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From acute to chronic pain: tapentadol in the progressive stages of this disease entity

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Abstract. – OBJECTIVE: Chronic pain is now recognized as a neural disease, which results from a maladaptive functional and structural transformation process occurring over time. In its chronic phase, pain is not just a symptom but also a disease entity. Therefore, pain must be properly addressed, as many patients still report unsatisfactory pain control despite on-going treatment. The selection of the therapy – taking into account the pathophysiological mechanisms of pain – and the right timing can result in a successful analgesic outcome. This review will present the functional and structural modifications leading to chronification of pain, focusing on the role of tapentadol in this setting.

MATERIALS AND METHODS: For inclusion in this review, research studies were retrieved via a keyword-based query of multiple databases (MEDLINE, Embase, Cochrane). The search was last updated in November 2016; no limitations were applied.

RESULTS: Functional and structural abnormalities of the nervous system associated with pain chronification have been reported in several conditions, including osteoarthritis, chronic back pain, chronic pelvic pain and fibromyalgia. Correct identification and treatment of pain in recurrent/progressive stage is crucial to prevent chronification and related changes in neural structures. Among analgesic drugs, tapentadol, with its dual mechanism of action (opioid agonist and noradrenaline reuptake blocker), has recently resulted active in pain control at both central and spinal level.

CONCLUSIONS: Tapentadol represents a suitable candidate for patients at early progressive stage of pain who have developed neuroplasticity with modification of pain pathways. The availability of different doses of tapentadol may help clinicians to tailor treatment based on the individual need of each patient, with the aim to enhance therapeutic appropriateness in the treatment of musculoskeletal and neuropathic pain.

Key Words:
Chronic pain, Recurrent chronic, Analgesics, Opioids, Tapentadol.

Introduction

Musculoskeletal pain is the leading cause of disability in the world, and chronic pain has a major impact on healthcare costs, direct and indirect[1,2]. The current understanding is that chronic pain should be considered as a specific neurological disease entity[3]. Specifically, pain chronification does not offer a protective function: pain progresses over time from a signal based on physiological alert mechanisms to a maladaptive response and then to a neurological disease, requiring proper pharmacological management[4,5]. This progression is the ultimate result of a process of functional and structural modifications of neurological structures due to neuroplasticity phenomena[6,7]. In more details, neuroplastic changes reflect the adaptive neurophysiological processes occurring as the result of altered afferent stimuli, which include nociceptive and neuropathic transmission to the spinal, subcortical and cortical areas[6]. Those stimuli may be initially beneficial; however, they may persist in a chronic state. Ultimately, neuroplastic changes within different areas of the central nervous system (CNS) may occur, explaining the transition from acute to chronic pain conditions.

The structural modifications that occur in chronic pain are among the main reasons for the

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poor efficacy sometimes shown by analgesic therapy[8,9]. Moreover, currently available analgesic options are not always applied in accordance with our growing understanding of the mechanisms underlying the etiology and chronification process of pain[10,11]. Analgesic drugs targeting specific neuroplastic processes involved in pain chronification have been developed[12-17].

Among them, tapentadol is characterized by a peculiar dual mode of action. This single molecule acts both as a μ-opioid receptor (MOR) agonist and as a norepinephrine reuptake inhibitor, thereby generating synergistic analgesic action[18]. The availability of multiple dosages of tapentadol may allow its use in all the intermediate steps involved in the process of transition from acute to chronic pain. This review will present the functional and structural modifications leading to chronification of pain, with a focus on the role of tapentadol in this setting.

Search Criteria

For inclusion in this review, research studies were retrieved via a keyword-based query (e.g. "pain chronification") of multiple database (MEDLINE, Embase, Cochrane). The search was last updated in November 2016; no limitations were applied. The abstract lists of major scientific congresses and the reference lists of the retrieved papers were also browsed. Papers were then considered for inclusion according to their relevance for the topic, as judged by the authors.

Pathophysiological Background

The standard classification of pain distinguishes between nociceptive pain (originating in tissues in response to a nociceptor stimulation or nociceptive stimulus) and neuropathic pain originating in the peripheral nervous system (PNS) or CNS as a result of damage to nerve fibres. In both cases, nociceptive impulses (Figure 1) then travel along A-delta fibres and C-fibres of first-order neurons (primary afferent fibres) and are transmitted to second-order neurons residing in the spinal cord dorsal horn[9,19-21]. These neurons transmit the pain impulse to the thalamus, where subliminal perception of pain occurs, giving rise to a series of physiological modifications, such as hypertension, tachycardia, and others. To enable the organism to locate the source of the pain stimulus, third-order neurons project impulses received from second-order neurons to the cerebral cortex.

