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ORIGINAL RESEARCH

# The Role of Dexketoprofen/Tramadol in Multimodal Therapy to Prevent Acute Postsurgical and Acute Low Back Pain from Developing into Chronic Pain: A Delphi Consensus Study

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## ABSTRACT

***Introduction***: Dexketoprofen/tramadol is a fixed-dose multimodal combination analgesic that significantly controls multiple acute pain states, and may have an important clinical application in providing pain control adequate to prevent the transition from acute to chronic postsurgical and low back pain. A consensus is needed to quantify and define the actual burden of postsurgical pain (PSP) and low back pain (LBP), which can support efforts toward effective approaches to manage potential pain chronification.

***Methods***: This study utilized a modified Delphi approach. A Scientific Committee set forth 28 statements on six themes about the burden of acute PSP and LBP, their potential transition to chronic pain, their pathophysiology, therapeutic

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approaches to stop this transition, and the role of multimodal analgesia in this context, specifically a fixed-dose combination oral product of dexketoprofen/tramadol. An international panel of healthcare professionals from various regions and relevant medical specialties participated in a Delphi study and were surveyed for consensus on a 5-point Likert scale with consensus defined as > 70% concordance. A round of online voting lasting 3 months and using an online survey platform was permitted for each participant.

***Results*:** A total of 100 experts completed the Delphi survey. All the 28 proposed statements reached consensus > 70% in the first round of voting. A fixed-dose combination product, specifically dexketoprofen/tramadol was recognized as a multimodal analgesic which could effectively relieve acute pain and act to prevent its transition to chronic pain. The high global burden of chronic PSP (CPSP) and chronic LBP (CLBP) was identified as well.

***Conclusions*:** Healthcare professionals who deal with pain recognize the burden of acute pain, the risks of acute pain transitioning to chronic pain, and inspire to avert the transition by providing effective multimodal control of acute pain. The role of fixed-dose combination analgesics, in particular dexketoprofen/tramadol, was recognized by consensus as an efficacious and safe therapy option for these acute pain syndromes.

A Video Abstract is available for this article. To view, please see the online version of the manuscript or follow the 'Digital Features' link. A Video Abstract for The Role of Dexketoprofen/Tramadol in Multimodal Therapy to Prevent Acute Postsurgical and Acute Low Back Pain from Developing into Chronic Pain: A Delphi Consensus Study (MP4 112565 KB)

**Keywords:** Analgesics; Delphi study; Dexketoprofen; Dexketoprofen/tramadol fixed-dose combination; Fixed-dose combination products; Multimodal analgesia; Opioids; Pain chronification; Pain; Tramadol

## Key Summary Points

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|---|
| *Why carry out this study?* |
| Acute pain can transition into chronic pain, but this transition may be averted (stopped) by adequate analgesia in the acute phase. Since in many acute pain syndromes, such as acute postsurgical pain (PSP) or low back pain (LBP), pain is poorly controlled (acute analgesia is inadequate). |
| a consensus is needed among experts as to the therapeutic options available to stop the transition from acute to chronic pain, to define unmet needs in stopping pain chronification, and to assess currently available analgesic options, such as an oral fixed-dose combination product of dexketoprofen/tramadol. |
| **What was learned from this study?** |
| The expert panel of 100 healthcare professionals dealing with various pain syndromes agreed on all statements, underscoring the need for optimal management of acute pain and awareness of the need to prevent the transition from acute to chronic pain. |
| The expert panel concurred on the value of multimodal analgesia to address multimechanistic forms of acute pain. |
| The expert panel recognized that pain is often multifactorial, and analgesia must accommodate this sometimes-complex pathogenesis. |
| The expert panel concurred that an oral fixed-dose combination product of dexketoprofen/tramadol used for up to 5 days may enhance pain control and reduce the risk of transitioning from acute to chronic pain because of its complementary pharmacokinetics and mechanisms of action. |

## DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.30272539

## INTRODUCTION

An oral fixed-dose combination analgesic product composed of dexketoprofen 25 mg and tramadol 75 mg is available in some European, American, and Asian countries for the short-term (up to 5 days) treatment of moderate-to-severe acute painful conditions [1]. It is one of several fixed-dose combination products, such as hydrocodone 7.5 mg combined with 400 mg ibuprofen, oxycodone 5 mg combined with 400 mg ibuprofen and other products that offer multimodal analgesia [2]. Multimodal analgesia is based on the use of two or more complementary analgesic agents with different mechanisms of action; besides effective pain control, an advantage of multimodal analgesia is that opioid analgesics may be used at lower doses, potentially reducing side effects, without sacrificing pain control [2]. Multimodal analgesics may offer additive benefits (the sum of two analgesics) or synergistic benefits (where the sum of the analgesia is greater than its parts); the design of such analgesics has been described in the literature [3]. A previous Delphi study found that dexketoprofen/tramadol is a rapidly acting, long-lasting, multimodal fixed-dose combination analgesic that is effective and generally well-tolerated in patients with moderate-to-severe acute pain [4]. Acute postsurgical pain (PSP) and low back painn (LBP) are prevalent acute pain conditions encountered frequently in clinical practice. A Delphi study has explored common clinical practices for the treatment of LBP [5].

While chronic pain is typically defined as painful symptoms that persist for more than 3 months, chronic primary pain is mechanistically distinct from acute pain [6]. Persistent pain is a term often used to describe pain that is moving beyond the temporal limits of acute pain but is not yet chronic. However, chronic pain involves central sensitization such that pain signals are aberrantly amplified and become disconnected from their original source [7]. As such, chronic pain may in some cases be a disease unto itself [8]. It is not helpful to think of chronic pain as merely long-lasting acute pain. Chronic pain poses many clinical challenges: it can be difficult to treat, has yet to be thoroughly elucidated, diminishes the patient's quality of life, and is associated with substantial burdens to the healthcare system [9]. Exacerbating this challenge is the high prevalence of chronic pain around the world.

While chronic pain is a global public health crisis, its prevalence varies by region for a number of reasons: population demographics (particularly age), definition of chronic pain, availability of analgesics [10], and other factors, one of which may be how effectively acute painful conditions are controlled. Besides suffering, social isolation, loss of function, diminished productivity, and higher healthcare costs, chronic pain is associated with depressed mood, cognitive dysfunction, fall risk, constipation, and sedation, particularly in older individuals [11]. Chronic pain is not rare. In Saudi Arabia, the prevalence of chronic pain has been estimated to be as high as 46.4% [12]. In Western Europe, chronic pain prevalence is 27% [13]. The China Pain Health Index completed in 2020 estimated chronic pain prevalence in that nation at 30% with marked strong regional variations [14]. In 2019, a study found that 20.5% of the USA population reported pain on most days or every day, frequently in the back [9]. Chronic pain prevalence in Peru is 38.5%, with about half of those individuals receiving no pharmacologic treatment [15]. It is not an overstatement to label chronic pain a silent epidemic or a major public health crisis.

Chronic low back pain (CLBP) is among the most frequent types of chronic pain syndrome anywhere in the world, with a particularly high prevalence (up to 18%) in low- and middle-income countries and prevalence of about 12% globally [10]. Postsurgical pain (PSP) is a normal, expected phenomenon in the acute period

following surgery and affects approximately 80% of all surgery patients; acute postsurgical pain follows a predictable trajectory with pain most severe immediately after the operation and decreasing daily intensity thereafter as the tissue heals. Chronic postsurgical pain (CPSP) persists long after the tissue has healed and becomes centralized, enduring months and even years after surgery. CPSP may be more intense than the acute surgical pain, pain sites may migrate, and it can have a neuropathic component; CPSP is both prevalent and under-treated [16]. In a study of patients who underwent a total hip or knee replacement, 38% and 53%, respectively, reported persistent pain a year after surgery [17]. About 40% of chronic pain is undertreated or entirely untreated [18].

