 hours.	No safety data reported. Branded tablets (from a well-known over the counter brand) were significantly more effective in relieving pain than unbranded (but identical) tablets.

Diener et al[106] Post hoc subgroup analysis	610 Treated for 3 independent episodes of severe headache (episodic tension headache or migraine)	**Acetylsalicylic acid-paracetamol-caffeine** 500 mg/400 mg/100 mg Placebo	Combination therapy was significantly more effective in providing pain relief than placebo ($P = 0.0008$) and median time to 50% pain relief was 1 hour and 24 minutes in active and 2 hours and 19 minutes in placebo arms.	Not reported
Fibromyalgia				
Bennett et al[107] Double-blind, randomized, placebo-controlled	315	**Tramadol-paracetamol** 37.5 mg/325 mg Placebo Mean daily dose 150 mg/1300 mg	Significantly better pain relief and health-related quality of life with combination therapy.	Discontinuation due to AEs was 19% for combination and 12% for placebo.
Painful diabetic neuropathy				
Ko et al[108] Open-label, randomized	163 Type 2 diabetes 25–75 years	**Tramadol-paracetamol** 37.5 mg/325 mg Gabapentin 300 mg Mean dose at final visit: Tramadol-paracetamol 158 mg/1371 mg Gabapentin 1575 mg	Comparable mean reductions in pain intensity and mean pain relief scores. Comparable improvements in quality of life.	Similar rates of AEs and discontinuation due to AEs for both groups.
Postoperative pain				
White et al[109] Double-blind, randomized, parallel-group	252 Ambulatory arthroscopic or laparoscopic tubal ligation	**Hydrocodone-paracetamol** 7.5 mg/750 mg Ketorolac 10 mg Placebo Every 6 hours for up to 3 days	No difference in pain relief between the active agents after arthroscopic procedures, both superior to placebo. No difference in pain relief between all 3 groups for laparoscopic procedures	AE incidences similar for both active agents, except higher incidence of postoperative dizziness for hydrocodone-paracetamol.
Sniezek et al[110] Double-blind, randomized	210 Mohs micrographic surgery and reconstruction for head and neck skin cancer	**Ibuprofen-paracetamol** Acetaminophen 1000 mg 400 mg/1000 mg **Codeine-paracetamol** 30 mg/325 mg Immediately after surgery and every 4 hours for up to four doses	Ibuprofen-paracetamol superior to other 2 treatments in pain control.	Higher rate of AEs on codeine-paracetamol compared with ibuprofen-paracetamol and paracetamol alone.
Rawal et al[93] Randomized, double-blind, double-dummy, parallel-group	261 Ambulatory hand surgery with intravenous regional anesthesia	**Tramadol-paracetamol** 37.5 mg/325 mg Tramadol 50 mg Before and immediately after surgery and every 6 hours thereafter	Comparable analgesic efficacy. Tramadol-paracetamol reduced tramadol consumption by 24%.	Fewer AEs with tramadol-paracetamol compared with tramadol monotherapy.

Abbreviations: AE, adverse event; bid, twice daily; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OTC, over the counter; qid, four times daily; SAE, serious adverse event; tid, three times daily.

Multimodal pain therapy

Nurse-prescribers are increasingly recognizing the value of multimodal pain treatments for managing acute and chronic pain syndromes. A multimodal approach simply refers to the use of more than one treatment strategy to address pain. Conservative treatments may include rest, hot or cold therapy, exercise, diet changes, weight loss, smoking cessation, massage, physical therapy, occupational therapy, and others. There is growing evidence in the literature on complementary and alternative medicine techniques, which may offer relief with minimal risk to patients open to this type of treatment. Common complementary and alternative medicine therapy for pain includes acupuncture, aromatherapy, music therapy, and herbal supplements.[54] Pharmacological pain treatment can then be added to this conservative base as needed, starting with nonopioid agents and progressing to fixed-dose combination products and, if necessary, to opioid therapy.

Patient education is an often neglected component in devising a comprehensive pain management plan for pain patients, and especially for those dealing with long-term or chronic pain. Patients should be encouraged to discuss their symptoms and questions about therapy with a qualified clinician or nurse. Patients on pharmacological therapy should be thoroughly informed about the drug(s) they are taking, dosing limits, potential side effects, and drug interactions.

