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EXPERT OPINION

Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain

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Abstract: Pain is the most common reason patients seek medical attention and pain relief has been put forward as an ethical obligation of clinicians and a fundamental human right. However, pain management is challenging because the pathophysiology of pain is complex and not completely understood. Widely used analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) have been associated with adverse events. Adverse event rates are of concern, especially in long-term treatment or at high doses. Paracetamol and NSAIDs are available by prescription, over the counter, and in combination preparations. Patients may be unaware of the risk associated with high dosages or long-term use of paracetamol and NSAIDs. Clinicians should encourage patients to disclose all medications they take in a "do ask, do tell" approach that includes patient education about the risks and benefits of common pain relievers. The ideal pain reliever would have few risks and enhanced analgesic efficacy. Fixed-dose combination analgesics with two or more agents may offer additive or synergistic benefits to treat the multiple mechanisms of pain. Therefore, pain may be effectively treated while toxicity is reduced due to lower doses. One recent fixed-dose combination analgesic product combines tramadol, a centrally acting weak opioid analgesic, with low-dose paracetamol. Evidence-based guidelines recognize the potential value of combination analgesics in specific situations. The current guideline-based paradigm for pain treatment recommends NSAIDs for ongoing use with analgesics such as opioids to manage flares. However, the treatment model should evolve how to use low-dose combination products to manage pain with occasional use of NSAIDs for flares to avoid long-term and high-dose treatment with these analgesics. A next step in pain management guidelines should be targeted therapy when possible, or low-dose combination therapy or both, to achieve maximal efficacy with minimal toxicity.

Keywords: NSAIDs, opioids, combination analgesics, moderate pain, severe pain, analgesics, tramadol/paracetamol

Introduction

Pain is the oldest medical problem and has been a challenge for doctors since the origin of humanity. While scientific and technological breakthroughs have improved care in many areas, eradicating diseases and advancing longevity, pain remains a global public health issue. The World Health Organization (WHO) has promoted and disseminated guidelines on pain management,[1] advocated for the use of analgesics, including opioids,[2] and encouraged national programs for palliative care and the relief of cancer pain.[3,4] Pain relief has been put forward as a fundamental human right.[5–8] The third international symposium on the Societal Impact of Pain held in May 2012 in Copenhagen has finalized a position paper, seeking that chronic pain be recognised as a disease by the governments of member states.[9] Despite pharmacological advances

and numerous guidelines or consensus documents to inform clinicians about the appropriate prescribing of analgesics, pain is often under-treated.[10–12] Inadequate analgesia may have roots in social, political, legal, cultural, and religious considerations, as well as the fundamental knowledge, differences in health care systems, and variations in clinical practice.[13–16] However, it remains the imperative of medical professionals to relieve pain as much as possible.[17–19] Regardless of the social and political factors complicating analgesic therapy, *not* treating pain is *not* an option and has been described as a "moral outrage."[20]

The European Study of the Epidemiology of Mental Disorders reported from a questionnaire (1659 respondents, all of whom were ≥75 years of age) that pain was the most commonly reported problem in this population (55.2%), far exceeding the rate of depression and anxiety (11.6%).[21] In Europe, it is estimated that 19% of the general population suffers from chronic pain.[22] A hospital-based survey in Germany reported that over 80% of patients (n = 438) experienced pain in the previous 3 months and pain was the main reason for hospital admission in over 60% of the cases.[23] In the USA, chronic pain affects more people every year than diabetes, heart disease, and cancer combined.[24,25] Chronic pain can occur in patients of any age, but it is more common among older individuals.[26] Inadequately treated persistent pain may be associated with a number of adverse outcomes in older people, including functional impairment, reduced mobility, falls, slower rehabilitation, decreased socialization, inadequate sleep, disturbed appetite, and changes in mood.[27] Pain negatively affects quality of life, adversely affects families, may result in lost or diminished productivity for society, and places a large burden on the health care system. In the USA in 2002–2003, over US$4 billion was spent on headache-related care alone, and this did not include over-the-counter medications, self-treatment, and inpatient treatment.[28] The total global health care burden related to all types of acute and chronic pain syndromes is difficult to assess.

Although pain management guidelines address specific types of pain, they frequently recommend nonsteroidal anti-inflammatory drugs (NSAIDs) in cases where tissue damage and inflammation are absent. Due to serious gastrointestinal, cardiovascular, and renal side effects, caution is recommended when using high-dose NSAIDs, particularly when taken long-term.[27,29] The appropriate use of NSAIDs, paracetamol, opioid analgesics, or combination products in the chronic pain population remains a subject of ongoing research.

Meeting details

A consensus meeting attended by all authors of this publication was held on November 20, 2010 in Paris, France, to discuss the use of high-dose NSAIDs, high-dose paracetamol, or tramadol/paracetamol (as an example of fixed-dose combination analgesics) for the management of moderate to severe pain from different etiologies. Tramadol/Paracetamol is – to our knowledge – the only fixed-dosed combination product where the dual mode of action of tramadol and the analgesic synergy between the two compounds have been proven in both preclinical studies (mouse model)[30,31] and companion human studies.[32,33] Presentations by five of the authors were followed by a group discussion and review of pain management issues regarding these drug classes and available guidelines/recommendations based on the clinical experiences of the participants. A manuscript was drafted, additional articles were reviewed and incorporated, and a final consensus was adopted by the group.

Pain management and underlying pain mechanisms

Pain management is complex for many reasons. Chronic pain may be broadly classified into nociceptive (pain owing to tissue disease or damage, including inflammatory and visceral pain), neuropathic (pain caused by somatosensory system disease or damage), and mixed syndromes (coexistence of nociceptive and neuropathic pain).[34] However, even the terminology of pain becomes challenging and contentious.[35] For example, the International Association for the Study of Pain is currently attempting to distinguish between "nociception" (a sensory process) and "pain" (a subjective phenomenon).[36]

Multiple mechanisms contribute to painful syndromes, including nociception, peripheral sensitization, central sensitization, phenotypic switches, ectopic excitability, structural reorganization, and compromised inhibitory systems.[37–41] Hypersensitivity causes a mild stimulus to provoke pain out of proportion to the stimulus. Hypersensitivity may be categorized academically as allodynia (pain response to nonnociceptive stimuli) or hyperalgesia (increased pain sensitivity in response to nociceptive stimuli),[37] although these phenomena may be difficult to distinguish clinically.

