REVIEW ARTICLE

Current Considerations for the Treatment of Severe Chronic Pain: The Potential for Tapentadol

Joseph Pergolizzi, MD*; Cayetano Alegre, MD†; David Blake, MB, ChB, FRCP‡; Jaime Calvo Alén, MD, PhD§; Roberto Caporali, MD¶; Hans-Raimund Casser, MD**; Gerardo Correa-Illanes, MD††; Pedro Fernandes, MD‡‡; Eugenio Galilea MD§§; Richard Jany, MD, PhD¶¶; Anthony Jones, MD, MA, FRCP***; Othmane Mejjad, MD†††; Jadranka Morovic-Vergles, MD, PhD‡‡‡; Ángel Oteo Álvaro, MD§§§; Francisco J. Radrigán Araya, MD¶¶¶; Maria Eugénia C. Simões, MD****; Generoso Uomo, MD††††

*Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; Naples Anesthesia and Pain Associates, Naples, Florida, U.S.A.; †Hospital Universitario Vall d'Hebrón, Barcelona, Spain; ‡Royal National Hospital for Rheumatic Diseases, Bath, U.K.; §Hospital Sierrallana Servicio de Reumatología, Torrelavega, Spain; ¶Università degli Studi di Pavia, Pavia, Italy; **DRK Schmerz-Zentrum Mainz, Mainz, Germany; ††Hospital del Trabajador de Santiago, Santiago, Chile; ‡‡Hospital da Luz, Lisbon, Portugal; §§Fundación San Cristobal, Santiago, Chile; ¶¶University Hospital Ruzinov, Bratislava, Slovakia; ***Salford Royal Hospitals NHS Foundation Trust, Manchester, U.K.; †††Clinique de l'Europe, Rouen, France; ‡‡‡University Hospital Dubrava, Zagreb, Croatia; §§§Hospital General Universitario Gregorio Marañón, Madrid, Spain; ¶¶¶Pontificia Universidad Católica de Chile, Santiago, Chile; ****Instituto Português de Reumatologia, Lisbon, Portugal; ††††Cardarelli Hospital, Naples, Italy.*

■ **Abstract** Studies suggest that around 20% of adults in Europe experience chronic pain, which not only has a considerable impact on their quality of life but also imposes a substantial economic burden on society. More than one-third of these people feel that their pain is inadequately managed. A range of analgesic drugs is currently available, but recent guidelines recommend that NSAIDs and COX-2 inhibitors should be prescribed cautiously. Although the short-term efficacy of opioids is good, adverse events are common and doses are frequently limited by tolerability problems. There is a perceived need for improved pharmacological treatment options.

Currently, many treatment decisions are based solely on pain intensity. However, chronic pain is multifactorial and

Address correspondence and reprint requests to: Joseph Pergolizzi, MD, Professor, Naples Anesthesia and Pain Associates, 4840 Sycamore Drive, Naples, FL 34119, U.S.A. E-mail: jpjmd@msn.com.

Submitted: May 11, 2011; Revision accepted: June 9, 2011
DOI. 10.1111/j.1533-2500.2011.00487.x

this approach ignores the fact that different causative mechanisms may be involved. The presence of more than one causative mechanism means that chronic pain can seldom be controlled by a single agent. Therefore, combining drugs with different analgesic actions increases the probability of interrupting the pain signal, but is often associated with an increased risk of drug/drug interactions, low compliance and increased side effects.

Tapentadol combines μ-opioid receptor agonism and noradrenaline reuptake inhibition in a single molecule, with both mechanisms contributing to its analgesic effects. Preclinical testing has shown that μ-opioid agonism is primarily responsible for analgesia in acute pain, whereas noradrenaline reuptake inhibition is more important in chronic pain. In clinical trials in patients with chronic pain, the efficacy of tapentadol was similar to that of oxycodone, but it produced significantly fewer gastrointestinal side-effects and treatment discontinuations. Pain relief remained stable throughout a 1-year safety study. Thus, tapentadol could possibly overcome some of the limitations of currently available analgesics for the treatment of chronic pain. ■

Key Words: chronic pain, multifactorial, causative mechanism, μ-opioid agonism, noradrenaline reuptake inhibition, synergism, opioid-sparing effect

INTRODUCTION

Epidemiological studies suggest that around 20% of adults in Europe experience chronic pain,[1–4] and that its severity correlates with a reduction in physical and mental health.[4] More than one-third of these individuals feel that their pain is inadequately managed and are dissatisfied with their treatment.[1,2,4] Severe chronic pain, in particular, presents a considerable burden for patients and can have a considerable impact on their quality of life, with a direct correlation to symptoms, such as anxiety, depression, and limited social functioning.[1,5]

Rheumatologists and orthopedists treat many patients with chronic pain, caused by conditions including osteoarthritis, rheumatoid arthritis, osteoporosis, low back pain and fibromyalgia. In July 2010, the International Advisory Board on Tapentadol for Rheumatologists and Orthopedists met for the first time in Brussels, Belgium. Its objectives were to enhance the understanding of patients with chronic pain, raise awareness of the inadequacy of current therapy, and explore possible strategies for improving pain management. Presentations on the unmet needs of chronic pain patients, a mechanism-based approach to its treatment, osteoporosis and tapentadol were combined with discussions and electronic questioning, which sought to establish the opinions and practice of the specialist audience. A number of consensus points was agreed during the meeting to indicate a possible way forward.

PREVALENCE AND IMPACT OF CHRONIC PAIN IN EUROPE

Studies consistently show that chronic pain affects around 1 in 5 adults in Europe.[1–3,6] One large-scale survey in 15 European countries and Israel found that 19% of 46,394 respondents had suffered pain for ≥ 6 months, had experienced pain in the last month and several times during the last week.[1] In each case, the intensity of pain had reached ≥ 5 on a 10-point Numeric Rating Scale (NRS; 1 = no pain, 10 = worst pain imaginable) during the most recent episode.[1] The prevalence varied considerably between countries, from 12% in Spain to 30% in Norway.[1]

An investigation by the European Commission concluded that pain affecting the muscles, joints, neck or back and lasting more than 3 months is experienced by approximately 25% of the European population.[7] The 2008 National Health and Wellness Survey questioned 53,524 adults in five European countries about pain; 22% had suffered from pain within the last month, of whom 44% experienced pain daily and 29% experienced pain 2 to 6 times per week.[4] The intensity of pain was severe in 23% of these patients, and moderate in a further 56%. Analysis of the patients with severe pain revealed that the most common condition was back pain (71%), followed by joint pain, and that cancer pain accounted for only 1%.[4] The severity of pain was found to correlate closely to reductions in physical health, mental health and social functioning, as measured by the Short Form-12 Questionnaire (SF-12; see Table 1).[6] Comorbidities, such as sleep difficulties (58%), insomnia (47%), anxiety (42%), and depression (35%) were around twice as common in patients with severe pain as in the general population.[4] Some 75% of these patients were of working age (18–64 years) and their work productivity and activity were profoundly affected; compared with the general population, they were only half as likely to be in full time employment, were absent from work five times as often, and their levels of activity impairment were twice as high.[4] Of the 13% of the U.K. population who have chronic

Table 1. Impact of Severe Pain on Physical Health, Mental Health, and Social Functioning[4]

	Severe Pain Mean (SD)	Moderate Pain Mean (SD)	No Pain Population Mean (SD)
SF-12 mental summary score	41.7 (12.4)	44.7 (11.4)	47.0 (10.6)
SF-12 physical summary score	32.0 (11.5)	42.3 (10.6)	50.1 (8.4)
SF-12 social functioning	36.2 (11.6)	42.8 (10.6)	46.7 (10.3)

pain, 49% take time off work and 25% lose their jobs.[1,8] Thus, the combination of distress, impaired functioning and reduced mobility imposed by chronic pain can seriously diminish the individual sufferer's quality of life.[1,5,9]

Chronic pain also imposes an economic burden on society. Taking the U.K. as an example, £3.8 billion is paid to people with chronic pain each year in the form of incapacity benefit.[10] There is also the annual cost of 4.6 million general practitioner (GP) appointments and £584 million for prescription analgesics;[8,11] people with severe chronic pain utilize disproportionately more healthcare resources than the general population, visiting healthcare providers twice as often and being hospitalized almost three times as often.[4] By far the biggest economic impact, however, is the result of chronic pain sufferers taking time off work. The total cost to the U.K. economy of back pain alone has been calculated at £12.3 billion each year, with 74% being due to loss of productivity.[8] This sum is equivalent to 22% of health expenditure and 1.5% of gross domestic product (GDP).[8] Germany spends even more—€48.96 billion—which is equivalent to 2.2% of GDP.[12]

CHRONIC PAIN THERAPIES CURRENTLY USED BY RHEUMATOLOGISTS AND ORTHOPEDISTS

Members of the Advisory Board, both rheumatologists and orthopedists, all agreed that pain therapy is of major importance in their specialties. The range of painful conditions treated includes osteoporosis, osteoarthritis, rheumatoid arthritis, low back pain and fibromyalgia, as well as neuropathic pain resulting from, for example, nerve root compression, carpal tunnel syndrome and complex regional pain. A consensus of guidelines relating to rheumatology (American College of Rheumatology, American Pain Society, European League Against Rheumatism) states that paracetamol is the first line drug of choice. Caution is urged with respect to COX-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and weak opioids are recommended only when analgesia is inadequate with other drugs.[13]

CONSENSUS POINT

Rheumatologists and orthopedists manage many different types of chronic pain.

