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REVIEW

Pathophysiologic Approach to Pain Therapy for Complex Pain Entities: A Narrative Review

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ABSTRACT

Pain management is challenging for both clinicians and patients. In fact, pain patients are frequently undertreated or even completely untreated. Optimal treatment is based on targeting the underlying mechanisms of pain and tailoring the management modality for each patient using a personalized approach. This narrative review deals with pain conditions that have a complex underlying mechanism and need an individualized and frequently multifactorial approach to pain management. The research is based on previously conducted studies, and does not contain any studies with human participants or animals performed by any of the authors. This is not an exhaustive review of the current evidence. However, it provides the clinician with a perspective on pain therapy targeting the underlying pain mechanism(s). When dealing with complex pain conditions, the prudent physician benefits from having a deep knowledge of various underlying pain mechanisms in order to provide a plan for optimal pharmacological pain relief to patients.

Keywords: Complex pain; Pain; Pain management; Pathophysiologic mechanisms; Pain pathophysiology; Pharmacological treatment

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Key Summary Points

The pathophysiology of pain may be very different from patient to patient.

Personalized medicine is the keystone of efficacious and safe therapy. This is especially true in some difficult pain syndromes.

The authors try to analyze the relevant literature in order to suggest the best therapy in complex patients.

INTRODUCTION

According to recent data, pain occurs in all demographics of the general population, with higher prevalence in some clusters such as the elderly [1]. Pain can be either acute or chronic; the latter refers to pain that persists past the normal healing time, and usually lasts or recurs for more than 3–6 months [2]. Pain may be nociceptive (somatic and visceral), neuropathic, nociplastic, or mixed [3]. Nociplastic is a new term, introduced by the International Association for the Study of Pain (IASP), and describes pain of unknown origin that arises from altered nociception, despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence of disease or lesion of the somatosensory system causing the pain [3]. Before an effective pain treatment plan can be established, recognizing the origin of the symptoms is crucial. Inflammation is the most frequent cause, but there is also pain of mechanistic origin, such as chronic osteoarthritis of the knee where the cartilage has eroded. However, the source of pain can also be obscured, which occurs in fibromyalgia, and is classified as chronic primary pain according to the IASP classification of pain for the International Classification of Diseases (ICD) 11 [4]. The classification system of chronic pain has evolved. The main overarching categories of chronic pain are primary and secondary pain. Secondary chronic pain is further divided into six categories: cancer-related pain, postsurgical or posttraumatic pain, secondary headache or orofacial pain, secondary visceral pain, and secondary musculoskeletal pain [5].

Participation of the Central Nervous System

Regardless of the origin of the pain or its duration, the central nervous system (CNS) is always involved. The CNS detects and interprets a wide range of thermal and mechanical stimuli as well as environmental and endogenous chemical irritants. Intense stimuli provoke acute pain, but recurrent stimuli, should protective reflexes fail, can lead to chronic pain through plasticity of the peripheral nervous system (PNS) and CNS as well as signal enhancement [6].

Personalized Management of Pain

Personalized management is a very important approach to pain management. In 2016, the National Health Service of England (NHS England) published its vision on personalized medicine [7]. According, they noted: "Personalized medicine is a move away from a 'one size fits all' approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients' health and targets therapies to achieve the best outcomes in the management of a patient's disease or predisposition to disease" [7]. However, the concept of personalized medicine is not new. Clinicians throughout the history of medicine have been working on tailoring care based on patients' individual needs. Specifically, in 2014, Hui and Bruera published their article on a personalized approach for managing cancer pain [8]. They stated: "Impeccable management of pain begins with appropriate assessment, which includes documentation of pain characteristics, determination of pain mechanism, identification of modulating factors, clarification of a personalized pain goal, and regular reassessments over time." According to the authors, the first step in the successful management of pain is the identification of its likely sources [8].

