

# The role of the therapist and neurologist in pain management in patients suffering from cardiovascular diseases

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**Abstract.** A large number of the population of the Russian Federation suffers from cardiovascular diseases, and many of these patients develop chronic pain syndromes as a result of the course of the disease. According to an agreement with the International Association for the Study of Pain, chronic pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Chronic pain syndrome (CPS) is a serious problem for medical professionals due to its complex natural history, unclear etiology and poor response to therapy. CPS is a poorly defined disease. Most authors consider constant pain lasting more than 6 months as a diagnosis, while others used 3 months as a minimum criterion. In chronic pain, the duration parameter is used arbitrarily. Some authors suggest that any pain that persists longer than the reasonably expected healing time of the affected tissues should be considered chronic pain. This article provides an overview of several pain syndromes that are a direct or indirect result of cardiovascular diseases. The role of the therapist in pain management in patients with cardiovascular diseases is also discussed.

## 1 Introduction

Chronic pain syndrome is a very serious health problem worldwide. Although its prevalence is difficult to calculate, it has been estimated that 10% of adults are diagnosed with chronic pain annually, and in a very recent meta-analysis, the prevalence of chronic pain among the population of developing countries as a whole was estimated at 18%. However, the treatment of chronic pain is still not completely satisfactory, probably due to the variety of persistent pain conditions of various etiologies, such as musculoskeletal, neuropathic, visceral and cancer-related pain, the pathophysiological mechanisms of which are only partially known.

Chronic pain is not only acute pain that lasts for several months, but also a disease in itself that has important social and clinical significance. Chronic pain is really common (up to 20% of the adult population) and affects all people at any age, even despite a slight increase in the incidence of the elderly. It is interesting that not only these epidemiological data are very similar to the data on cardiovascular diseases, but it is also well demonstrated that there

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is an increased frequency of simultaneous occurrence of chronic pain and cardiovascular diseases. Finally, new research has shown that chronic pain shares a genetic variant with depression and cardiovascular diseases.

Therefore, it is important to better understand whether chronic pain affects the functioning of the heart and whether there are common mechanisms between these two diseases. There are more and more observational data indicating some correlation between chronic pain and cardiovascular diseases.

## **2 Materials and methods**

At the beginning of the study, a collection of scientific articles, medical literature and publications related to the treatment of chronic pain syndrome in patients with cardiovascular diseases was carried out. Medical journals and official medical recommendations were used for this purpose. After collecting the literature, the selection and analysis of scientific and medical sources was carried out, paying special attention to works containing information about the role of the therapist in pain management in patients with cardiovascular diseases. Publications were included that represented current research, reviews and expert opinions. The data obtained were systematized on key topics, including the diagnosis of pain, principles of treatment, the role of the therapist and his functions in pain management in patients with cardiovascular diseases. Based on the collected and analyzed information, conclusions were drawn about the significance and effectiveness of the therapist's role in pain management in patients with cardiovascular diseases. The research methods made it possible to conduct an extensive analysis of the literature and highlight the key aspects of the therapist's role in pain management in patients with cardiovascular diseases, which became the basis for writing this article.

## **3 Results**

Chronic pain can occur as a consequence of dysfunction of nociceptive circuits at any level of the nervous system, which leads to increased perception of pain (hyperalgesia and allodynia) and even spontaneous pain. Tissue damage and inflammation lead to a decrease in the threshold and an increase in the sensitivity of the peripheral endings of nociceptors, which leads to hypersensitivity to pain – a process known as peripheral sensitization. On the other hand, central sensitization is a phenomenon of increased function of neurons and circuits of central pain pathways caused by increased membrane excitability and synaptic efficiency, as well as a decrease in inhibition. Peripheral and central sensitization is a manifestation of the extraordinary plasticity of the somatosensory nervous system in response to inflammation or injury, and they are the main causes of chronic pain. Functional changes in neurons, including changes in neurotransmitter synthesis and signal transmission, as well as changes in the expression and traffic of receptors and ion channels, can cause sensitization of pain pathways [1]. In addition, accumulating evidence suggests that non-neuronal cells, mainly immune and glial cells, play an active role in the pathogenesis and resolution of chronic pain, releasing neuroactive mediators that modulate pain [2]. Among these non-neuronal cells, the most studied to date are glial satellite cells, macrophages and T cells of the peripheral nervous system, as well as microglia and astrocytes of the central nervous system. Interestingly, nociceptive neurons can also secrete active substances on glial and immune cells, which can also contribute to the neuroinflammatory process that is involved in chronic pain [3]. Thus, there is a genuine cross-interaction between neurons, immune cells and glial cells, which in recent years has attracted the attention of many scientists studying pain in order to expand