Timely and effective acute pain treatment is crucial to interrupt the cascade of events in the nervous and immune systems that can allow acute pain to transition into chronic pain [19, 20]. According to an expert-consensus definition, "pain chronification" describes the process by which transient pain progresses into persistent and then chronic pain owing to alterations in pain information processing caused by an imbalance between pain amplification and pain inhibition [7]. The risk, degree, and time course of pain chronification is determined by the interplay of multiple factors, notably genetics, environment, and biopsychosocial factors [7]. Effective acute pain control is crucial and available evidence supports the use of multimodal pain treatments in many situations, although the exact components of effective multimodal care vary on the basis of the patient, the cause of pain, and the setting [21, 22]. In real-world clinical practice, acute pain is not always effectively treated [20, 23], and this can lead to chronic pain, particularly in the cases of CPSP and CLBP [23–26]. In a community study, the rate of transition from acute low back pain to CLBP was 32.2% at 3 months and 80.6% at 6 months [27]. The prevalence of CPSP varies on the basis of the type of surgery and other factors, affecting 5–85% of patients, with highest rates following thoracic surgeries, amputations, mastectomies, and joint replacement procedures [28].

The aim of this Delphi study was to survey healthcare professionals who deal with pain to help define and quantify the burden of PSP and LBP and strategies to prevent the transition to CPSP and CLBP. In order to mitigate potential bias, the experts included came from a variety of medical disciplines and different geographical regions. The objective was to seek expert consensus in terms of how acute pain is defined, managed, and approached, specifically with the goal of preventing the transition from acute to chronic pain. The ability to identify and clinically apply risk factors for pain syndromes such as CLBP can create prognostic models that can identify patients at elevated risk for developing chronic pain and lead to better care [29]. A lack of universally accepted consensus definitions has compromised care for patients and has contributed to inconsistent understanding of risk factors that may lead to the transition from acute to chronic pain [30] In this regard, the study focused more on consensus in regard to treatment than the mechanisms of chronification of postsurgical pain.

The study is particularly interested in the use of an oral fixed-dose combination analgesic product of dexketoprofen/tramadol in these settings, with respect to if and how it might interrupt acute pain and avoid the transition to chronic pain. The study sought to better define the awareness among physicians as to the current nature and risks associated with acute PSP and acute LBP and their risk of chronification, seeking a translational consensus among international pain experts on the current therapeutic options, practices, and unmet clinical needs. Moreover, the consensus will help to define the role and suitability of multimodal analgesia in this setting. The investigators believe that the substantial and increasing burden of CPSP and CLBP on patients, the healthcare system, and society at large demand further elucidation to guide prescribing choices for moderate-to-severe acute pain in these two specific settings of postoperative pain and acute to subacute LBP. To the best of the knowledge of the authors, no similar Delphi study of this nature on the transition

from acute to chronic pain has been conducted previously.

## METHODS

This study is based on a modified Delphi method [31], illustrated in Fig. 1. The Delphi method is an indirect, anonymous, iterative process which seeks to achieve expert consensus on real-world, complex problems [32]. A scientific committee of established pain specialists or experts in pain management met in person on 9 June 2022 to draft preliminary statements on the basis of an extensive literature search on the subject of the current management of low back pain and post-surgical pain with a focus on the potential therapeutic role of dexketoprofen/tramadol for acute pain management. The opinions offered by the scientific committee were grouped together for a total of 28 statements, subdivided into six thematic topics. All statements were referenced in the medical literature. See Table 1. The main themes were to define the burden of moderate-to-severe PSP and LBP, the mechanisms and implications of their transition to CPSP and CLBP, the role of multimodal analgesia in acute pain conditions and its potential to stop the transition from acute to chronic pain. The survey asked specifically about an oral fixed-dose combination product of dexketoprofen/tramadol for short-term use in acute pain care.

An expert panel was selected on the basis of expertise in pain management, with efforts to select healthcare professionals from different geographical regions and medical specialties, subspecialties, and disciplines. Publications in peer-reviewed journals on pain-related topics and active membership in medical and scientific societies related to pain were also considered. The expert panel was presented with the 28 statements for ranking, including the references in support of the statements. All voting was done online using a survey platform. The scientific committee did not vote in the Delphi rounds. The expert panel ranked each statement on a 5-point Likert scale, with 1 = strongly disagree, 2 = disagree, 3 = partially agree, 4 = agree, and 5 = strongly agree.

After the initial round of voting, the scientific committee was to analyze the results. Where

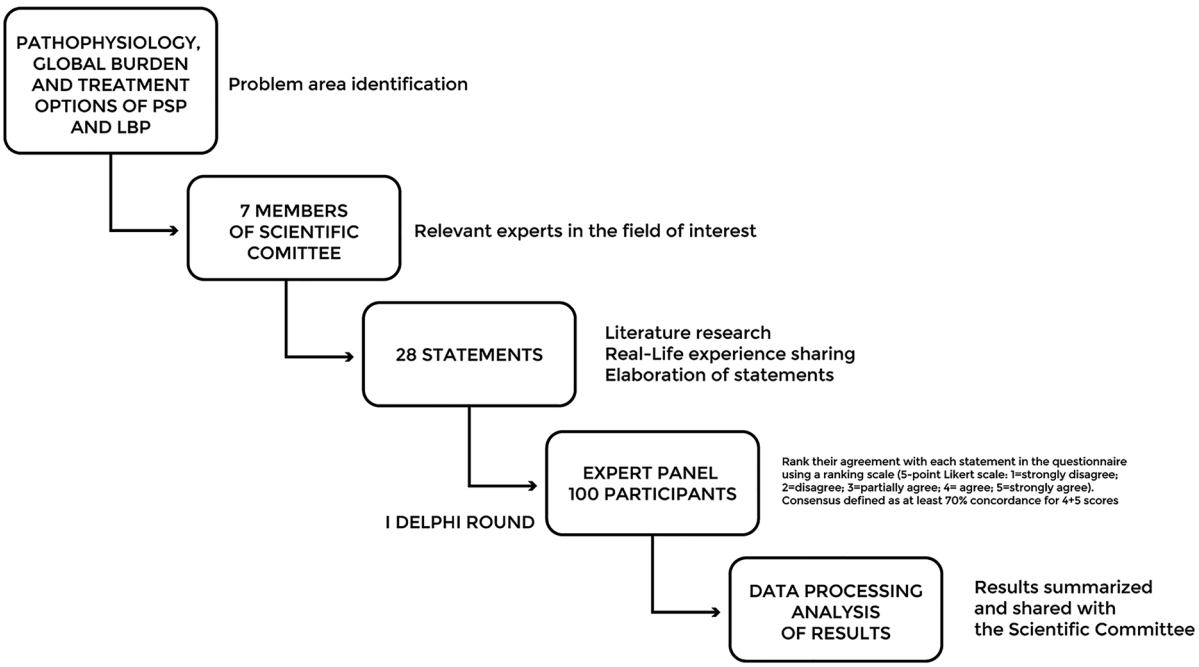


**Fig. 1** Flow chart of the modified Delphi method

**Table 1** The scientific committee drafted 28 statements, grouped into six themes and supporting references [7, 16, 19–21, 24, 41, 43, 46, 49, 50, 54, 56, 59, 63–75]