The mechanisms may act in different ways. Nociception requires an intact central nervous system; changes in the central nervous system are evident in chronic pain patients.[42] Primary afferent or sensory neurons play an important role in nociceptive pain processing, thus involving the peripheral

nervous system.[42] Inflammation, altered sympathetic and catecholaminergic function, changes in somatosensory processing in spinal cord and brain, pressure, temperature, neuropathic components, along with psychological factors, may also play a role in acute and chronic pain syndromes.[43] The transition from acute to chronic pain is not thoroughly understood, but it is likely to involve the interaction among immune, endocrine, and nervous systems[44] and, therefore, progressing central and peripheral sensitization.[45] Other factors no doubt play a role. A study of trauma patients (n = 290) identified as risk predictors for the transition to chronic pain – that is, pain that persists beyond 3 months: older age, female sex, past alcohol dependence, the amount of morphine equivalents administered on the day of assessment, and attitudes about pain control.[46] A two-dimension positron emission tomography scan study of 20 cancer patients found preferential activation of the prefrontal cortex in patients with chronic pain but not in similar patients without pain.[47] The prefrontal cortex is associated with emotional response, which may account for the emotional component of chronic pain.

In certain rheumatic pain conditions, selective serotonin reuptake inhibitors, serotonin and noradrenalin reuptake inhibitors, as well as tricyclic antidepressants have been shown to exert an analgesic effect that is distinct from their ability to treat depression, fatigue, and sleep disturbances.[48,49] However, the evidence for the efficacy of these drugs in treating common pain syndromes (headache, low back pain, fibromyalgia, postherpetic neuralgia, and others) remains equivocal and, at times, conflicting.[50,51] This suggests that these common pain syndromes may involve different pain mechanisms.

The accurate assessment of pain is challenging because pain perception is subjectively reported and may be influenced by the patient's attitude about health, disease, and personal expectations.[52] These differences may be more than just idiosyncratic. For example, men and women not only experience pain differently, they may respond to analgesics differently.[53]

Pain may be a potentially serious comorbid condition, affecting medical and surgical outcomes.[23] Maladaptive chronic pain may even be regarded as a disease in its own right.[37] As such, it is crucial to devote our attention to better understanding and superior management of patients dealing with acute and chronic pain. The identification and increased understanding of the multiple mechanisms of pain has been a major advance.

Commonly used agents in the treatment of pain

Since the dawn of medicine, clinicians have treated pain (Table 1). As early as 3000 BC, natural salicylates were applied for the treatment of pain and Hippocrates reported on the analgesic efficacy of opium as early as 400 BC. However, in early medicine, these narcotics enjoyed a dubious reputation because of their potential for misuse, potentially life-threatening side effects, and withdrawal symptoms.[54] Chemistry-based anti-inflammatory therapy began in 1897 with the discovery of aspirin, leading to advances in other pharmacological options, including NSAIDs. In 1986, the WHO proposed its well-known "pain ladder," which calls for the treatment of cancer pain based on level of pain intensity rather than the underlying mechanism, in that it advocates the use of nonopioid agents (such as aspirin, paracetamol, and NSAIDs) for mild pain, weak opioids for moderate pain (tramadol), and strong opioids (morphine) for severe pain.[1] The multimechanistic nature of pain is recognized in the WHO ladder insofar as it includes adjuvant medications to treat pain.

When the WHO ladder was introduced in 1986, oxycodone, hydromorphone, and buprenorphine did not exist. Tramadol was not available worldwide until the 1990s. Transdermal delivery systems for opioids were unknown in 1986. Methadone, not listed on the WHO pain ladder, existed in 1986, but its analgesic benefits in treating cancer pain were unknown. The first guidelines for neuropathic pain management were not published until the first decade of the 21st century[55–58] and the neuropathic treatment model differs from the WHO ladder (opioids are adjuvants in neuropathic pain management). Thus, in particular, the pain model should be updated with new pharmacological agents (new opioids, gabapentinoids, etc) according to new insights into adjuvant and multimodal therapies.[59] It should also be noted that all treatment options may be combined with nonpharmacological approaches and patients may benefit from these multidisciplinary efforts.

Weighing the risks of treatment with high-dose NSAIDs and paracetamol

Paracetamol or acetaminophen is frequently grouped with NSAIDs, but it is actually an aniline analgesic. The terms "paracetamol" and "acetaminophen" reflect only geographical differences: "acetaminophen" is the term used in the USA, Canada, Hong Kong, Iran, and certain Latin American countries, such as Colombia, while "paracetamol"

Table 1 Milestones in analgesic agents

Year	Event
3000 BC	First description of the use of myrtle leaves as systemic pain treatment
Approximately 400 BC	Hippocrates reports on the pain-relieving properties of opium in treating internal diseases and diseases of women
1527	Paracelsus prescribes opium with other agents as an analgesic
1680	Thomas Sydenham introduces Sydenham's laudanum (opium mixed with wine and herbs), which becomes a popular home remedy
1803	Friedrich Sertürner discovers the active ingredient in opium – morphine
1827	Merck and Company begin first commercial manufacture of morphine
1877	Synthesis of paracetamol (acetaminophen) at Johns Hopkins University is completed, but the drug would not be used in patients for another 10 years
1890	Morphine, legal in the USA, is taxed by Congress
1895	Bayer Company adds acetyls to morphine to reduce side effects to create a drug that would be marketed in 1898 as Heroin (trade name)
1897	Discovery of aspirin, named for *Spiraea* (meadowsweet), one of many salicylate sources used to treat pain in the nineteenth century
1905	USA bans opium (but not opioid drugs)
1910	Heroin, marketed as a cough suppressant and morphine substitute, is taken off the market when it is found it is more addictive than morphine
1914	The Harrison Narcotics Act in the USA requires physicians and pharmacists who prescribe or dispense narcotics to register (and pay a tax)
1953	Paracetamol (acetaminophen) first marketed in the USA by Sterling-Winthrop Company
1955	McNeil Laboratories first markets Tylenol® brand (paracetamol) in the USA
1956	Frederick Stearns and Company first markets Panadol in the UK
1963	Development of nonsteroidal anti-inflammatory drugs (NSAIDs)
1971	Understanding of the mechanism of action of aspirin
1990–1991	Discovery of cyclooxygenase-2 (COX-2)
1992	COX-2 drug development
1998–1999	Celecoxib and rofecoxib introduced
2004–2006	Rofecoxib withdrawn from market
2005	Warning of increased cardiovascular risk must be added to labeling for all NSAIDs in US (FDA requirement)
2006–2010	Warnings and dose restrictions on NSAIDs
2009	Dextropropoxyphene withdrawn from market in the European Union
2010	FDA launches Safe Use Initiative
2010	Propoxyphene withdrawn from market in the USA

Abbreviation: FDA, US Food and Drug Administration.