our knowledge of how neuroimmune and neuroglial mechanisms contribute to the emergence of chronic pain conditions.

Patients suffering from chronic pain conditions rarely turn to a medical professional with pain as the only medical condition. Approximately half of all patients have one or more concomitant diseases, with cardiovascular diseases being the most common [4].

Cardiovascular diseases are the leading cause of death for both men and women of African-American, Hispanic and Caucasian origin. Interestingly, some conditions with chronic pain, such as osteoarthritis (OA), are associated with an increased risk of cardiovascular disease. An effective and safe treatment of pain requires a holistic approach to therapy. Taking into account patient-specific factors, including the type of pain, patient preferences, costs, concomitant medications and comorbidities, can help clinicians develop a safe and effective treatment plan. This article examines how concomitant cardiovascular disease can play a role in the choice of both opioid and non-opioid drugs for pain relief, using two examples of patients with cardiovascular diseases, chronic OA and diabetic peripheral neuropathy [5].

We will consider options for the treatment of chronic pain syndrome in patients suffering from cardiovascular diseases.

Patient 1: Chronic osteoarthritis pain with a history of MI and hypertension [6].

A 48-year-old obese man went to the clinic with difficulty breathing and chronic OA pain in his right hip and knee, which limited his ability to perform daily duties at work. In the past, he had a history of myocardial infarction, complicated by heart failure and hypertension. He tried over-the-counter acetaminophen (650 mg every eight hours as needed) to no avail. The patient started taking over-the-counter ibuprofen (800 mg three times a day) a week before the appointment to the clinic for pain control, which, according to him, helped somewhat. In addition, he reported that his arterial hypertension was controlled by lisinopril (20 mg orally daily) with a blood pressure of 119/72 mmHg during this visit. The patient was willing to try physical therapy, but also sought medication to get back to work.

Treatment options and recommendations.

Physiotherapy and over-the-counter medications.

Although the focus of this article is on pharmacological treatment options for patients with chronic pain, additional non-pharmacological approaches suitable for each patient should be considered. For example, individuals with chronic OA may be considered and discussed with the patient physical exercise, weight loss, walking aids and physiotherapy/occupational therapy. The Clinical Practice Guide for the non-surgical treatment of osteoarthritis of the hip and knee joints contains a recommended algorithm for the treatment of patients with chronic OA of the knee and hip joints [7]. Recommendations include physical therapy with the addition of acetaminophen or oral nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy or without it, followed by duloxetine or tramadol as second-line options or as an alternative to oral NSAIDs. Patients at risk or with known cardiovascular diseases are advised to avoid NSAIDs and consider using acetaminophen as a first-line remedy. Patients with mild or moderate pain associated with knee joint OA may also be recommended topical administration of capsaicin or intra-articular corticosteroids if the pain is moderate or severe and does not respond to first- or second-line therapy.

NSAIDs and acetaminophen.

NSAIDs and acetaminophen are approved for the treatment of osteoarthritis and other chronic pain conditions [8]. The proposed mechanism of their action is to inhibit prostaglandin synthesis by inhibiting central cyclooxygenase (COG) enzymes. Although oral NSAIDs are recommended as first-line medications for patients with general OA, and doctors of the Cardiological Association recommend using NSAIDs with caution in patients with cardiovascular diseases. This caution is due to the fear that NSAIDs may increase the risk of

serious cardiovascular events, including myocardial infarction (MI), stroke and the development or aggravation of heart failure [9].

