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## Review

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# CHRONIC PAIN AND NEUROIMMUNE POSSIBLE PREDICTIVE FACTORS: REVIEW

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Secondary post-traumatic and post-operative pain is a problem that is increasingly encountered by medical professionals in Ukraine today in the conditions of war. Chronic pain is an independent nosological unit, which is a severe complication of many performed surgical procedures. Chronic pain as a result of surgical interventions occurs up to 10% of patients. It develops significantly often after amputations (50–85%), thoracotomies (5–65%), cardiosurgical interventions (30–55%), and chest surgeries (20–50%). Long-term post-operative pain is one of the primary, mostly unrecognized clinical problems.

It can be assumed that patients whose wounds do not heal in time have a predisposition to the development of secondary chronic pain. The long healing process of the wound surface is directly related to the following features: the wound microbiota, the resistance of microorganisms to antibiotics, the group of antibacterial agents chosen for treatment and the duration of exposure to the drug.

Understanding the interaction between microorganisms and the sensory systems of neurons can reveal more information for the putative pain mechanisms study.

In recent years, much attention has been paid to studying the concept of pain sensitization. Inflammation and nerve damage contribute to increased pain signaling, stimulating wound hyperalgesia. These processes can directly affect the formation of long-term post-operative pain.

Among the key problematic factors that contribute to the appearance of remote peripheral neuropathy, the duration of administration, increased dosage, and possible combinations of antimicrobial drugs should be highlighted, as well as the persistence and exacerbating of manifestations of local inflammation with the participation of resistant opportunistic bacteria that colonize the lesion and can directly produce metabolites vital activities, pathogenicity factors with pro-inflammatory properties. This allows us to assume a significant role of persistence in the primary lesion of antibiotic-resistant opportunistic bacteria, as well as antibiotic therapy as a delayed iatrogenic factor, as predictors of the formation of chronic pain syndrome in the wounded.

**Keywords:** Chronic pain, postoperative pain, antibiotic resistance, peripheral neuropathy.

## Introduction

Chronic pain is one of the dominant diseases of humanity in the modern world, which leads to limitations in mobility and daily activities. Of course, a sudden change in the way of performing daily functions initiates the development and change of the patient's psycho-social status, anxiety and depression, and a decrease in the quality of life, which is also a risk factor for premature death. Chronic pain is an unpleasant sensory and emotional experience associated with actual or perceived tissue damage that persists for over three months [1, 2].

More than 230 million people undergo surgical treatment worldwide each year, and the number is increasing annually [3].

Secondary post-traumatic and post-operative pain is a problem that is increasingly encountered by medical professionals in Ukraine today in the conditions of war. Chronic pain is an independent nosological unit, which is a severe complication of many performed surgical procedures. It is estimated that up to 80% of patients experience post-operative pain of varying intensity. Acute post-operative pain occurs in 10–50% of people after routine surgery, while chronic pain as a result of surgical interventions has up to 10% of patients. It develops significantly often after amputations (50–85%), thoracotomies (5–65%), cardiosurgical interventions (30–55%), and chest surgeries (20–50%). Long-term post-operative pain is one of the primary, mostly unrecognized clinical problems [4]. Over 20 surgical, psycho-social, inherent, and surrounding factors are known as risk factors. The main pre-operative factors are psychological disorders, altered perception and pain, inherent factors, insomnia, and catastrophizing. Determinants of the abnormal healing process which are related to surgical interventions might be different techniques, nerve impairment, and long ischemia. In the remote period, hyperalgesia, medicines, radiation therapy, re-operation, and many other personality characteristics serve as important factors. Unfortunately, there are currently no definitive proper measures for the prevention and treatment of post-operative pain since the process of chronic pain appearance is still not fully understood. However, many neurotransmitters are known, and various pain mechanisms are considered. Of course, it is evident that such measures should suppress central sensitization. Gabapentinoids are effective because of their ability to specifically affect the neuropathic type of pain. Still, the data from the literature remain contradictory. Analysis of 11 studies showed that gabapentin characterizes gabapentin was described as capable of influencing post-operative pain. At the same time, in the Cochrane review and meta-analysis, such properties of gabapentin have been disproved [5].

This means that not all determinants for pain formation arising after surgical interventions have been sufficiently studied.