Suggestions for Developing Strategies Against Pain

According to the previous statements, it is well understood that the management of pain needs to target all of the different pathophysiological mechanisms that may cause pain. Several pain specialists have also stressed this [9]. Throughout the years, an initiative called CHANGE PAIN has evolved. The major objectives of the CHANGE PAIN International Advisory Board were to enhance the understanding of chronic pain and to develop strategies for improving pain management [9]. CHANGE PAIN

conducted a survey which, among others, pointed out a basic lack of knowledge among physicians regarding the differences between nociceptive and neuropathic pain [10]. Moreover, Varrassi et al. stated: "Increasing physicians' knowledge of the pharmacological options available to manage these different pain mechanisms offers the promise of better treatment decisions and more widespread adoption of a multimechanistic approach" [11]. In their opinion, managing pain could include the use of two agents from different medication classes or one agent acting through different mechanisms. When physicians do not address the mechanisms responsible for pain, there is an increased risk of initiating a "vicious circle," where both doses and their side effects progressively increase [10]. A cross-sectional study in Europe revealed that medical schools still provide little education regarding pain, which could be responsible for the continued high prevalence of pain [12]. A close examination of the pathophysiological mechanisms of pain would include all of the cells of the CNS, and would offer new perspectives on pain control [13, 14] and open the possibility for the development of new pharmacological substances [15, 16] or lead to the novel use of existing agents for different types of pain.

It is also important for clinicians to become aware of the multifactorial nature of chronic pain in order to make pharmacological decisions based on the underlying mechanistic factors of the pain [15]. Therefore, it is crucial that clinicians who treat patients with chronic pain are knowledgeable regarding current theories of the development of chronic pain, and understand the differences between nociceptive and neuropathic pain and how they develop. An understanding of peripheral sensitization and the local release of inflammatory mediators that attract immune cells after injury is crucial, as well as an understanding of the process of central sensitization. The latter is the result of persistent transmission of pain signals from the periphery to the spinal cord [17].

Different Mechanisms of Pain and Central Sensitization

A number of different mechanisms are involved in central sensitization, which involves the peripheral input of a nociceptive stimulus to a dorsal horn synapse and the concomitant release of substance P and glutamate into the synaptic cleft. These include presynaptic *N*-methyl D-aspartate (NMDA) receptors and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and the signal is transmitted to the thalamus. There, microglial cells release inflammatory modulators, after activation of the toll-like receptor 4 (TLR4). The role of the NMDA receptors is crucial, because their prolonged activation after repetitive stimuli leads to their increasing density, which in turn enhances the signal to the thalamus [18, 19]. Allodynia, hyperalgesia, spontaneous pain, and secondary hyperalgesia indicate central sensitization. Another characteristic of central sensitization is the wind-up phenomenon, where the same unchanged stimulus causes increasingly intense sensations of pain [20]. Wind-up can be prevented up to a point by ketamine, an NMDA antagonist [21]. However, ketamine cannot fully reverse central sensitization [22, 23]. Another cause of central sensitization could be a defect of the descending inhibitory control (DIC) system, which is present in various pain conditions [24, 25] Therefore, knowledge of the multiple causative mechanisms of pain and pain syndromes, along with their molecular components, is fundamental in creating proper treatment plans, especially in complex patients [11, 17, 26].

OBJECTIVES

Because a very important task for clinicians is the effective management of pain in their patients by targeting the causative triggering mechanisms, this review aims to bring together published work that has shed light on the above mechanisms and, at the same time, offers insight into current or promising pain-relieving pharmacological treatments.

METHODS

We searched relevant articles within the PubMed, Scopus, and Cochrane databases, considering publications up to May 2019. All searches used the following research key words: (pathophysiology OR underlying mechanism OR cause) AND (pain OR painful OR pain syndromes) AND (pharmacological therapy OR pharmacological approach OR pharmacological treatment OR pharmacological strategy). The primary search was supplemented with a secondary search using the bibliographies of the articles retrieved. Only full-length original articles were accepted, and the search was limited to English-language publications. Because knowledge regarding pain mechanisms is evolving so rapidly, the primary search focused on articles within the last 15 years. All retrieved articles were reviewed by title, abstract, and the article itself when its content was not clearly indicated by the title and abstract. The inclusion criteria were as follows: (1) the article referred to acute or chronic pain, and a specific pathophysiological mechanism was suggested in the article, and (2) the authors suggested a treatment plan or a medication therapy that would target the underlying mechanism. We tried to focus on the main complex categories of pain, such as neuropathic pain, and special populations such as the elderly. The perspective suggested here can be used by clinicians to guide their efforts in dealing with pain experienced by their patients. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

The article selection process is shown in Fig. 1. According to the new classifications of chronic pain [5], we attempted to cover as many clinical conditions as possible, indicating a possible representative for each category. As a result, we elaborated on the pathophysiological mechanisms and the proposed pharmacological approach for the following: chronic neuropathic pain, chronic primary pain and more specifically fibromyalgia, chronic visceral pain, central post-stroke pain, pain in complex regional pain syndrome, and low back pain. Finally, a group of patients that is continually growing and, in our opinion, needs particular attention is the elderly population, who were included in our review.