A cohort study conducted in Denmark among 82,000 patients with a history of MI and the use of NSAIDs showed that the use of selective and non-selective NSAIDs increases the risk of cardiovascular death or recurrent MI by 45%. A large meta-analysis of 639 studies showed that the use of selective COG-2 inhibitors (such as celecoxib) increased the risk of fatal MI, non-fatal MI and stroke by 37%. Complementing these data, a recent published longitudinal study on the role of NSAIDs in the growth of cardiovascular diseases in patients with OA showed that the use of NSAIDs increases the risk of congestive heart failure, coronary heart disease and stroke by 23-64%. Due to this increased risk of MI and stroke, the FDA labeled all NSAIDs with a "black box" warning about serious cardiovascular thrombotic complications [9].

Although all NSAIDs have a built-in warning about cardiovascular complications, some of them may be more dangerous than others, although current data are contradictory. The PRECISION study was a multicenter randomized double-blind incomplete study involving 24081 patients, which compared the risk of cardiovascular death, nonfatal MI and nonfatal stroke among patients with arthritis who required celecoxib at a dose of 100 mg/day, ibuprofen at a dose of 600 mg/day daily. or naproxen at a dose of 375 mg / day. The study showed that the daily use of celecoxib in patients with arthritis and increased cardiovascular risk was not inferior to ibuprofen and naproxen in terms of cardiovascular complications after 3 years of follow-up. The frequency of cardiovascular complications was approximately 2-3% in each of the groups [11].

On the other hand, a meta-analysis of 87 studies showed that the cardiovascular risk was slightly higher with the use of selective COG-2 inhibitors compared with non-selective NSAIDs such as ibuprofen, diclofenac or naproxen. Of the non-selective NSAIDs, diclofenac demonstrated the highest cardiovascular risk. This discovery may be due to the fact that diclofenac is somewhat more selective against COG-2 compared to ibuprofen or naproxen. Naproxen appears to be the safest of NSAIDs for patients with cardiovascular diseases. Clinical trials have shown that naproxen is not associated with an increased cardiovascular risk compared to other non-selective NSAIDs [12].

In addition to increasing the risk of serious cardiovascular thrombotic complications, the use of NSAIDs is also associated with an increased risk of exacerbation of heart failure. NSAIDs reduce pain by reducing prostaglandin synthesis, but the kidneys need prostaglandins to maintain renal perfusion and water-salt balance. The use of NSAIDs in patients with heart failure can increase blood pressure and accelerate fluid retention, which leads to worsening of symptoms and can potentially lead to an exacerbation requiring hospitalization. Topical NSAIDs, including methyl salicylate or diclofenac gel or patches, may be considered as monotherapy or additional therapy in patients with osteoarthritis of the hand or knee joint. Due to the topical application of the drug, minimal systemic absorption is expected when taking the drug, which can potentially reduce the risk of cardiovascular complications. However, local NSAIDs warn of serious cardiovascular thrombotic complications in the same way as oral NSAIDs, despite significantly lower systemic bioavailability.

NSAIDs have an additional warning about serious gastrointestinal bleeding (GIB), ulceration and perforation. Like the kidneys, the stomach needs prostaglandins to create a protective film that prevents damage to the gastric mucosa by an acidic environment. By reducing prostaglandin synthesis, NSAIDs eliminate this line of defense, which leads to an increased risk of GIB and ulceration. NSAIDs can also prolong a patient's bleeding time by reducing platelet adhesion and aggregation. This problem is important for patients with pre-existing cardiovascular diseases, since many of these patients are already taking aspirin, antiplatelet drugs and/or anticoagulants that have a similar effect. Due to this

pharmacodynamic interaction of drugs, patients receiving both NSAIDs and aspirin, antiplatelet and/or anticoagulant therapy should be monitored for bleeding and anemia. Caution should be exercised when using NSAIDs with anticoagulants such as rivaroxaban or apixaban.

The results of ROCKET AF and ARISTOTLE studies have shown that the use of NSAIDs in combination with anticoagulants can independently increase the risk of major bleeding. Patients taking anticoagulants should consider alternative pain medications [13].