| N° | Statement | Supporting reference |
|---|---|---|
| Theme A | ***Burden of moderate-to-severe acute postsurgical pain and low back pain (statements 1–5)*** | |
| 1 | Acute pain is the main reason for up to 70% of visits to emergency departments, and many hospitalized patients experience acute pain during their stay | Castroman 2022<br>*Narrative review, incidence data from Keating 2011* |
| 2 | Acute PSP is poorly managed in about 80% of patients and represents a reason for hospital readmissions following ambulatory surgery in over 30% of cases | Castroman 2022<br>*Narrative review, incidence data from Coley 2002* |
| 3 | Acute LBP is one of the main reasons for physician visits worldwide, with a prevalence of care-seeking among patients with LBP varying from 67% in the USA to 48% in Europe | Buchbinder 2020<br>*Editorial, prevalence data from Beyera 2019* |
| 4 | Persistent PSP is associated with increased morbidity, decreased quality of life, sleep and mood disorders, as well as it is an economic burden for the patient and the healthcare system | Montero 2022<br>*Narrative review* |
| 5 | Acute LBP is the leading global cause of disability in all genders, and is accompanied by a significant clinical and socioeconomic burden in high, middle, and low-income countries | Buchbinder 2020<br>*Editorial, data from Global Burden of Disease Study, Vos 2017* |
| Theme B | ***Transition from acute-to-chronic pain, mechanisms of pain chronification, and strategies to prevent pain chronification (statements 6–11)*** | |
| 6 | Acute postsurgical pain is expected during approximately the first month following surgery; however, pain may persist after 1 month (persistent or subacute postsurgical pain, PPSP) or 2 months (chronic postsurgical pain, CPSP) in 10–50% of patients | Castroman 2022<br>*Narrative review*<br>Montero 2022<br>*Narrative review* |
| 7 | Acute LBP has a presumed favorable prognosis; however, if it is not effectively and adequately treated, it will become a chronic and disabling condition that is difficult to manage | Stevans 2021<br>*Cohort study conducted in parallel with a multisite pragmatic cluster randomized trial involving 77 centers with 6 months of follow-up* |
| 8 | The development and maintenance of many chronic pain syndromes, including chronic LBP and PSP, appear to arise from an imbalance between amplified ascending signals and inadequate activation of the descending inhibitory pathway, associated with structural and functional maladaptive neuroplastic changes within the central and peripheral nervous system. This ultimately results in peripheral and central nervous system sensitization, causing pain chronification | Morlion 2018<br>*Review based on an international meeting of the Change Pain Chronic Advisory Board Meeting in 2016* |
| 9 | Early recognition and effective management of acute pain is of crucial importance to interrupt the cascade of events that could lead to acute pain to progress to chronic pain | Hanna 2022<br>*Review from Roma Pain Days scientific sessions*<br>Linton 2018<br>*Topical review of stepped-care approach to acute pain* |
| 10 | Since quality of postoperative pain management appears to influence pain chronification, efforts should be undertaken to reduce the risk of chronic pain states by effectively treating postoperative acute pain, employing multimodal analgesic techniques that target peripheral and central mechanisms as well as any psychological risk factors that increase a patient's likelihood of developing chronic conditions | Pak 2018<br>*Review of pain mechanisms* |
| 11 | The duration of severe pain during the first 24 h after surgery has been shown to be a risk factor for CPSP and offers a new management goal in its prevention | Montero 2022<br>*Narrative review*<br>Fletcher 2015<br>*Observational study* |
| Theme C | ***Pathophysiology of postsurgical pain and low back pain (statement 12)*** | |

**Table 1** continued

| N° | Statement | Supporting reference |
|---|---|---|
| 12 | Acute pain is assumed to be predominantly nociceptive in nature. It results from noxious stimulation from tissue damage causing the release of inflammatory mediators. Drugs reducing peripheral inflammatory mediator activity, and thereby leading to reduced peripheral sensitization, are a useful component of multimodal analgesia | Chen 2021<br>*Narrative review*<br>Pak 2018<br>*Narrative review* |
| Theme D | ***Therapeutic options and unmet needs in acute pain management. (statements 13–15)*** | |
| 13 | Optimal analgesia should balance effective pain relief with the minimal acceptable side effects: NSAID/opioid combinations have additive or synergistic analgesic efficacy, allowing a reduction of opioids and NSAIDs dosage, hence minimizing undesirable adverse effects and improving function recovery | Pergolizzi 2014<br>*Narrative review*<br>Varrassi 2017<br>*Narrative review* |
| 14 | Acute pain should be promptly treated and better controlled, in order to prevent chronification and to improve patients' outcomes, achieving early rehabilitation and functional recovery. This requires the implementation of available evidence-based guidelines, better clinician awareness of the complications of untreated acute pain, a more patient-centric approach, and the development of predictive models that will guide preventative interventions for those at risk and therapies for those already with chronic pain | Pergolizzi 2014<br>*Narrative review*<br>Expert opinion of the scientific committee |
| 15 | To date, there is no single intervention that prevents the development of chronic pain. However, usual approaches, such as "wait and see", do not only ignore LBP complexity, natural history and disability trajectories, but also prevent timely intervention, thus increasing the likelihood of acute pain becoming chronic | Linton 2018<br>*Topical review of stepped-care approach to acute pain* |
| Theme E | ***Multimodal approach as the pillar in acute pain management and importance of fixed-dose combinations (statements 16–20)*** | |
| 16 | The synergy created when multimodal regimens are used to target individual components of the peripheral and central pain pathways provides effective pain control at lower analgesic dosing, reducing risk of adverse effects, while enhancing early function recovery | Polomano 2017<br>*Review utilizing a case-based approach*<br>Hanna 2023<br>*Narrative review* |
| 17 | Multimodal analgesia, or the use of a variety of analgesic and coanalgesic medications and techniques combined with nonpharmacological interventions, has been recommended by national and international guidelines for the treatment of PSP pain both in children and adults | Chou 2016<br>*Clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council* |
| 18 | The multifactorial nature of acute LBP supports a multimodal treatment approach. As both nociceptive/inflammatory and neuropathic components may be present, combining analgesic agents with different modes of action is a rational, important and effective treatment strategy | Muller-Schwefe 2017<br>*Review based on proceedings of a panel meeting* |
| 19 | Oral multimodal analgesia for hip and knee arthroplasty is increasingly employed as part of enhanced recovery protocols aimed at reducing early PSP and promoting early discharge, while minimizing undesirable side effects from analgesic monotherapy | Golladay 2017<br>*Review based on a symposium* |
| 20 | Advantages of fixed-dose combination analgesics include reduction of the total number of pills needed to manage pain, possibly improved adherence, fewer side effects owing to the reduced doses of each single compound and, in the case of fixed-dose combinations involving an opioid and a nonopioid agent, opioid-sparing effects | Raffa 2003<br>*Review*<br>Raffa 2010<br>*Review* |
| Theme F | ***The dexketoprofen/tramadol pharmacological profile and clinical efficacy in acute pain management and prevention of pain chronification (statements 21–28)*** | |

**Table 1** continued

| N° | Statement | Supporting reference |
|---|---|---|
| 21 | The unique multi-mechanistic or multimodal combination of dexketoprofen/tramadol provides a broad-spectrum analgesia: the analgesic (and antiinflammatory) action of dexketoprofen and its central action; the opioid receptor activation by tramadol and the indirect activation of central descending monoaminergic pathways by tramadol, with consequent inhibition of the nociceptive transmission to the brain | Varrassi 2017<br>*Narrative review* |
| 22 | In moderate-to-severe acute pain following surgery, the complementary pharmacokinetic profiles of the individual components of the dexketoprofen/tramadol fixed-dose combination have achieved effective analgesia, fast onset, long duration and a favorable tolerability profile | Varrassi 2017<br>*Narrative review* |
| 23 | Oral dexketoprofen/tramadol fixed-dose combination offers effective multimodal analgesia to treat acute PSP in day-case surgery, major abdominal and orthopedic surgeries, enabling patients to quickly return to their normal daily activities | Derry 2016<br>*Cochrane systematic review*<br>Gay-Escoda 2019<br>*Randomized controlled trial* |
| 24 | In patients with moderate-to-severe acute LBP, oral dexketoprofen/tramadol produced significantly greater pain reduction compared with diclofenac/thiocolchicoside | Meloncelli 2020<br>*Observational study* |
| 25 | Irrespective of pain intensity at baseline, oral dexketoprofen/tramadol analgesic efficacy was superior to tramadol/paracetamol as soon as 30 min and up to 4–6 h in day-case surgery such as third molar tooth extraction | Hanna 2021<br>*Randomized controlled trial* |
| 26 | In patients undergoing total hip arthroplasty, oral dexketoprofen/tramadol fixed-dose combination provided greater pain relief than that achievable by each component alone, with a sustained effect up to 5 days of treatment | McQuay 2016<br>*Randomized controlled trial* |
| 27 | Owing to the unique complex mechanism of action and its efficacy in the fast and sustained control of acute pain, oral dexketoprofen/tramadol fixed-dose combination may reduce the risk of pain chronification | Varrassi 2019<br>*Delphi study* |
| 28 | Currently, there is no optimal analgesic agent or pain control regimen that can reliably prevent the chronification of acute pain, but available evidence supports the superior efficacy in terms of pain control achieved by using two-drug combinations that have complementary mechanisms of action, such as oral dexketoprofen/tramadol fixed-dose combination | Derry 2016<br>*Cochrane systematic review*<br>Gay-Escoda 2019<br>*Randomized controlled trial*<br>Meloncelli 2020<br>*Observational study*<br>Montero 2022<br>*Narrative review* |

*CPSP* chronic postsurgical pain, *LBP* low back pain, *NSAID* nonsteroidal antiinflammatory drug(s), *PSP* postsurgical pain

there was no consensus, the statements would be re-evaluated, reworded, or excluded. The ratings for each statement were then summarized by using the median and consensus was achieved on the basis of interquartile ranges for continuous numeric scales [33]. The threshold for consensus was 70% of respondents awarding scores of 4 or 5 [34]. Multiple rounds of voting were permitted, if needed.