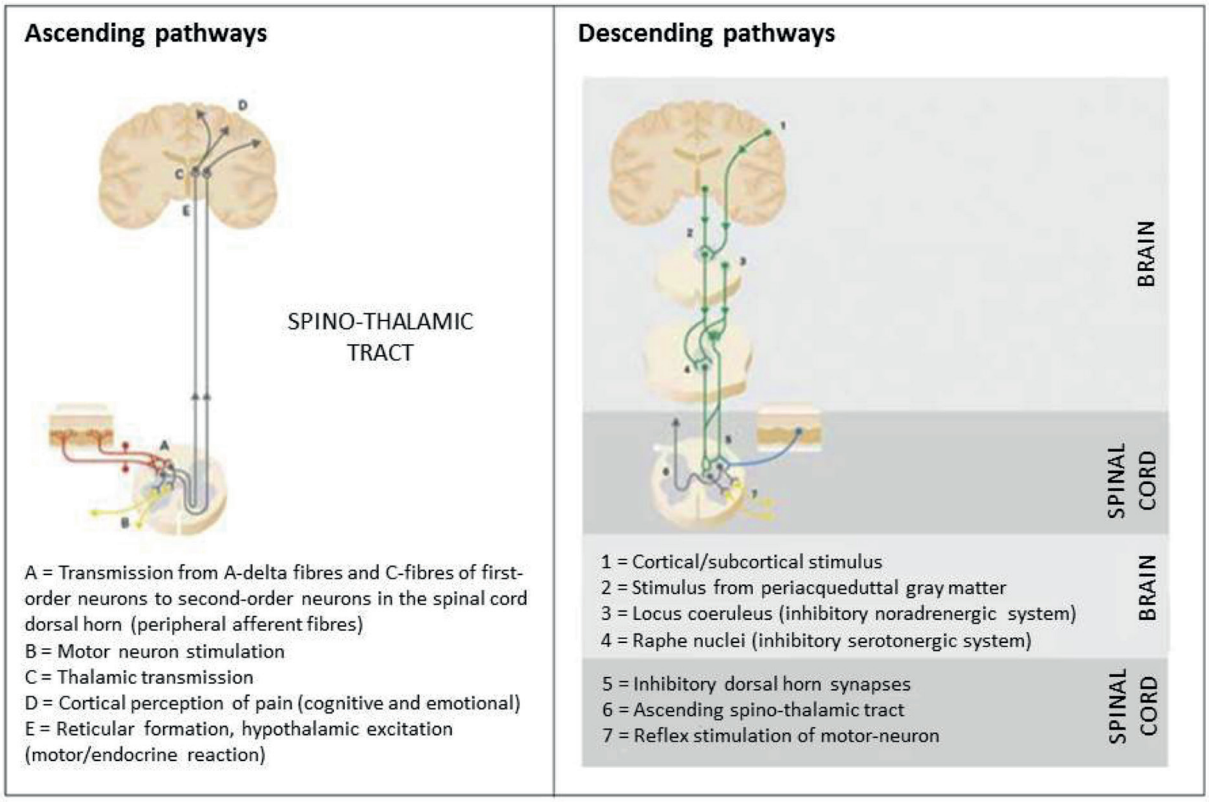

Figure 1. Ascending and descending pathways involved in pain transmission and modulation (modified from[3]).

However, the transmission of noxious stimuli along the ascending pathways is conditioned by the action of descending modulatory pathways, which, especially at the spinal level, may modify the intensity and characteristics of the perceived pain. At spinal synapses, the descending pathways promote the release of endogenous opioids, norepinephrine, serotonin (5-HT) and gamma-aminobutyric acid (GABA), which control the transmission between primary and secondary neurons[22].

Over the last years, mounting attention has been paid to the pathophysiological mechanism driving the shift from acute (i.e., physiological) to chronic (i.e., pathological) pain. This process of pain chronification is based first on functional changes and then encompasses structural alterations of the CNS[5].

Peripheral and Central Sensitisation

From an early stage (few hours) the neural structures involved in acute inflammatory pain start to undergo plastic modifications. This leads to peripheral sensitisation, in which peripheral nociceptors reduce their activation threshold and increase their responsivity to noxious stimuli. If the cause of the inflammatory pain resolves in a short period (a few days), the plastic modifications also regress[23]. However, if the stimulus persists, high-frequency transmission is upheld with massive release of glutamates and neuro-modulating peptides, ultimately leading to modifications of spino-thalamic neurons and interneurons, a phenomenon known as central sensitisation. Central sensitisation may then involve other supraspinal integration structures such as the thalamus and cortex and constitutes the basis for chronification of pain[24]. These short-term modifications are of a functional nature (e.g. recruitment of silent synapses and synaptic reinforcement) and are reversible. On the other hand, structural plasticity phenomena follow over time (sprouting/shrinking of fibres, neuronal death), and they are difficult to reverse[25].

