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Research progress of nociplastic pain in the clinical treatment of chronic pain diseases

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Abstract. Chronic pain is increasingly developing into a worldwide health problem. Due to the money and treatment required for care and rehabilitation, as well as the complexity of the various types of pain, chronic pain sufferers often bear a huge financial burden as well as a psychological one. According to statistics, 23% of chronic pain sufferers have suicidal thoughts. In 2017, the third category pain named "nociplastic pain" was proposed for the first time by the International Association for the Study of Pain (IASP) which is disparate with the first kind ‘nociceptive pain “and the second pain “neuropathic”. The physiological mechanisms behind this type of pain are not known. However, it is commonly thought to be associated with a hypersensitivity response in the central nervous system and can be resulted in chronic nociceptive pain, so nociplastic pain is able to occur by itself, and can combine with other pain. At the same time, this type of pain affects the central system and produces other derived symptoms. Examples include stimulation of the limbic system, including impaired processing of emotions by the amygdala, amplified pain perception, sleep disturbances, increased fatigue and sensitivity to external environmental stimuli. There are no very clear and obvious diagnostic criteria or methods, and clinical detection is difficult. Due to the many symptoms, patients usually undergo multiple tests, with high medical costs and a poor prognosis. Patients suffer both physical and psychological distress. The disease with its complexity characteristic leads the difficulty for doctors to diagnosis it plagues patients with the condition, while increasing the difficulty of medical diagnosis and the cost of medical treatment. This article synthesizes the existing developments in outcomes in nociplastic pain from introduction and classification to diagnosis and treatment, it discusses the existing research findings.

Keywords: nociplastic pain, chronic pain, treatment.

1. Introduction

The International Society for the Study of Pain views pain as an uncomfortable emotional experience associated with actual (or potential) damage within the tissue. This definition goes some way to explaining that pain is something that needs to be assessed subjectively by the patient, reflecting the reflexes of the patient and capable of responding to painful stimuli. Nociplastic pain is a category of pain first introduced by the IASP in 2017, which differs from injurious and neuropathic pain by associating previously indescribable or unexplained pain with 'central sensitization' of nerve centres, defining a category of pain that is difficult to be expressed subjectively by the patient, excluding pain that has no obvious external damage to nociceptive pain receptors and no clear disease causing nerve

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damage, but is triggered by altered sensation [1]. It excludes pain that is triggered by altered sensitisation, without any obvious external injury or nociceptive pain receptor activation, and without clear disease-causing nerve damage [1]. The prevalence of nociplastic pain is highly variable. The prevalence varies depending on the disease the patient is suffering from. It is a mixed pathophysiology of pain, which manifests clinically as chronic overlapping pain. Typically, the prevalence is generally higher in women. The percentage of the General population who has suffered from nociplastic pain is at the value of 5% to 15% [2]. About 30% to 50% of the cosmopolitan population is Deeply influenced by Chronic pain [3].

Chronic pain is usually of long duration (usually lasting more than 12 weeks), and Patients usually present with acute or dull pain, manifests itself as flaming feeling or aching sensation in or around the affected area, can be present in multiple parts of the body and appear persistent [3]. Diagnosing chronic pain is therefore very difficult and the cause is not always clear, greatly affecting the quality of life of a patient. The main difference between nociplastic pain and chronic pain is that chronic pain is divided into primary pain and secondary pain, but they are not the same. Instead of the primary pain as a concept of diagnostic criterion, nociplastic pain is just one pain kind, which means they do not belong to the same dimension, but it is undeniable that many nociplastic pains are transformed from chronic pain [1].

This paper presents existing research on the concept of nociplastic pain, how the mechanisms behind it differ from other pains, and a disease-specific classification to help the reader gain insight into this type of pain, as well as talking about the existing diagnostic and treatment modalities and the gaps in existing research.

2. What is the difference between the nociceptive pain and neuropathic pain and nociplastic pain

Chronic pain can be a huge financial burden and according to research, the area of illness that causes the greatest prevalence is musculoskeletal disorders, which means that care and rehabilitation requires a great deal of money and time [4, 5]. People with chronic pain are at high risk of suicide rates, with the incidence of attempted suicide almost four times higher in people with chronic pain than in those without the condition. Patients with chronic pain have a poorer sense of life experience and a higher rate of suicide: between 5% and 23% of patients have attempted suicide [6].