is used in Europe, Africa, and most of Asia. The drug is sometimes abbreviated to "APAP" in all geographic regions. The mechanism of action of paracetamol is not well understood and several models have been proposed, all of which have certain strengths and limitations.[60] Paracetamol is metabolized mainly by conjugation with sulfate and glucuronide, with about 5% to 10% of the drug oxidized by the cytochrome P450 metabolic pathway (mostly CYP2E1 and CYP3A4) to a toxic electrophilic metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI). NAPQI is subsequently detoxified by glutathione and eliminated in the urine or bile.[61] If any residual NAPQI is not detoxified in this manner, it may bind to hepatocytes, where it can lead to cellular necrosis. At appropriate doses in healthy individuals, the small amounts of NAPQI produced by paracetamol metabolism can be effectively eliminated with glutathione. However, at higher doses, paracetamol is associated with serious hepatic toxicity.[62] In fact, paracetamol toxicity is the leading indication for liver transplantation in the UK[63] and one of the most common causes of poisoning[64] and acute liver failure[65] in the USA. Paracetamol has also been linked to hypertension,[66–68] which is probably caused by the considerable sodium content present in each paracetamol tablet. Thus, there are still unanswered questions about these side effects, including their extent.[69–71]

NSAIDs encompass a diverse group of drugs that reduce pronociceptive and proinflammatory prostaglandins and other chemical mediators by inhibiting their biotransformation in the arachidonic cascade, a reaction catalyzed by cyclooxygenase (COX) isoenzymes.[72] In this way, they are similar to aspirin.[73]

The safety of many drugs, including pain drugs, has not been studied in as much detail as safety issues of NSAIDs and especially selective COX-2 inhibitors (coxibs). Nonselective NSAIDs block COX, namely COX-1 and

COX-2, blocking the synthesis of prostaglandins and consequently shunting arachidonic acid into the lipoxygenase pathway, producing leukotrienes. Leukotrienes are powerful bronchoconstrictors and impair mucociliary clearance, resulting in increased mucus production, mucus filtration, and edema. Obviously, NSAID use has been associated with bronchospasm.[74] Coxibs selectively block COX-2 and include such drugs as celecoxib, valdecoxib, and rofecoxib, limiting the COX-1-related inhibition to vital housekeeping functions. All NSAIDs are associated with dose-dependent toxicity, manifesting as gastrointestinal symptoms, including dyspepsia, ulceration, and bleeding, as well as cardio-renal complications including fluid retention, hypertension, and renal dysfunction.[75–77] A recent study found even short-term use of NSAIDs was associated with increased risk of death in patients with a history of myocardial infarction (hazard ratio 1.45; 95% confidence interval: 1.29–1.62).[78]

For such reasons, NSAIDs, including coxibs, should not be prescribed as a panacea for all pains, but restricted to pain related to tissue damage and/or inflammation, in accordance to their mechanism of action.[79–81] NSAIDs are to be used cautiously, in patients with or at elevated risk for cardiovascular disease[29,78,79,81–84] or gastrointestinal complications.[79,81,85]

Pharmacological aspects: why combinations might be better than single agents

Rarely does a single known mechanism cause pain. Obviously, no single analgesic agent can fully address multiple mechanisms of pain. Combination analgesic products have been effective because they activate multiple pain-inhibitory pathways and offer a broader spectrum of relief.[86] This may include multiple afferents and pathways as well as multiple processes.

Combination analgesics might reduce adverse events.[86] A given analgesic provides pain relief at a specific dosage and is associated with dose-dependent adverse effects. Combining analgesics may allow for lower doses of the individual agents, with doses possibly low enough to significantly reduce potential adverse events. While the theory of combination analgesic products holds promise, combination products require rigorous scrutiny and testing since not all combinations are ideal.

Combining two or more agents may result in an additive or synergistic analgesic effect.[86,87] When agents are combined, the combination effect may be greater than, less than, or the same as the predicted magnitude of effect, resulting in synergistic, sub-additive, or additive effects, respectively. Such effects are calculated mathematically based on the concept of dose equivalence, defined as doses of each drug that yield the same magnitude of effect when each is used by itself. These calculations compare actual versus expected effects in graphic representations of dose combinations known as isoboles[88–92] (Figure 1). Isobolographic analysis is well accepted and has been used with many drug combinations.[93,94] Drugs with a constant potency ratio have linear isoboles of additivity,[93–95] but drugs with variable potency ratios can be analyzed as well.[96] Receptor saturation of the agents can also be assessed.[97]

Combination analgesic products are common and include, but are not limited to, such products as Empirin® (paracetamol + codeine), Vicodin® (paracetamol + hydrocodone), Percocet® (paracetamol + oxycodone), and Zaldiar® or Ultracet® (paracetamol + tramadol). Table 2 lists selected studies of fixed-dose combinations with paracetamol, all of them having demonstrated good efficacy in several chronic pain conditions.

As an example of fixed-dose combination, the participants of the meeting discussed tramadol/paracetamol because this product has been more extensively evaluated than other combination products. The theoretical rationale for the combination agents described needs to be backed by clinical evidence because, in some cases, additive benefits do not result in clinically meaningful differences. Tramadol/Paracetamol is – to our knowledge – the only fixed-dose combination where both the dual mechanism of action of tramadol and the analgesic synergy between the two compounds have been demonstrated in both preclinical studies (mouse model) and human companion studies using essentially the same study design.[30–33] Table 3 provides an overview of the relevant results. Further study of tramadol/paracetamol combination analgesia in chronic pain syndromes is warranted to better evaluate long-term safety and efficacy.

According to these and later studies, the mechanisms of action of tramadol may be described, respectively as: a weak agonist effect at the μ-opioid receptors, inhibition of serotonin reuptake, and inhibition of norepinephrine reuptake.[98]

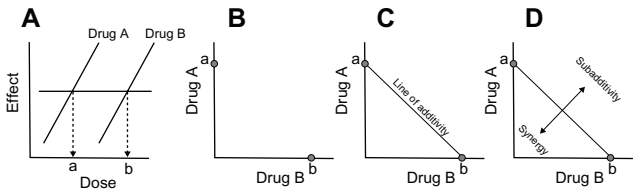

Figure 1 Representation of isobolographic analysis. Equi-effective doses of two drugs are determined (**A**) and graphed on Cartesian coordinates (**B**). The predicted effect of various ratios of combinations of these drugs is simple additivity (**C**). Actual results on, above, or below the predicted line of additivity (**D**) are indicative of additive, sub-additive, or supra-additive (synergistic) interaction, respectively.