In some types of musculoskeletal pain, for instance, the process is based on an inflammatory nociceptive input. The initial excitation and peripheral sensitisation of nociceptors associated with tissue damage may produce a nociceptive input to the central systems that would be sufficient to cause central sensitisation of neurons in the dorsal horn and/or at higher levels[26]. In such a context, persistence of the peripheral nociceptive input in combination with initial reduction in the efficacy of some inhibitory systems such as the GABAergic systems may result in chronification.

Descending Pathways in the Modulation of Pain

Descending modulatory pathways – both facilitatory and inhibitory – originating in the supraspinal centers, influence the perception of pain and modulate the activity of nociceptors at the level of the spinal cord dorsal horns through an increase or decrease in the propagation of signals to the brain[27]. The action of neurotransmitters, including endogenous opioids, norepinephrine and serotonin, underlies the modulation of the noxious stimulus. In particular, MOR agonists directly influence and inhibit transmission of pain signals along the ascending pathways and, in addition, are involved in the modulation of supraspinal pain signals through their action at the level of descending pathways[5,9,22]. While noradrenergic pathways have an inhibitory effect on the transmission of pain, which also continues in case of neuropathic pain or chronic pain[28], serotonin may also have a facilitatory effect particularly in the advanced stages of chronicity and is, therefore, pro-nociceptive[29]. An imbalance between amplified ascending signals and inadequate activation of the descending inhibitory pathway seems to underlie the development and maintenance of many chronic pain syndromes (Figure 2). Animal studies also suggest that effective involvement of the inhibitory descending pathways protects against the development of chronic pain[30]. Moreover, other studies in animal models demonstrate that μ-opioid receptor agonism is particularly relevant in acute nociceptive pain, while the inhibitory activity of noradrenaline reuptake is important in chronic neuropathic pain[31].

Clinical Evidence

The functional and structural modifications of the nervous system in response to pain have an immediate clinical relevance. The diagnosis of chronic pain in a patient with active chronification and neuroplasticity phenomena should not rely only on the duration of symptoms alone. Thus, chronic pain is more than just "pain that has lasted for 3 or 6 months". Chronic pain[32,33] is defined according to three main features: (i) widespread pain which is diffused beyond the site of the primary lesion and does not necessarily follow innervation territories; (ii) pathological pain (mixed, nociceptive and neuropathic pain) which has lost its physiological protective function; and

(iii) loss of response to the so-called "simple analgesics" (non-steroid anti-inflammatory drugs -NSAIDs- and paracetamol), since the chronification process has involved superior structures of the CNS and has lost its immediate association with inflammation. An algorithm for the classification of central sensitization pain has been proposed based on the above-definitions (Figure 3)[33].

The presence of functional and structural abnormalities of the nervous system and their clinical relevance has been shown in some conditions, including osteoarthritis (OA), chronic back pain (CBP), chronic pelvic pain (CPP), and fibromyalgia (FMS).

Osteoarthritis

Patients with OA show some sensory abnormalities including widespread loss of cutaneous vibration sensitivity, hypoesthesia to punctate mechanical, pinprick and thermal stimuli and mechanical allodynia[32]. Also, pain in areas of their body and skin becomes referred and does not match the innervation territories of peripheral nerves or nerve roots.

This referred pain in OA is mediated by central sensitization nociceptors, continuously firing (ectopically) in and around the affected joint. The central sensitization in patients with OA has been supported by some studies[34-36]. As a further confirmation of pain sensitisation in OA patients, a meta-analysis of 15 studies pooled data on pressure pain threshold (PPT) and heat pain threshold (HPT)[37]. The point estimate was large for differences in PPTs between knee OA participants and controls [-0.85; confidence interval (CI): -1.1 to -0.6], and moderate for PPT differences between knee OA participants with high symptom severity *vs.* those with low symptom severity (0.51; CI: -0.73 to -0.30). A small point estimate was also reported for differences in HPTs between knee OA