2.1. Nociceptive pain

The Symptoms of nociplastic pain include combined peripheral and central pain sensitization, hyperresponsiveness to painful and non-painful sensory stimuli, Related features -Fatigue -Sleep disturbances, Cognitive impairment (difficulty concentrating), Sensitivity to environmental stimuli (light, heat, sound), Emotional processing disorders: anxiety and depressed mood [7]. The International Association for the Study of Pain defines nociceptive pain as pain that is caused by actual or threatened damage to non-neural tissues. nociceptive pain is caused by tissue damage or inflammation caused by toxic irritation of C-fibres and is a form of reflex that protects the body briefly from a potentially harmful environmental stimulus and spares the body from deep injury. The somatosensory system does not have any lesions or pathology in nociceptive pain. nociceptive pain is divided into two main categories, one is somatic pain, which includes the surface trunk, skin mucosa, subcutaneous tissue, deep trunk, muscles, joints and tendons, and the second is visceral pain, which is pain in the internal organs. With signs of nociceptive pain, the patient will usually express pain that is superficial, localized, with a burning sensation of skin burns, cuts, dull wounds and a burning sensation [7]. Deeper somatic pain may be painful like arthritis, visceral pain, which may be vague or sharp. Inflammatory pain also falls under the umbrella of nociceptive pain. Usually, pain is a manifestation of real tissue damage. It does not normally cause serious consequences due to the activation of injury receptors, but once it is transformed into chronic pain, it leads to peripheral and central sensitisation [7].

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2.2. Neuropathic pain

Neuropathic pain is the second type of pain. The International Association for the Study of Pain defines neuropathic pain as pain caused by a lesion or disease of the somatosensory nervous system. When a neurological lesion occurs in or around the centre, the area innervated by the damaged nerve may be directly or indirectly associated with sensation in the spinal cord and cerebral regions damaged by the disease. Thus, an important feature of most types of neuropathic pain is the paradoxical combination of loss of sensation and pain: the area of pain with or without hypersensitivity. There are different types of neuropathic pain, including neuropathic pain, neuropathic deafness pain, neuronal pain and central pain. For neuropathic pain, the patient usually presents with a constant burning or stabbing pain, paroxysmal pain, chills or a strange sound caused by touch. Neuropathic pain also produces corresponding changes in pathophysiology, including ectopic activity of damaged or adjacent nerves, peripheral and central sensitisation of DRG or central pathways by a range of molecular mechanisms. Again, neuropathic pain is a complex disorder and difficult to treat [8].

Nociplastic pain is a third type of pain, distinct from the previous two types of pain, nociceptive pain caused by inflammation or tissue damage and neuropathic pain caused by nerve damage. It may be a combination of nociceptive pain that becomes chronic pain, but once it has become this type of pain, there is no substantial damage from acute trauma.

It is often thought to have an important relationship with sensitisation of the central nerve sensory processing pain system. Its symptoms encompass a more multifaceted, multifocal pain that is more widespread and intense and usually causes other central nervous system symptoms such as fatigue, sleep, memory and mood problems in addition to those of the disorder itself. Typical disorders are fibromyalgia, Tension headaches, chronic diffuse pain, chronic musculoskeletal pain etc. [2].

3. Causes

This pain can probably be modelled as a biopsychosocial and it is difficult to go into the causes. The causes may be multiple or overlapping and are usually not obvious or explicit. Susceptibility factors include, first and foremost, genetic aspects. The genetic aspect may be influenced by environmental exposure and family history, including a family history of pain, and performance genetics. The second aspect is that pain may be historically transformed from nociceptive pain to chronic pain, for example, as one of the bottom-up development triggered by pain surrounding the regional area (peripheral pain) , like osteoarthritis, which causes neurological sensitisation, or top-down response mechanism braked by the central system , which can be combined with overlapping pain conditions, such as rheumatism, gastrointestinal stress syndrome, and these persistent pain causing pain sensitisation. The third aspect is psychological, associated with emotional trauma, physical abuse, or certain sources of irritation [2, 9].

CS (central sensitization) explains why many chronic pain sufferers complain that their pain is unbearable and that it interferes with their lives to a degree that far exceeds the actual detectable causative factors, the degree of pain caused by damaged tissue or damaged nerves [4]. The International Association for the Study of Pain (IASP) describes the concept of central pain as "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input". Nociceptive neurons cannot be seen by non-interventional situations, so it is difficult to imagine how to detect nociceptive neuronal responses from the central nervous system.