Table 2 Selected clinical studies using fixed-dose combination products with paracetamol

Study	N	Agents	Results	Comments
Postoperative pain				
Dental				
Fricke et al[139] Double-blind, randomized	200	• **Tramadol/APAP** 37.5 mg/325 mg • **Tramadol/APAP** 75 mg/650 mg • **Hydrocodone/APAP** 10 mg/650 mg • Placebo • Single dose	• Comparable analgesia between tramadol/ATAP 75 mg/650 mg and hydrocodone/APAP but better tolerability for tramadol/ATAP • Nausea and vomiting were 50% lower with tramadol/APAP 75 mg/650 mg than with hydrocodone/APAP	Removal of ≥2 impacted third molars
MacLeod et al[140] Double-blind, randomized, parallel-group	82	• **Codeine/APAP** 30 mg/1000 mg • APAP 1000 mg • 3 doses over 8 hours	• Combination significantly more effective in pain control • Similar AE incidences	Removal of impacted third molars
Edwards et al[141] Meta-analysis, randomized studies	5 studies	• **Tramadol/APAP** 75 mg/650 mg or 112.5 mg/975 mg • Tramadol 75 mg • Single dose	• NNT for at least 50% pain relief over 6-hour period: – 2.6 tramadol/APAP – 9.9 tramadol	NNH was 5.4 (4.0–8.2) for tramadol/APAP and 5.0 (3.7–7.3) for tramadol
Jung et al[142] Randomized	128	• **Tramadol/APAP** 75 mg/650 mg • **Codeine/APAP/ibuprofen** 20 mg/500 mg/400 mg • Single dose	• Comparable onset of analgesia, analgesic efficacy, and safety profile	Extraction of ≥1 impacted third molar requiring bone removal
Litkowski et al[143] Double-blind, randomized, placebo-controlled, parallel-group	249	• **Oxycodone/ibuprofen** 5 mg/400 mg • **Oxycodone/APAP** 5 mg/325 mg • **Hydrocodone/APAP** 7.5 mg/500 mg • Placebo • Single dose	• Oxycodone/Ibuprofen with significantly better pain relief than other treatments • AE rate of oxycodone/ibuprofen similar to placebo and 2-fold lower to other 2 active agents	Removal of 2 or more impacted third molars
Daniels et al[144] Double-blind, randomized, parallel-group, placebo-controlled	678	• **Ibuprofen/APAP** 400 mg/1000 mg • **Ibuprofen/APAP** 200 mg/500 mg • **Ibuprofen/codeine** 400 mg/25.6 mg • **Codeine/APAP** 30 mg/1000 mg • Placebo • Single dose	• Both doses of ibuprofen/APAP with significantly more effective pain relief than placebo and codeine/APAP • Ibuprofen/APAP 400 mg/1000 mg significantly superior to ibuprofen/codeine; ibuprofen/APAP 200 mg/500 mg noninferior to ibuprofen/codeine • AE rates were higher for codeine combinations	Removal of ≥3 impacted third molars
Other procedures				
White et al[145] Double-blind, randomized, parallel-group	252	• **Hydrocodone/APAP** 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/APAP	Ambulatory arthroscopic or laparoscopic tubal ligation
Palangio et al[146] Double-blind, randomized, placebo-controlled	180	• **Hydrocodone/ibuprofen** 15 mg/400 mg • **Oxycodone/APAP** 10 mg/650 mg • Placebo • Single dose	• Both active combinations provided significantly better pain relief than placebo; hydrocodone/ibuprofen superior to oxycodone/APAP at some time points • AEs similar for active agents	Obstetric or gynecological surgery
Smith et al[132] Double-blind, randomized, placebo-controlled	305	• **Tramadol/APAP** 75 mg/650 mg • **Codeine/APAP** 60 mg/600 mg • Placebo • Mean daily dose: – tramadol/APAP 163 mg/1415 mg – codeine/APAP 130 mg/1296 mg	• Both active combinations provided significantly greater pain relief than placebo; scores were similar for tramadol/APAP and codeine/APAP • Tramadol/APAP was better tolerated than codeine/APAP but AE rates were similar for both active groups	Orthopedic and abdominal surgery

(*Continued*)

Table 2 (*Continued*)

Study	N	Agents	Results	Comments
Sniezek et al[147] Double-blind, randomized	210	• APAP 1000 mg • **Ibuprofen/APAP** 400 mg/1000 mg • **Codeine/APAP** 30 mg/ 325 mg • Immediately after surgery and every 4 hours for up to 4 doses	• Ibuprofen/APAP superior to other 2 treatments in pain control • Higher rate of AEs under codeine/APAP compared with ibuprofen/APAP and APAP alone	Mohs micrographic surgery and reconstruction for head and neck skin cancer
Rawal et al[148] Randomized, double-blind, double-dummy, parallel-group	261	• **Tramadol/APAP** 37.5 mg/325 mg • Tramadol 50 mg • Before and immediately after surgery and every 6 hours thereafter	• Comparable analgesic efficacy, fewer AEs with tramadol/APAP compared with tramadol monotherapy • Tramadol/APAP reduced tramadol consumption by 24%	Ambulatory hand surgery with iv regional anesthesia
Musculoskeletal pain				
Mullican and Lacy[131] Double-blind, randomized	462	• **Tramadol/APAP** 37.5 mg/325 mg • **Codeine/APAP** 30 mg/300 mg • Mean daily dose: – Tramadol/APAP 131 mg/1133 mg – Codeine/APAP 105 mg/1054 mg	• Comparable efficacy, better tolerability for tramadol/APAP	Chronic, nonmalignant low back pain and osteoarthritis pain
Serrie et al[149] Observational, prospective, open-label, in clinical practice (ELZA), mean therapy duration 16.6 days	5495	• **Tramadol/APAP** 37.5 mg/325 mg • Mean daily dose 139 mg/1203 mg	• Significant reduction from baseline in mean pain intensity score • 4.2% of patients with AEs	Majority of patients had musculoskeletal pain
Mejjad et al[150] Observational, prospective, open-label, in clinical practice (SALZA), median treatment 30 days	2663	• **Tramadol/APAP** 37.5 mg/325 mg • Mean daily dose 143 mg/1235 mg	• Marked reduction from baseline in mean pain intensity score (from 6.1 ± 1.6 at baseline to 3.0 ± 1.8 at final assessment) • 91% of patients were satisfied or completely satisfied • Rate of AEs was 4.5%	Patients aged ≥ 65 years, primarily with musculoskeletal pain
Osteoarthritis				
Emkey et al[151] Double-blind, randomized, placebo-controlled	306	• **Tramadol/APAP** 37.5 mg/325 mg • Placebo • Mean daily dose 154 mg/1332 mg	• Significant pain relief, significant improvement in medical assessments, physical function, and subject's and investigator's overall assessment • 13% of tramadol/APAP and 4% of placebo patients discontinued owing to AEs	Add-on for patients with inadequate pain control by celecoxib or rofecoxib
Corsinovi et al[152] Randomized, single-blind	154	• Average dose at end of study: – **Oxycodone/APAP** 16 mg/900 mg – **Codeine/APAP** 115 mg/1916 mg • Conventional therapy (NSAIDs, APAP, COX-2 inhibitors)	• Significantly greater pain reductions for oxycodone/APAP and codeine/APAP compared with conventional therapy • AE rates did not differ between groups	Elderly females
Pareek et al[153] Randomized, open-label	199	• **Aceclofenac/APAP** 100 mg/500 mg bid • Aceclofenac 100 mg bid	• Combination superior in pain intensity differences, sum of pain intensity differences, peak pain intensity differences and patients'/ investigators' assessments • Combination had more rapid onset of action • AE rate similar in both groups	Knee flare-up
Pareek et al[154] Randomized, double-blind	220	• **Etodolac/APAP** 300 mg/ 500 mg bid • Etodolac 300 mg bid	• Compared with etodolac monotherapy, etodolac/APAP was superior in reducing pain intensity and improvement of function • Results noticeable within 30 minutes of first dose • Similar AE rates for both groups	Knee flare-up