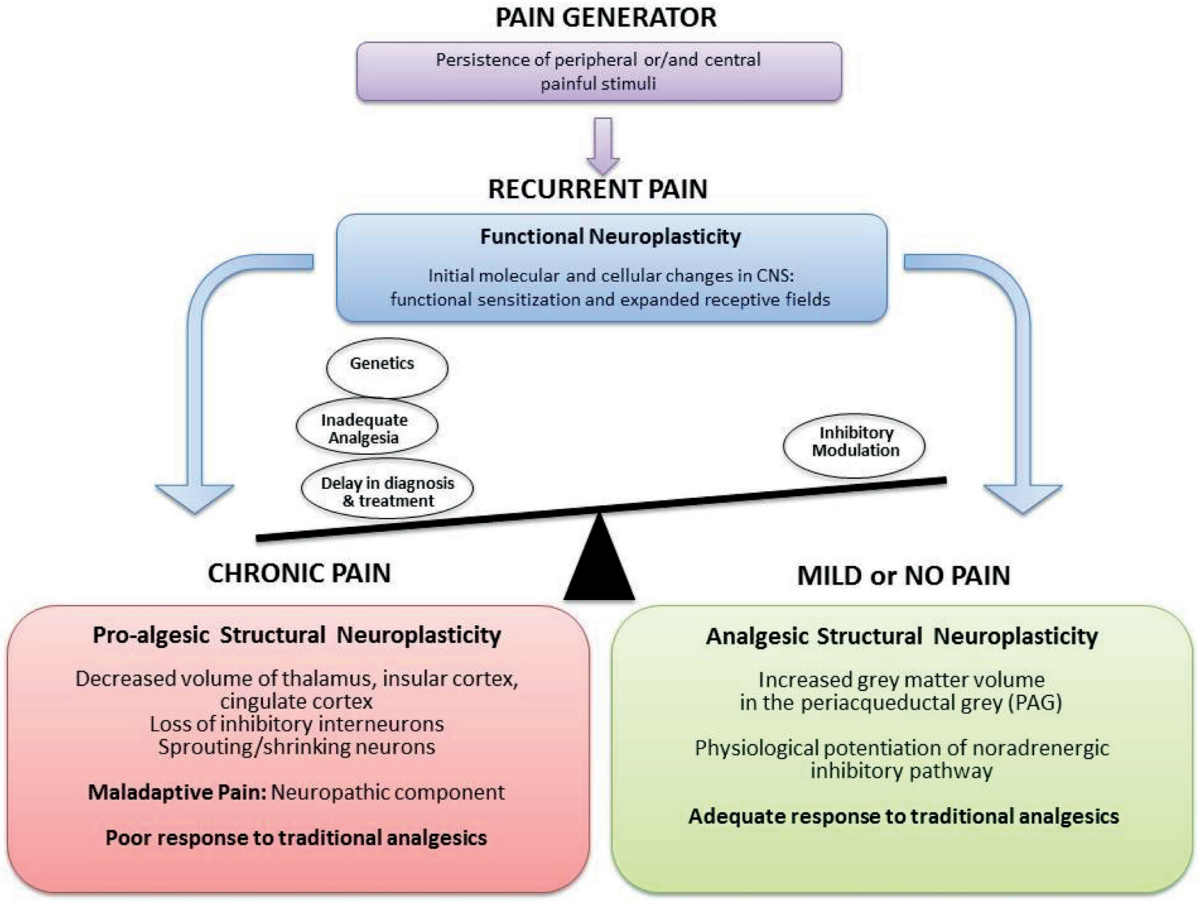

Figure 2. Pain chronification is the result of an imbalance between enhanced ascending nociceptive inputs and inadequate inhibitory descending system.

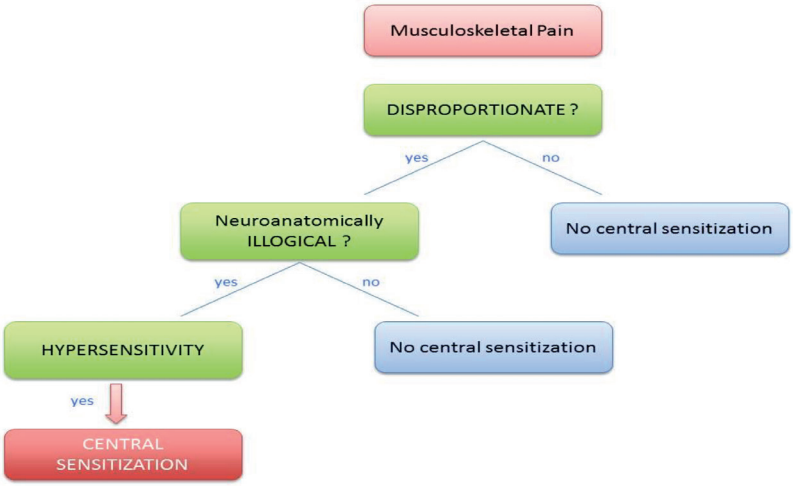

Figure 3. Algorithm for the classification of musculoskeletal pain (modified from[33]).

participants and controls (-0.42; CI: -0.87 to 0.02). Moreover, in a very recent cross-sectional study, 53 people with knee OA scheduled to undergo primary total knee arthroplasty were studied[38]. Pain frequency maps revealed enlarged areas of pain, especially in women; in particular, enlarged areas of pain were associated with higher knee pain severity (rs = 0.325, p <0.05) and stiffness (rs = 0.341, p <0.05), lower pressure pain thresholds at the knee (rs = -0.306, p <0.05) and epicondyle (rs = -0.308, p <0.05), and higher scores with the Central Sensitization Inventory (rs = 0.456, p <0.01). The authors of this study concluded that expanded distribution of pain was correlated with some measures of chronic sensitization in individuals with knee OA. Recently, increased pain sensitivity distantly from the knee reflects widespread hyperalgesia, thus further supporting chronic sensitization in patients with knee OA.