CS is a category of central nervous system dysfunctions. In the brain, the regions involved in processing the acute sensation of acute pain mainly include the prefrontal cortex, the anterior cingulate cortex CS will increase the perception of this area and CS will enhance brain processing activity in the brain stem and the dorsolateral parietal cortex. CS also involves alterations in the activity of brain-controlled nociceptive-promoting pathways. CS also means impaired endogenous analgesia. This refers to pathways emanating from the brainstem that release neurotransmitters to inhibit nociceptive purification in the spinal cord [4].

Taken together, these CNS dysfunctions contribute to increased reactivity to various sensory inputs. For example, when encountering light, hearing sound, and environmental cold and heat changes and

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pressure, CS is always used as a new starting point, so that doctors do not simply consider the substantive muscles and bones when diagnosing patients' diseases, but transform to the regulation of the central nervous system, that is, the problem of the root cause of pain [4].

4. Classifications of nociplastic pain

The supraspinal mechanism is manifested in the patient's enhanced response to painful stimuli, hyperactivity and connectivity of brain areas associated with pain, and decreased brain activity in areas involved in pain inhibition. Downstream inhibitory pathways are diminished. Cerebrospinal fluid concentrations of substance P and glutamate are elevated. Changes in the size and shape of grey and white matter areas involved in pain processing. Spinal mechanisms respond to regional aggregation of signals from different pain sites, spinal cord reorganization, amplification of spinal reflex conduction [2]. The following are common classifications of nociplastic pain: chronic widespread pain and fibromyalgia, complex regional pain syndrome. Chronic primary verbal and orofacial pain. Chronic visceral pain syndrome, chronic primary musculoskeletal pain (check the specific terms correctly)

4.1. CWP& FM

Chronic widespread pain (CWP) is defined as pain in at least four to five areas of the body10 and encompasses all three quadrants of the body: upper, lower, right and left lateral, neck, back, abdomen or chest. CWP is defined as pain in the upper, lower, right and left quadrants lasting more than three months and has a prevalence of roughly 7%-15% in school-age children, 11.4% in females and 11.4% in adolescents aged 13 to 19 years. The overall prevalence is 4.1% for males and 3.8% for females. In epidemiology, fibromyalgia (FMS) is defined as the presence of chronic widespread pain with a range of symptoms associated with chronic fatigue, sleep disturbances and amplification of damage to nerve signals within the central nervous system. The prevalence is 1.3% in children and adolescents and up to 3.5%-6.2% in children aged 15 to 19 years [10]. FM affects roughly 2% of the world's population [11].

CNS sensitisation, also known as central nervous system sensitisation, (or CS) is now thought to be the main cause of FM. This sensitisation mainly leads to an imbalance in the pathways of inhibition and allodynia from the downstream of pain. This phenomenon of CS is seeming to have more persuasive power than peripheral sensitisation in a range of pathogenic mechanisms. However, it is a broad concept involving complex pathophysiological mechanisms. Some important clinical signs of FM include widespread, chronic, like widespread musculoskeletal pain with highly pain sensitivity, combined with ectopic pain and nociceptive sensitisation, but without identifying partly structural pathology of muscles, ligaments and joints. Patients always complaint about a range of other associated symptoms of the central nervous system, fatigue, sensory abnormalities, sleep problems, joint stiffness, cognitive problems, depression and anxiety [11].

4.2. Chronic primary musculoskeletal pain

Chronic primary musculoskeletal pain, referred to as MSK, is a primary form of nociplastic pain with no identifiable tissue abnormalities. It is understood anatomically as an unchanged injury, but patients complain of pain in muscles, tendons, bones and joints. The cause of chronic primary musculoskeletal pain has been proposed as central sensitisation, and regional MSK is often thought of as myofascial pain syndrome (MPS). The main difference between primary musculoskeletal pain and secondary musculoskeletal pain is that primary musculoskeletal pain is in the third category of pain Nociplastic pain, whereas secondary musculoskeletal pain is nociceptive pain, the symptoms of primary musculoskeletal pain are usually pain and other sensory stimuli with dysfunctional processing, but without substantial tissue damage. Patients often describe the symptoms as sharp, burning, painful and diffuse sensations, with generalized physical fatigue, vegetative symptoms, mood disturbances, sleep disturbances, and psychosocial factors. Patients may have signs of autonomic dysfunction. Also, primary musculoskeletal pain present in Nociplastic pain can cause a similar or greater reduction in quality of life than secondary skeletal pain than neuropathic pain. Rates of msk are higher in

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psychiatric, pathological cognitive impairment and other comorbid pain compared to nociceptive versus neuropathic pain [12].