Osteoarthritis

Osteoarthritis usually develops in people over 50 years of age and is characterized by damage to the articular cartilage, osteophyte formation, and synovitis. Risk factors include obesity, previous joint injury or structural damage. The joints most frequently involved are the knees, hips, spine and small joints of the hands, although any joint may become affected. Treatment goals are to relieve pain, reduce stiffness, preserve mobility and increase muscle strength to prevent joint instability and limit further joint damage.

A Canadian study found that the most commonly prescribed analgesic for osteoarthritis was paracetamol (68.6%), followed by intra-articular corticosteroids (65.7%), NSAIDs/cyclooxygenase-2-selective inhibitors (COXIBs; 50.5%) and hyaluronans (43.8%), whereas fewer than 20% of patients received opioids.[14] Rheumatologists are more likely than family medicine specialists or general internal physicians to recommend exercises or heat and cold therapy, and to explain the principles of joint protection.[15] NSAIDs may be more effective than paracetamol in osteoarthritis patients, especially for short-term use.[16] In patients with osteoarthritis of the hip or knee, transdermal fentanyl provides significantly better pain relief than placebo ($P < 0.007$), but nausea, vomiting and somnolence are more frequent.[17] Similarly, tramadol has been shown to produce significantly better pain relief than placebo, and also a significant improvement in physical function.[18] A Cochrane database study of 10 clinical trials, in which patients with osteoarthritis received various opioids (codeine, fentanyl, morphine, oxycodone, oxymorphone), found they were more effective than control interventions (paracetamol 3000 mg daily; ibuprofen 1200 mg daily) at relieving pain and improving function, but produced more side effects.[19]

Osteoporotic Disease

Osteoporosis is a common skeletal disorder, characterized by compromised bone strength and an increased risk of fracture, which severely affects patients' quality of life[20] and may even lead to increased mortality.[21,22] Although the condition itself is not primarily a painful disorder, the complications may be very painful. Fractures and their sequelae are the major cause of acute and chronic pain and disability.[23,24] Acute pain may subsequently become chronic as a result of altered spinal biomechanics and myofascial fatigue.[25,26] Osteoporosis causes inadequate repair of bone microfractures,[27] and this may also contribute to the patients' pain. The most important therapeutic goals are to improve the integrity of the bones with antiosteoporotic treatment, reduce the incidence of fragility fractures and improve the patient's quality of life. Effective analgesia is essential to reduce pain and preserve mobility. This minimizes progressive bone loss, new fractures and further pain, as well as facilitating early participation in gymnastic programs.

A range of drugs can effectively prevent and treat osteoporosis. Specific antiosteoporotic therapies, such as antiresorptives or anabolic agents, may also provide analgesia. There is some evidence that calcitonin significantly reduces pain in patients with osteoporosis by direct modulation of nociception in the CNS.[28] Surgical therapy and orthopedic treatment, such as orthoses and infiltrations of local anesthetic, may also be prescribed. The available analgesic agents include NSAIDs, COX-2 inhibitors, and weak and strong opioids. Despite the need to avoid inadequate analgesia, even patients suffering from severe pain are often initially prescribed NSAIDs. Opioids are used infrequently, although resting pain and pain on movement can both be significantly reduced by a potent opioid.[29] One reason for the limited use of opioids may be fear of side effects, although allowances tend to be made for the dangerous adverse events associated with NSAIDs.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune, systemic, inflammatory disorder that principally attacks synovial joints, but may cause systemic damage to other organs such as the kidneys and lungs. The disease process produces synovitis, which often leads to destruction of the articular cartilage and ankylosis of the joint. Rarely, it can produce diffuse inflammation in the lungs, pericardium, pleura and sclera, as well as nodular lesions, most commonly in the subcutaneous tissue. Before the era of treatment with biologic agents, the destruction of joints was the usual outcome. Today, treatment aims to alleviate the current symptoms, preserve mobility and prevent joint destruction, the overall objective being to achieve remission of the disease with freedom from joint pain and synovitis.

A retrospective database study that analyzed prescriptions given to patients with rheumatoid arthritis (n = 23,342) between 1995 and 2004 found that over this period:

- the proportion of patients receiving a disease-modifying antirheumatic drug (DMARD) increased from 62% to 71%.
- glucocorticoids decreased from 46% to 38%.
- NSAIDs increased from 33% to 38%.
- "narcotic" agents increased from 38% to 55%.[30]

Also, 22% of the patients were receiving a biologic agent by 2004.[30]

In an open-label trial of opioid-naïve patients with severe pain caused by rheumatoid arthritis, transdermal fentanyl significantly decreased pain intensity and significantly improved function.[31] Nearly all the participants were satisfied with their treatment.[31] Low dosage combinations of oxycodone and paracetamol have been shown to be a good alternative to NSAIDs, reducing pain intensity and disease activity, and decreasing disability.[32] In a randomized, placebo-controlled, 1-week study, adding tramadol/paracetamol to existing rheumatoid arthritis therapy produced significantly greater pain relief, but physical function was not significantly different.[33] However, the incidence of adverse events was higher in the tramadol/paracetamol group (57.6% vs. 22.4%), and 19% of this group discontinued treatment owing to side effects.

Fibromyalgia

Fibromyalgia affects muscle and connective tissue, and is characterized by chronic widespread pain and allodynia.[34] Other symptoms, include fatigue, sleep disturbance, joint stiffness, restless leg syndrome, numbness and cognitive dysfunction. The cause is unknown, but there is evidence that fibromyalgia patients perceive pain and other noxious stimuli differently from healthy individuals.[35]

The alpha2delta agonist pregabalin, and the highly selective serotonin-noradrenaline reuptake inhibitors (SNRIs) duloxetine and milnacipran, have been approved in the U.S.A. for treating fibromyalgia. However, only about half the fibromyalgia patients treated pharmacologically experience a 30% reduction in symptoms, suggesting that additional therapies are required.[36]

Analgesic Tolerability and Side Effects

The mechanism of action of paracetamol has not yet been elucidated, but almost certainly involves the brain and/or spinal cord.[37] It is less effective but safer than NSAIDs,[38] although potential safety risks include internal bleeding and liver damage, when products containing it are taken to excess.[39]

NSAIDs inhibit COX enzymes, which catalyze the conversion of arachidonic acid to prostaglandins. This inhibition can lead to undesirable organ toxicities, including gastrointestinal ulceration and bleeding.[40,41] The development of COX-2 inhibitors was originally thought to offer a solution to this problem, but these agents have now been associated with an increased risk of cardio-renal effects.[42,43] New guidelines for older adults by the American Geriatrics Society recommend that nonselective NSAIDs and COX-2 selective inhibitors be considered rarely, with caution, in highly selected individuals.[44] Moreover, 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.[44] Similarly, guidelines from the British Society for Rheumatology and IASP Musculoskeletal Taskforce for managing chronic pain recommend that NSAIDs should be avoided in patients over 65 years of age, as well as in those who have risk factors such as asthma, cardiovascular disease, impaired renal function or who are taking comedication that increases the likelihood of gastrointestinal bleeding.[45] In other patients, these agents should be given at the lowest effective dose for the shortest possible time.[45]

Opioids are agonists at one or more of the three major opioid receptors (μ, δ, and κ), which are located along pain pathways and throughout the CNS. Activation of the receptors inhibits the transmission of pain signals along pain pathways by decreasing the presynaptic release of neurotransmitters and hyperpolarizing postsynaptic neurons.[46] These agents are commonly used to treat moderate to severe chronic pain because the dose can usually be adjusted to achieve the required pain relief.