At a physiological level, animal models of OA have shown that ectopic sprouting of sensory and sympathetic nerve fibers occurs in the painful arthritic joint and may be involved in the generation and maintenance of arthritic pain. Understanding the factors that drive this neuroplasticity, whether this pathologic reorganization of nerve fibers contributes to chronic joint pain, and how the phenotype of sensory and sympathetic nerves changes with age may provide insight into better pharmacologic targets for controlling aging-related joint pain[39,40].

Chronic Back Pain

Central sensitization leading to chronic pain plays a major role also in CBP, and it is associated with major structural alterations also at CNS. Apkarian et al[41] compared brain morphology of 26 CBP patients to matched controls. Patients with CBP showed 5-11% less neocortical gray matter volume than controls; by way of comparison, the magnitude of this decrease is equivalent to the gray matter volume lost in 10-20 years of normal aging. The decreased volume was also related to pain duration, indicating a 1.3 cm^3 loss of gray matter for every year of chronic pain. Moreover, gray matter density was reduced in bilateral dorsolateral prefrontal cortex and right thalamus and was strongly related to pain characteristics in a pattern distinct for neuropathic and non-neuropathic CBP. These results imply that CBP is accompanied by brain atrophy and suggest that the pathophysiology of chronic pain includes thalamocortical processes.

In a more recent research, Fritz et al[42] investigated the association of CBP and regional gray matter volume in 111 individuals with CBP and 432 pain-free controls, accounting for effects of medication. CBP was associated with decreased regional gray matter in the ventrolateral prefrontal cortex (PFC) and dorsolateral PFC, both the ventral and dorsal medial PFC, and the anterior insula. Pain intensity showed a weak negative correlation with gray matter volume in the left dorsolateral PFC, ventro-lateral PFC, and anterior cingulate cortex. The CBP sample showed alterations in regions commonly associated with pain processing and emotional demands.

Noteworthy, treating chronic pain can restore normal brain function: Seminowicz et al[43] acquired magnetic resonance imaging (MRI) scans from chronic CBP patients before (n = 18) and 6

months after (spine surgery or facet joint injections; n = 14) treatment. The control group included 16 controls. After treatment, patients had increased cortical thickness in the left dorsolateral PFC. Increased thickness correlated with the reduction of both pain and physical disability. Additionally, increased thickness in the primary motor cortex was associated specifically with reduced physical disability, and the right anterior insula was associated specifically with reduced pain. Left PFC activity during an attention-demanding cognitive task was abnormal before treatment, but following normalized treatment.

Chronic Pelvic Pain

In women with CPP, central changes similar to those identified in other pain conditions have been documented[44]. Specifically, these include alterations in the behavioral and central response to noxious stimulation, changes in brain structure (both increases and decreases in the volume of specific brain regions), altered activity of both the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (ANS) and psychological distress. The presence of these changes has the potential to both exacerbate symptoms and to predispose these women to the development of additional chronic conditions. In more details, As-Saine et al[45] applied voxel-based morphometry to determine whether women with CPP and with and without endometriosis display changes in brain morphology in regions known to be involved in pain processing. Four subgroups of women participated: 17 with endometriosis and CPP, 15 with endometriosis without CPP, 6 with CPP without endometriosis, and 23 healthy controls. Compared with controls, women with endometriosis-associated CPP displayed decreased gray matter volume in brain regions involved in pain perception, including the left thalamus, left cingulate gyrus, right putamen, and right insula. Women with CPP without endometriosis also showed decreases in gray matter volume in the left thalamus. Such decreases were not observed in patients with endometriosis who did not have CPP. Therefore, it is possible to conclude that CPP is associated with changes in regional gray matter volume. Given that dysmenorrhea is often a prestage of CPP, these data suggest that pain chronification is marked by a decrease in regional gray matter volume in the pain system. On the other hand, those women who remain relatively "pain-free" do not show these decreases. In contrast, they show an increase in gray matter volume in the antinociceptive system, which might be adaptive. These findings support the use of adjunctive medication targeting the CNS in these women.