4.3. Complex regional pain syndrome

Complex regional pain syndrome, known as CRPS, is a neuropathic pain, characterized primarily by a marked inflammatory response and autonomic nature, a chronic pain caused by spontaneous or irritation, usually in the arms, legs, hands and feet of patients following surgical fractures or trauma to the limbs. It usually occurs more than six months after the injury and the main causes of CRPS are peripheral nervous system dysfunction, central sensitisation, autonomic changes, inflammatory and immune changes, psychological and genetic factors, which are likewise thought to contribute to the development of CRPS. The main symptoms of CRPS are severe prolonged severe pain, changes in skin color and temperature (vasomotor disorders), loss of bone mass CRPS is usually divided into two categories, the first being those with a definite event and cause of injury, and the second being syndromes that develop after nerve injury, where spontaneous pain or pain hyperactivity occurs, when the pain is not necessarily confined to the area of injury. Patients usually express their prolonged, severe pain in this way: a persistent, burning, pins-and-needles sensation that spreads throughout the arm, leg, and the affected area often shows increased sensitivity and is unusually painful to touch the skin [13].

Epidemiology indicates that 0.07% of the hospitalized population from 2017 to 2011 were diagnosed with CRPS in the U.S. In terms of risk factors, the most common factor was 42% fractures, 21% blunt injuries, 12% surgery, and 7% carpal tunnel syndrome, but the overall prevalence was relatively low [14].

4.4. Chronic primary headache and orofacial pain

Chronic primary headache and orofacial pain is considered to occur for greater than three months and the patient is in pain for more than half of the day. Trigeminal autonomic headache, chronic migraine, chronic burning mouth pain and chronic tension-type headache all fall under this pain [2, 15].

The prevalence is probably between 16.1% and 33.2% and the actual prevalence of COFP appears to be around 25%, with 10% of COFP resulting in a remarkable reduction in the patient's quality of life, sleep disturbances and disability problems [16].

4.5. Chronic visceral pain

Chronic visceral pain is pain from any part of the body in the internal organs. There are six subgroups of chronic visceral pain syndromes as follows: chest, upper abdomen, abdomen, bladder and pelvis. Pain syndromes to bowel stress syndrome, which is the main classification of IASP. Each syndrome is identified by the organ it affects. They often overlap with each other, with problems of visceral hypersensitivity, dysmotility, this improves the processing of sensations from the central nervous system and enhances immune function and mucosal action [2, 15].

5. Diagnosis and treatment

Any of the following hypersensitivities induced by the site of pain: static mechanical allodynia, dynamic mechanical allodynia, hot and cold touch induced pain.

Dynamic mechanical abnormal pain: the skin is stroked with a gentle brush and the patient is asked if he/she feels pain. Static mechanical abnormal pain is usually assessed by palpating the finger with a four-kilogram weight; palpation is pressure palpation. Cold abnormal pain is assessed by keeping the metal at room temperature of 20 degrees and heating the same object with water afterwards, abnormal pain can also be assessed by performing a quantitative sensory test for pain hypersensitivity, a response indicating abnormal central sensory processing.

History of pain sensitivity: tactile sensitivity, pressure sensitivity, motor sensitivity, hot and cold sensitivity.

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History of pain allergy, where the patient is allergic to touch, pressure, movement or hot or cold pain, e.g. may feel uncomfortable or painful with the skin rubbing against clothing or belts, pressure from a bra, uncomfortable sitting in a chair for long periods of time. The pain increases in times of heat or cold or environmental changes [1].

Presence of co-morbidities: More sensitive hearing, light response, odour, sleep disturbances with frequent night waking, fatigue (like CTS), cognitive problems (difficulty concentrating, memory impairment) [1].