The goal of a Delphi study is to offer qualitative expert opinion rather than statistical generalizability; therefore, this study sought a large sample size for the expert panel to present a broad diversity of perspectives and clinical experiences as well to reduce the risk of bias that a smaller sample or a sample from a specific geography or medical discipline might present. Many Delphi studies use samples of 20 or 30 respondents, but the goal was to seek a wider range of clinical experiences in order to mitigate potential bias that could arise had the sample been smaller or had come from a single geographical region or medical discipline. By definition, a Delphi study is a consensus-driven, iterative, qualitative study and it is not possible to present a formal calculation of statistical power. A total of 103 experts were selected to offer the best replicability of results and to represent the heterogeneous clinical settings involved [35].

The emphasis in our study was on achieving expert consensus, rather than illuminating the mechanisms that may allow acute pain in the postoperative setting to transition to chronic pain.

Voting by the expert panel was anonymous. To provide depth to the analysis, results were to be grouped by five concordance ranges, with the fifth level indicating the greatest degree of agreement (> 80%). The cutoff for concordance was > 70%. This value was set by the protocol and may vary, because other Delphi studies use different consensus thresholds. Delphi studies were first developed in 1953 by the Rand Corporation and represents one of two main approaches to achieving an expert consensus, the other being the nominal group technique [36, 37]. Delphi methods are adaptable to the research requirements and there is no standard methodology set forth in terms of how to calculate the panel size or the

**Table 2** Theme A: burden of moderate-to-severe acute postsurgical pain and low back pain

| | % Agreement | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **4+5** |
| Statement 1: acute pain is the main reason for up to 70% of visits to emergency departments, and many hospitalized patients experience acute pain during their stay | 1 | 0 | 0 | 34 | 65 | 99 |
| Statement 2: acute post-surgical pain (PSP) is poorly managed in about 80% of patients and represents a reason for hospital readmissions following ambulatory surgery in over 30% of cases | 1 | 5 | 9 | 47 | 38 | 85 |
| Statement 3: acute low back pain (LBP) is one of the main reasons for physician visits worldwide, with a prevalence of care-seeking among patients with LBP varying from 67% in the USA to 48% in Europe | 1 | 0 | 2 | 37 | 60 | 97 |
| Statement 4: persistent PSP is associated with increased morbidity, decreased quality of life, sleep and mood disorders, as well as it is an economic burden for the patient and the healthcare system | 1 | 0 | 1 | 23 | 75 | 98 |
| Statement 5: acute LBP is the leading global cause of disability in all genders, and is accompanied by a significant clinical and socioeconomic burden in high-, middle-, and low-income countries | 1 | 2 | 1 | 27 | 69 | 96 |

Note that only consensus is reported in this table, with the degree or percentage of agreement moderate in columns 1 through 5. Column 1 indicates no agreement. Columns 2 through 5 all achieve the threshold of agreement, but are stratified by degree, so that column 2 is 70% or higher consensus, column 3 is 75% or greater, and column 4 is 80% or greater. Column 5 is the highest degree of concordance. Thus, the results of columns 4 added to column 5 show those who "agree" or "strongly agree" with the statement

consensus threshold, [36] but many Delphi studies set the consensus threshold at 70–75% [34]. Consensus values are sometimes as low as 50% or as high at 90% [34]. The consensus threshold of 70% was set before the study began as part of the study protocol, which is necessary for good practice [34]. In reviewing the literature, we found a Delphi study on musculoskeletal pain that utilized a 40% threshold [38], which must be considered low. The median consensus threshold in Delphi studies is 75%. However, the higher the consensus threshold is set, the more refined the questions must be as Delphi rounds advance [39]. There is no standard value set for number of panelists, number of questions, number of rounds, number of items on the Likert scale, or consensus threshold for Delphi studies, but protocols are defined in advance [40]. The 70% value was selected because it falls within the range of typical and accepted threshold values (70–75%) and it was not so high that questions needed to be formulated in a highly specific way. Our goal was to encourage discussion and achieve a consensus definition and setting a consensus level too high or too low might have thwarted this objective.

### Ethical Approval

No ethical approval was required for this consensus study, which was conducted according to the Delphi technique to assess agreement among participants, all of whom are also coauthors of the paper.

## RESULTS

A team of seven experts convened to address the pathophysiology, global burden, and treatments of postsurgical pain and low back pain with the objective of interrupting the transition of acute pain to chronic pain. Following a literature search and clinical experience, the scientific committee established six main areas of interest (see Table 1) and from there drew up 28