(*Continued*)

Table 2 (*Continued*)

Study	N	Agents	Results	Comments
Doherty et al[155] Double-blind, randomized, parallel-group	892	• Ibuprofen 400 mg tid • APAP 1000 mg tid • **Ibuprofen/APAP** 200 mg/500 mg tid • **Ibuprofen/APAP** 400 mg/1000 mg tid	• Ibuprofen/APAP, at nonprescription doses, confers modest short-term benefits • Decreases in hemoglobin by ≥1 g/dL occurred in all groups but were twice as frequent in patients taking 2 combination tablets daily compared with monotherapy	≥40 years of age Chronic knee pain, 85% osteoarthritis
Conaghan et al[156] Open-label, randomized, parallel-group	220	• 7-day **buprenorphine patches** (range 5–25 μg/hour) + APAP 1000 mg qid • **Codeine/APAP** range 16–60 mg/1000 mg qid	• Noninferiority of patch + APAP to codeine/APAP combination regarding analgesic efficacy • Comparable incidence of AEs • High withdrawal rates in both groups	• Hip and/or knee pain • ≥60 years of age
Low back pain				
Palangio et al[157] Double-blind, randomized, parallel-group	147	• **Hydrocodone/ibuprofen** 7.5 mg/200 mg • **Oxycodone/APAP** 5 mg/325 mg • Mean daily dose: – Hydrocodone/ibuprofen 13.5 mg/360 mg – Oxycodone/APAP 11 mg/715 mg	• No significant differences between the groups in efficacy and AEs	Acute pain
Ruoff et al[158] Double-blind, randomized	318	• **Tramadol/APAP** 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	Chronic pain
Perrot et al[159] Double-blind, randomized, parallel-group	119	• **Tramadol/APAP** 37.5 mg/325 mg • Tramadol 50 mg • Mean daily dose: – Tramadol/APAP 172 mg/1495 mg – Tramadol 227 mg	• Comparable analgesic efficacy with significantly fewer AEs with tramadol/APAP • Tramadol/APAP reduced tramadol consumption by 24%	Subacute pain
Fibromyalgia				
Bennett et al[160] Double-blind, randomized, placebo-controlled	315	• **Tramadol/APAP** 37.5 mg/325 mg • Placebo • Mean daily dose 150 mg/1300 mg	• Significantly better pain relief and health-related QoL with combination therapy • Discontinuation due to AEs was 19% for combination and 12% for placebo	
Rheumatoid arthritis				
Lee et al[161] Double-blind, randomized, placebo-controlled	277	• **Tramadol/APAP** 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	Add-on for patients with inadequate pain control by conventional NSAIDs and DMARDs
Raffaeli et al[162] Open-label, case series	29	• **Oxycodone/APAP** 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 • No serious AEs	Patients under rheumatoid arthritis therapy with biological drugs were excluded
Painful diabetic neuropathy				
Freeman et al[130] Double-blind, randomized, placebo-controlled, parallel-group	313	• **Tramadol/APAP** 37.5 mg/325 mg • Placebo • Mean daily dose 158 mg/1365 mg	• Significantly greater improvements for all measures of pain intensity, sleep interference, and global impression as well as several QoL measures and mood • AE rate was 60% for the combination and 59% for placebo, nausea, dizziness, and somnolence significantly more common under combination • Discontinuation due to AEs was 8% for combination and 6.5% for placebo	

(*Continued*)

Table 2 (*Continued*)

Study	N	Agents	Results	Comments
Ko et al[129] Open-label, randomized	163	• **Tramadol/APAP** 37.5 mg/325 mg • Gabapentin 300 mg • Mean dose at final visit: – Tramadol/APAP 158 mg/1371 mg – Gabapentin 1575 mg	• Comparable mean reductions in pain intensity and mean pain relief scores • Comparable improvements in QoL • Similar rates of AEs and discontinuation due to AEs for both groups	Patients with type 2 diabetes aged 25–75 years Dose adjusted to effect, no rescue medication during maintenance phase

Abbreviations: AEs, adverse events; APAP, paracetamol (acetaminophen); bid, twice daily; DMARD, disease-modifying antirheumatic drug; iv, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; NNH, number needed to harm; NNT, number needed to treat; qid, four times per day; QoL, quality of life; tid, three times per day.

Table 3 Companion studies demonstrating mode of action of tramadol/paracetamol fixed-dose combination

	Dual mechanism of action of tramadol		Analgesic synergy between tramadol and paracetamol	
	Mouse and rat model[30]	**Healthy male volunteers[32]**	**Mouse model[31]**	**Healthy volunteers[33]**
Design		Double-blind, randomized, placebo-controlled, crossover		Double-blind, randomized, placebo-controlled, crossover
Agents	Tramadol iv	• Tramadol 100 mg oral dose • 3 hours later, either placebo injection or yohimbine iv 0.1 mg kg^{-1} + placebo or yohimbine + naloxone (μ opioid antagonist) 0.8 mg iv	Oral: • APAP • Tramadol • Tramadol/APAP using different fixed dose ratios (TRAM/APAP ratios tested were: 1000:1, 100:1, 20:1, 3:1, 1:1, 1:3, 1:5, 1:5.7, 1:19, 1:50, 1:100: 1:200, 1:800, and 1:1600)	iv infusions: • APAP 650 mg • Tramadol 75 mg • Tramadol/APAP 37.5 mg/325 mg • Placebo
Methods	• Mouse acetylcholine-induced abdominal constriction test • Rat air-induced abdominal constriction test • Mouse/rat hotplate and tail-flick tests • Yohimbine (α_2-adrenoceptor antagonist) and ritanserin (5HT2A/2C antagonist) antagonism in rats and mice	• Induction of pain by electrical stimulus • Assessment of subjective pain threshold (pain intensity rating) and objective pain threshold (R III nociceptive reflex) for 8 hours after tramadol intake	• Acetylcholine bromide injection 30 minutes after analgesia delivery • Assessment: occurrence of a single abdominal constriction response • Estimation of ED_{50} from individual dose–response curves	• Induction of acute pain and mechanical hyperalgesia by transcutaneous electrical stimulation at high current densities • Drugs were delivered in a 15-minute infusion starting 30 minutes after onset of electrical stimulation • Assessments before, during, and 150 minutes after infusion
Results	• Tramadol produced dose-related anti-nociception in all tests • This anti-nociceptive activity was completely antagonized by naloxone • Administration of yohimbine or ritanserin blocked anti-nociceptive activity produced by tramadol but not the one produced by morphine	• Tramadol induced a significant increase in both thresholds • Yohimbine almost totally reversed the subjective (67%) and objective (97%) anti-nociceptive effect of tramadol for 2.8 hours • Addition of naloxone abolished tramadol effects (79% for subjective, 90% for objective pain threshold)	ED_{50} values: • Tramadol 5.5 ± 0.4 • APAP 164.9 ± 24.5	Pain reduction (correction for placebo effects) • Tramadol 11.7% ± 4.2% • APAP 9.8% ± 4.4% • Tramadol/APAP 15.2% ± 5.7% Anti-hyperalgesic effect (correction for placebo effects) • Tramadol 7.4% ± 8.1% • APAP 34.5% ± 14% • Tramadol/APAP 41.1% ± 14.3%
Conclusions	The results suggest that tramadol-induced anti-nociception is mediated by opioid (μ) and nonopioid (inhibition of monoamine uptake) mechanisms	$Alpha_2$-adrenoceptor antagonism reverses tramadol effects, thus pointing to significant role of monoaminergic modulation and synergy with opioid antagonism in tramadol anti-nociception		Supra-additive effects of the combination regarding analgesia and anti-hyperalgesia