A retrospective analysis of 230 orthopedic spine clinic cases found that 66% of the patients had received opioids.[47] These opioids (eg, oxycodone, tramadol, fentanyl, and others) had been prescribed either alone or in combination. Although the severity of pain was significantly reduced and tolerance was not a problem, 58% of the patients reported side effects.[47] A meta-analysis of 18 clinical trials in osteoarthritis patients found that opioids significantly decreased pain intensity and conferred modest functional benefits, but recommended that they be used with caution and only for short periods, because of potentially severe adverse events.[48] Fifteen randomized placebo-controlled trials were included in a systematic review of 1145 patients with chronic noncancer pain.[49] The short-term efficacy of opioids was good; the mean decrease in pain intensity in most studies was at least 30% with opioids and was comparable in neuropathic and musculoskeletal pain. However, about 80% of patients experienced at least one adverse event, with constipation (41%), nausea (32%), and somnolence (29%) being most common, and only a minority of patients in these studies went on to long-term management with opioids.[49] These results suggest that opioids can provide effective analgesia in severe chronic pain, but the dose that can be administered may be suboptimal, because it is limited by tolerability problems.

Gabapentin and pregabalin appear to inhibit the release of excitatory neurotransmitters by blocking voltage-gated calcium channels,[50,51] but this mechanism may also be responsible for the side effects of these agents, which include somnolence, dizziness, balance problems, and cognitive impairment.[52,53] However, in randomized, placebo-controlled trials in patients with diabetic neuropathy or postherpetic neuralgia, adverse events were typically mild to moderate and usually subsided within approximately 10 days of the initiation of treatment.[52,53]

CHRONIC PAIN TREATMENT—PATIENTS' UNMET NEEDS

Although they differ in detail, numerous national and international guidelines give broadly similar recommendations for the treatment of chronic pain. However, there is evidence that incorporation of these guidelines into daily practice is marginal,[54,55] and probably less than optimal for some patients.[56] One of

the best known is the World Health Organisation's (WHO's) three-step pain ladder, which recommends nonopioids for step I, weak opioids for step II and strong opioids for step III.[57] Treatment decisions are based solely on pain intensity—the only criterion determining the specific step to which the patient is allocated. However, chronic pain is often multifactorial and rational pain management should take into account the context of the pain and the treatment preferences of the patient.[58,59] Furthermore, effective relief from chronic pain often requires a multimodal strategy, combining optimal pharmacological therapy with other treatment modalities such as physiotherapy, psychologic therapy, activities of daily living (ADL) aids, patient education and peripheral stimulation.

The general lack of consensus or consistency in treating chronic pain is clearly indicated by data from the internationally accepted information provider IMS Health (International Medical Statistics) for 2008 (Figure 1)[59]. Huge differences exist in the consumption of analgesics between different European countries, in terms of both quantity and the specific agents used. For example, opioids are prescribed much more readily in northern Europe than in the south and east.

One recent German study discovered that the average time from onset of pain until consultation with a GP was 3 years, and until referral to a specialist pain center was 12 years.[60] In almost half these cases, referral was at the request of the patient. However, at 6 and 12 months after the first contact with the specialist pain center, only 20% of the patients had improved with respect to pain intensity and psychometric data.[60]

In routine clinical care, 50% of patients with chronic pain do not obtain satisfactory pain relief.[61] Of the respondents reporting chronic pain in the Breivik survey, 40% felt that their pain was not well-managed, and 64% of those taking prescription medicines said their pain was inadequately controlled at

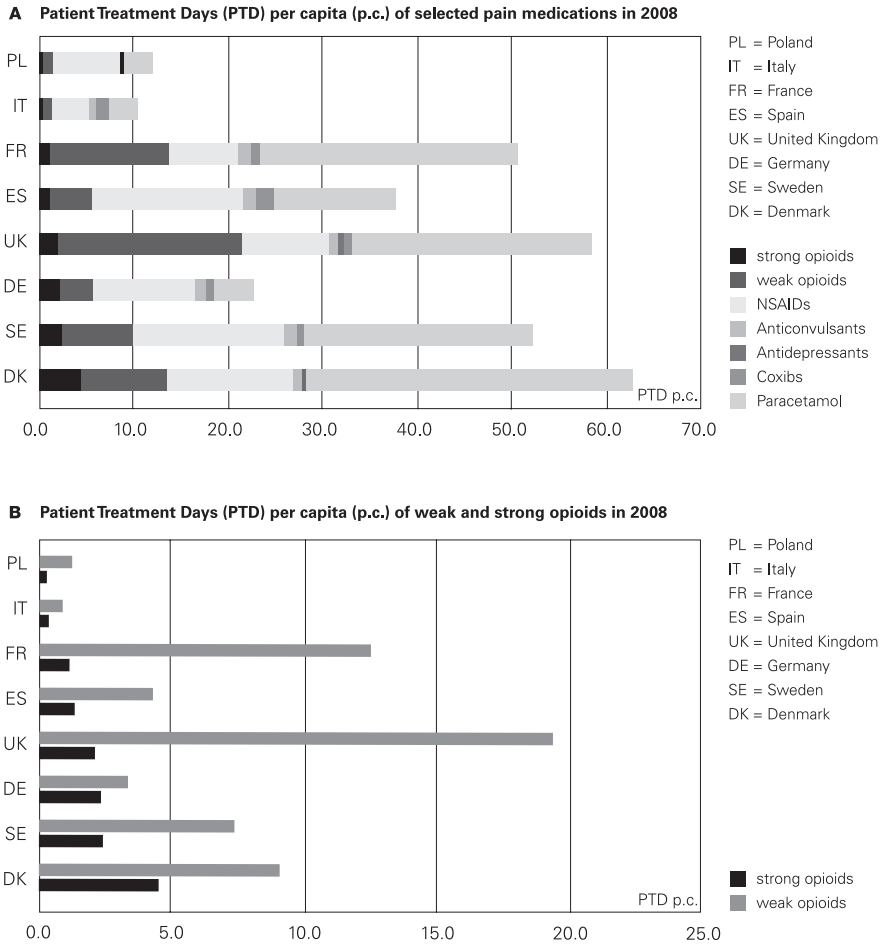

Figure 1. Differences in consumption of analgesics (A) and opioids (B) in Europe in patient treatment days per capita (PTD) (Varrassi et al.).[59]

times.[1] It has also been recorded that 28% of people experiencing severe chronic pain take only over-the-counter analgesics—or none at all.[6] These shortcomings in the management of chronic pain are partly due to persistent barriers restricting the use of strong opioids—related to such issues as tolerability, abuse potential, regulation and cultural values—and a belief that certain types of pain are not amenable to opioid analgesia, which is widely held but has no supporting evidence. Moreover, they suggest a need for improved pharmacological treatment options.

THE COMPLEXITY OF TREATING CHRONIC PAIN

Pain perception generally involves transduction at the neuron, conduction of pain signals along peripheral nerves, and onward transmission from the dorsal horn of the spinal cord to the brain. At the same time, modulating responses from the brain influence the patient's perception of pain, response, and the long-term effects. A normal response to acute pain, which is caused by external or internal tissue damage, is protective and adaptive.

However, the experience of pain results from activation of the pain matrix in the brain, which may arise from a number of possible triggers, and chronic pain may have no peripheral origin. Pain is a dynamic, bidirectional process and persistent pain is associated with neuroplastic changes throughout the nervous system. These changes—such as altered peripheral neuronal activity—may affect pain perception, sometimes causing intense pain even when tissue damage is limited or nonexistent, because the mechanisms involved are different from those of normal, acute pain.[62] In some chronic pain conditions, such as osteoarthritis, recurrent acute pain may be superimposed upon underlying persistent pain, and adequate long-term management of both types of pain is required.