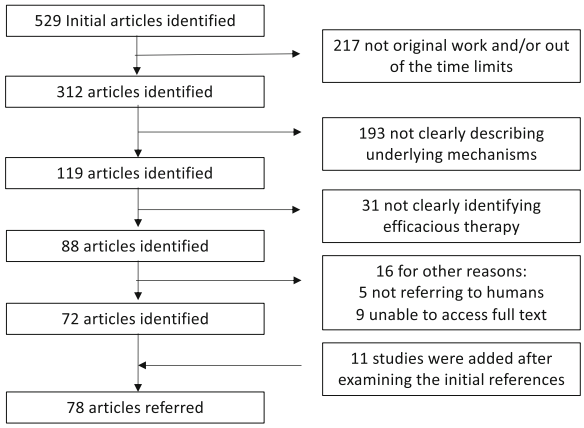

Fig. 1 Selection of referred papers

PATHOPHYSIOLOGICAL APPROACH AND PHARMACOLOGICAL PAIN MANAGEMENT

Chronic Neuropathic Pain

Mechanism of Pain

Neuropathic pain can have multiple causes and be peripheral, central, or mixed. It arises as the direct result of a disease or lesion of the central and/or peripheral somatosensory nervous system, and it should be distinguished from nociceptive pain and treated differently [27]. These lesions produce and maintain spontaneous ectopic activity by way of voltage-gated neuronal sodium channels and transient receptor potential channels, which manifests as thermal hyperalgesia and pain attacks [27]. These channels can be modulated with medicines such as carbamazepine, lidocaine, and capsaicin, with resulting pain relief [28]. An important aspect of neuropathic pain is central sensitization, which manifests as intensified spontaneous pain, mechanical allodynia, or hyperalgesia, all of which can be modulated with medicines

including gabapentin, pregabalin, and opioids, with resulting pain relief [28]. Moreover, in healthy individuals there is a descending system in the CNS that can modulate nociceptive impulse transmission [27]. By inhibiting the reuptake of the neurotransmitters needed for this path, antidepressants can lead to pain relief [28]. Treatment of this type of pain is extremely important, considering its influence on patients' quality of life [29].

Treatment Plan

Therefore, the suggested pharmacotherapy for neuropathic pain is as follows:

(a) Tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, which act through the potentiation of the descending nociceptive inhibitory pathways by presynaptic inhibition of the reuptake of serotonin and norepinephrine, two monoaminergic neurotransmitters. TCAs also block voltage-dependent sodium channels and have sympatholytic properties, and should be given in an individually titrated dose [30]. Both are considered first-line medications. The last update of the relevant Cochrane review also supports this, pinpointing diabetic neuropathy and postherpetic neuralgia as benefiting the most from this category of medication [31].

(b) Gabapentinoids, which act on the α2-d-subunit and inhibit the activation of calcium influx [30], and are recommended as a first-line medication. The evidence suggests that although they are not expected to benefit more than half of the patients, this category of medications should always be considered [32].

(c) Weak (e.g., tramadol) or strong opioids (e.g., morphine, buprenorphine) for resistant pain. Opioids act as agonists primarily at the μ-opioid receptors, which are located in both the CNS and PNS. Tramadol exerts an additional effect on the descending pain-suppressing system by inhibiting the reuptake of norepinephrine and serotonin [30]. The use of opioids, although controversial, is being reserved for occasions when either more rapid relief is necessary or when pain is significantly resistant, leaving them as a second-line recommendation. The 2013 Cochrane review regarding opioids for neuropathic pain does not conclude that opioids are better than placebo for long-term use and highlights their multiple side effects [33].

(d) μ-Opioid receptor agonist norepinephrine reuptake inhibitors such as tapentadol should also be used wisely, like high-potency opioids [30].

(e) Topical treatments such as lidocaine patches, which block sodium channels, or the capsaicin 8% patch, which leads to reversible degeneration of nociceptive afferent fibers in the skin, are being recommended as a second-line option for the treatment of painful peripheral neuropathy [30]. However, the relevant Cochrane remains inconclusive regarding the efficacy, awaiting for newer evidence [34].