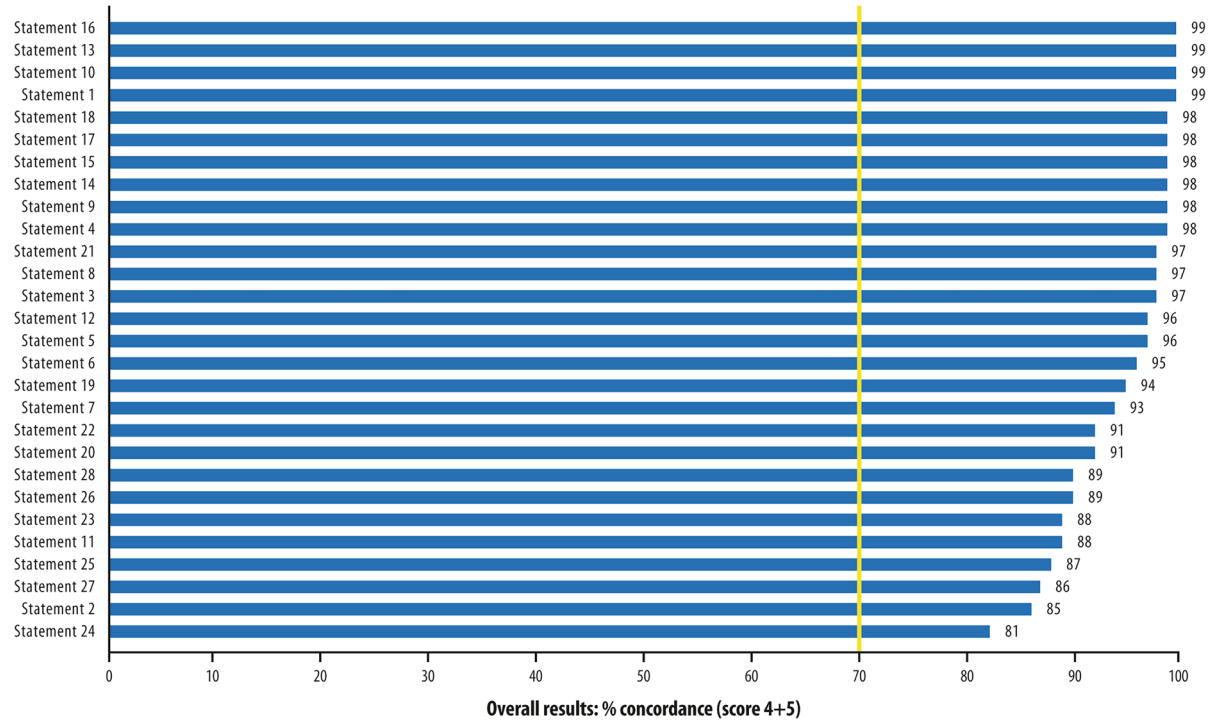


**Fig. 2** Concordance across statements

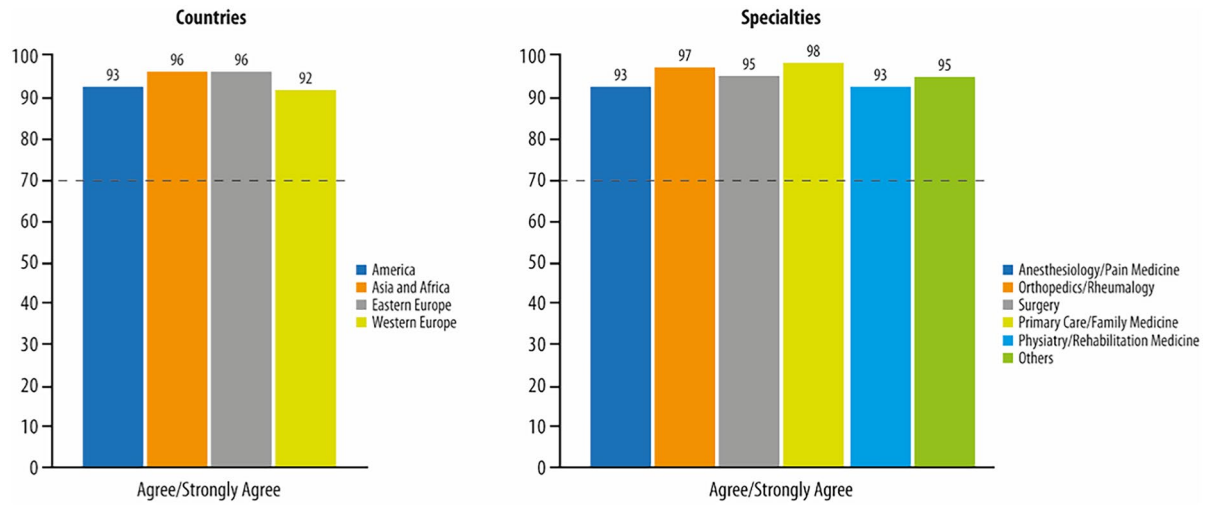


**Fig. 3** Average concordance rate in subgroups divided per count specialties

statements grouped thematically. All statements had references, which were presented to the panel.

An expert panel was recruited of 102 healthcare professionals, of whom 100 completed the survey. (See Table 2). Two of the panelists started the survey but left the answers blank; they did not offer any explanations as to why they did not participate. The expert panel had a heterogeneous geographical distribution (39% from Western Europe, 24% from Eastern Europe, 21% from Asia and Africa, 16% from North and South America). Expertise areas included anesthesiology and pain medicine (63%), general practice or family medicine (11%), orthopedics or rheumatology (9%), surgery (5%), physiatry and rehabilitation medicine (4%), and the remaining 8% came from other specialties, including neurology, internal medicine, and pharmacology. Most of the participants were academic experts (61%), while 39% were clinical experts. The estimate mean age of experience was 23.28 years (SD ± 9.55). Most respondents were physicians; one held a PharmD degree. Panelists were considered key opinion leaders in their respective regions or fields, as evidenced by publication of pain-related articles in peer-reviewed medical journals and active participation in local, national, or international specialty society activities. Owing to the subjective nature of "expert" status, there were no objective criteria set in terms of number of published articles, number of medical society memberships, or number of presentations given.

Voting took place from July to October 2022. Only one round of voting was required to achieve consensus on all statements.

Consensus was defined as at least 70%, ranking the statement as a 4 or 5, in the first round of voting (see Figs. 2 and Tables 2, 3, 4, 5, 6, and 7). For 16 of the statements, there was 95–99% consensus. For four statements, consensus was 90–95%. Seven statements reached consensus levels of 85–90%. One statement achieved consensus at 80–85%. Analyses stratified voting by nationality and specialty and found that agreement was equally distributed across such subgroups (see Figs. 3 and 4). Note that statement 2 did not reach consensus among the surgeons, orthopedists, or rheumatologists; this statement reported that inadequate management of post-surgical pain in 80% of surgical patients and that such inadequately controlled pain was a reason for hospital readmission following day surgery. Likewise, statement 25 did not reach consensus among surgeons; this statement said that the analgesic efficacy of dexketoprofen/tramadol was superior to that of tramadol/paracetamol (acetaminophen) 30 min to 4–6 h after day surgery, regardless of pain intensity. In this


**Fig. 4** Concordance divided by theme in: **a** the general practitioner group; **b** the anesthesiologist group; **c** the orthopaedics/rheumatologists group; **d** in the physiatry/rehabilitation medicine doctors group; and **e** in the surgeons group. DKP/TRAM: dexketoprofen/tramadol

connection, it is important to note that those two statements achieved consensus, with 85% and 95% consensus level reported, respectively.

The greatest consensus within a theme was achieved on statements 1 through 5 regarding the burden of acute PSP and LBP. There was also strong concordance with respect to theme B about the importance of early recognition of acute pain and prompt, effective treatment to interrupt the cascade of events that could progress to chronic pain. In this section, the lowest level of agreement (88%), related to statement 11, which indicated that the duration of severe pain in the first 24 h after surgery was a risk factor for CPSP. See Table 3, Figs. 2 and 5.

A high consensus (96%) was reached with respect to the complexity of the pathophysiology of PSP and LBP. See Table 4 and Figs. 2 and 5.

There was robust agreement about the need for a therapeutic option to manage acute pain, reaching 98–99%. See Table 5, Figs. 2 and 5. Likewise, 91–99% agreed that the multimodal approach to acute pain management was important and multimodal analgesics, such as

**Table 3** Theme B: transition from acute to chronic pain, mechanisms of pain chronification, and strategies to prevent pain chronification,

| | % Agreement | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 4+5 |
| Statement 6: acute postsurgical pain is expected during approximately the first month following surgery; however, pain may persist after 1 month (persistent or subacute post-surgical pain, PPSP) or 2 months (chronic postsurgical pain, CPSP) in 10–50% of patients | 1 | 4 | 0 | 50 | 45 | 95 |
| Statement 7: acute LBP has a presumed favorable prognosis; however, if it is not effectively and adequately treated, it will become a chronic and disabling condition that is difficult to manage | 1 | 4 | 2 | 32 | 61 | 93 |
| Statement 8: the development and maintenance of many chronic pain syndromes, including chronic LBP and PSP, appear to arise from an imbalance between amplified ascending signals and inadequate activation of the descending inhibitory pathway, associated with structural and functional maladaptive neuroplastic changes within the central and peripheral nervous system. This ultimately results in peripheral and central nervous system sensitization, causing pain chronification | 1 | 1 | 1 | 37 | 60 | 97 |
| Statement 9: early recognition and effective management of acute pain is of crucial importance to interrupt the cascade of events that could lead acute pain to progress to chronic pain | 1 | 0 | 1 | 13 | 85 | 98 |
| Statement 10: since quality of postoperative pain management appears to influence pain chronification, efforts should be undertaken to reduce the risk of chronic pain states by effectively treating postoperative acute pain, employing multimodal analgesic techniques that target peripheral and central mechanisms as well as any psychological risk factors that increase a patient's likelihood of developing chronic conditions | 1 | 0 | 0 | 20 | 79 | 99 |
| Statement 11: the duration of severe pain during the first 24 h after surgery has been shown to be a risk factor for CPSP and offers a new management goal in its prevention | 1 | 1 | 10 | 38 | 50 | 88 |

oral fixed-dose combination products play an important role in multimodal pain control. See Table 6, Figs. 2 and 5.