Pain may be classified in different ways according to its duration, site, cause, or pathogenesis. Acute nociceptive pain may be defined as an adaptive, transient pain in response to a noxious stimulus, such as temperature (eg, burns, frostbite), chemicals (eg, acid), or mechanical injury (eg, crushing or cutting). The pain pathways function normally in this type of pain, which essentially has a warning function.[63] In neuropathic pain, an injury or lesion of the brain or spinal cord produces spontaneous pain, hyperalgesia and fluctuations in pain sensitivity to stimuli. This type of pain is maladaptive, with both the structure and function of the pain pathways being compromised.[63] In France, a nationwide postal survey of the general population produced 23,712 responders. Of these, 6.9% (n = 1631) reported having pain with neuropathic characteristics, which was moderate to severe in 5.1% (n = 1209).[64]

However, in humans this approach to the classification of pain is of unproven physiologic relevance. In neuropathic pain, sensations that would normally be interpreted as nonpainful are perceived as painful, as a result of higher levels of nociceptive traffic being presented to the pain matrix. The patterns of response to different types of pain within the pain matrix, however, are fairly similar; the main components of the matrix are activated during nociceptive, neuropathic, and psychogenic pain. Increasing evidence suggests that the psychologic context of the pain is very important in determining the brain's response. Psychologic traits have proved effective in predicting patients' response to therapy, but no attempts at classification have so far produced reliable improvements in therapeutic response at the individual patient level—this remains a challenge for the future.

Early, effective analgesic drug treatment of acute nociceptive pain aims to prevent or reverse chronification, activate endogenous pain control, improve physical function, and allow psychosocial rehabilitation. If left untreated, the peripheral neurons involved in transduction may undergo sensitisation as a result of persistent pain, tissue injury, or inflammation. This peripheral sensitisation causes formerly subthreshold stimuli to be capable of triggering action potentials, so that the frequency and duration of pain signals is increased.[63] The increased flow of pain signals, in turn, sensitizes the neurons in the dorsal horn of the spinal cord and further amplifies the sensation of pain.[65] This process is repeated once more when signals from the dorsal horn reach the brain. The changes in neuronal properties (plasticity) produced in the brain and spinal cord constitute central sensitisation, which can profoundly affect the experience of pain.[65]

Chronic pain (maladaptive pain syndromes) may be nociceptive, neuropathic, or mixed (both mechanisms may be present) (Figure 2). It may result from peripheral tissue damage or inflammation (nociceptive), or damage to the peripheral or central nervous system (neuropathic), and may be driven mainly by abnormal psychologic processes (psychogenic). The contribution of these different factors may be determined with

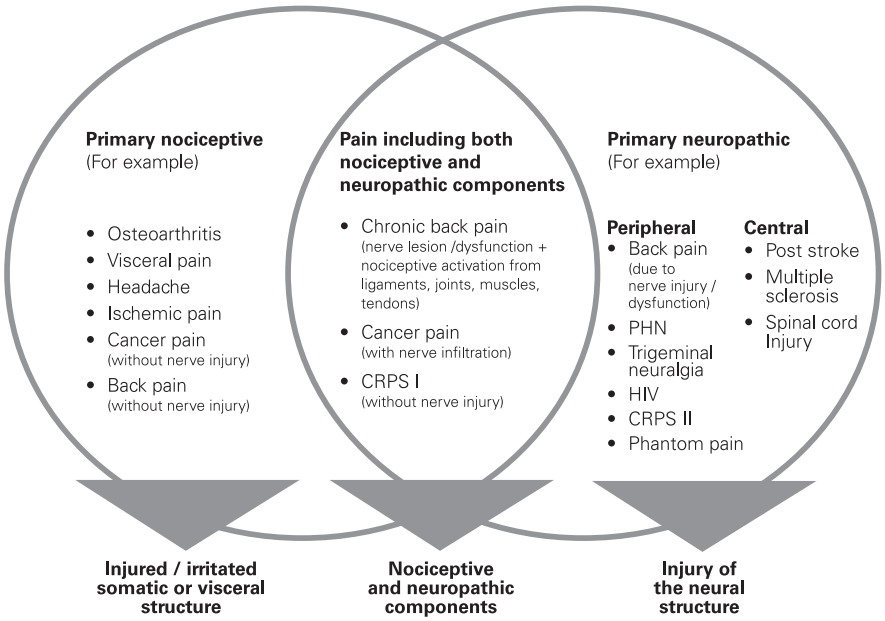

Figure 2. The occurrence of neuropathic and nociceptive components in various conditions, emphasizing the complexity of chronic pain.

varying levels of certainty depending on the physical and psychologic assessment. However, a substantial level of clinical judgement is often required, particularly as all three components may be present in different proportions over time. When assessing a patient with chronic pain, the clinician must always have in mind the biopsychosocial pain model, which acknowledges the interplay of physical, psychologic, and social factors.[66–68] As pain becomes chronic, psychosocial factors become increasingly important. Patients may develop depression, anger, fear of the future and frustration, or may become inactive and withdrawn. The challenge for the physician is to work with patients to overcome the biopsychosocial pain cycle and empower them to take control of their pain.

Clinical assessment is the crucial first step in effective pain management, to identify any organic cause of the pain and associated comorbidities. This requires a full history of pain and its treatment, general medical history, psychosocial assessment, physical examination, and any necessary laboratory tests.[69] Usually, the analysis of pain patients is based on the cause of pain (eg, osteoarthritis, diabetic neuropathy), but this ignores the possibility that different mechanisms may be involved; physicians should rather be guided by the type and intensity of pain, and the underlying mechanisms involved.[70] This can be difficult, however, because there may be no close correlation between the mechanism(s) and the symptoms experienced.[71,72]

Many analgesic drugs are available, which act at different points on the pain pathway (Figure 3), but no single agent completely addresses the analgesic needs of all patients. Currently, the management of severe chronic pain is often inadequate because of the difficulty of achieving a balance between sufficient analgesia and tolerability.[59] The impact that this has on quality of life produces high rates of treatment discontinuation (> 20%) even over short periods, particularly as a result of adverse events.[74] In one 13-month study of transdermal fentanyl and morphine in patients with back pain, 20% withdrew during the first month and a further 29% during the remaining period.[75] Switching to an alternative analgesic is one possible solution. Another is prescribing additional medications specifically to target a troubling side effect, although this may lead to drug/drug interactions associated with polypharmacy, or reduce compliance.[76]

CONSENSUS POINTS

No single agent completely addresses the analgesic needs of all patients.

Currently, the analgesics used to treat severe pain have limitations, including gastrointestinal and CNS tolerability issues, that often result in less than adequate pain relief.

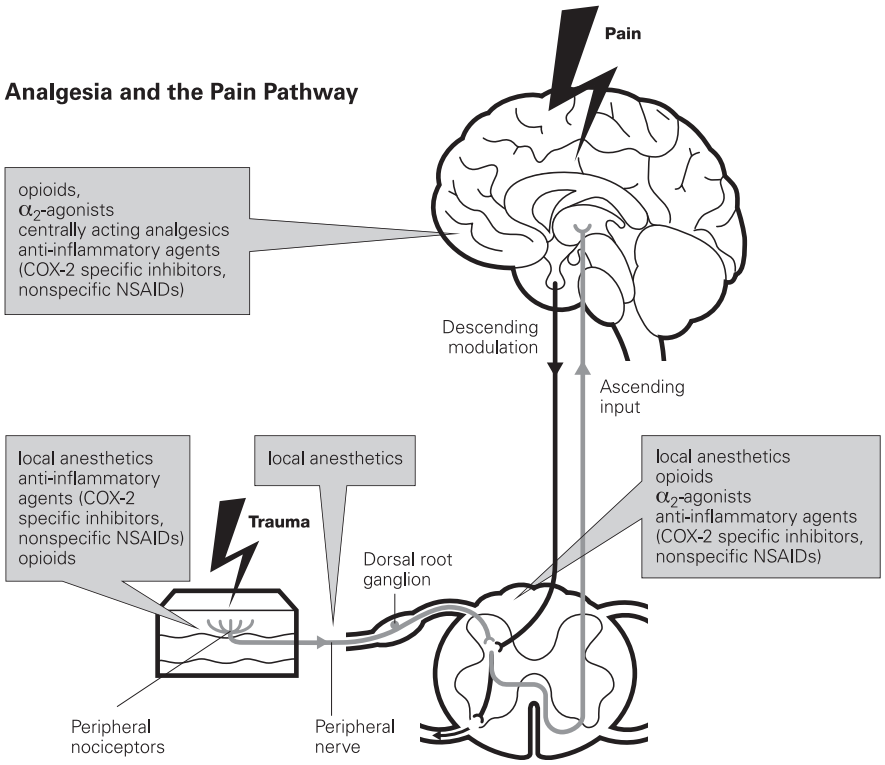

Figure 3. Analgesia and the pain pathway (adapted from Gottschalk and Smith).[73]

Chronic pain often involves more than one causative mechanism and is seldom controlled by a single agent,[77] so combining drugs that possess different mechanisms of action increases the probability of interrupting the pain signal.[59,78,79] Advisory Board members confirmed that they used this strategy in the majority of patients with severe chronic pain, because it was necessary to address multifactorial symptoms.