An important component of multimodal pain therapy is the concept that there is no "magic pill". Some patients have the unrealistic expectation that they can simply take one tablet to relieve 100% of their pain. Patients should be encouraged to think of their pain and pain treatments in percentages. For example, regular massage may relieve about 20% of a patient's pain. Instead of dismissing this as insufficient, the patient should build on it. An exercise program may relieve another 30% of the patient's pain. Together, massage and exercise might therefore decrease the patient's pain by 50%. If an analgesic product is then 50% effective, a multimodal therapeutic approach involving massage, exercise, and drug therapy could reduce 100% of the patient's pain. While this is an imperfect analogy, it may be a useful illustration to help patients understand better the fundamental concept underlying multimodal therapy.

Positioning of fixed-dose combinations on the WHO cancer pain ladder

Paradigms of pain management are often based on the older concept that all pain is nociceptive. The WHO cancer pain ladder[127] describes pain and treatments based on pain intensity rather than the nature of the pain (Figure 3).

Over the years, several modifications have been proposed, including adaptations to accommodate other pain types.[128]

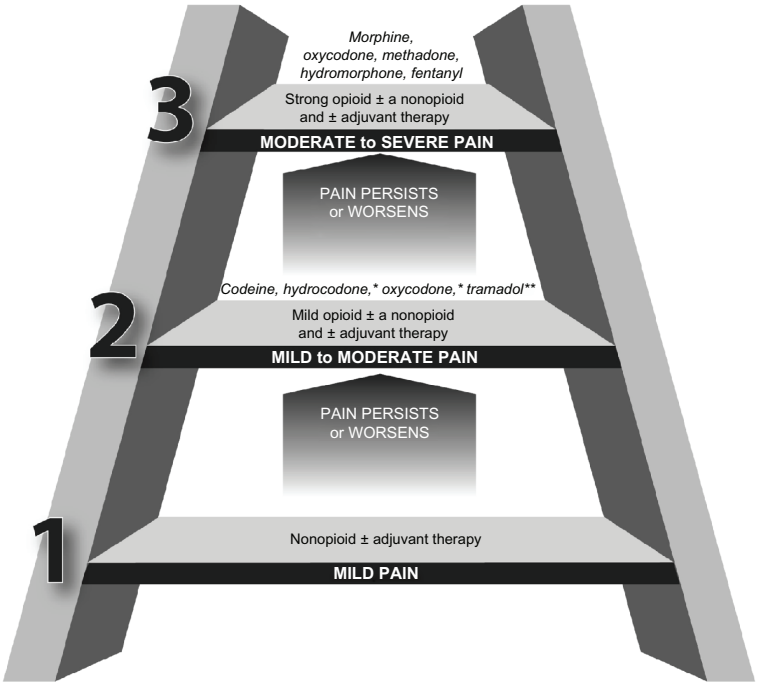

Figure 3 The World Health Organization pain ladder bases therapeutic choices on pain intensity and makes no provision of neuropathic or mixed pain syndromes.
Notes: *In fixed-dose combination products, such as oxycodone and paracetamol or hydrocodone and paracetamol; **considered a step 2 opioid but is also available in fixed-dose combination product of tramadol and paracetamol.
Adapted from World Health Organization pain ladder.[127]

Although created in 1986, the WHO pain ladder is still used to help clinicians understand the "ramp" of progressively stronger analgesics, but it is intended for cancer pain and does not apply well to some conditions like arthritis pain, where NSAIDs are more effective than opioids. Combination products, such as tramadol-paracetamol, were not available in 1986 and it is debatable as to where this and other fixed-dose combination products would fit onto the original WHO ladder. Fixed-dose combination products are basically an unmarked rung on the ladder, because different experts might classify them as step 1 or step 2 analgesics, or between steps 1 and 2, if for instance a step 1 analgesic like paracetamol is combined with a step 2 opioid like tramadol.

Conclusion

Pain is a serious, prevalent, and frequently undertreated condition that can often be effectively and safely managed or even alleviated. Because pain is frequently multimechanistic, multimodal pain therapies including administration of a combination drug may be effective with good tolerability. The pharmacological armamentarium for pain is large and includes topical analgesics, nonopioid agents (such as paracetamol and NSAIDs), weak and strong opioids, and fixed-dose combination products. Proper product selection should take into account the patient's age, condition, type of pain, comorbidities, and balance safety with effectiveness. Fixed-dose combination products, such as tramadol-paracetamol, offer important advantages that a nurse-prescriber should consider, in that they may be opioid-sparing without sacrificing efficacy. Pain should be treated promptly and effectively to restore the patient to full function, avoid pain chronification, and preserve quality of life.

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