Vranken [35] proposed several other treatments for neuropathic pain for patients who cannot tolerate the side effects of the first-line pharmacological treatment. For example, the muscle relaxant baclofen exerts its analgesic effect via an agonistic effect on the inhibitory GABAβ receptors, while mexiletine, an oral analog of lidocaine, can be used if a trial lidocaine infusion has been effective for the patient [35]. Moreover, clonidine, as an α2-adrenoceptor agonist, can be used in neuropathic pain [35], as well as ketamine [35]. Transdermal buprenorphine has also been used successfully for central neuropathic pain [36]. Palmitoylethanolamide (PEA) has been recommended for chronic neuropathic pain, as well [15, 16].

For the effective management of neuropathic pain a combination medication therapy might be of utmost importance. However, a Cochrane systematic review did not succeed to suggest the value of any specific combination [37].

Chronic Primary Pain (Fibromyalgia)

Mechanism of Pain

It has been suggested that fibromyalgia is the result of two different mechanisms affecting the CNS: on the one hand, hyperreactivity of the CNS, and on the other hand the decreased capacity of the CNS to modulate pain [38]. A probable cause for the latter could be the decreased activity of the serotonergic/noradrenergic pathways [39]. Hauser et al. suggested that "the cerebrospinal fluid levels of the main noradrenaline metabolites, as well as the serum levels of serotonin, tryptophan, and 5-hydroxyindoleacetic acid are lower in fibromyalgia patients, whereas those of pronociceptive neurotransmitters such as glutamate, nerve growth factor, and substance P are increased" [39]. Emerging evidence also shows that glial cells may play a role in maintaining central sensitization by producing various chemokines and cytokines [40]. PNS abnormalities seem to have their own role in the pathogenesis as well. Fibromyalgia patients have functional impairment of small nerve fibers and reduced small fiber density [41]. It has been suggested that certain interventions to limit peripheral input might improve pain, allodynia, and hyperalgesia. Moreover, it is important to note that other sources of comorbid pain can increase central sensitization; therefore, comorbidities should be properly treated [42]. Finally, Calandre et al. mention other factors that may lead to fibromyalgia, including polymorphisms in the catechol-*O*-methyltransferase (COMT) gene or alterations in the hypothalamic–pituitary–adrenal axis, abnormal autonomic nervous system functioning, disruptions of sleep architecture, and dysfunctional dopaminergic neurotransmission. In addition, certain psychological or physical factors may play a role in fibromyalgia [43]. This topic was recently reviewed, and a new hypothesis has been proposed [44].

Treatment Plan

The main categories proposed are as follows: antidepressants, antipsychotic medications, dopaminergic agonists, anticonvulsants, muscle relaxants, cannabinoids, opioids, melatonin and its analogs, NMDA antagonists, and 5-HT3 receptor antagonists such as modafinil and armodafinil (non-amphetamine stimulants that release dopamine and noradrenaline in the CNS and histamine in the hypothalamus) [45].

Among the above-mentioned agents, pregabalin and gabapentin are currently mainly used to treat chronic pain, improve sleep, and enhance health-related quality of life, and the TCA amitriptyline is widely used as first-line treatment for fibromyalgia [46]. It is important to note that the combinations of amitriptyline plus fluoxetine or pregabalin plus duloxetine have been shown to be more effective than either medicine alone [46], and tramadol administered alone or together with paracetamol has been shown to reduce pain by 30% [45].

The most recent recommendations from the European League Against Rheumatism (EULAR) regarding pharmacological therapy for pain in fibromyalgia included duloxetine, pregabalin, and tramadol (with or without paracetamol) for severe pain. When severe sleep problems were also present, low-dose amitriptyline was suggested, as were cyclobenzaprine or pregabalin to be taken at night [47].

However, many patients do not respond to the above treatments, indicating the need for developing new medicines or reformulating older ones in order to target the pathogenesis of fibromyalgia [45]. It is worth mentioning that some new potential agents are being investigated, including IMC-1 (a fixed-dose combination of the anti-herpes virus nucleoside analog famciclovir and the anti-herpes virus active COX-2 inhibitor celecoxib), neurotrophins, mast cell stabilizers, and mirogabalin (which is more specific for calcium channels than pregabalin or gabapentin) [45]. An interesting study from Del Giorno et al. [48] evaluated the therapeutic efficacy of duloxetine combined with pregabalin in patients suffering from fibromyalgia, and the possible added benefit of the lipid-signaling molecule PEA. The combination of duloxetine and pregabalin had previously been suggested [49], and was well documented to exert anti-inflammatory, analgesic, and pain-relieving effects in both

preclinical and clinical studies. The authors concluded that adding PEA to an initial combination therapy of pregabalin plus duloxetine improved the outcome of fibromyalgia, and that when an additional medication is needed, PEA could serve as an optimal option [48]. Non-pharmacological treatments for fibromyalgia may also be appropriate, for example postural counseling [50].