Loose combinations of agents (ie, not in fixed proportions) are predicated upon a good knowledge of pharmacology and may produce additive or synergistic effects for analgesia[80,81]—although the evidence is limited—but they risk drug/drug interactions, noncomplementary pharmacokinetic profiles, low compliance and increased side effects. Also, there is no guarantee that two drugs administered simultaneously will produce any clinical benefit.[82] On the positive side, drugs with different actions can be titrated independently to suit the individual patient, as long as time is taken to explain any potential side-effects and the clinician has a good working knowledge of the relevant pharmacology.

Fixed combinations are common and are designed either to address different underlying mechanisms (eg, a low-dose opioid plus a nonopioid, such as codeine/paracetamol)[83,84] or to minimize side effects. Examples of the latter include an opioid plus its antagonist to reduce gastrointestinal side effects (eg, oxycodone/naloxone)[85] and a NSAID plus a gastric protective agent for the same purpose (eg, diclofenac/misoprostol).[86] Another approach is to combine more than one mechanism of action in a single molecule, as in tapentadol. This novel centrally acting analgesic is both a μ-opioid receptor agonist (MOR) and a noradrenaline reuptake inhibitor (NRI),[87] the first example of a new pharmacological class called MOR-NRI.[88]

TAPENTADOL—PRECLINICAL TESTING

The analgesic properties of tapentadol (3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride) reside in a single enantiomer with the chemical formula $C_{14}H_{23}NO{\cdot}HCl$ and do not require metabolic activation.[89] It diffuses passively across the blood–brain barrier, following its concentration gradient—there is no known active transport mechanism. The two mechanisms are complementary; μ-opioid agonism is primarily effective against acute, moderate to severe pain, whereas noradrenaline reuptake

inhibition is particularly suitable for treating chronic pain.[90,91] Tapentadol is metabolized mainly in the liver via phase II glucuronidation to produce inactive metabolites,[92] and there are no clinically relevant interactions with enzymes of the P450 cytochrome system.[93] Plasma protein binding is low, so other medications are unlikely to be displaced from plasma proteins, and tapentadol therefore has a low potential for pharmacokinetic drug–drug interactions.[93]

In binding assays, tapentadol has only a moderate affinity for the μ-opioid receptor (Ki = 0.1 μM in rats),[89] which is about 50 times lower than that of morphine and may be associated with fewer opioid-like side effects.[94] The Ki value in a rat synaptosomal noradrenaline reuptake assay is 0.5 μM.[89] The two mechanisms contribute to the production of analgesia in different ways. Ascending pain messages are interrupted at synapses in the spinal cord, where μ-opioid agonism acts in two ways; binding to presynaptic neurons decreases calcium ion reflux and blocks the release of glutamate and other neurotransmitters, whereas binding to postsynaptic neurons inhibits their activity by producing hyperpolarisation of the neuronal membrane. Supraspinally, tapentadol's μ-opioid agonism changes the balance between the release of noradrenaline (inhibitory) and serotonin (inhibitory and facilitatory) by the descending pain pathways.[95] This action is enhanced by noradrenaline reuptake inhibition, which raises noradrenaline levels in the synaptic cleft, increasing the activation of α-2 receptors and inhibiting second order neurons. The differentiation between additive or synergistic effects of two drugs can be demonstrated by isobolographic analyses, whereas proving dual synergistic mechanisms in a single agent requires modification of this approach.[96] However, as can be demonstrated in acute and neuropathic preclinical pain models, there is compelling evidence for a true synergism between the two mechanisms of action of tapentadol.[97,98] Tapentadol also has very little effect upon serotonin reuptake,[87] which avoids the effects of increased serotonin on the enteric nervous system (constipation, nausea, and vomiting).

Efficacy

Broad analgesic efficacy has been demonstrated in various animal models of nociceptive, inflammatory, visceral, mono- and polyneuropathic pain, in mice, rats, rabbits, and dogs.[87,89] These used a range of different stimulus modalities (thermal, tactile, chemical, and electrical) and administration routes (intravenous, intraperitoneal, oral, intrathecal, and intracerebroventricular). Despite its 50-fold lower affinity for the μ-opioid receptor compared with morphine, in models of nociceptive pain the potency of tapentadol was only 2.5 times lower than morphine.[94] These consistent findings suggest that noradrenaline reuptake inhibition contributes to the analgesic effect of tapentadol, which is higher than would be expected from its μ-opioid agonist activity alone. In models of neuropathic pain, tapentadol demonstrated an even higher potency than morphine (ED_{50} = 0.32 mg/kg vs. 0.65 mg/kg in diabetic neuropathy) and also a significant inhibition of hyperalgesia at doses below those required for antinociception.[94] Additional evidence for tapentadol's efficacy in neuropathic pain states comes from a later study in a rodent model of diabetic peripheral neuropathy, in which tapentadol inhibited thermal hyperalgesia, but morphine did not.[99]

The relative importance of the two mechanisms in acute and chronic pain has been investigated by combining tapentadol with the μ-opioid antagonist naloxone or the α-2 antagonist yohimbine. It can be seen from Figure 4 that μ-opioid agonism makes a greater contribution to analgesia in acute pain (naloxone shifts the dose-response curve further to the right than yohimbine), whereas noradrenaline reuptake inhibition plays the major role in chronic pain.[97] This experiment also determined receptor fractional occupation from the brain concentration of tapentadol and its dissociation constant for each binding site. Isobolographic analysis of occupation-effect data, and a theoretically equivalent methodology that determined interactions from the effect scale, both demonstrated very pronounced synergistic interaction between the two mechanisms of action.[98]

CONSENSUS POINT

Tapentadol's pharmacological profile shows that it acts as an MOR-NRI and provides analgesic efficacy via two distinct mechanisms of action.

Tolerability

Constipation, nausea, and vomiting are frequent side effects of opioids and often lead to poor compliance. The inhibitory effects of morphine and tapentadol on gastrointestinal motility have been investigated using

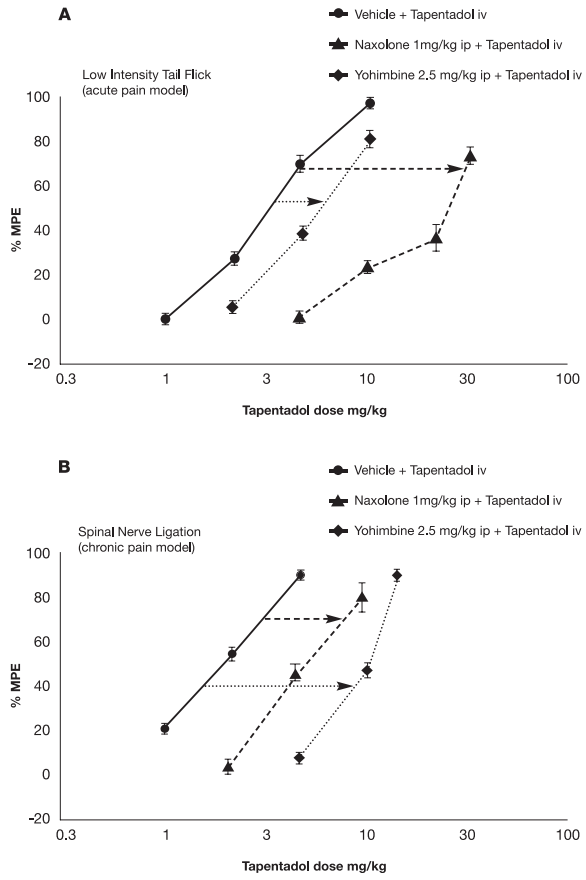

Figure 4. Differential contribution of MOR agonism and NA reuptake inhibition in acute and chronic pain models (adapted from Schröder et al.).[97] In acute pain, antagonising μ-opioid agonism with naloxone moves the dose-response curve further to the right than antagonising noradrenaline reuptake inhibition with yohimbine, showing that μ-opioid agonism makes a greater contribution to the compound's analgesic effect. In chronic pain, the opposite is true; noradrenaline reuptake inhibition contributes more to analgesia.