Theme F explored the pharmacological profile of dexketoprofen/tramadol as a therapeutic option to manage acute pain in light of preventing pain chronification. Statements 21 through 28 addressed this topic and achieved concordance in the range of 81–97%. Of these statements, the lowest agreement was 81%, which was reached on statement 24, stating that dexketoprofen/tramadol was effective in the management of LBP. See Table 7, Figs. 2 and 5.

## DISCUSSION

This study found broad and robust consensus about 28 statements addressing the incidence and prevalence of acute pain, the challenges of preventing acute pain from transitioning into chronic pain, and the need for analgesic products, such as fixed-dose combination analgesics to offer multimodal therapy to interrupt pain chronification. While differences were not noted by region, there were some differences by professional specialty that deserve consideration. In particular, surgeons, orthopedists, and rheumatologists disagreed on the prevalence of PSP in various settings, in contrast with pain specialists and general practitioners with regard to statement 2. This difference may be owing to the different perspectives of various medical

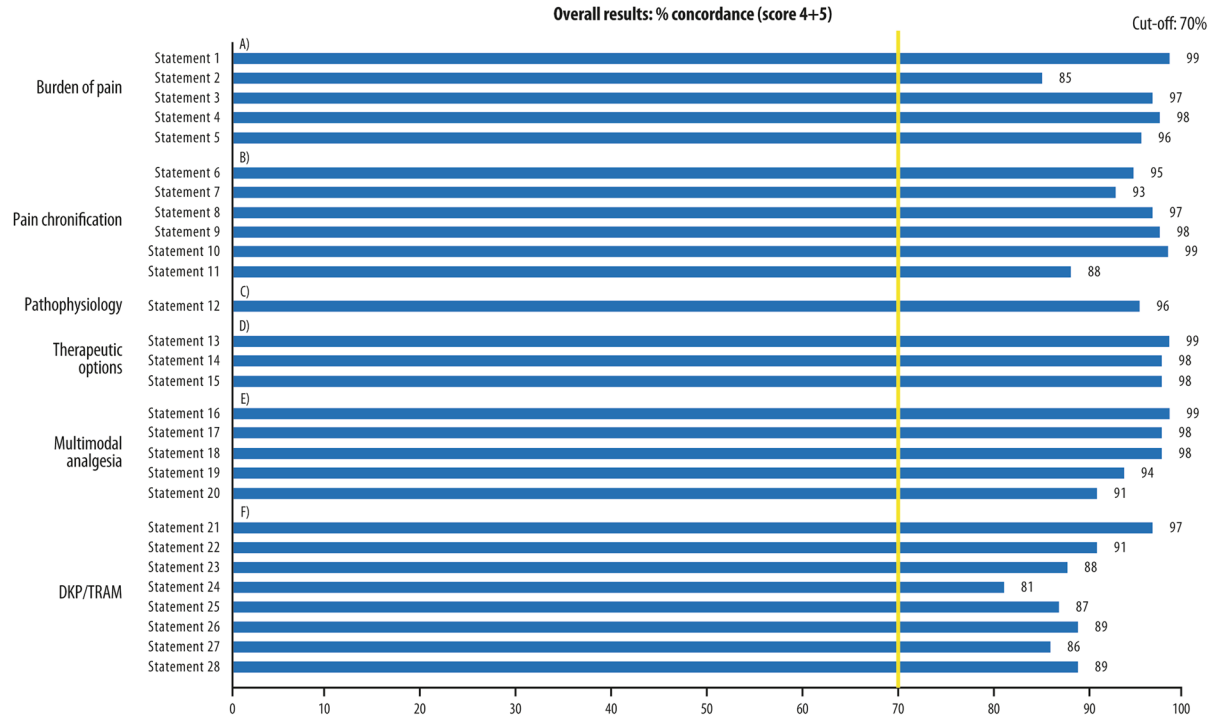


**Fig. 5** Concordance divided by theme in the overall responders. DKP/TRAM: dexketoprofen/tramadol

**Table 4** Theme C: pathophysiology of postsurgical pain and low back pain

| | % Agreement | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 4+5 |
| Statement 12: acute pain is assumed to be predominantly nociceptive in nature. It results from noxious stimulation from tissue damage causing the release of inflammatory mediators. Drugs reducing peripheral inflammatory mediator activity, and thereby leading to reduced peripheral sensitization, are a useful component of multimodal analgesia | 1 | 0 | 3 | 34 | 62 | 96 |

disciplines, since surgeons treat patients at a different point in the continuum of care than other physicians and may be less likely to treat patients dealing with persistent PSP months after surgery. In other words, inadequate postoperative pain control may be evident to clinicians downstream from the surgical suite more than those performing surgery. However, it is important to recognize that this is speculation, and further study is needed to affirm this conclusion. Likewise, there were specialty-specific differences with regard to item 25 about the superiority of DKP/TRAM compared with tramadol/paracetamol combination products, when such analgesics were used in day surgery, as soon as 30 min and up to 4–6 h in day-case surgery, regardless of pain intensity levels at baseline. The example cited in the statement was dental surgery, specifically a third-molar extraction. This is a very specific question, and respondents may have had limited experience with ambulatory or day surgery, may not be familiar with dental surgery, or may not have worked with patients about 6 h after a day surgery. Indeed, survey responses were clearly colored by specialty, because different specialists treat different types of pain (rheumatologists versus surgeons, for example) at different points on the

**Table 5** Theme D: therapeutic options and unmet needs in acute pain management

| | % Agreement | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 4+5 |
| Statement 13: optimal analgesia should balance effective pain relief with the minimal acceptable side effects: NSAID/opioid combinations have additive or synergistic analgesic efficacy, allowing a reduction of opioids and NSAIDs dosage, hence minimizing undesirable adverse effects and improving function recovery | 1 | 0 | 0 | 32 | 67 | 99 |
| Statement 14: acute pain should be promptly treated and better controlled, in order to prevent chronification and to improve patients' outcomes, achieving early rehabilitation and functional recovery. This requires the implementation of available evidence-based guidelines, better clinician awareness of the complications of untreated acute pain, a more patient-centric approach, and the development of predictive models that will guide preventative interventions for those at risk and therapies for those already with chronic pain | 1 | 0 | 1 | 20 | 78 | 98 |
| Statement 15: to date, there is no single intervention that prevents the development of chronic pain. However, usual approaches, such as "wait and see," do not only ignore LBP complexity, natural history and disability trajectories, but also prevent timely intervention, thus increasing the likelihood of acute pain becoming chronic | 1 | 0 | 1 | 37 | 61 | 98 |

**Table 6** Theme E: multimodal approach as the pillar in acute pain management and importance of fixed dose combinations

| | % Agreement | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 4+5 |
| Statement 16: the synergy created when multimodal regimens are used to target individual components of the peripheral and central pain pathways provides effective pain control at lower analgesic dosing, reducing risk of adverse effects, while enhancing early function recovery | 1 | 0 | 0 | 26 | 73 | 99 |
| Statement 17: multimodal analgesia, or the use of a variety of analgesic and coanalgesic medications and techniques combined with nonpharmacological interventions, has been recommended by national and international guidelines for the treatment of PSP pain both in children and adults | 1 | 0 | 1 | 26 | 72 | 98 |
| Statement 18: the multifactorial nature of acute LBP supports a multimodal treatment approach. As both nociceptive/inflammatory and neuropathic components may be present, combining analgesic agents with different modes of action is a rational, important, and effective treatment strategy | 1 | 1 | 0 | 26 | 72 | 98 |
| Statement 19: oral multimodal analgesia for hip and knee arthroplasty is increasingly employed as part of enhanced recovery protocols aimed at reducing early PSP and promoting early discharge, while minimizing undesirable side effects from analgesic monotherapy | 1 | 1 | 4 | 37 | 57 | 94 |
| Statement 20: advantages of fixed-dose combination (FDC) analgesics include reduction of the total number of pills needed to manage pain, possibly improved adherence, fewer side effects owing to the reduced doses of each single compound and, in the case of FDCs involving an opioid and a nonopioid agent, opioid-sparing effects | 1 | 2 | 6 | 38 | 53 | 91 |