Abbreviations: APAP, paracetamol (acetaminophen); ED_{50}, the dose of a drug that is pharmacologically effective for 50% of the population exposed to the drug or a 50% response in a biological system that is exposed to the drug; iv, intravenous.

In a preclinical model, it has been shown that the nonopioid component in tramadol may enhance its potency ratio relative to morphine in neuropathic pain models.[99] Tramadol can increase the risk of convulsions in patients who are taking medicinal products reducing the seizure threshold such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics. 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 medicines such as selective serotonin reuptake inhibitors.[100] The second component in this fixed-dose combination, paracetamol, appears to act at both central and peripheral pathways,[101] but its exact mechanism(s) of action has/have yet to be thoroughly elucidated. The maximum recommended adult dose of paracetamol is 4 g/day.[102,103] At therapeutic doses, paracetamol is rarely associated with hepatotoxicity.[104]

Complementary pharmacokinetics of tramadol/paracetamol in combination enhance the probability of effective pain relief (Figure 2) and supra-additive effects of the combination regarding analgesia and anti-hyperalgesia have been demonstrated in a human pain model.[33] Clinical studies have shown good efficacy and safety of this fixed-dose product for a variety of pain conditions.[105,106] Details from selected studies can be found in Table 2.

Mitigation strategies when prescribing high-dose NSAIDs or high-dose paracetamol

Before high-dose paracetamol or high-dose NSAIDs are considered for patients, mitigation strategies should be undertaken, including the review of patients to verify if they are appropriate candidates for such therapy in light of their comorbidities and co-medications.[107] Upper gastrointestinal adverse effects can be mitigated by proton pump inhibitors.[108–112] Patients on long-term high-dose paracetamol or NSAID therapy should be educated as to the potential risks of these drugs, the doses, and the fact that these agents may be contained in a variety of prescription and over-the-counter products. In the USA, this has been called a "do ask, do tell" strategy, where clinicians are encouraged to ask patients about their use of concomitant medications, including over-the-counter products and, by the same token, patients are encouraged to fully disclose to their clinicians all of the drugs they take.[113] For many patients, it may be appropriate to use a low-dose combination product for maintenance, with occasional NSAIDs to treat breakthrough episodes. An individualized approach to mid- and long-term pain management is required in light of the potential risks and benefits of analgesic agents (Table 4).[114]

The mitigation of adverse events is more than just a matter between clinician and patient. We recommend the use of plain language in labeling over-the-counter products and prescribed medications that contain paracetamol and/or NSAIDs to help patients in monitoring their own daily and cumulative doses. Comprehensive educational efforts are required to alert patients to the dangers of many over-the-counter analgesics and to inform them of appropriate doses and how to calculate them. Many patients consider over-the-counter products "harmless" and may take these agents casually. Patient education should include "do ask, do tell," such that patients understand the importance of discussing with their clinicians all drugs they take.

Current guidelines and pain management in specific populations

When it comes to pain management, there is no lack of literature, including consensus statements and guidelines.

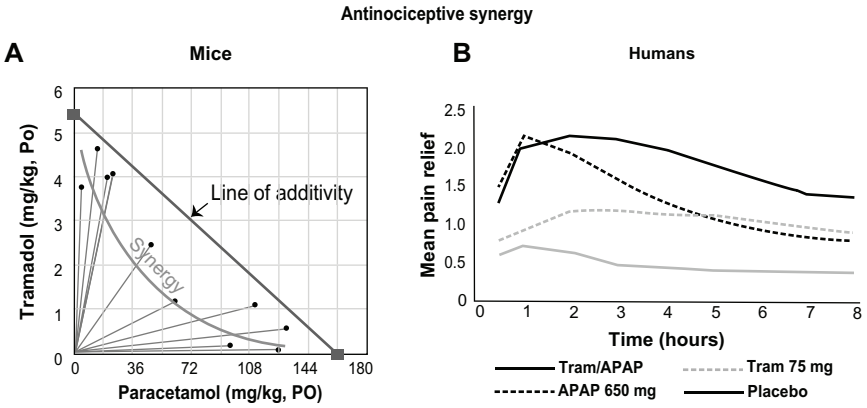

Figure 2 Mean pain relief with (**A**) tramadol/paracetamol (Tram/APAP) compared with (**B**) paracetamol 650 mg alone (APAP 650 mg), tramadol 75 mg alone (Tram 75 mg), and placebo.
Notes: (**A**) Adapted from *Life Sciences*, 58(2), Tallarida RJ, Raffa RB, Testing for synergism over a range of fixed ratio drug combinations: replacing the isobologram, PL 23–PL 28, Copyright (1996), with permission from Elsevier.[31] (**B**) Adapted from an FDA Executive Summary [web page on the Internet; McNeil background package to the Nonprescription Drug Advisory Committee]. 2002.[168]

Table 4 Mitigation strategies that may be useful for patients receiving paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management

Area of concern	Mitigating strategies
Labeling of paracetamol, acetaminophen, and combination products, particularly over-the-counter preparations	Plain language labeling Patient education initiatives about high-dose, long-term, and cumulative doses of paracetamol and NSAIDs "Do ask, do tell" approach
High-dose paracetamol seems necessary	Consider lower doses of paracetamol in combination with other pain medication due to risk of hepatotoxicity, hypertension, and gastrointestinal complications
High-dose NSAID seems necessary	Consider lower doses used in combination with other pain relievers on account of increased risk for gastrointestinal complications and particularly in light of risk factors (old age, ulcer history, smoking, comorbidities) Add proton pump inhibitor Limit dose
NSAID seems necessary in a patient with a cardiovascular risk	Consider the lowest possible dose of NSAIDs or avoid NSAIDs altogether. An alternative might be a low-dose fixed combination product