the charcoal passage test and the prostaglandin (PGE_2)-induced diarrhea model in mice.[89] In both cases, tapentadol had a weaker inhibitory effect than morphine at equianalgesic doses,[89] which may be due to tapentadol's noradrenergic component having an "opioid-sparing" effect. Equianalgesic doses of tapentadol and morphine have also been compared in an emesis model in ferrets; the incidence of retches and vomits was significantly lower in the tapentadol group, and the duration of these effects was shorter.[89]

The development of tolerance has been investigated in rats, using the chronic constriction model of neuropathic pain. In animals receiving vehicle or equianalgesic doses of tapentadol or morphine, complete tolerance was significantly delayed in the tapentadol group (23 days) compared with the morphine group (10 days).[87] Tapentadol has also been shown to produce less physical dependence than morphine.[89] Studies in Chinese hamster ovary cells and guinea-pig papillary muscles, as well as in rats, rabbits, and dogs, demonstrated a favorable cardiovascular safety profile.[89]

TAPENTADOL—CLINICAL TRIALS

Tapentadol has been developed in immediate release (IR) and prolonged release (PR) tablet formulations. Both formulations have been approved in Europe. In the U.S.A., the IR formulation has already gained approval, and the PR formulation is awaiting registration. The clinical development program has involved more than 800 healthy volunteers and 7,000 patients around the world.

Acute Pain

Bunionectomy is a standardized pain model that produces a predictable level of moderate to severe postsurgical pain. In a randomized, double-blind study, 901 bunionectomy patients received tapentadol IR (50 or 75 mg), oxycodone IR (10 mg), or placebo every 4–6 hours for 72 hours following surgery.[100] The primary endpoint was the sum of pain intensity differences after 48 hours (SPID48). Tapentadol demonstrated dose-dependent efficacy that was significantly better than placebo, and noninferior to oxycodone. The incidence of nausea and/or vomiting was significantly lower for tapentadol 50 mg and numerically lower for tapentadol 75 mg than for oxycodone.[100]

CONSENSUS POINT

Tapentadol has been shown to be clinically effective in treating acute postoperative pain.

Chronic Pain

Tapentadol PR has been investigated in three double-blind, randomized, placebo-controlled, multicenter trials in patients with chronic low back pain (1 trial; $n = 981$) or osteoarthritis (2 trials; $n = 2{,}020$), all following a similar design. A 3-week titration phase enabled subjects with moderate to severe pain (≥ 5 on an 11-point NRS) to reach their optimal dose of

tapentadol PR, oxycodone controlled release (CR), or placebo. This was followed by a 12-week maintenance phase, when patients could adjust the dose, but were not allowed rescue medication. The primary endpoint was the mean change in pain intensity, using the last observation carried forward (LOCF) imputation.

In the low back pain trial, optimal doses of opioid in both active treatment groups produced statistically significant reductions in pain intensity compared to placebo over the entire maintenance period (both $P < 0.001$),[101] but the incidence of treatment-emergent adverse events (TEAEs) was significantly lower for tapentadol than for oxycodone ($P < 0.05$). Gastrointestinal side effects, including constipation, nausea, and vomiting, were among the most commonly reported adverse events (placebo, 26.3%; tapentadol PR, 43.7%; oxycodone CR, 61.9%). The odds of experiencing constipation or the composite of nausea and/or vomiting were significantly lower for tapentadol PR than for oxycodone CR (both $P < 0.001$).[101] Over the whole study period, only 5.3% of the patients in the tapentadol group discontinued treatment owing to gastrointestinal side effects, compared with 18.3% in the oxycodone group.

In a pooled efficacy analysis of the two osteoarthritis studies, tapentadol clearly separated from placebo ($P < 0.001$) whereas oxycodone did not [data on file]. In both studies, discontinuations owing to gastrointestinal side effects were again lower in the tapentadol group than in the oxycodone group (7.3% vs. 26.9% and 11.6% vs. 28.7% [data on file]. In all three studies, there was a clear difference in treatment discontinuations for any reason between tapentadol and oxycodone, particularly during the titration phase [data on file].

A meta-analysis of all three studies demonstrated that tapentadol PR was noninferior to oxycodone CR in terms of efficacy ($P < 0.001$).[102] The results of analyses of 30% and 50% responders, patient global impression of change, Short Form-36 domains (except general health; Figure 5), and the EuroQol 5-Dimension health status index were all significantly better for tapentadol PR than for oxycodone CR (all $P \leq 0.048$).[102] Statistically better results for tapentadol were also demonstrated for gastrointestinal side effects ($P < 0.001$), and overall treatment discontinuations ($P < 0.01$)[102].

A clinical study with a randomized-withdrawal design has investigated the efficacy and safety of

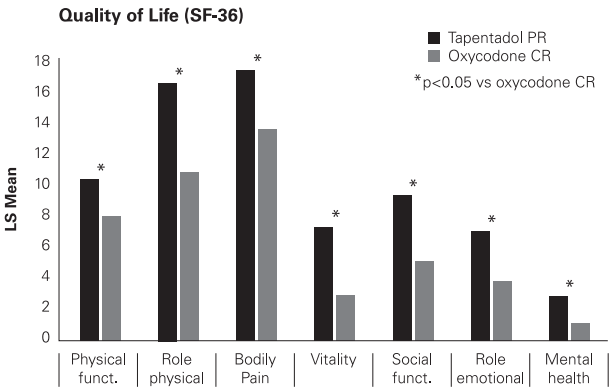

Figure 5. Results of the SF-36 health status questionnaire from a pooled analysis of three clinical studies with tapentadol PR in low back pain and osteoarthritis patients (Lange et al.; data on file).[102]

tapentadol in 588 patients with painful diabetic neuropathy, who were dissatisfied with their current treatment and had an average NRS score of ≥ 5.[103] Subjects were titrated to an optimal dose of tapentadol PR (100–250 mg twice a day) during a 3-week open-label phase. Those who responded (≥ 1 point reduction in pain intensity) were randomized 1:1 to receive either the optimal dose of tapentadol or placebo during the subsequent 12-week double-blind, fixed dose, withdrawal phase. The primary endpoint—to show a statistically significant difference in the maintenance of a clinically important improvement in pain intensity—was achieved, and tapentadol was well-tolerated by these patients.[103]

Long-term safety has been evaluated in a Phase III, open-label, randomized study in 1,117 patients with osteoarthritis or chronic low back pain.[104] Patients were randomized 4:1 to receive tapentadol PR or oxycodone CR. After titrating to their optimum dose over a period of 1 week, subjects were encouraged to stay on a stable dose for the 51-week maintenance phase, but allowed to adjust it if necessary, to reflect clinical practice. Efficacy was assessed as the average pain intensity over the previous 24 hours, using an 11-point numerical rating scale (NRS). Tapentadol provided stable, long-term relief from chronic low back or osteoarthritis pain over the period of the study and was also associated with significantly lower levels of constipation (22.6% vs. 38.6%; $P < 0.001$), nausea (18.1% vs. 33.2%; $P < 0.001$), and vomiting (7.0% vs. 13.5%; $P = 0.002$) than oxycodone.[104] In the tapentadol and oxycodone groups, respectively, gastrointestinal TEAEs led to discontinuation in 8.6% and 21.5% of patients.[105]

CONSENSUS POINTS

Tapentadol has proved to be efficacious in chronic pain and demonstrated a substantial reduction in gastrointestinal and CNS side effects compared with oxycodone.

Study data indicate that tapentadol may offer an analgesic opportunity that overcomes some of the limitations of currently available analgesics for treating chronic pain.

Tapentadol is an appropriate choice when there is a need for strong analgesics.