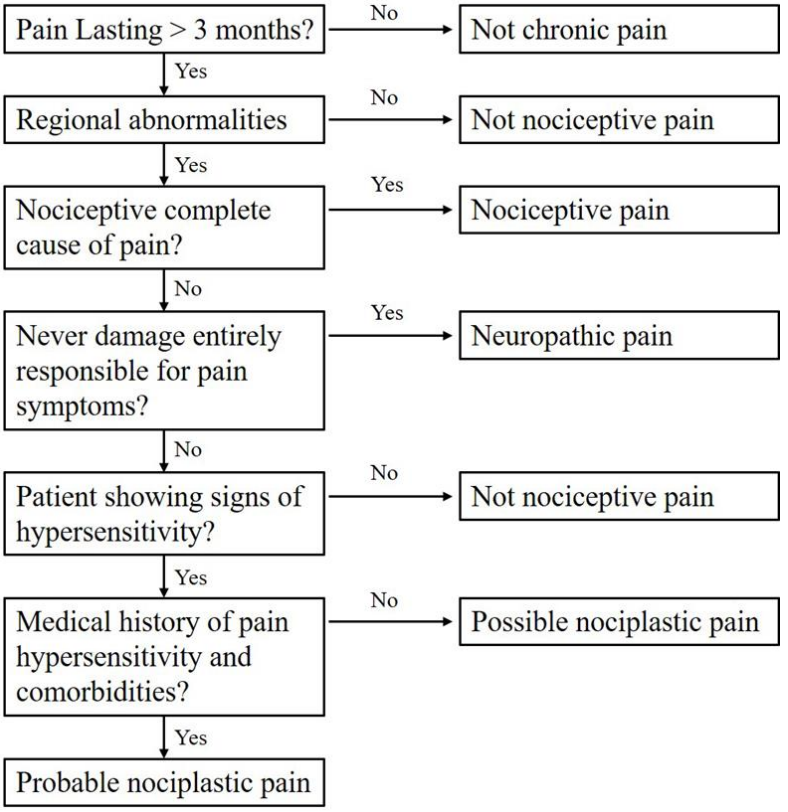

Figure 1. The dio diagram of the nociplastic pain occurrence [1, 2].

The clinical assessment: which is mainly comprehensive as it is always combined with CNS-related symptoms, is a very important diagnostic mechanism that distinguishes it from others, including sleep disturbances, fatigue, mood disorders, cognitive impairment, hypersensitivity to stimuli. The diagnosis requires attention to the patient's pain traits, other physical and psychological symptoms caused by pain, and the diagnosis of co-morbidities and similar conditions (figure 1 and table 1). Genetic history includes family history, traditional childhood history and other central symptoms, fatigue, cognitive problems, multiple environmental sensitivities and psychological symptoms. In contrast to healthy individuals, patients' reduced sleep quality is a major problem contributing to poor prognosis, thus keeping patients' health in a vicious cycle. Sleep deprivation is also associated with increased pain sensitivity, cognitive deficits, and mental and physical fatigue in a worsening manner. They often describe fatigue as the inability to perform an activity after a heavy body. Mental fatigue includes drowsiness and lack of concentration, but is also associated with sleep disturbance problems, and emotional problems include depression and anxiety. Diagnosis should be done with empathy, increasing the patient's sense of confirmation and informing them of the true existence of the symptoms to avoid unnecessary excessive panic [2].

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Table 1. General principles for the diagnosis of nociplastic pain according to clinical history [2].

Patient's chief complaint.	Functional examination
1) The patient complains of pain problems	6) Full physical examination to determine possible peripheral pain triggers
2) Presence of easy fatigue and sleep disturbances	7) Selective examination for symptoms: laboratory tests, imaging tests or other specific tests
3) Mood disorders and memory problems	8) Choose the appropriate questionnaire according to the patient's sleep, emotional state and physical fatigue.
4) Other somatic disorders with increased sensitivity to sensory stimuli	9) Seeking the patient's rating for the description of the pain assessment.
5) Multi-organ system symptoms in addition to the area of pain complained of	

6. Treatments

The goal of treatment should be to relieve symptoms rather than eradicate them, while focusing on the patient's ability to reduce the functional effects caused by pain and to improve the patient's quality of life. Excessive depression about treatment can lead to exacerbation of the disease and a poor prognosis, but excessive optimism can likewise lead to an overwhelming sense of fallout and a poor prognosis [2].