In patients with cardiovascular diseases, acetaminophen is the preferred first-line drug for OA, since there is no warning about cardiovascular risk on its label. Acetaminophen has been shown to reduce pain at rest, movement, sleep and general pain in patients with knee and hip joint OA compared to placebo. Unlike NSAIDs, acetaminophen does not have an anti-inflammatory effect, so it may not be an appropriate option for patients with pain caused by inflammation. The typical dosage of acetaminophen for OA is from 325 to 1000 mg every four to six hours, the maximum dose is 4 grams per day. In patients with hepatic dysfunction or taking warfarin, the recommended maximum daily dose is reduced to 2 g per day, since the liver is necessary for the metabolism and excretion of acetaminophen [14].

It is important to note that acetaminophen is available as a standalone drug, but can also be found in combination medications such as hydrocodone/acetaminophen or over-the-counter medications. It is recommended to train patients to control the daily intake of acetaminophen to make sure that the patient does not take more than the recommended daily amount. The current ACR guidelines for the treatment of osteoarthritis recommend that patients undergo an adequate routine examination of acetaminophen at a dose of 2-3 grams for several weeks before being considered immune.

#### Opioids and tramadol.

Prescription opioids are commonly prescribed and used to treat many types of pain. However, the long-term effectiveness of opioids in chronic pain is limited. Patients with OA are recommended to use opioids for moderate or severe knee or hip pain in patients who are contraindicated or do not respond to other treatments. Opioid use is associated with serious risks, including addiction, abuse, overdose, respiratory and central nervous system depression, and cardiovascular changes. Short-term use of opioids can lead to hypotension and fainting, even in therapeutic doses. Long-term use of opioids has also been associated with cardiovascular mortality and the development of atrial fibrillation [15].

Unlike other opioids, the synthetic mu-opioid receptor agonist tramadol has a low risk of side effects from the cardiovascular system. In addition, tramadol inhibits the reuptake of norepinephrine and serotonin (similar to the antidepressants venlafaxine and duloxetine), which may contribute to its effectiveness in the treatment of chronic pain. Due to the mechanism of inhibition of serotonin reuptake by tramadol, the use of tramadol with other serotonergic agents may increase the risk of developing serotonin syndrome, therefore, it should be carefully monitored at the beginning of treatment. Signs and symptoms of serotonin syndrome include tremor, hyperreflexia, mydriasis, sweating, confusion, agitation, and cardiovascular changes such as tachycardia, high blood pressure, and arrhythmias.

#### Intra-articular corticosteroids.

Glucocorticoids, such as prednisone, are often used to treat various inflammatory conditions, including rheumatoid arthritis. However, even short-term use (<1 month) of glucocorticoids can cause side effects, including hyperglycemia, hypertension, dyslipidemia and fluid retention. The mechanism of steroid-induced hypertension is not fully understood, but it is believed that it is due to an increase in peripheral vascular resistance and sodium and water retention. Due to the effect of glucocorticoids on blood pressure and fluid retention, the use of glucocorticoids in uncontrolled hypertension and heart failure is not recommended. Although oral glucocorticoids are not recommended for the treatment of OA, intra-articular injection of corticosteroids may be recommended for patients with moderate to severe OA in

the knee or hip joint with signs of local inflammation that have proved ineffective or contraindicated for other treatment methods [16].

We will re-examine the case of patient 1.

Due to the presence of a cardiovascular history in this patient, the use of oral NSAIDs, opioids and corticosteroids should be avoided. NSAIDs can cause hypertension and lead to sodium and water retention, which can worsen heart failure. As noted, he went to the clinic with difficulty breathing, which may be due to taking ibuprofen. The patient tried acetaminophen, but used it only as needed, not according to a schedule. If the patient wishes, he can re-take acetaminophen at a dose of 650 mg every 6 hours prescribed for pain. In addition, he could use topical capsaicin or topical NSAIDs as an adjunct therapy due to the reduced risk of systemic absorption and side effects. If the patient continues to experience pain when taking acetaminophen and additional local therapy after a few weeks, you can try to start taking tramadol at a dose of 100 mg every 6 hours as needed.

