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Review Article

Pharmacological Evaluation of Covid 19 Vaccine in Acute and Chronic Inflammatory Neuropathies

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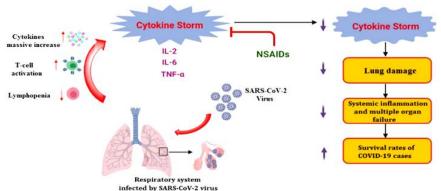
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ABSTRACT

Neuropathic pain is a type of chronic pain that is resulted from illness, infection, or injury or is associated with these problems. Of course, neuropathic pain is not a direct result of these factors. Nerve pain is usually a complication of illness or injury. Patients with neuropathic pain suffer from burning, stabbing, and lightning pain. The neuropathic pain in some patients is persistent. Studies revealed that there is no evidence that anesthetics interfere with the immunogenic effects of the Covid-19 vaccine. In international guidelines, therapeutic interventions that require anesthesia are also prohibited after the Covid-19 vaccine is given. In the case of anesthesia but recommended, if possible, to delay surgery until complete immunity to vaccination is achieved. Some anesthetics and surgeries use anesthetics. These drugs are used to numb specific areas of the body or induce sleep to prevent pain and discomfort. Topical anesthetics and general anesthetics are two common types of these drugs. Researchers at the National Institute of Health Research of the Islamic Republic of Iran prepared a leaflet study to assess the interaction of the first group of anesthetics, namely anesthetics, on the immunogenic effects of vaccines. Studies show no studies or evidence directly assessed the influence of anesthetics on the immunogenicity of the Covid-19 vaccine. At the same time: There is also no evidence that the use of anesthetics interferes with the immunogenic effects of the Covid-19 vaccine.

GRAPHICAL ABSTRACT



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Introduction

Pain is an unpleasant sensation caused by a harmful stimulus, and its purpose is primarily to defend and protect against injury [1-4]. Chronic pain is defined as limited, intermittent, or persistent pain that affects the normal function of tissues for more than twelve weeks. Unlike acute pain, chronic pain is often felt without apparent reason [5-7].

Chronic pain is caused by a combination of biological, psychological, and social factors and often requires a multifactorial approach to manage it (Figure 1). The source of chronic pain may be neurogenic (neurological), nociceptive (pain from tissue damage), or psychological. Treatment of patients with pain due to structural causes such as intervertebral disc pain, degenerative joint disease, or inflammatory

disorders such as pain caused by rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, or other painful conditions such as pain Tissue infarction is different from each other [8-10]. The patient's immobility and the resulting problems in the muscles and joints, weakening the patient's immune system and predisposing to other diseases, sleep problems, loss of appetite and poor nutrition of the patient, dependence on drugs, more dependence than usual on family members and caregivers, excessive unreasonable use of medical services, failure to provide appropriate services in the workplace or disability, separation of a person with chronic pain from society and family and introversion, anxiety, and fear of the cause He noted pain, feelings of hopelessness, depression, and suicide [11].

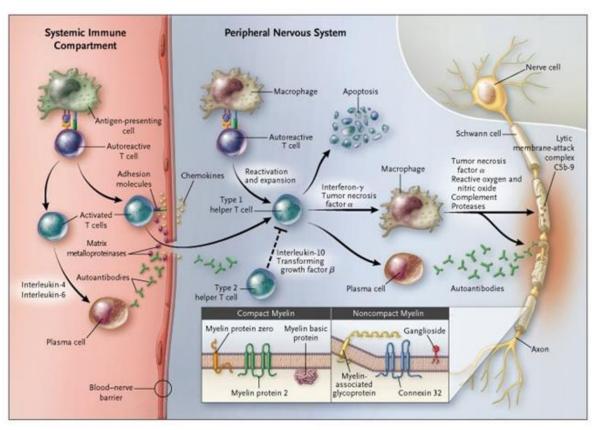


Figure 1: Chronic Inflammatory Demyelinating Polyneuropathy [12]

Chronic pain is a major clinical challenge. The general approach and initial treatment strategy appropriate for chronic pain depend on an accurate assessment of the cause and the type of chronic pain syndrome. Chronic pain is usually difficult to treat, and in most cases, it is not possible to get rid of the pain completely. Primary

management of a patient with chronic pain includes targeted treatment of pain [13]. If there is no improvement with non-drug interventions in the first stage, drug treatment is selected according to the type of pain and clinical condition and response to treatment. Finally, nerve block is an alternative to persistent pain

that has responded well to previous treatments [14-16].

Non-pharmacological chronic pain management methods are very diverse and include mental and acupuncture techniques and physical methods. There is no single cure for chronic pain. Chronic pain management begins with non-pharmacological methods, and if the appropriate response is not appropriate, appropriate drug treatments are selected.