Chronic Visceral Pain

Mechanism of Pain

Identifying the specific underlying causes of chronic visceral pain is very important for its proper management. The inflammatory process begins in the gastrointestinal (GI) tract and is then transmitted through various receptors and ion channels to the CNS. Therefore, targeting those portions of the GI tract could be ideal in terms of reducing side effects and providing novel opportunities for the pharmacological treatment of chronic visceral pain. Moreover, in chronic visceral pain, the aforementioned receptors and ion channels have undergone pathological changes, and as a result there is enhanced nociceptive signaling [51].

A significant correlation has been demonstrated between serotonin polymorphisms and chronic visceral pain severity. For example, in patients with irritable bowel syndrome, it was observed that plasma serotonin concentrations were reduced in patients with constipation but elevated in those with diarrhea [52]. Therefore, there has been considerable interest in these receptors as possible therapeutic targets [52]. A possible role of genetic polymorphisms coding for anti-inflammatory and proinflammatory interleukins (IL), α-2 adrenergic receptors, and serotonin and cholecystokinin (CCK) receptors has also been suggested [52].

Treatment Plan

An effective treatment plan might target pronociceptive mechanisms by blocking sodium channels with lidocaine, potassium channels with retigabine, or voltage-gated calcium channels with gabapentin or pregabalin. Protease-activated receptor 2 blockers could also be useful, as well as histamine receptor blockers such as ebastine. Agonists against serotonin, tachykinin, or purine, and glutamate receptor antagonists such as ketamine have also been shown to reduce visceromotor pain. Additionally, recent evidence highlights increases in antinociceptive mechanisms in models of chronic visceral pain, which present novel targets for pharmacological treatment of this condition. These mechanisms are up-regulated during inflammatory or chronic visceral hypersensitivity states. Potential targets include the receptors for oxytocin, GABA, cannabinoids, opioids, and TRPM8, along with protease-activated receptor 4 (PAR4) and guanylate cyclase-C receptors [51]. The physician should be aware of all of the different mechanisms that may apply in each individual case and which agents may be effective when pharmacotherapy must switch from an agonist to an antagonist (e.g., against serotonin receptors), which is necessary for individualized treatment. The clinician has several options in the armamentarium against chronic visceral pain, including laxatives, antidiarrheals, antispasmodics (mebeverine hydrochloride, hyoscine butylbromide, and peppermint oil), probiotics, fecal microbiota transplantation, and serotonin receptor agonists (tegaserod, prucalopride, renzapride) and antagonists (alosetron, ramosetron). In addition, anti-inflammatory therapies such as rifaximin, corticosteroids, mast cell stabilizers, and mesalazine may be used [52].

Central Post-Stroke Pain

Mechanism of Pain

Central post-stroke pain is caused by CNS lesions. Although the pathogenesis of central post-stroke pain remains unknown, the suggested underlying causes include hyperexcitation of the damaged sensory pathways, damage to the central inhibitory pathways, or a combination of the two. It is likely that various neurotransmitters are involved in this process [53]. Initially, the thalamus was believed to be the cause of pain by failing in its inhibitory role. However, there is also evidence suggesting that various cortical structures such as the anterior

cingulate cortex are involved, leading to allodynia. The pathways that mediate cold sensation or other impairments in the spinothalamic paths could also account for the generation of the pain [53].

Treatment Plan

For pharmacological treatment, the first-line medication is the adrenergic antidepressant agent amitriptyline. However, its effect is frequently incomplete, and many patients do not tolerate high doses. Lamotrigine, an antiepileptic, was also found to be effective and can be used as an alternative or add-on therapy. GABAergic medicines with potential calcium channel-blocking effects, such as gabapentin or pregabalin, have also recently emerged as a potentially useful therapy. Fluvoxamine and mexiletine may be used adjunctively in some patients [53]. Transdermal buprenorphine may also be useful in some cases [36].