Fibromyalgia

Similar findings were also reported for patients with fibromyalgia. Kuckinald et al[46] investigated anatomical changes in the brain associated with fibromyalgia. In a study of 10 female fibromyalgia patients and 10 healthy controls, fibromyalgia patients had significantly less total gray matter volume and showed a 3.3 times greater age-associated decrease in gray matter than healthy controls. This means that each year of fibromyalgia is equivalent to 9.5 times the loss of gray matter associated with normal aging. Also, fibromyalgia patients demonstrated significantly less gray matter density than healthy controls in several brain regions. In a subsequent study of 25 fibromyalgia patients, 10 fibromyalgia patients with major depression (MD) and 35 healthy controls, fibromyalgia patients had lower pressure pain thresholds than patients with MD and controls, and they reported higher pain intensity[47]. Upon unilateral pressure pain stimulation, increased bilateral cortical activation was revealed in fibromyalgia patients compared to controls. Fibromyalgia patients also displayed a stronger contralateral activity over the dorsolateral PFC than patients with MD. These data provide further evidence for altered central nervous processing in patients with fibromyalgia and the distinction between FMS and MD.

Clinical Features of Pain Chronification

According to available evidence, the process of chronification of pain can be divided into three consecutive stages. The first stage is characterized by the presence of acute, localized pain. In the second stage, the pain has not yet become chronic but it starts to change its characteristics in accordance with functional changes in neural structures. In the third and final stage, the pain has become a medical entity (Figure 4)[2]. Musculoskeletal pain for example starts out localized, then extends regionally and spreads more and more as time passes. In clinical practice, it is paramount to recognize each stage and establish appropriate treatment with the aim to prevent the progression of pain to a chronic state.

Stage I: acute pain

A patient with initial musculoskeletal problems presents some time-limited episodes of localized

pain with intensity proportional to the lesion. The pain resolves with anti-inflammatory drugs. However, such episodes must not be underestimated or ignored given that even in the earliest stages, they may be sufficient to trigger the progressive stage.

Stage II: progressive recurrent pain

The transition from acute pain to chronic pain is characterized by the onset of more intense episodes of pain. The interval between these episodes may be entirely pain-free or there may be mild persistent pain[2]. This stage is often characterized by an increase in susceptible areas, a phenomenon that correlates directly with spinal sensitisation. This further highlights the importance of spinal phenomena in the chronification process[22]. The primary care physician has a major role in this initial stage, in which there is simultaneous progression of two diseases: the underlying musculoskeletal disease (osteoarthritis, for example) and the pain itself as a disease, which now can be defined as "recurrent". The in-depth investigation of patient's clinical history is crucial. Pain in the recurrent stage tends to display some periodicity (e.g., monthly), typically lasts a relatively short time, and, in some cases, does not resolve completely between one episode and the next (persistence). The pain is probably still responsive to effective treatment, and therefore the initiation of appropriate therapy is paramount.

Stage III: chronic pain

Over time, the plastic modifications of the nociceptive pathways lead to chronification of the pain. In this stage, the pain syndrome is consolidated and well structured. The pain transmission and modulation pathways have now lost their physiological characteristics and have assumed some pathological properties. As the complexity increases, the disease becomes more difficult to control and stabilize.

Selecting the Right Treatment

The selection of the proper analgesic treatment must take account of the clinical and subjective characteristics of the patient, and address at the same time the underlying pathogenic mechanisms of the pain, including the neuroplasticity