However, it can be assumed that patients whose wounds do not heal in time have a predisposition to the development of secondary chronic pain. The long healing process of the wound surface is directly related to the following features: the wound microbiota, the resistance of microorganisms to antibiotics, the group of antibacterial agents chosen for treatment and the duration of exposure to the drug (Fig. 1).

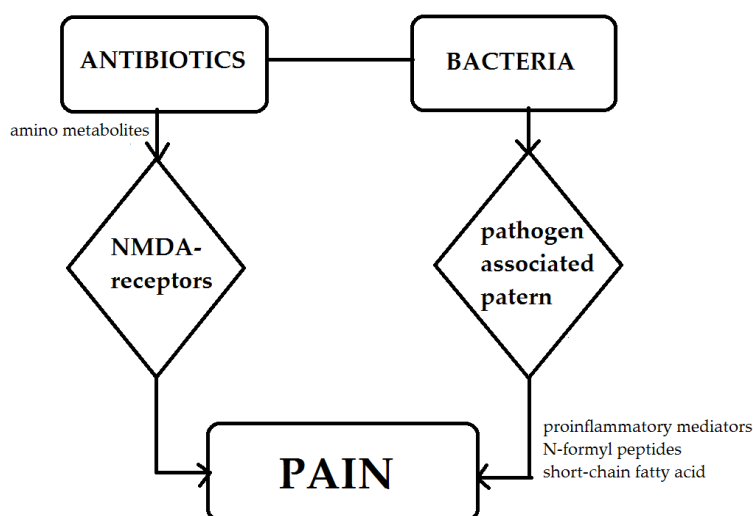


Figure 1. Neuroimmune factors of pain formation in patient with active inflammatory process

Clinically, bacterial infections cause inflammation and pain, a neuroimmune body response. During inflammation, immune cells, acting on peripheral nerve endings, trigger the mechanism of activation of the sensation of pain [6].

Understanding the interaction between microorganisms and the sensory systems of neurons can reveal more information for the putative pain mechanisms study. Some studies described that the nociceptor signal is activated in response to substances of vital activity of pathogenic bacteria. This process induces pain, which stimulates neurogenic inflammation and neuroimmune processes as protective reactions of the human body. The basis of the structure of the cell wall of gram-negative bacteria is lipopolysaccharides, which are associated with pathogenic structures and are secreted by bacteria into the surrounding tissues during the infectious process [7]. Also, it is known that tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a major cytokine that activates the production of other cytokines associated with pain sensation. Cytokine storm initiate primary afferents and spinal cord sensitization. Nociceptors are also activated under the influence of interleukins IL-1 $\beta$  and IL-6. Toll-like receptors that support the cascade immune response are also activated [8].

It is known that both bacterial, fungal and viral infections are associated with pain. Microorganisms affect the mechanisms of pain formation directly and indirectly. In the first case, pathogenic factors secrete virulence factors (toxins) and damage tissues. Pathogen recognition receptors of the host's immune system are activated and detect harmful factors. It has been proven that toxins and pathogen-associated substances can affect sensory structures, causing pain. Also, pain occurs directly due to tissue damage [9].

We analyzed published works for 2014–2024 in the medical databases PubMed, Google Scholar, Medline and Cochrane Library. All studies were related to the search for answers to questions about additional possible factors in the formation of secondary chronic post-operative and post-traumatic pain. Possible factors, such as the neurotoxic effect of antibiotics and the influence of wound microbiota, were considered. The exclusion group consisted of clinical cases, abstracts, books, monographs regardless of the year of publication, and studies published before 2014. The search was conducted using the following keywords: “chronic postsurgical pain,” “antibiotics neurotoxicity,” “antibiotic resistance,” “peripheral neuropathy,” and “NMDA-receptors.”