**Table 7** Theme F: DKP/TRAM pharmacological profile and clinical efficacy in acute pain management and prevention of pain chronification

| | % Agreement | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 4+5 |
| Statement 21: the unique multi-mechanistic or multimodal combination of tramadol/dexketoprofen (DKP/TRAM) provides a broad-spectrum analgesia: the analgesic (and antiinflammatory) action of dexketoprofen and its central action; the opioid receptor activation by tramadol and the indirect activation of central descending monoaminergic pathways by tramadol, with consequent inhibition of the nociceptive transmission to the brain | 1 | 0 | 2 | 37 | 60 | 97 |
| Statement 22: in moderate-to-severe acute pain following surgery, the complementary pharmacokinetic profiles of the individual components of the DKP/TRAM FDC has achieved effective analgesia, fast onset, long duration, and a favorable tolerability profile | 1 | 0 | 8 | 44 | 47 | 91 |
| Statement 23: oral DKP/TRAM FDC offers effective multimodal analgesia to treat acute PSP in day-case surgery, major abdominal, and orthopedic surgeries, enabling patients to quickly return to their normal daily activities | 1 | 3 | 8 | 42 | 46 | 88 |
| Statement 24: in patients with moderate-to-severe acute LBP, oral DKP/TRAM produced significantly greater pain reduction compared with DIC/THIO (diclofenac/thiocolchicoside) | 2 | 0 | 17 | 41 | 40 | 81 |
| Statement 25: irrespective of pain intensity at baseline, oral DKP/TRAM analgesic efficacy was superior to TRAM/paracetamol as soon as 30 min and up to 4–6 h in day-case surgery such as third molar tooth extraction | 1 | 1 | 11 | 37 | 50 | 87 |
| Statement 26: in patients undergoing total hip arthroplasty (THA), oral DKP/TRAM FDC provided greater pain relief than that achievable by each component alone, with a sustained effect up to 5 days of treatment | 1 | 0 | 10 | 38 | 51 | 89 |
| Statement 27: owing to the unique complex mechanism of action and its efficacy in the fast and sustained control of acute pain, oral DKP/TRAM FDC may reduce the risk of pain chronification | 1 | 2 | 11 | 43 | 43 | 86 |
| Statement 28: currently, there is no optimal analgesic agent or pain control regimen that can reliably prevent the chronification of acute pain, but available evidence supports the superior efficacy in terms of pain control achieved by using two-drug combinations that have complementary mechanisms of action, such as oral DKP/TRAM FDC | 1 | 1 | 9 | 41 | 48 | 89 |

continuum of care. The inclusion of multiple specialists in this Delphi study was to ascertain where there were robust consensus and near-universal agreement versus areas where specialists diverged. Deeper analysis of these differences would necessitate further investigation, but it is clear that while all specialties treat patients in pain, pain symptoms, mechanisms, and treatments differ by underlying pathology and clinical situation. Chronic LBP is not the same as acute postsurgical pain. Caution is advised when interpreting our findings or generalizing them into all specialty areas.

Nevertheless, there is widespread and strong consensus that acute pain must be diagnosed accurately, treated promptly, and controlled to block the potential transition of acute to chronic pain. While both PSP and LBP represent major burdens on the healthcare system, there are some important distinctions that may come into play. Following surgery, PSP is normal, expected, and follows a more or less predictable trajectory

[19]. Left untreated, it is well established that PSP may develop into subacute postsurgical pain or CPSP [24]. As such, prompt, effective pain control for surgical patients was deemed important by the vast majority of the experts. Pain intensity in the immediate postoperative period has been correlated with the development of CPSP [41, 42]. In fact, the percentage of time a patient endures severe pain in the first 24 h after surgery is considered a risk factor for CPSP, which presents a clear target for the clinical team [16, 24]. There is evidence that supports what many clinicians intuitively know: treating acute PSP quickly effectively lessens the risk for CPSP [24].

Less attention is granted to prompt analgesia for acute LBP, which may be owing to the fact that back pain is a common complaint with a generally favorable prognosis. The prevailing "wisdom" in medicine is that acute LBP typically resolves within 3 months with conservative treatment. However, a recent systematic review found that a median of 26% of those who were diagnosed with acute LBP eventually develop CLBP [43].

The chronification of PSP to CPSP involves a different pathophysiology than the transition of LBP to CLBP; the conditions differ fundamentally and are generally managed by different physicians with different therapeutic approaches. While the Delphi study achieved overall consensus, important differences were apparent by medical specialty. This emerged most markedly with statement 11, which reported that the duration of severe pain in the first 24 h after surgery was a risk factor for CPSP and, as such, could be an important management goal to prevent CPSP. The surgeons in the group agreed with this statement (100%), while physiatry and rehabilitation medicine doctors (75%), orthopedists and rheumatologists (78%), and general practitioners (82%) were more divided. This suggests that the clinical recognition of pain and its consequences varies depending on the vantage point of the clinician; those immediately concerned with surgery and perioperative care were more likely to understand the risk factor of prolonged and intense postsurgical pain than those who were not involved in perioperative care, such as general practitioners. PSP tends to be nociceptive with an inflammatory component, and there was strong consensus (96%) that pharmacologic reduction of proinflammatory mediators might, in turn, reduce peripheral sensitization and improve analgesia [41, 44, 45]. In particular, prolonged inflammation and neuroinflammation can result in peripheral and central nervous system sensitization [46]. A multimodal approach therapy combines two or more complementary analgesics with different mechanisms of action to address the many factors contributing to acute pain [47].

The vast armamentarium of pain relievers exists in part because pain can be caused by any number of distinct mechanisms, and in certain circumstances, combination analgesic products can be more effective than a single agent [48]. The use of two complementary analgesics with different mechanisms of action may offer additive or synergistic analgesic benefits, target more than one type of pain, and potentially reduce side effects because smaller doses can be effective [49, 50]. For instance, a patient may require a higher dose of an opioid analgesic for acute pain than the opioid dose needed when that opioid is combined with a nonopioid pain reliever. Multimodal analgesia has been found to be safe and effective, even in pediatric and geriatric patients [24]. Fixed-dose combination products offer dosing convenience, reduce the pill burden, and may enhance patient adherence to therapy [49].

Multimodal or combination drug therapy demands the use of two or more analgesics with complementary mechanisms of action, ideally offering enhanced or synergistic analgesic benefits. However, not all combination products are equally effective in all settings. The STARDOM2 clinical trial utilizing the cocrystal of tramadol–celecoxib as an analgesic in patients who underwent an abdominal hysterectomy failed to meet its primary end point and could not demonstrate superiority over tramadol 100 mg four times a day monotherapy [51]. However, the same fixed-dose combination product was superior to tramadol alone in STARDOM1, a study of oral surgery patients [52].

Dexketoprofen combined with tramadol is an established fixed-dose combination oral

analgesic with unique pharmacological properties. It appears to be as effective as a double dose of racemic ketoprofen but with a more rapid onset of action; the safety profile of dexketoprofen/tramadol is in many cases superior to the safety profiles of certain nonsteroidal antiinflammatory drugs (NSAIDs) used in monotherapy [2]. Tramadol itself may be considered a "new-generation opioid," in that it activates mu-opioid receptors including a traditional opioid but has a dual mechanism of action because it also simultaneously inhibits monoamine reuptake [2]. The synergistic interactions between tramadol and dexketoprofen are important and have been established in preclinical studies [53]; its safety profile is superior to that of opioid monotherapy [2]. Tramadol has no relevant clinical effects on the cardiovascular or pulmonary systems and is associated with less opioid-induced constipation and bowel dysfunction than conventional opioids such as morphine or oxycodone; in addition, the abuse potential of tramadol is lower than that of other opioids [2, 48].