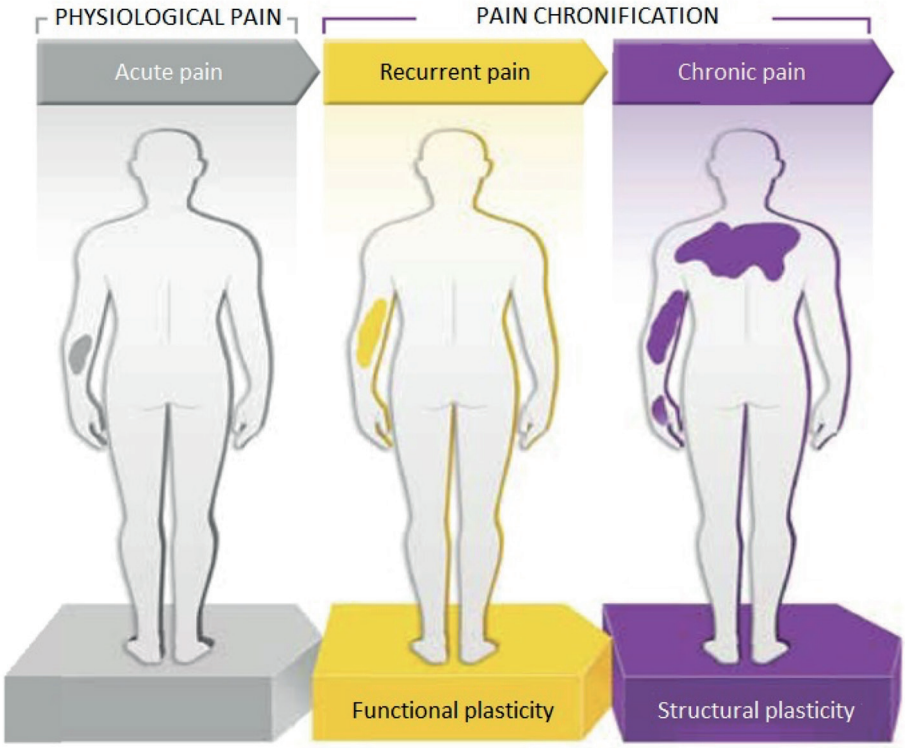

Figure 4. Progression of pain. Acute musculoskeletal pain starts out circumscribed, and then becomes chronic over time by developing from progressive/recurrent to chronic pain. From a clinical point of view, recurrent pain is characterized by repeated, localized and intense episodes of pain and development of changes in sensitivity (allodynia, hyperalgesia). In contrast, chronic pain is more diffuse and continuous, with the impairment of the patient's mental and physical health. The severity of the lesion and the intensity of pain commonly lessen in this stage. Modified from[2].

processes which lead to chronification and transformation of the symptoms, and which differ in the various stages involved in the progression of pain from symptom to disease (Table I). Also, a multimodal and multimechanistic approach to pain management must be considered. For instance, in the case of OA, treatment of pain should pursue three goals: inhibit peripheral mechanisms of pain and inflammation, treat central pain mechanisms, and reduce progression of joint destruction (peripheral pain generators)[48]. While these goals were described for OA, they may also be applied to other conditions. Two basic criteria should be met when choosing the analgesic strategy: therapeutic appropriateness and timing. In particular, the selected drug must be capable of targeting the main mechanisms responsible for chronic pain, while tackling central sensitisation and controlling the nociceptive and neuropathic components[4]. According to these criteria, acute pain accompanied by an inflammatory phenomenon (post-traumatic inflammation, for example) arising from torn muscles, minor trauma or transient musculoskeletal pain can be treated by NSAIDs and paracetamol. Subsequently, in cases where the pain exhibits signs of progression (increase in susceptible areas, secondary allodynia), the use of NSAIDs is no longer sufficient because spinal sensitisation phenomena attributable to underlying functional plasticity are modifying the course of the pain disease. Furthermore, although appropriate in the presence of inflammatory pain, NSAIDs are not recommended for prolonged treatment because of the risk of adverse reactions, especially those involving the kidney, gastrointestinal tract, coagulation and cardiovascular systems, and are not suitable for treating neuropathic pain[49-51]. This stage of recurrent progressive pain is particularly important because its identification and treatment (which differs from acute treatment and should be continued for 3 or 4 weeks) may have a major impact on the natural course of the disease. Last, patients with moderate-to-severe chronic pain often require opioid analgesics for effective pain control[7]. On timing, the use of the right analgesic from the very initial stages of musculoskeletal pain can help prevent, slow down, and possibly reverse those pathological alterations leading to chronification and therefore prevent pain chronification and, in so doing, improve the patient's quality of life. Once the chronic stage has been reached and the pain syndrome has stabilized, therapeutic intervention may no longer fully reverse the alterations in the nervous system. The modulation of the noradrenergic pathway using appropriate treatments may, in principle, be able to modulate neuropathic pain. To this end, the inhibition of serotonin and noradrenaline reuptake has been proposed[52,53]. Also, nerve injury down-regulates MOR expression via an epigenetic mechanism[54]. The descending noradrenergic tone delays the appearance of ipsilateral mechanical allodynia, cold allodynia, and heat hyperalgesia following nerve injury via an alpha 2-adrenoceptors mediated mechanism[30,55]. In the spinal dorsal horn, noradrenaline released from descending pathways originating in the pontine A5-A7 cell groups attenuates pain by inhibitory action on alpha 2-adrenoceptors on central terminals of primary afferent nociceptors (presynaptic inhibition), by direct alpha 2-adrenergic action on spinal pain-relay neurons (postsynaptic inhibition), and by alpha 1-adrenergic activation of inhibitory interneurons[56]. Moreover, alpha 2-adrenoceptors on axon terminals of

Table I. Course of pain and appropriate treatments.

	Pathology (examples)	Therapeutic options
Acute pain (episodic and circumscribed)	Torn muscles, minor trauma, sprains, mild and transient musculoskeletal pain	NSAIDs Paracetamol Paracetamol in combination with weak opioids
Progressive recurrent pain (functional neuroplasticity)	Early osteoarthritis, myalgia, tension headaches, tendinitis, arthritis	Tapentadol PR 25 mg to 75 mg twice daily Low-dose strong opioids + adjuvants
Chronic pain (structural neuroplasticity)	Low back pain, osteoarthritis, fibromyalgia, cervicobrachialgia, radiculopathy, slipped disc, spinal stenosis	Tapentadol PR 50 mg to 250 mg twice a day Full-dose strong opioids + adjuvants

excitatory interneurons might contribute to spinal control of pain. At supraspinal levels, the effect of noradrenergic system on pain has varied depending on many factors such as the type of the adrenoceptor, pathophysiological condition, and the brain area. In general, the baseline pain sensitivity is only little influenced by the noradrenergic system, whereas in injured conditions the noradrenergic system contributes to feedback inhibition of pain.