Yet, pain is undertreated. Up to 27% of people with constant or daily musculoskeletal pain never seek treatment and many people with chronic pain seek medical help for the first time only after a year or more of pain.[115] It may be inferred that many people feel pain as something they have to live with or that clinicians are unable to treat pain effectively. Between 28% and 54% of patients with musculoskeletal pain under medical care do not take any prescription analgesics.[115] Further, patients may have serious concerns about analgesics; for example, 65%–77% of pain patients considering opioid analgesics have fears of tolerance or addiction.[115]

Many guidelines for the management of pain in specific populations exist.[27,29,79,81,116–127] These guidelines are largely evidence-based documents, but at times the absence of evidence is construed as the evidence of absence. Important topics in pain management, such as, but not limited to, the transition from acute to chronic pain, are not addressed by the guidelines. In general, the guidelines tend to stress avoidance of adverse events at the expense of efficacy in the treatment of moderate to severe pain. The American Heart Association scientific statement recommends a stepped-care approach to pharmacological therapy for musculoskeletal pain patients with known cardiovascular disease or at risk for ischemic heart disease that emphasizes avoidance of potential risk at the expense of pain relief.[29]

Elderly patients

Chronic pain is both common and especially challenging to treat in geriatric patients, who often suffer from comorbidities. Chronic pain adversely affects the quality of life, mobility, and mood, and may limit daily activities and social pursuits in patients of all ages, but younger patients may be more resilient or better able to cope with these limitations than older patients. According to the most recent guidelines issued by The American Geriatrics Society, NSAIDs for the treatment of chronic pain should be avoided in patients aged 75 years or older; NSAIDs should be "considered rarely, and with extreme caution, in highly selected individuals."[27] Paracetamol should be considered as the initial and ongoing therapy of choice except for patients with a known liver disease. The maximum recommended daily dose of paracetamol is 4 g/24 hours and should not be exceeded. This maximum daily intake must include hidden sources in other medications. All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy.[27]

Overview on experience with fixed-dose tramadol/paracetamol in the treatment of moderate to severe pain in nonacute conditions: differences to NSAIDs

NSAIDs are frequently prescribed analgesic agents but recent warnings – including a US Food and Drug Administration labeling proposal that all NSAIDs should be prescribed at the lowest possible doses for the shortest possible duration[128] – have caused many clinicians to reevaluate these effective painkillers. Recently, new combination analgesic products based on scientifically reasonable design have been introduced to the market to offer effective analgesia with a good risk/benefit ratio. The combination product tramadol/paracetamol may be an important aid for the treatment of acute and chronic pain syndromes (Table 5).

Pain involving multiple mechanisms, can be safely and effectively treated with combination analgesics, for example,

Table 5 Comparison of nonsteroidal anti-inflammatory drugs (NSAIDs) with tramadol/paracetamol fixed-dose combination

	Selective and nonselective NSAIDs	Tramadol/paracetamol combination
Pain severity	For mild to moderate pain	For moderate to severe pain
Clinical application	Wide, including rheumatic disorders, headaches, visceral pain	Wide, indicated for symptomatic relief of moderate to severe pain
Acute vs chronic pain	Both	Both
Neuropathic pain	No, exclusively for pain related to tissue damage and/or inflammation	Yes[129,130]
Anti-inflammatory effect	Yes	No
Pediatric use	Yes	No
Geriatric use	With caution[27]	May be appropriate[27,150]
Use in patients with renal failure	No[163]	Not recommended for severe renal insufficiency (creatinine clearance < 10 mL/min) but may be used at reduced dose in patients with moderate renal insufficiency (creatinine clearance between 10 and 30 mL/min) Tramadol is removed only very slowly by hemodialysis or hemofiltration, so post-dialysis administration to maintain analgesia is usually not required
Co-medications	Caution with diuretics, anticoagulants, angiotensin-converting-enzyme inhibitors	Caution with other central nervous system depressants, selective serotonin reuptake inhibitors[164]
Use with concomitant opioids	May be synergistic[86]	Overdose considerations
Use with anticonvulsants	Not known	Not known

tramadol/paracetamol.[129,130] However, there are few direct comparative studies of combination products – for instance, codeine/paracetamol versus tramadol/paracetamol.[131–133]

Long-term pain management recommendations often feature NSAIDs as a first-line treatment for rheumatic diseases,[134,135] with added opioid combination analgesics for flares.[136–138] A possible new paradigm would be to treat pain first with opioid combination analgesics then use NSAIDs to manage flares. Table 6 summarizes the strengths and weaknesses of NSAIDs versus tramadol/paracetamol fixed-dose combination products.

Recent guidelines for pain management and the position of paracetamol, NSAIDs, and fixed-dose combinations such as tramadol/paracetamol are shown in Table 7.

Consensus statements

The group arrived at several consensus statements. These follow, grouped by topic.

Pain management

- There are many reasons why pain management is complex, including the classification of pain, mechanisms, knowledge, individualization, lack of universally accepted guidelines, social and psychological factors, as well as various influences from the health care system itself. Nevertheless, *not* treating pain is *not* an option.
- Individualization of treatment in patients suffering from moderate to severe pain should be the ultimate goal of the health care team.
- Pain management guidelines must take into consideration the type of pain, its intensity, the particular patient characteristics, and expected duration of treatment. This requires a multidimensional approach, which creates difficulty in making generalized recommendations.
- Many evidence-based guidelines for pain management are available, but none is universally accepted by all health care providers. These guidelines may benefit

Table 6 Strengths and weakness of tramadol/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs)

	NSAIDs	Tramadol/paracetamol
Strengths	• Frequently prescribed • Ubiquitous • Gold standard for many conditions: ibuprofen • Well tolerated short term • Over-the-counter availability	• Recent combination of established analgesics with scientifically and clinically based rationale • Good benefit–risk balance • No specific warnings
Weaknesses	• Recent warnings • Safety profile (gastrointestinal, renal, and cardiovascular risks) • Coadministration with other drugs	• Combination therapy not well established • Difficult to differentiate from tramadol immediate release, tramadol extended release • Not well tolerated short term

Table 7 Summary of guidelines and recommendations for paracetamol (APAP), nonsteroidal anti-inflammatory drugs (NSAIDs), and combination products such as tramadol (tram)/paracetamol