### **Antibiotic therapy: modern problems**

The discovery of antibiotics is one of the most significant discoveries in the practical field of medicine and humanity. The first studies in this direction were carried out since the beginning of the 1900s. Thus, the first antibiotic was discovered in 1920 and was called salvarsan. However, the discovery of penicillin by Fleming, Florey and Chain in 1945 is considered the beginning of the era of antibiotics. Indeed, it was a kind of revolution in the field of medicine, because it directly allowed to reduce the level of complications and mortality from infectious diseases. Many medical manipulations and procedures have become possible. However, in the 21st century, we are on the threshold of a “post-antibiotic” era. Misuse of antibiotics has created new risks of returning to the era of antimicrobial ineffectiveness as the number of resistant pathogens increases. Humanity may face the same problem again more than 100 years later. For example, according to the forecasts of the government of Great Britain, in the absence of immediate decisions and actions, by 2050, deaths from infections not susceptible to drugs will increase, with approximately 10 million cases every year [10].

The traditional approach to evaluating effectiveness examines the relationship between the time of exposure to an antibiotic and the response to them of clinically significant microorganisms, which predicts the effectiveness of therapy in patients. Pharmacokinetics can vary significantly in different groups of patients, taking into account certain individual characteristics. For example, the severity of infection, renal function, liver function, body weight, and anatomical abnormalities can significantly alter drug clearance, volume of distribution, and protein binding. Taking into account the effect of antibiotics on the patient's microbiota is essential in developing an optimal treatment regimen, given that the issue of the development of resistance of commensal bacteria is a prognostic negative factor [11–13].

Also, the consequences of combined antibiotic therapy for severe bacterial infections caused by *Pseudomonas* spp., *Acinetobacter* spp., and *Enterobacteriaceae* are highly controversial topics. Of course, one cannot deny the possible advantages of a combination of antimicrobials compared to their monotherapy. The desired expected effects are a broader antibacterial spectrum, a synergistic effect, and a reduced risk of developing resistance during treatment. At the same time, excessive use of combinations should be avoided by antimicrobial agents, it can cause toxicity, superinfection, formation of non-sensitive strains, and higher costs of medical care [14, 15].

However, the problem of overcoming resistance to antibiotics is not the only issue related to their use, to which modern medicine needs to find answers. Of course, the problem of antibiotic therapy, like any other medicine, is the occurrence of many possible side reactions associated with their use. Adverse drug reaction is a concept that is considered an expected and harmful reaction that occurs during drug use. Adverse reactions occur in outpatients and hospitalized patients and may manifest as disorders of varying severity. According to the literature, adverse reactions occur in 5–10% of hospitalizations, and up to 0.1–0.3% of adverse reactions can be serious and cause death [16].

Antibiotics are estimated to be among the most widely used drugs in clinical settings. Despite the undeniable benefits of antibacterial agents, one serious adverse effect is neurotoxicity. This is the factor that can lead to serious complications and even death. Convulsions, encephalopathy, optic neuropathy, peripheral neuropathy (PN) and exacerbation of myasthenia gravis are important examples of neurotoxic side effects associated with antibiotic use. Among all groups of antibiotics, quinolones and beta-lactams are most often mentioned as neurotoxic. However, it should be noted that several other classes of antibiotics, especially aminoglycosides and tetracyclines, antituberculosis drugs also hurt the nervous system [17].

### Comparison of the study of resistance and neurotoxicity of antibiotics

We conducted a comparative analysis of the activity of studying such problems of antibiotic therapy as resistance and neurotoxicity.

**Table 1**

**Comparative analysis of the activity of studying the problems of resistance and neurotoxicity of antibiotics**

Keywords	antibiotic resistance		antibiotic neurotoxicity	
database	2003–2013	2014–2024	2003–2013	2014–2024
PubMed	2666	8787	24	58
GoogleScholar	49500	47700	17700	17200

The search was conducted in the medical scientific-metric databases PubMed and Google Scholar, comparing the number of publications for 2014–2024 and the previous ten years, that is, in the period 2003–2013. The same keywords were used in each scientific metric base: “antibiotic resistance” and “antibiotic neurotoxicity” (Table 1).

In the Medline National Library of Medicine, the number of publications was compared since this database allows for distribution according to various criteria. The same keywords, “antibiotic resistance” and “antibiotic neurotoxicity,” were used; search results were 1,678 and 34, respectively.

### N-methyl-D-aspartate receptors

Despite the small amount of information regarding the mechanism of neuropathic pain, there is evidence of dysfunction in the opioid and glutamatergic systems. Glutamate receptors of the N-methyl-D-aspartate (NMDA) type are important for normal work of the nervous system, covering the fundamentals of excitatory neurotransmission to synaptic plasticity, learning, and memory complexities. NMDA receptors have long been the subject of research in transmitting excitatory input from primary sensory neurons to the brain [18, 19].