Successful chronic pain management requires dealing with all the unpleasant physical and mental conditions that lead to pain. Non-

pharmacological therapies include a wide range of therapies that include exercise therapy, psychological interventions (e.g., cognitive-behavioral therapy, psychotherapy, and patient education), various skin stimulation techniques, massage therapy, and immobilization [17-19]. Acupuncture, muscle relaxation, music therapy, hypnosis, or physiotherapy.

The choice of pharmacological or non-pharmacological treatments is based on various factors observed in the patient, including age, associated problems, type of pain, access, cost, and patient preferences (Figure 2) [18].

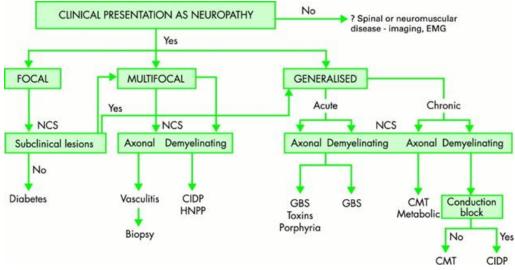


Figure 2: Clinical Evaluation & investigation of the neuropathy [28]

Are vaccines safe and effective for people with inflammatory neuropathy?

Another concern is the potential risk of recurrence after vaccination in patients with autoimmune neuropathies. Only retrospective studies have examined this issue in Guillain-Barre and CIDP. Only one Guillaume patient experienced disability after the vaccine was given, and only one CIDP patient developed symptoms that needed treatment. In contrast, the symptoms were mild and resolved spontaneously in the other patients. Given these limitations, these studies show little likelihood of worsening Guillain-Barre symptoms and CIDP vaccination. No study has evaluated the effect of vaccination in patients with inflammatory neuropathy [29].

Peripheral neuropathy is diagnosed when a person notices some of these symptoms and sees a doctor. Occasionally, when a doctor examines a patient for other reasons, such as an incision in the leg, they notice peripheral neuropathy. At other times, neuropathy is diagnosed during a checkup for diabetes [30-32]. Your doctor may order blood tests to diagnose possible causes of peripheral neuropathy. Your doctor may refer you to a neurologist for further assessment. The neurologist may also order other tests for the patient. Prescribing new tests depends on the probable cause of the disease, based on the patient's symptoms and medical history. These tests include blood tests, x-rays, scans, or other tests [33-35].

Non-opioid Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most popular medications for chronic pain, despite their many side effects. NSAIDs relieve milder forms of pain, such as pain from muscle and joint problems, and reduce inflammatory symptoms such as swelling and burning. These drugs are widely used to manage chronic pain and vary in strength, duration of

action, method of administration, increased risk of ulceration and bleeding, and gastrointestinal and cardiovascular complications. The spectrum of NSAIDs' action reflects their ability to generally reduce arachidonic acid-derived inflammatory cascade products [36].

Depending on the ability of these drugs to inhibit each of these isoenzymes, the risk of side effects of these drugs will be different. Concerning NSAIDs, the maximum effective dose can be determined. After passing this amount, there is no expected increase in analgesic effect, and only the side effects of the drug increase. Injectable types of these drugs are also available in Iran, but for chronic diseases and long-term daily use, the injectable type of these drugs recommended [37]. Cardiovascular side effects of NSAIDs should be considered because of the need for long-term use of these drugs to manage chronic pain. In 2015, the US food and drug administration stressed the need to affix a warning label on the packaging of NSAIDs to increase the risk of cardiovascular complications and the risk of heart attack and stroke. Recent studies published in the BMJ medical Journal show that short-term use of this class of drugs may also increase the risk of heart attack and stroke. Hypertension and cardiovascular events probably occur due to decreased production of prostaglandins and prostacyclin's and possible increase in water and salt retention following renal effects due to medications [38-40].

NSAIDs with non-selective effects on COX enzymes and NSAIDs with selective effects on these enzymes, such as celecoxib, can increase the risk of cardiovascular disease, including stroke, myocardial infarction, hypertension, atrial fibrillation, congestive heart failure. On the other hand, studies have shown that people who used two-drug antiplatelet therapies, such as aspirin and clopidogrel, were exposed to bleeding events after cardiovascular events were 3.3 cases per 100 people-years. And this risk has increased with the addition of NSAID treatment to 7.6 accidents per 100 people per year.