The expert consensus recognized the effectiveness of dexketoprofen/tramadol for postoperative analgesia, which has been evaluated in several randomized clinical trials, with 738 patients receiving the fixed dose combination [4, 54–58]. Statement 25 reported that the use of oral dexketoprofen/tramadol is effective in day surgery procedures and is superior to the analgesic benefit of tramadol combined with paracetamol (acetaminophen), regardless of the intensity of pain at baseline [59]. A small, real-world study from Asia ($n=11$) confirms the effectiveness and suitability of dexketoprofen/tramadol for managing PSP [60, 61]. A larger, multicenter international study of real-world acute pain management in Asia enrolled 599 acute pain patients, of whom 68.6% suffered acute postsurgical pain from a variety of different surgeries [62]. In most patients, pain intensity as measured on a numeric rating scale reduced significantly over baseline, with 65% of patients experiencing > 30% pain reduction over baseline within 8 h after the first dose. The majority of patients (95.7%) reported they were satisfied with the dexketoprofen/tramadol analgesic (rating it "good," "very good," or "excellent") [62].

The consensus agreement of dexketoprofen/tramadol as a serviceable analgesic was stronger for surgical patients than for those with low back pain (81% consensus). This lower number may be owing to the lack of high-quality evidence supporting the use of dexketoprofen/tramadol for LBP, but it may also trace back to the fact that many of the panelists do not routinely treat acute LBP. Anesthesiologists (80%) and physiatry/rehabilitation medicine physicians (75%) were the least convinced of the use of dexketoprofen/tramadol for acute LBP. There is a paucity of high-quality evidence from large studies that support the use of dexketoprofen/tramadol in LBP, which may have impacted survey results. The recent DANTE study ($n=538$) was designed to evaluate the use of dexketoprofen/tramadol for LBP, but it failed to meet its primary end point of time to pain reduction, defined as a score on the numeric rating scale of less than 4 or a reduction in pain intensity > 30% 8 h after the first dose when compared with placebo [58]. However, dexketoprofen/tramadol achieved superiority over tramadol alone in the secondary end points of pain reduction 8 h after the first dose and in the 5-day multiple-dosing phase of the study [58]. The DANTE study was not yet published when this Delphi study was conducted, and it cannot be known if and how its results might have affected consensus. The fixed-dose combination product of dexketoprofen/tramadol is not approved in all markets, but studies of its short-term use to manage acute postoperative pain report tolerability and good safety [55, 58, 63]. Longer-term use is not as well studied. No drug is completely without adverse effects. Both dexketoprofen, as an NSAID, and tramadol, as an opioid, are associated with adverse events when used alone. The proper selection of appropriate patients for this agent is crucial. For example, dexketoprofen is contraindicated in patients with a history of gastrointestinal bleeding, renal or hepatic dysfunction, and cardiac problems, while tramadol should not be used by patients taking a monoamine oxidase (MAO) inhibitor or other types of serotonergic drugs [55]. In a study of 606 patients who underwent abdominal hysterectomy, the combination product has a 9.4% rate of adverse events compared with 15%

in patients who received dexketoprofen alone and 13% of those who received tramadol alone. One serious adverse event occurred in this study; it was a psychotic episode in one patient who had been administered the combination product [55].

This Delphi study has strengths and weaknesses. The main strength of the study is that it was based on a large cohort of 100 experts in pain management from numerous countries and medical disciplines, providing a broad and multifaceted global view of the topic. Our method allowed for anonymous responses which encouraged the clinicians to share their actual approaches and honest opinions. Very strong support emerged in the survey for preventing acute pain from transitioning into chronic pain through multimodal analgesia. While the study did not allow us to draw reliable conclusions based on respondent specialty, it did allow for a broad overview of the subject.

The strength of these findings may support healthcare professionals worldwide in gaining a deeper understanding of the burden and unmet needs associated with post-surgical pain (PSP) and low back pain (LBP). The results also highlight the potential role of multimodal analgesia in preventing the chronification of pain in these conditions. Furthermore, the consensus on the role of the fixed-dose combination of dexketoprofen and tramadol provides valuable insights into its appropriate clinical application and therapeutic potential in the management of PSP and LBP. These findings may also prompt further research into the effectiveness of multimodal analgesia in preventing the transition from acute to chronic pain. Ultimately, the insights gained from this consensus could assist clinicians in optimizing the management of patients with PSP and LBP, with multimodal analgesia considered as a strategic option to mitigate the risk of pain chronification. The statements about the use of specific multimodal products may have allowed some bias to enter the study, since we did not evaluate all multimodal or other analgesic agents. Experts who agreed with statements relating to specific products should not be taken as endorsements of the use of these products.

There are limitations to this study. There was a lack of high-quality evidence-based results for some of the statements; however, expert consensus was utilized and it has a long tradition in medicine as a valid tool to guide clinicians toward preferred therapeutic approaches even in the absence of large randomized clinical trials or official guidelines for specialty societies. This study encompassed 28 statements but did not address the very important role of nonpharmacologic approaches to specific conditions, particularly LBP. The pool of experts used in our study were not randomly selected and there was further self-selection bias in the fact that it was limited to those experts willing to join a Delphi study. Moreover, the panelist experience was not quantifiable with average relevant publications owing to topic wideness. There were no negative statements about dexketoprofen/tramadol offered in the survey. Finally, this study was limited to LBP and CPSP, two distinct acute painful conditions with different pathophysiologies. These two conditions were selected because they are highly prevalent, frequently encountered in clinical practice, and can transition into chronic pain conditions, but their pathogenesis and mechanisms differ. This Delphi study covered a wide range of topics from clinically ubiquitous pain conditions (acute postsurgical pain and back pain), pain management strategies, the transition from acute to chronic pain, and then experiences using a specific multimodal product. It was our goal to cover this range of topics, but the breadth of our study may be viewed as a potential limitation. Finally, specialists at some points diverged in their opinion which may be a reflection of their specialty, the type of pain, and population they treat, or the point at which they are on the continuum of care. Caution should be exercised in interpreting our results, which may not be generalizable to all patient populations or all specialties.

## CONCLUSIONS

In this Delphi study, an expert panel strongly agreed that acute pain is often inadequately treated and effective treatment of acute pain

may prevent the transition from acute-to-chronic pain. Treating acute pain in light of chronification requires a greater understanding of pain pathophysiology, which is often multimechanistic in nature. The panel agreed that multimodal analgesia is beneficial and effective, and agreed with statements supporting the use of dexketoprofen/tramadol. This Delphi study evaluated specifically PSP and LBP, two prevalent but distinct conditions. The Delphi study supports the use of a fixed-dose combination analgesic such as dexketoprofen/tramadol for up to 5 days to provide acute pain control and blunt the risk of a transition to chronic pain.

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***Data Availability.*** The datasets generated during the current study are available from the corresponding author on reasonable request.

## *Declarations*

***Conflict of Interest.*** Giustino Varrassi received a grant from the Menarini Group, as the main investigator of this study. Giustino Varrassi is a consultant of several companies, including but not limited to: Abbott, Berlin-Chemie, Dompé, Menarini Corporate. Giustino Varrassi is an editorial board member of Pain and Therapy. Giustino Varrassi was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Since this study was conducted. Maria Dolma Gudez-Santos received a grant from the Menarini Group for participation in this study, as an international expert. She is a consultant and speaker for A. Menarini Philippines. Magdi Hanna received a grant from the Menarini Group for participation in this study, as an international expert. He is a consultant for a few companies, for scientific support. Magdalena Kocot-Kępska received a grant from the Menarini Group for participation in this study, as an international expert. She is speaker for several companies: Berlin-Chemie Menarini, Stada, KRKA, Molteni, Novartis, Adamed, Bausch, Polpharma, Sandoz, Takeda, Zentiva. Antonio Montero Matamala received a grant from the Menarini Group for participation in this study, as an international expert. He is consultant and speaker for Menarini. Marco Antonio Narvaez Tamayo received a grant from the Menarini Group for participation in this study, as an international expert. He is consultant and speaker for Menarini, Grunenthal, Tecnofarma, Breskot Pharma, Inti B/Braun and P&G. Serge Perrot received a grant from the Menarini Group for participation in this study, as an international expert. He is consultant and speaker for Menarini, Sanofi, Pfizer, Grunenthal, Sandoz, Abbvie.

***Ethical Approval.*** No ethical approval was required for this consensus study, which was conducted according to the Delphi technique to assess agreement among participants, all of whom are also coauthors of the paper.

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