Pain in Complex Regional Pain Syndrome

Mechanism of Pain

Complex regional pain syndrome (CRPS) is frequently seen as a post-traumatic disorder characterized by a non-dermatomal, severe, continuous pain in the affected limb and is associated with sensory, motor, vasomotor, sudomotor, and trophic disturbances. CRPS is usually precipitated by trauma or surgery [54]. The pathophysiology of CRPS is multifactorial, with recent studies suggesting it may be an exaggerated inflammatory response to trauma or surgery. Both peripheral and central mechanisms are thought to play a role in the initiation and maintenance of CRPS [55, 56]. Recent studies focusing on inflammatory processes in CRPS found higher levels of proinflammatory cytokines in blister fluid in the form of tumor necrosis factor alpha (TNFα) of the affected extremity compared with the unaffected extremity, and this could suggest a role for local inflammatory processes in CRPS [56]. Elevated levels of proinflammatory cytokines have also been found in the serum, plasma, and cerebrospinal fluid of patients with CRPS [57], which may be involved in peripheral nociceptor activation and sensitization [58].

Another explanation for the pathogenic mechanisms of CRPS is neurogenic inflammation mediated by calcitonin gene-related peptide (CGRP) and substance P. This is thought to be an underlying mechanism for such symptoms as edema, vasodilation, and increased sweating [55].

CRPS is also described as an autoantibody-mediated autoimmune disease, where immunoglobulin G mediates inflammation [59]. According to Bharwani et al., deep-tissue microvascular ischemia–reperfusion injury along with various human leukocyte antigen (HLA) associations and cortical reorganization could play an important role in CRPS and pain [54]. It has also been proposed that CRPS is a small fiber neuropathy, as it has many similarities to other generalized small fiber-predominant polyneuropathies [60].

Treatment Plan

Accordingly, as additives to physiotherapy and invasive treatments, the choice of medication is based on the mechanism deemed most prominent in each specific CRPS case/patient [54]. The different medications that can be used include free radical scavengers, immunomodulating medications (bisphosphonates, glucocorticoids, TNFα antagonists, thalidomide), and immunoglobulin to fight against inflammation. Achieving a change in pain perception is an important aspect of care. Gabapentin has been shown to lead to a reduction in pain symptoms in CRPS and may be used in the treatment of neuropathic pain. If intractable pain persists, treatment with intravenous administration of low-dose ketamine in long-standing cases may be considered. Should the patient suffer from so-called cold CRPS caused by vasomotor changes, a calcium channel blocker, α-sympathetic blocker, or phosphodiesterase-5 (PDE5) inhibitor can be considered. Finally, muscle relaxants or antispasmodics offer another approach, as intrathecal baclofen has been shown to have a positive effect on dystonia in patients with CRPS [54].

Low Back Pain (LBP)

Mechanism of Pain

Low back pain (LBP) encompasses three distinct sources: axial lumbosacral, radicular, and referred pain. For that reason, there are many different pathophysiological mechanisms in play [61]. Despite the fact that LBP has been the subject of much study and clinical effort, no clear-cut effective treatment has yet emerged. Continuing efforts should be made to understand the pathology, diagnosis, and method of treatment for LBP [62]. The source(s) of pain should be identified and specifically targeted. The most common causes of LBP are myofascial pain [63], facet-mediated pain due to either degeneration [64] or OA [61], discogenic pain [65, 66, 67], failed back surgery syndrome (FBSS) [68, 69], spinal stenosis pain [70], and sacroiliac joint pain [71].

Treatment Plan

Treatment in LBP should be specific and should target the main cause of pain, which is usually inflammation. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to provide short-term pain relief [72]. While tramadol has shown limited analgesia, with mild functional improvement for chronic LBP, strong opioids may offer significant analgesia and improved function at 3 and 6 months, as shown in selected randomized trials [73]. Recent guidelines from the National Institute for Health and Care Excellence (NICE) for the treatment of low back pain recommend exercise as a key part of any treatment program, and a "cautious, stepwise approach" to pharmacological therapy [74]. The use of TCAs has shown beneficial effects for LBP treatment by exerting analgesia primarily through serotonin and norepinephrine reuptake inhibition, sodium channel blockade, and NMDA antagonism [72]. Additionally, serotonin norepinephrine reuptake inhibitors (SNRIs) offer another pharmacological treatment for chronic LBP, as they inhibit serotonin and norepinephrine reuptake, which is important for descending pain inhibition [72]. Lastly, pharmacological treatment of LBP may include antiepileptics. While gabapentin has shown analgesic efficacy for chronic LBP with radiculopathy, only topiramate has been studied for chronic axial LBP with evidence of effective analgesia and improved quality of life [75].