The specific chemicals that can pass through the membrane of NMDA receptors are still unknown. Activation of NMDA receptors contributes to the formation of central sensitization. As a result of the activation of nociceptive afferent fibers, glutamate is released in the spinal cord; the NR2B subunit is activated and ion permeability changes.

An increase in the excitability of the postsynaptic potential additionally leads to the separation of  $Mg^{2+}$  from the NR2B subunit, increasing the excitability level of this potential, and as a result, pain increases. Also, endogenous pain perception systems are activated in response to neuropeptides such as substance P and neurokinin A. In this way, there is a basis for developing adaptive neuroplastic processes that can contribute to the “pain memory” formation [20, 21].

The most well-known and researched NMDA receptor antagonists are magnesium and ketamine. It is believed that due to their mechanism of action, they can have a pain-relieving effect, which is why they are associated today with new possibilities in treating post-operative pain and various acute and chronic pain conditions [22].

In recent years, much attention has been paid to studying the concept of pain sensitization. Inflammation and nerve damage contribute to increased pain signaling, stimulating wound hyperalgesia. These processes can directly affect the formation of long-term post-operative pain [23].

### **Peripheral neuropathy**

Peripheral neuropathy (PN) occurs in 1% to 7% of cases in the general population, with a predominance in people over the age of 50. The causes described in various literature sources are diabetes, mechanical impact on the nerve, alcohol, toxins, drugs, heredity, and nutritional deficiency. The causes of peripheral neuropathy in 25–46% of patients are not established [24–26].

Pain, which is a manifestation of peripheral neuropathy, is obviously the result of the chronic generation of action potentials of the damaged nerve. Distorted nerve activity is a serious mechanism and factor in neuropathic pain. Early application of local anesthetics to the damaged nerve area can reduce neuropathic pain. PN is divided into acute and chronic, depending on the duration of symptoms. If acute neuropathy is usually identical to emergency conditions, then chronic neuropathy develops over several months. Also, depending on the manifestations and the damaged structure, PN can be sensory (PSN) and motor (PMN). PNS is formed when the interaction of the somatic and autonomic nervous systems is disturbed. In simple words, PSN is impaired perception of information from the environment by the sensory organs and/or impaired transmission of information from sensory organs to the brain. Different symptoms depend on the nerve damage. The main manifestations of PSN are increased and changed sensitivity and an increased feeling of pain. Symptoms characteristic of PMN are progressive muscle weakness, fasciculations or convulsions. Psychological disorders and sleep problems are also frequent secondary effects. According to the International Association for the Study of Pain (IASP), neuropathic pain, which is often a manifestation of the development of peripheral neuropathy, is associated with damage to the somatosensory nervous system work and chronic pain [27].

Qualitative signs of peripheral sensory nerve damage are tingling, burning, or electric shock sensations. Such symptoms meet the clinical criteria used in questionnaires to diagnose neuropathic pain [28].

Literature data confirms that pain is a common symptom in the European population of elderly patients. They often have comorbid conditions and are at increased risk of polypharmacy and, therefore, adverse events, iatrogens, and possible hospitalizations. Pain is one of the most frequent complaints that creates the need for medication. The effectiveness of painkillers has not been thoroughly investigated, as elderly patients are not usually included in clinical trials. Drugs used for the management of neuropathic pain can cause dangerous effects for older people, such as pronounced sedation, the possibility of falls, and cognitive impairment [29].

### **Antibiotic therapy and neurotoxicity: possible connections**

Antibiotics are estimated to be among the most widely used drugs in clinical settings among all age groups. At the same time, metronidazole usually causes only mild side effects, severe neurotoxic effects are rarely mentioned, for example, effects on peripheral nerve endings and encephalopathy. The relationship between metronidazole use and resulting neurotoxicity remains unclear. Some studies have suggested that free radicals damage the nervous system, and the formation of a thiamine-like chemical that is formed from metronidazole can lead to a neuropathy similar to a nutritional deficiency. On the other hand, some scientists believe that metronidazole and its metabolites provoke the degeneration of axons of nerve fibers.