Guideline	APAP	NSAIDs	Combination (tram/APAP)	Comments
Osteoarthritis (OA)				
Management of OA Altman overview[117]	1st	(Yes)	Yes	NSAIDS for anti-inflammatory action
Early management of OA Altman overview[118]	1st	(2nd)	3rd	Oral NSAIDs at their lowest effective dose; long-term use should be avoided
NICE OA guideline[81]	1st	2nd with PPI	–	Oral NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time
OARSI guidelines[79]	1st	(2nd)	–	Oral NSAIDs at lowest effective dose; long-term use should be avoided
ACR Guidelines[165]				
Hand OA	No	1st	–	Topical or oral NSAIDs; topical NSAIDs for persons ≥75 years of age recommended
Knee OA	1st	2nd	–	Health care providers should be aware of the warnings and precautions associated with topical and oral NSAIDs
Hip OA	1st	2nd	–	Oral NSAIDs; no recommendation on topical NSAIDs
Rheumatoid arthritis (RA)				
NICE RA guideline[119]	1st	(2nd + PPI)	1st (compound analgesics in general)	Oral NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time
BSR guidelines for early RA[120]	2nd (as add-on)	(1st)	2nd (as add-on)	Long-term use of NSAIDs at lowest effective dose. At present, the use of single or compound analgesics or anti-inflammatory drugs (including coxibs) has to be settled with each individual patient No clear recommendations
BSR guidelines for long-term treatment of RA[121]	–	2nd as add-on with PPI	–	No clear recommendations
EULAR recommendations early arthritis[122]	–	(Yes)	–	NSAIDs after careful evaluation of gastrointestinal, renal, and cardiovascular status
Fibromyalgia				
EULAR recommendations for fibromyalgia[123]	Yes	–	–	Tramadol is one of the analgesics of choice
APS guidelines for fibromyalgia[124]	No	No	3rd	Tricyclic antidepressants first, serotonin reuptake inhibitors (SSRIs) alone or in combination with tricyclics second. Paracetamol not recommended as monotherapy, only in combination
Low back pain				
European guidelines for chronic nonspecific low back pain[125]	–	(Yes)	(Yes)	NSAIDs should only be used for exacerbations or short-term periods (up to 3 months)
APS/ACP guidelines[126]	1st	(1st)	–	Oral NSAIDs at their lowest effective dose, for the shortest possible time required
NICE. Low back pain guideline[127]	1st	2nd (+ PPI for patients aged > 45 years)	–	Weak opioids and strong opioids are suggested for more severe pain, but no combinations
Musculoskeletal pain				
Schnitzer, guidelines for chronic musculoskeletal pain[116]				NSAIDs not for long-term use or in patients with risk factors; second
Osteoarthritis	1st	No or 2nd	2nd	for short-term use

(*Continued*)

Table 7 (*Continued*)

Guideline	APAP	NSAIDs	Combination (tram/APAP)	Comments
Low back pain		2nd	1st	Young, healthy individuals could receive NSAIDs alone or at a reduced dose combined with paracetamol/tramadol
following injury	2nd as add-on	(1st)	3rd	
Rehabilitation	1st	1st for pain in motion and for inflammation	2nd as add-on	
Specific patient populations				
AGS geriatric guidelines[27]	1st	(2nd) + PPI or misoprostol	(2nd)	For paracetamol, maximum daily recommended dosages of 4 g per 24 hours should not be exceeded and must include "hidden sources" Nonselective NSAIDs and COX-2 selective inhibitors may be considered *rarely, and with extreme caution*, in highly selected individuals All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy Maximal safe doses of paracetamol or NSAIDs should not be exceeded when using *fixed-dose opioid combination* agents
AHA guidelines[29]	1st	(3rd)	–	NSAIDs at their lowest effective dose + ASA 81 mg and PPI for patients at increased risk of thrombotic events
Neuropathic pain				
Dworkin et al[166]	–	–	–	Tramadol is recommended as second-line treatment Standard treatments such as NSAIDs and paracetamol have no proven efficacy against neuropathic pain although they are frequently prescribed for patients with neuropathic pain[167]

Notes: –, not mentioned in guideline; 1st, first-line therapy; 2nd, second-line therapy; 3rd, third-line therapy; NO, not recommended; Yes, recommended but not first-, second-, or third-line recommendation; (Yes), recommended with caution.
Abbreviations: ACR, American College of Rheumatology; ACP, American College of Physicians; AGS, The American Geriatrics Society; AHA, American Heart Association; APS, American Pain Society; ASA, acetylsalicylic acid; BSR, British Society for Rheumatology; COX, cyclooxygenase; coxibs, selective COX-2 inhibitors; EULAR, European League Against Rheumatism; NICE, National Institute for Health and Excellence; PPI, proton pump inhibitor.

by addressing topics such as the chronicity of pain, barriers to treatment, patient preferences influencing pain therapy, and practical clinical considerations. Current guidelines mostly contain strong evidence for pharmacological approaches; however, they would benefit from the addition of considerations related to the evidence or absence of evidence of risks of drugs and inclusion of nonpharmacological treatment options.

The use of NSAIDs and paracetamol in chronic pain management

- NSAIDs and paracetamol are commonly used and commonly recommended agents for the management of pain and are helpful for many patients. However, they are not without potential risks, especially in the elderly and in patients with renal, gastrointestinal, or cardiovascular disease. High doses and long-term use of NSAIDs to manage moderate to severe pain have been associated with tolerability issues, including serious adverse events.
- Fixed-dose combinations provide a multi-mechanistic analgesic approach. Clinical studies have demonstrated effective management of various types of moderate to severe pain with mostly good tolerability.
- A new approach to managing arthritis-related pain is to consider the long-term use of low-dose combination products for moderate to severe pain, and reserving NSAID use for acute flares related to inflammation.

The role of fixed-dose combinations in chronic pain management using tramadol/paracetamol as an example

- Tramadol/Paracetamol may offer distinct advantages in certain patient populations and for certain types of pain, compared with high doses of NSAIDs or paracetamol or when NSAIDs or paracetamol are expected to be used for long durations. However, long-term studies of fixed-dose combinations are required.
- Potential advantages of a fixed-dose tramadol/paracetamol analgesic product include a broader analgesic spectrum, a complementary pharmacokinetic profile, potentially synergistic analgesic effect, greater convenience (possibly resulting in better compliance, thus, improved therapy), and an improved ratio of efficacy to adverse effects.

Conclusion

Pain management is a global challenge to clinicians and, despite the plethora of evidence-based guidelines, all analgesic options must be individually assessed and weighed for specific risks and benefits in a given patient. Many effective analgesics exist but are associated with adverse events. NSAIDs and paracetamol are effective pain relievers, but recent studies have raised safety concerns, particularly when these agents are used at high doses, long-term, or in special patient populations. Opioid analgesics are effective but are associated with adverse events as well as concerns over tolerance and addiction. Finding an analgesic product that offers both effective pain relief and a good safety profile has led to increasing interest in combination products.

Combination agents may offer analgesic synergy that allows them to provide effective analgesia at reduced doses. However, careful study of combination agents is warranted, as such combination products might also exacerbate side effects. New fixed-dose combination products may offer an improved method of treating the newly recognized multi-mechanistic nature of pain. Studies of fixed-dose combinations such as tramadol/paracetamol for the treatment of chronic pain syndromes are promising, showing safe and effective pain relief with good tolerability and safety profiles.

A new practice paradigm may be to use low-dose paracetamol or fixed-dose combination products, and NSAIDs to manage acute flares. However, further studies are warranted to establish the long-term efficacy and safety of these products.

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