At this point, it is worth mentioning that some authors have suggested the addition of PEA to a multimodal therapeutic regimen for the treatment of FBSS in treatment-resistant patients [69]. In that study, treatment with PEA was found to significantly decrease pain intensity. PEA is a mechanism-modifying approach in pain management and was shown in earlier studies to exert anti-inflammatory, analgesic, and neuroprotective action [76] through inhibition of mast cell and microglial activation [13, 77].

Pain in the Elderly

Mechanism of Pain

The world's population is aging, and the elderly endure a great variety of pain due to the physiological changes associated with growing old [13, 14]. In the elderly, peripheral nerves display functional, structural, and biochemical changes mainly involving the Aδ fibers. Persistent neuroinflammation is promoted in older individuals by mast cells and microglia, which become more sensitive to noxious stimuli and less capable of regulation by homeostatic endogenous systems (primed microglia) (Fig. 2) [15]. Another characteristic of aging is an overall increase in central sensitization, due to limited descending inhibitory capacity and altered responses to heat pain in the middle insular cortex and primary somatosensory cortex. In general, the pain threshold increases with age, while the threshold for pain tolerance remains unchanged or decreases [15].

Treatment Plan

When treating pain in the elderly, physicians should never forget the physiological modifications (Table 1) significantly affecting pharmacological consequences of drug administration, including the potential side effects. Nausea and vomiting, bowel dysfunction, and somnolence are the main treatment-

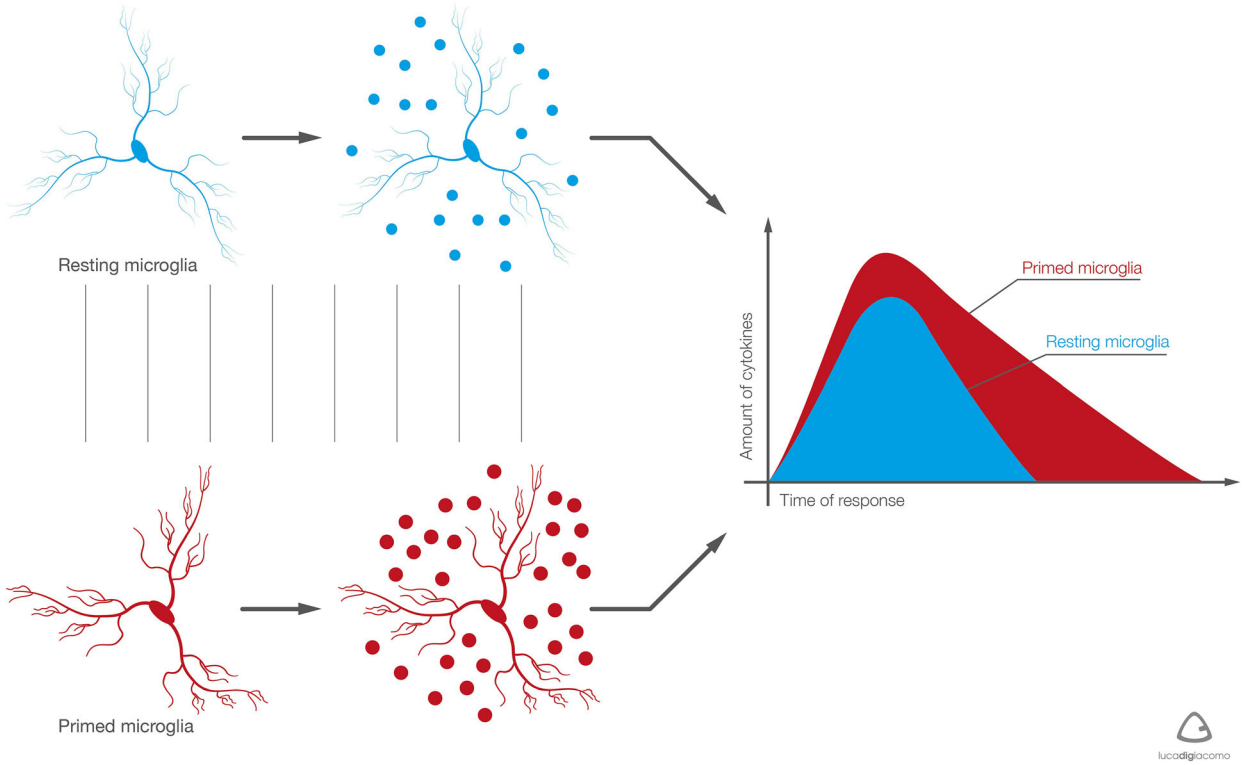

Fig. 2 Resting and primed microglia ([79] Reproduced with permission from Fusco M., Paladini A., Skaper S. et al. Chronic and neuropathic pain syndrome in the elderly: Pathophysiological basis and perspectives for a rational therapy. Pain Nurs Mag. 2014;3:94–104)