CONCLUSIONS

Rheumatologists and orthopedists manage many different chronic pain conditions that clearly present a considerable problem to society, both in terms of individual distress and economic impact. Current pain management strategies are in many cases inadequate, partly because of the limitations of existing pharmacological agents; for example, it is difficult to achieve the necessary balance between effective analgesia and tolerability when prescribing strong opioids, leading many patients to discontinue treatment. The gastrointestinal side effects of these agents—constipation, nausea, and vomiting—present a particular problem.

The combination of μ-opioid agonism and noradrenaline reuptake inhibition in a single molecule clearly differentiates tapentadol from other centrally acting analgesics. Preclinical testing has shown that these two mechanisms produce analgesic efficacy in a wide variety of nociceptive and neuropathic pain models. Tapentadol also possesses antihyperalgesic properties and a better side effect profile than existing strong opioids, most probably as a result of its ''opioid-sparing'' effect and absence of serotonergic properties. It may offer particular benefits in the treatment of chronic pain conditions with a neuropathic component, which is often the case in severe low back pain, because of its noradrenaline reuptake inhibition. In clinical trials, the efficacy of tapentadol has been comparable to oxycodone, but the incidence of adverse events—especially gastrointestinal side effects—has been consistently lower. In a long-term safety trial, tapentadol provided stable relief from chronic pain for almost a year with no evidence of tolerance development; this is particularly relevant to rheumatologists, whose patients may take analgesics for extended periods. The experts stated that tapentadol has the potential for managing moderate to severe pain in various acute and chronic pain indications, due to its multimechanistic analgesic approach.

ACKNOWLEDGEMENTS

This article was based on a meeting held in Brussels, Belgium, on July 9th and 10th, 2010, and was supported by an unrestricted educational grant from Grünenthal GmbH, Aachen, Germany.

The following authors received honoraria to attend the meeting in Brussels: Joseph Pergolizzi, Cayetano Alegre, David Blake, Jaime Calvo Alén, Roberto Caporali, Hans-Raimund Casser, Gerardo Correa, Pedro Fernandes, Eugenio Galilea, Richard Jany, Anthony Jones, Othmane Mejjad, Jadranka Morovic-Vergles, Ángel Oteo Álvaro, Francisco J. Radrigán Araya, Maria Eugénia C. Simões, Generoso Uomo.

The authors thank Derrick Garwood Ltd, Cambridge, U.K., for editorial support, which was sponsored by Grünenthal GmbH, Aachen, Germany.

REFERENCES

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287–333.

2. Sjøgren P, Ekholm O, Peuckmann V, Grønbaek M. Epidemiology of chronic pain in Denmark: an update. *Eur J Pain*. 2009;13:287–292.

3. Rustoen T, Wahl AK, Hanestad BR, Lerdal A, Paul S, Miaskowski C. Prevalence and characteristics of chronic pain in the general Norwegian population. *Eur J Pain*. 2004;8:555–565.

4. Langley PC. The prevalence, correlates and treatment of pain in the European Union. *Curr Med Res Opin*. 2011;27:463–480.

5. Langley PC, Müller-Schwefe G, Nicolaou A, Liedgens H, Pergolizzi J, Varrassi G. The societal impact of pain in the European Union: health-related quality of life and healthcare resource utilization. *J Med Econ*. 2010;13:571–581.

6. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: results from a cross-sectional survey. *Eur J Pain*. 2006;10:127–135.

7. European Commission. Health in the European Union: Special EUROBAROMETER 272. 2007. Available at: http://ec.europa.eu/health/ph_publication/eb_health_en.pdf [last accessed on September 7th, 2010].

8. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain*. 2000;84:95–103.

9. Gore M, Brandenburg NA, Hoffman DL, Tai KS, Stacey B. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain*. 2006;7:892–900.

10. Department of Work and Pensions. DWP quarterly statistical summary. August 12th 2009. ISSN: 1462-9798.

11. Belsey J. Primary care workload in the management of chronic pain: a retrospective cohort study using a GP database to identify resource implications for UK primary care. *J Med Econ*. 2002;5:39–52.

12. Wenig CM, Schmidt CO, Kohlmann T, Schweikert B. Costs of back pain in Germany. *Eur J Pain*. 2009;13:280–286.

13. Schnitzer T. Update on guidelines for the treatment of chronic musculoskeletal pain. *Clin Rheumatol*. 2006;25(suppl 1):S22–S29.

14. DeHaan M, Guzman J, Bayley M, Bell M. Knee osteoarthritis clinical practice guidelines—how are we doing? *J Rheumatol*. 2007;34:2099–2105.

15. Mazzuca S, Brandt K, Katz B, et al. Comparison of general internists, family physicians, and rheumatologists managing patients with symptoms of osteoarthritis of the knee. *Arthritis Care Res*. 1997;10:289–299.

16. Batlle-Gualda E, Román J, Carbonell J, Tornero J, Fortea J. Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial. *Osteoarth Cartil*. 2007;15:900–908.

17. Langford R, McKenna F, Ratcliffe S, Vojtassak J, Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. *Arthritis Rheum*. 2006;54:1829–1837.

18. Kean W, Bouchard S, Gossen E. Women with pain due to osteoarthritis: the efficacy and safety of a once-daily formulation of tramadol. *Pain Med*. 2009;10:1001–1011.

19. Nuesch E, Rutjes A, Husni E, Welch V, Juni P. Oral or transdermal opioids for osteoarthritis of the knee or hip (review). *Cochrane Database*. 2009;7:CD003115.

20. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res*. 2000;15:1384–1392.

21. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*. 1999;353:878–882.

22. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1999;159:1215–1220.

23. Lydick E, Martin A, Yawn B. Impact of fears on quality of life in patients with a silent disease: osteoporosis. *Clin Ther*. 1996;18:1307–1315.

24. Bayles CM, Cochran K, Anderson C. The psychosocial aspects of osteoporosis in women. *Rheumatology*. 2000;35:279–286.

25. Lukert B. Vertebral compression fractures: How to manage pain, avoid disability. *Geriatrics*. 1994;49:22–26.

26. Gold DJ. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. *Bone*. 1996;18:1855–1895.

27. Hahn TJ. Metabolic bone disease. In: Lavin N ed. *Manual of Endocrinology and Metabolism*. Baltimore, MD: Lippincott Willams and Wilkins; 2009: 362–380.

28. Gennari C. Analgesic effect of calcitonin in osteoporosis. *Bone*. 2002;5(suppl):67S–70S.

29. Ringe JD, Faber H, Bock O, et al. Transdermal fentanyl for the treatment of back pain caused by vertebral osteoporosis. *Rheumatol Int*. 2002;22:199–203.

30. Grijalva C, Chung C, Stein C, Mitchel EF, Griffin M. Changing patterns of medication use in patients with rheumatoid arthritis in a Medicaid population. *Rheumatology*. 2008;47:1061–1064.

31. Berliner M, Giesecke T, Bornhovd K. Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. *Clin J Pain*. 2007;23:530–534.

32. Raffaeli W, Pari C, Corvetta A, et al. Oxycodone/acetaminophen at low dosage: an alternative pain treatment for patients with rheumatoid arthritis. *J Opioid Manag*. 2010;6:40–46.

33. Lee EY, Lee EB, Park BJ, et al. Tramadol 37.5-mg/acetaminophen 325-mg combination tablets added to regular therapy for rheumatoid arthritis pain: a 1-week, randomized, double-blind, placebo-controlled trial. *Clin Ther*. 2006;28:2052–2060.

34. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33:160–172.

35. Schweinhardt P, Sauro K, Bushnell M. Fibromyalgia: a disorder of the brain? *Neuroscientist*. 2008;14:415–421.

36. Staud R. Pharmacological treatment of fibromyalgia syndrome: new developments. *Drugs*. 2010;70:1–14.

37. Raffa RB, Pergolizzi JV, Tallarida RJ. The determination and application of fixed-dose analgesic combinations for treating multimodal pain. *J Pain*. 2010;11:701–709.

38. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2004;63:901–907.

39. Liver injury related to the use of acetaminophen. FDA: Joint meeting of the Drug Safety and Risk Management Advisory Committee Nonprescription Drugs Advisory Committee and Anesthetic and Life Support Drugs Committee, Notice of Meeting Federal Register 74:28 April 24, 2009. Available at: http://edocket.access.gpo.gov/2009/pdf/E9-9380.pdf [last accessed June 30th, 2011].

40. Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Amer J Epidemiol*. 1995;141:539–545.

41. Lanas A, Perez-Asia MA, Feu F, et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal antiinflammatory use. *Amer J Gastroenterol*. 2005;100:1685–1693.

42. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954–959.

43. Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension*. 2004;44:140–145.

44. American Geriatrics Society. April 21st, 2009. AGS Clinical Practice Guideline: Pharmacological Management of Persistent Pain in Older Persons. Available at: http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/persistent_pain_executive_summary [last accessed October 1st, 2011].

45. British Society for Rheumatology and IASP Musculoskeletal Taskforce. British Society for Rheumatology and IASP Musculoskeletal Pain Taskforce Guidelines for the Integrated Management of Musculoskeletal Pain Symptoms (IMMsPS), 2008. Available at: http://www.hope–academic.org.uk/painresearch/Guidelines_for_the_Management_of_Musculoskeletal_Pain_Short.pdf [last accessed February 15th, 2011].

46. Schumacher MA, Basbaum AI, Way WL. Opioid analgesics and antagonists. In: Katzung BG ed. *Basic and Clinical Pharmacology*. New York, NY: McGraw Hill; 2007: 489–510.

47. Mahowald M, Singh J, Majeski P. Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum*. 2005;52:312–321.

48. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. *Osteoarth Cartil*. 2007;15:957–965.

49. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–380.

50. Gajraj NM. Pregabalin for pain management. *Pain Pract*. 2005;5:95–102.

51. Field MJ, Cox PJ, Stott E, et al. Identification of the α2-δ-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. *Proc Natl Acad Sci USA*. 2006;103:17537–17542.

52. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: Evidence from randomized, placebo-controlled clinical trials. *Clin Ther*. 2003;25:81–104.

53. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003;60:1524–1534.

54. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999;354:581–585.

55. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8:287–313.

56. Victor TW, Alvarez NA, Gould E. Opioid prescribing practices in chronic pain management: guidelines do not sufficiently influence clinical practice. *J Pain*. 2009;10:1051–1057.

57. World Health Organisation. *Cancer Pain Relief with a Guide to Opioid Availability*. 2nd ed. Geneva: World Health Organisation; 1996.

58. Woolf CJ, Max MB. Mechanism-based pain diagnosis: issues for analgesic drug development. *Anesthesiology*. 2001;95:241–249.

59. Varrassi G, Müller-Schwefe G, Pergolizzi J, et al. Pharmacological treatment of chronic pain—the need for CHANGE. *Curr Med Res Opin*. 2010;26:1055–1069.

60. Schulte E, Hermann K, Berghöfer A, et al. Referral practices in patients suffering from non-malignant chronic pain. *Eur J Pain*. 2009, 14: 308.e1–308.e10.

61. Galvez R. Variable use of opioid pharmacotherapy for chronic noncancer pain in Europe: causes and consequences. *J Pain Palliat Care Pharmacother*. 2009;23:346–356.

62. Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci*. 2002;5(suppl):1062–1067.

63. Woolf C. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140:441–451.

64. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*. 2008;136:380–387.

65. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895–926.

66. Edwards D, Gatchel R, Adams L, Stowell AW. Emotional distress and medication use in two acute pain populations: jaw and low back. *Pain Pract*. 2006;6:242–253.

67. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007;133:581–624.

68. Becker N, Bondegaard Thomsen A, Olsen AK, Sjøgren P, Bech P, Eriksen J. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. *Pain*. 1997;73:393–400.

69. American Pain Society. *Pain Control in the Primary Care Setting*. Glenview, IL: American Pain Society; 2006.

70. Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. *Life Sci*. 2004;74:2605–2610.

71. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959–1964.

72. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911–1920.

73. Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Physician*. 2001;63:1979–1984.

74. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther*. 2005;7:R1046–R1051.

75. Kalso E, Simpson KH, Slappendel R, Dejonckheere J, Richarz U. Predicting long-term response to strong opioids in patients with low back pain: findings from a randomized, controlled trial of transdermal fentanyl and morphine. *BMC Med*. 2007;5:39.

76. Harris JD. Management of expected and unexpected opioid-related side effects. *Clin J Pain*. 2008;24(suppl 10):S8–S13.

77. Davis MP. What is new in neuropathic pain? *Support Care Cancer*. 2007;15:363–372.

78. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. *J Clin Pharm Ther*. 2001;26:257–264.

79. Besson M, Piguet V, Dayer P, Desmeules J. New approaches to the pharmacotherapy of neuropathic pain. *Expert Rev Clin Pharmacol*. 2008;1:683–693.

80. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324–1334.

81. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain*. 2008;12:804–813.

82. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. *J Pain*. 2010;11:462–471.

83. Raffa R. Pharmacological aspects of successful long-term analgesia. *Clin Rheumatol*. 2006;25:S9–S15.

84. Raffa RB, Pergolizzi JV, Segarnick DJ, Tallarida RJ. Oxycodone combinations for pain relief. *Drugs Today*. 2010;46:379–398.

85. Clemens KE, Mikus G. Combined oral prolonged-release oxycodone and naloxone in opioid-induced bowel dysfunction: review of efficacy and safety data in the treatment of patients experiencing chronic pain. *Expert Opin Pharmacother*. 2010;11:297–310.

86. Kristiansen IS, Kvien TK, Nord E. Cost effectiveness of replacing diclofenac with a fixed combination of misoprostol and diclofenac in patients with rheumatoid arthritis. *Arthritis Rheum*. 1999;42:2293–2302.

87. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel μ-opioid receptor agonist/norepinephrine reuptake inhibitor with broad–spectrum analgesic properties. *J Pharmacol Exp Ther*. 2007;323:265–276.

88. Kress H (Editorial). Tapentadol and its two mechanisms of action: Is there a new pharmacological class of centrally acting analgesics on the horizon? *Eur J Pain*. 2010;14:781–783.

89. Tzschentke TM, De Vry J, Terlinden R, et al. Tapentadol hydrochloride. *Drugs Fut*. 2006;31:1053–1061.

90. Casy AF, Parfitt RT. *Opioid Analgesics*. New York, USA: Plenum Press; 1986.

91. Carter GT, Sullivan MD. Antidepressants in pain management. *Curr Opin Investig Drugs*. 2002;3:454–458.

92. Terlinden R, Ossig J, Fliegert F, Lange C, Göhler K. Absorption, metabolism, and excretion of 14C-labeled tapentadol HCl in healthy male subjects. *Eur J Drug Metab Pharmacokinet*. 2007;32:163–169.

93. Kneip C, Terlinden R, Beier H, Chen G. Investigations into the drug-drug interaction potential of tapentadol in human liver microsomes and fresh human hepatocytes. *Drug Metab Letters*. 2008;2:67–75.

94. Tzschentke TM, Jahnel U, Kögel B, et al. Tapentadol hydrochloride: a next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. *Drugs Today*. 2009;45:483–496.

95. Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: Descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci*. 2004;25:613–617.

96. Hartrick CT, Rozek RJ. Tapentadol in pain management. A μ-opioid receptor agonist and noradrenaline reuptake inhibitor. *CNS Drugs*. 2011;25:359–370.

97. Schröder W, De Vry J, Tzschentke TM, Jahnel U, Christoph T. Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. *Eur J Pain*. 2010;14:814–821.

98. Schröder W, Tzschentke TM, Terlinden R, et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. *J Pharmacol Exp Ther*. 2011;337:312–320.

99. Christoph T, De Vry J, Tzschentke TM. Tapentadol, but not morphine, selectively inhibits disease-related thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Neurosci Lett*. 2010;470:91–94.

100. Daniels S, Casson E, Stegmann JU, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin*. 2009;25:1551–1561.

101. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother*. 2010;11:1787–1804.

102. Lange B, Kuperwasser B, Okamoto A, et al. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther*. 2010;27:381–399.

103. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin*. 2011;27:151–162.

104. Grond S, Kuperwasser B, McCann B, et al. Long-term safety and gastrointestinal tolerability of tapentadol extended release or oxycodone controlled release in patients with chronic low back or osteoarthritis pain [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1495.

105. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Pract*. 2010;10:416–427.