Peripheral neuropathy with a short period of metronidazole treatment (not more than four weeks) develops infrequently, although the risk of peripheral nerve impairment is high with a total received dose of more than 42 g; however, this effect is reversible after discontinuation of drug therapy. Cerebellar dysfunction, visual disturbances, vestibulotoxicity, cochleotoxicity, ataxic gait, dysarthria, and convulsions are possible side effects that develop as a result of metronidazole use. Combinations of metronidazole in combination with a group of cephalosporin antibacterial agents and carbapenems are successfully used against anaerobic bacteria. Metronidazole dosage can vary in infectious processes caused by anaerobic bacteria, but the most common dosage encountered is 500 mg intravenously three times a day. Symptoms completely disappeared in almost all patients. Thus, impressions of peripheral nerves rarely occur when using a total dose of metronidazole less than 42 g. Using higher doses of metronidazole likely increases the risk of neurotoxic effects, but it should be noted that these effects are not persistent and may disappear after the drug is stopped [30–31].

However, according to some experts, metronidazole should be included in drugs with a probable neurotoxic effect. When using it, the possible consequences of its appointment should be considered [32–34].

In another study of 5,357 patients with sporadic peripheral neuropathy and 17,285 controls, oral fluoroquinolones were associated with an increased risk of peripheral nerve impairment. The risk of side effects from the use of fluoroquinolones became higher every day with each additional day and persisted for six months after the end of their treatment. Compared with the use of amoxicillin and clavulanate, when no significant risk was established. The number of patients with side effects after the average course of fluoroquinolones was the largest in men and elderly patients. Recently, the Food and Drug Administration (FDA) required changes to the package insert to emphasize this adverse effect of fluoroquinolones [35].

Also, the FDA recommends using fluoroquinolones only in cases of infectious processes in which other agents are ineffective due to the high risk of toxicity. In Europe, the European Medicines Agency carried out the safety review. Despite the recognition of the risk of peripheral neuropathy, there is limited data to quantify both the relative and absolute risk from exposure to fluoroquinolones. To our knowledge, only one observational study on this topic, a case-control study using US administrative claims data, reported an increased risk of peripheral neuropathy in those currently taking fluoroquinolones. The study aimed to quantify the relative and absolute risk of peripheral neuropathy with fluoroquinolones and explore potential associated risk factors. Simultaneous use of other drugs may increase the risk of affecting peripheral nerve fibers.

The mechanisms of damage to peripheral nerve fibers resulting from fluoroquinolone treatment are unknown. Fluoroquinolones are regularly studied for their safety and possible risks of developing chronic effects on the muscles and nervous system. Morales et al. conducted a case-control study that demonstrated an association between fluoroquinolone use and a higher risk of neuropathy than in fluoroquinolone-naïve patients. The highest risk occurs in men aged over 60. The strength of this study was that the control group used other different antibiotics that did not increase the risk of neuropathy [36–38].

In conclusions: Traumatic injuries that require surgical treatment are accompanied by the appearance of factors that create prerequisites for the formation of post-operative pain syndrome and require the fastest possible correction. Secondary post-operative chronic pain is an important issue today, especially in the Ukrainian population, because it significantly limits functional capacity, worsens the quality of the patient's life and affects the change in his social status. Antimicrobial therapy, as an integral component of treatment tactics for the wounded during the acute post-traumatic period, simultaneously with therapeutic effectiveness, has several negative long-term consequences, especially in cases of long-term systemic use and the need to use several means of different pharmacological groups. Neurotoxicity is one of the main understudied side effects of long-term multicomponent antibiotic therapy, which has not been thoroughly studied to date. Among the key problematic factors that contribute to the appearance of remote peripheral neuropathy, the duration of administration, increased dosage, and possible combinations of antimicrobial drugs should be highlighted, as well as the persistence and exacerbating of manifestations of local inflammation with the participation of resistant opportunistic bacteria that colonize the lesion and can directly produce metabolites vital activities, pathogenicity factors with pro-inflammatory properties. This allows us to assume a significant role of persistence in the primary lesion of antibiotic-resistant opportunistic bacteria, as well as antibiotic therapy as a delayed iatrogenic factor, as predictors of the formation of chronic pain syndrome in the wounded.

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