limiting symptoms in seniors [78]. Positive results in the treatment of pain for the aged can only be achieved by using innovative therapeutic strategies based on a knowledge of the patient's real needs and in consideration of age-related changes in pain perception, pain processing, and the immune system which may modify responsiveness to painful stimuli [13, 14, 79]. As stated previously, microglia, mast cells, and astrocytes are very important to pain perception, so they can serve as targets for the control of persistent pain. Because PEA has a high ratio of efficacy to risk, it may be an excellent co-treatment for the burgeoning elderly population with chronic pain [15].

Patients with cognitive decline constitute an important geriatric subpopulation [80]. For instance, in Alzheimer's disease (AD), neuropathological changes selectively impact the affective-motivational component of pain (medial pathway) more than the sensory-discriminative dimension (lateral pathway), which impairs the patient's ability to assess a painful experience. Combined with an unchanged pain threshold and a higher tolerance of painful stimuli typical of the elderly, AD patients have been observed to have a higher tolerance for intense pain that alters their experience of chronic pain [80]. However, in other studies these changes were inconsequential, indicating no selective reduction in the emotional aspects of the pain experience in these patients [81]. Another key point for AD patients is their altered response to analgesic medicines, in that they have little to no placebo effect, requiring a higher dose of pain medication to obtain an analgesic effect [82]. Moreover, changes in the blood–brain barrier in AD patients can influence the effect of centrally acting pain medications such as opioids. For example, pain perception in vascular dementia may increase because of white matter lesions in pathways ascending to the thalamus, such as the spinothalamic tract, while pain perception in Lewy body dementia

Table 1 Physiological modifications in the elderly, and their influence on pharmacological therapy

Parameter modification	Pharmacological effect	Example medications affected
Increased fat mass Reduced lean mass Reduced body water	Increased duration of lipophilic drugs effects Increased plasma concentration of water-soluble drugs	Local anesthetics Opioids
Reduced serum albumin	Increased free-medication availability	Anticonvulsants NSAIDs
Reduced hepatic and renal clearance	Increased medicine half-life and increased dose-related side effects from medications that undergo first-pass metabolism	Local anesthetics Opioids
Reduced cytochrome P-450 function	Possible toxic medicine-medicine interactions	Local anesthetics Opioids SNRIs SSRIs
Increased reactivity of glia [74]	Increased need for anti-inflammatory medications	Corticosteroids NSAIDs

SSRIs selective serotonin reuptake inhibitors

may be altered due to brain atrophy and damage caused by Lewy bodies [80].

Of paramount importance is that both underreported or underestimated pain and comorbidities and polypharmacy are formidable barriers to effective pain control in the elderly. Avoiding potentially dangerous medications such as neuroleptics and benzodiazepines as pain relievers, and initiating treatment with non-opioid analgesics or gradual titration of pain regimens are crucial. SNRIs can be considered as adjuvants and/or as an alternative to NSAIDs and opioids [80].

One additional obstacle in the elderly is compliance to therapy. This may be reduced when fixed-dose combinations of medicines are prescribed [83]. Pain is always multifactorial. Hence, considering a multimodal approach to therapy is essential, especially in complex patients with many comorbid conditions.

Limitations

This is not an exhaustive review of the current evidence. However, it provides the clinician with a perspective on pain therapy targeting the underlying pain mechanism(s) in complex pain syndromes. A further limiting aspect is that the review focuses on just a few complex pain syndromes. Further reviews on other pain syndromes will be necessary, using the same methodology.

CONCLUSIONS

When pain is complex, a multimechanistic approach to pain control may be required in order to address the different pain mechanisms involved. Clinicians treating patients with chronic pain in such complex painful conditions must understand the underlying pathophysiology and appropriate treatment regimens, which likely involve combination therapy using analgesic and adjuvant agents. The optimal modality will be found by tailoring the right therapy for the right patient, ensuring the best possible compliance with therapy.

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