Treatment should focus on individualization and precision. There is an overall division into non-pharmacological and pharmacological treatments. Non-pharmacological treatment is always the first choice. Non-pharmacological treatment includes the management of internal needs of the self, life management, emotional management, psychotherapy, physiotherapy, etc. Management of the self includes maintaining a normal, routine, biological rhythm, continuous participation in life's social activities, implicit segmentation of expectations, encouragement, recognition and self-affirmation of oneself. Maintaining good lifestyle habits, including participation in health-related physical activities, physical activity, appropriate exercise, focusing on diet and weight management, improving sleep quality and reducing stress. Combine this with some psychotherapy, including cognitive behavioral therapy. However, some studies have pointed that cognitive behavioral therapy is less effective, and there are other hypnotherapy and psychodynamic therapies. If psychiatric co-morbidity, (depression, anxiety, etc.) develops, this should be combined with psychotherapy and medication.

Other physiotherapy treatments such as naturopathy, acupuncture, laser therapy, shock waves, etc. Medication management is divided into analgesic drugs and centrally acting drugs. Analgesic drugs include muscle relaxants, non-steroidal anti-inflammatory drugs and acetaminophen as well as opioids. However, opioids are not as effective for nociplastic pain as they are for nociceptive pain, and opioids may have a lower effect. Centrally acting drugs act as pain modifiers and include mainly tricyclic antidepressants, 5-hydroxytryptamine-norepinephrine reuptake inhibitors, plus octopentin and other membrane stabilisers. These include priligylparaben and duloxetine. Other neuromodulation includes brain stimulation and transcutaneous pathways and other centrally acting drugs. Cannabis-based drugs, but further research is needed.

7. Conclusion

Overall, nociplastic pain is still a relatively new concept in pain, and research into its mechanisms is not yet clear, with central hypersensitivity currently proposed as the single most important etiological basis. There are its currently classified relevant five diseases all of which are more than difficult to overcome long term, nociplastic pain is more of a dependent, painful symptom in an existing disease. From a diagnostic point of view, there is no clear or definitive series of objective tests, functional tests

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are not yet directly diagnostic, and the difficulty of diagnosis is compounded by the correlation of similar diseases. At the same time, because of its multiplicity and niche nature is not yet understood by many hospital doctors, increasing the difficulty of diagnosis, while doctors do not understand the failure to detect the cause of the disease, giving rise to greater psychological pressure and burden, may prescribe a series of related diseases under the examination and treatment, resulting in over-testing, medical waste. In terms of treatment direction, there is more of a bias towards long-term comprehensive treatment, including physical, psychological, physiotherapy and pharmacological treatment. Due to the diffuse and widespread nature of the disease, finding a breakthrough in treatment is also a gap in existing research. Patients can be caught in a vicious cycle of symptoms, making it difficult to find relief from pain and breakthroughs. For this type of pain, it is now important to eliminate the symptoms, and being able to eliminate certain symptoms such as sleep disturbances can go some way to reducing the vicious cycle. In terms of medication, there are still controversies and gaps, such as the fact that opioids are not very effective for this type of pain, but instead lead to problems such as sleep that further worsen the development of symptoms. Therefore, in addition to discussing a range of objective treatments, patients should themselves remain optimistic and positive about their illness, seeing it as a long-term process, but also, and more importantly, needing the companionship and encouragement of those around them. Patients should have the right psychology and be clear that the aim is to alleviate the disease to the greatest extent possible, not to eradicate it or get rid of it, but to improve the quality of life and gradually restore several functions to normal life. The range of symptoms it produces is assessed in terms of frequency, e.g. the frequency of a symptom was originally five times a week but can now go to once a week to once a month, to verify the degree of symptom relief by reducing the frequency, even if it is encouraging to oneself. Due to the widespread nature of the disease, it is important to avoid over-testing over-medication. Patients need to focus on maintaining stability in their living environment and to be in a stable emotional and mood state. This paper therefore summarizes the existing research on nociplastic pain in terms of causes, disease classification, diagnostic modalities, and treatment, as a new type of pain. This paper argues that there is a need for greater medical and social acceptance, understanding and encouragement of these patients. It is also worthwhile to conduct more extensive research and studies to help more patients with this type of pain in the future.

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