Tapentadol in the chronification of pain

Recent evidence demonstrating the importance of the descending noradrenergic pathways in the chronification processes suggests the usefulness of drugs with a targeted effect on norepinephrine reuptake to restore the equilibrium in the descending pathways. Drugs like tapentadol may act in this line by strengthening synaptic inhibition systems in the spinal cord and by preventing or eliminating some of the conditions resulting in the maladaptive plasticity of the synapses themselves[57]. A Cochrane Collaboration review on neuropathic pain reports that numerous studies demonstrate the superior efficacy of combining two different modes of action[58]. The reason for the poor efficacy of a drug with a single mechanism of action, especially for mixed types of pain, lies in the fact that nociceptive pain and neuropathic pain do not arise from the same pathogenic mechanisms and therefore require different therapeutic approaches[59]. Thanks to its dual mechanism of action – MOR agonism and norepinephrine reuptake inhibition – tapentadol is an important therapeutic option which differs from classical opioids such as morphine and oxycodone: while its analgesic efficacy is similar to that of other strong opioids, it has considerably fewer side effects[57], including lower potential of abuse[60,61]. This favorable efficacy/safety profile may be attributed, at least in part, to the synergic effect of the two analgesic mechanisms, which enables the use of an opioid with lower affinity for μ-opioid receptors (about 50-fold lower than morphine), in turn reducing the risk of side effects, notably gastrointestinal. Moreover, tapentadol has a low risk of drug interactions, and for that reason may be particularly suitable for the treatment of patients on multiple medications. Interestingly, tapentadol does not behave as morphine during a chronic treatment: it is, in fact, able to induce internalization of μ-opioid receptors, whereas morphine does not, therefore suggesting a different molecular mechanism at receptor level[62]. Tapentadol activity both on the central and spinal level has recently been demonstrated, which also makes the drug a suitable candidate for patients who have developed neuroplasticity that has modified pain pathways and rendered traditional analgesic therapies ineffective. In a randomized trial, diabetes patients who interrupted tapentadol after titration maintained a lower intensity of pain compared with baseline values; those who continued tapentadol experienced a further reduction of pain intensity[63]. Similar findings were reported by another study[64]. Niesters et al[57] analyzed 24 patients with diabetic polyneuropathy (DPN) who were randomized to receive daily treatment with tapentadol sustained-release (SR) [average daily dose 433 (31) mg] or placebo for 4 weeks. Conditional pain modulation (CPM) and offset analgesia were measured before and on the last day of treatment[57]. Before treatment, none of the patients had significant CPM. At week 4 of treatment, CPM was significantly activated by tapentadol SR and coincided with significant analgesic responses. CPM increased from 9.1 ±5.4% (baseline) to 14.3 ±7.2% (placebo) and 24.2 ±7.7% (tapentadol SR, $p < 0.001$ *vs.* placebo); relief of DPN pain was also greater in patients treated with tapentadol than placebo ($p = 0.028$). Tapentadol analgesic effect in chronic pain patients with DPN appeared, therefore, dependent on activation of descending inhibitory pain pathways as observed by CPM responses. This dosage and duration of treatment should take advantage of the two mechanisms of action of the drug, i.e. in tackling the pain as a symptom and intervening in the neuroplastic processes responsible for chronification. Given these premises, tapentadol at doses of 50 mg to 250 mg twice daily (BID) may be helpful to treat severe chronic pain[65], the ideal median dosage being 150 mg BID for at least three months.

Conclusions

Continuing advances in our understanding of the pathophysiological mechanisms underlying pain have revealed the importance of central mechanisms. In particular, a stage of initial progression has now been identified. This is important because intervention at this point with drugs like tapentadol – appropriate from the point of view of its two mechanisms of action and the availability of low doses – can have an impact on the neuroplastic transformations leading to chronification, by blocking or at least slowing

down those processes. The availability of a wide range of doses – including the recent addition of a 25 mg formulation – enables clinicians to adjust treatment to suit the needs of the patient and the characteristics of the pain in the individual case. The range of choices available helps maximize therapeutic appropriateness both in the initial stages of chronification and in the long-term treatment of the main forms of chronic musculoskeletal pain (such as osteoarthritis and lumbago) and neuropathic pain.

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Conflict of interest

All Authors served as speakers for several pharmaceutical companies.

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