Patient 2: DPN with a history of uncontrolled hypertension and MI after CABG

A 64-year-old man with diabetic peripheral neuropathy sought help in treating his pain. He has a history of type 2 diabetes mellitus, chronic kidney disease (creatinine clearance CrCl 50 ml/min), hypertension and atrial fibrillation. He went to the clinic for the first time with numbness and tingling in his legs and would like to start taking medications to alleviate his symptoms. Currently, he takes lisinopril (40 mg) and amlodipine (5 mg) orally daily for his hypertension. His blood pressure during this visit was 166/94 mmHg. Currently, his atrial fibrillation is controlled by taking metoprolol tartrate 50 mg orally twice a day and amiodarone (200 mg) orally daily.

Treatment options and recommendations.

Antidepressants.

Antidepressants that inhibit the reuptake of norepinephrine and serotonin have been found to help reduce neuropathic pain by enhancing the analgesic effect in the spinal cord. Antidepressants that inhibit both norepinephrine and serotonin reuptake, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, have been found to be more effective in reducing neuropathic pain than antidepressants that inhibit serotonin reuptake alone. Various guidelines recommend tricyclic antidepressants (TCAD) as first-line remedies for neuropathic pain. One of the significant side effects of TCAD is the cardiovascular risk associated with taking medications. TCAD should be prescribed with caution to patients with a history of cardiovascular diseases, including myocardial infarction, stroke, tachycardia and conduction disorders, since TCAD can slow down cardiac conduction, increase the QTc interval, cause or worsen arrhythmias, worsen coronary heart disease and cause tachycardia and orthostatic hypotension. TCAD doses of more than 100 mg per day have been associated with sudden cardiac death. Thus, cardiologists recommend that patients at risk of serious arrhythmias and coronary heart disease should completely avoid taking TCAD medications [17].

SNRI (duloxetine and venlafaxine) are also recommended as first- and second-line medications for neuropathic pain. Duloxetine is currently approved by the FDA for the treatment of neuropathic pain, while venlafaxine is used over the counter. Both drugs inhibit the reuptake of norepinephrine, which leads to an increase in the peripheral level of norepinephrine, which causes an increase in blood pressure. The effect of inhibition of norepinephrine reuptake by venlafaxine is dose-dependent and manifests itself at doses of 150 mg or more. For this reason, SNRIs may not be an appropriate option in patients with uncontrolled hypertension; however, the demonstrated effect on blood pressure appears to be dose-dependent. In addition, it was found that venlafaxine causes prolongation of the QTc interval in both therapeutic and supratherapeutic doses, therefore, in patients with risk factors for prolongation of the QTc interval, basic monitoring of QTc may be appropriate. In addition, both duloxetine and venlafaxine require dose adjustment in patients with impaired

renal function. Patients with hepatic dysfunction should avoid taking duloxetine, and the dose of venlafaxine should be adjusted accordingly. In addition, SNRI have a significant pharmacodynamic interaction with aspirin, antiplatelet drugs and anticoagulants. The uptake of serotonin by platelet cells is a key component of platelet aggression. Thus, inhibition of serotonin reuptake by SNRIS may increase the risk of bleeding. This risk increases up to 3 times with the simultaneous use of SNRI with NSAIDs, aspirin, antiplatelet drugs and / or anticoagulants [18,19].

Patients receiving SSRIs and NSAIDs, aspirin, antiplatelet and/or anticoagulant therapy should be monitored for signs and symptoms of bleeding.

**Gabapentinoids.**

In addition to antidepressants, gabapentin and pregabalin are recommended as first-line remedies for neuropathic pain.

Gabapentin is not used for neuropathic pain, while pregabalin is approved by the FDA for the treatment of various pain symptoms, including diabetic peripheral neuropathy, fibromyalgia and neuropathic pain. Gabapentinoids are a good first-line remedy with minimal side effects from the cardiovascular system. Common side effects of gabapentinoids include dizziness, drowsiness, sedation, and peripheral edema. The recommended initial dose of gabapentin is from 100 to 300 mg orally before bedtime or in divided doses titrated until the desired effect is achieved with a maximum daily dose of 3600 mg. It is recommended to start taking pregabalin with a dose of 75 mg twice a day, titrating until the desired effect is achieved with a maximum daily dose of 450 mg. In addition, in patients with impaired renal function and  $\text{CrCl} < 60 \text{ ml / min}$ . it may be necessary to adjust the dose of both drugs. Titration of the dose should be carried out slowly every 3-7 days to reduce side effects [20].

Additional second-line drugs for the treatment of neuropathic pain include tramadol, topical capsaicin and opioids.

We will re-examine the case of patient 2.

Due to atrial fibrillation in this patient, TCA testing would be unsafe and could exacerbate both arrhythmia and uncontrolled hypertension. In addition, SNRIS can worsen his blood pressure. Gabapentinoids may be the most appropriate for this patient, as they are recommended as the first line for neuropathic pain and have minimal side effects from the cardiovascular system. Due to impaired renal function, the patient should adjust the dose of gabapentinoids. One of the options for this patient could be the administration of gabapentin at a dose of 300 mg once a day and titration until the desired effect is achieved with a maximum dose of 700 mg twice a day due to kidney function.

## **4 Discussion**

When choosing pharmacological therapy for the treatment of chronic pain conditions such as osteoarthritis and diabetic peripheral neuropathy, it is important to conduct a complete examination of the patient before choosing an analgesia regimen. Patient-specific factors, including comorbidities, can help practitioners choose the safest and most effective treatment for a patient's pain.

The treatment of chronic pain requires a "multidimensional approach" that includes medical, psychological and social elements, like most of the treatment of CVD. However, for such an approach to be successful, a person living with chronic pain must be able to solve multifactorial problems. This requires personal, financial, family and community resources, as well as the will and understanding to direct them to solving the problem.

The cardiological aspects of the treatment of chronic pain syndrome are an important area of study, especially in the context of pain management in patients with cardiovascular diseases. In this context, the therapist's role in pain management in such patients is also critically important.

Diagnosis and evaluation of pain syndrome.

The therapist plays a key role in the diagnosis and assessment of the nature and intensity of pain syndrome, which helps to determine the optimal strategies for the treatment and management of pain in patients with cardiovascular diseases.

A comprehensive approach to treatment.

The therapist focuses on a comprehensive approach to treatment, including pharmacotherapy, non-drug pain management methods, as well as psychological support to ensure the best results in patients with chronic pain syndrome and cardiovascular diseases.

Optimization of drug therapy.

The attending physician is actively involved in optimizing drug therapy, taking into account the peculiarities of the patient's cardiovascular system in order to prevent possible undesirable effects and drug interactions.

Education and enlightenment.

In the treatment of chronic pain syndrome, the attending physician performs an important function in educating and educating patients about pain management strategies, compliance with treatment recommendations and lifestyle changes necessary to improve the state of the cardiovascular system and reduce pain.

Cooperation with a cardiologist.

The therapist works closely with the cardiologist to determine the optimal treatment strategy adapted to the specific needs and characteristics of each patient, which contributes to improving the quality of life and well-being of patients.

Thus, it is necessary to draw the following conclusions. Chronic pain conditions in patients with cardiovascular diseases require a special approach to treatment. Consideration of concomitant diseases and patient factors is important for choosing a safe and effective treatment. Opioids and tramadol may be the preferred painkillers for patients with chronic pain and cardiovascular disease. Intra-articular corticosteroids may be a treatment option for patients with osteoarthritis and uncontrolled hypertension. Antidepressants, gabapentinoids and other medications can be used to treat neuropathic pain. It is important to conduct a full examination of the patient before choosing an analgesic treatment.

Effective pain management in patients with cardiovascular diseases and chronic pain syndrome requires a comprehensive approach. The role of the therapist in this process is extremely important, from the diagnosis and evaluation of pain syndrome to the optimization of drug therapy. The therapist also plays an essential role in educating and educating patients, helping them to take an active part in managing their condition. In addition, cooperation with a cardiologist is important for adapting treatment to the individual needs of patients, which contributes to improving their quality of life and overall well-being.

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