In general, cardiovascular and gastrointestinal events appear to increase with increasing dose

and frequency of administration. However, naproxen may be an exception because of the increased risk of myocardial infarction or stroke at lower doses than usual. 220 mg every 12 hours has also been observed. At the same time, at higher doses, the antiplatelet effects of this drug become more stable and possibly reduce cardiovascular events. Studies have shown that patients with most no history cardiovascular disease who require short-term (less than one month) or intermittent treatment with this class of drugs, naproxen appears to have the highest level of cardiovascular safety among drugs. With this category, it is recommended to use naproxen, another non-selective drug such as ibuprofen is a reasonable alternative. Nonselective drugs should be prescribed for the minimum effective dose and the minimum duration of treatment. According to PRECISION, selective cyclooxygenase-2 the inhibitor, celecoxib, has not been associated with an increased risk of cardiovascular disease (CVD) in patients with osteoarthritis compared to other drugs (NSAIDs), as seen in Figure 3. More than 24,000 patients receiving daily medications to treat their osteoarthritis pain and at risk for cardiovascular disease were randomly assigned to receive celecoxib 100 mg twice daily and ibuprofen 600 mg three times daily. Or naproxen at a dose of 375 mg twice daily. Patients were treated for an average of 20 months and followed up for about 30 months.

As a result, contrary to the results of previous studies, the rate of cardiovascular events with celecoxib similar to naproxen and ibuprofen was observed. One of the limitations of the study mentioned by the research group is the lack of a control group. Therefore, these findings as the safety of celecoxib in patients with cardiovascular disease should not be interpreted. Therefore, the results of the mentioned trial cannot change the current clinical approach, and it is still recommended that patients at high risk of cardiovascular disease generally avoid taking celecoxib or other NSAIDs. Acute renal failure, acute tubular glomerulopathy, necrosis, nephrotic syndrome, acute interstitial nephritis, water and electrolyte disturbances, and of these drugs. nephropathy are among the renal complications

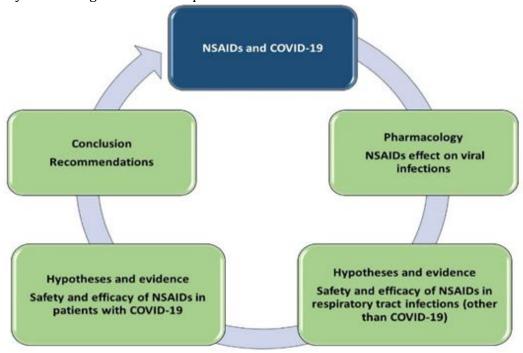


Figure 3: NSAIDs and COVID-19 [42]

Acute renal failure due to these drugs is due to inhibition of COX-1 and a lesser extent, inhibition of COX-2 in the kidneys, resulting in decreased production of prostaglandins. Decreased production of prostaglandins further leads to constriction of the afferent arteries, decreased renal blood flow, increased creatinine and blood urea nitrogen, and fluid retention in the body. COX-2-specific inhibitors, such as celecoxib, also inhibit prostaglandin production and renal complications and are not superior to other NSAIDs (Figure 4). Indomethacin has the highest risk of renal ischemia among NSAIDs, and aspirin has the lowest risk. Piroxicam, diclofenac, naproxen, and ibuprofen are among the two drugs in terms of these side effects.

Gastrointestinal side effects of NSAIDs often occur in patients with diarrhea, headache, nausea, constipation, rash, dizziness, bloating, stomach pain, and indigestion. Gastrointestinal side effects are caused by decreased production of prostaglandins and bicarbonate and the acidic properties of the drugs. Although the sources associated with the most and the most negligible gastrointestinal side effects have varied in different sources, in general, the incidence of these side effects may be remembered as

ibuprofen> diclofenac> naproxen> tolmetin> indomethacin> piroxicam.

Vaccine's work based

Vaccine's work is based on properly preparing a person's immune system (the body's natural defenses) to identify and protect against a specific disease. Most research on Covid 19 vaccines involves reacting to a protein (in whole or in part) found only in the Covid 19 virus. When a person is vaccinated, an immune response is triggered. Most Covid 19 vaccines require two doses to be safe. If a person becomes infected with the virus after vaccination, the immune system can detect the virus and is ready to attack. Vaccination is a simple, safe, and effective way to protect people against harmful diseases. Covid 19 vaccines protect us against disease by creating an immune response to SARS-Cu-2, the virus that causes Covid 19. This immunity helps you fight off the virus. It also means that you protect the people around you. If you get vaccinated, your risk of infecting other people around you is significantly reduced. This is especially important for people at risk for severe disease caused by Covid 19, including health care providers, the elderly, and people with underlying medical conditions. After vaccination, immunity to Covid 19 will continue for at least 6 to 8 months, as far as we know. Even if you are vaccinated, you are less likely to get Covid 19. No vaccine is 100% protective. Therefore, it is essential to continue public health practices, such as physical distance,

masks, and frequent hand washing. When a large portion of the population is vaccinated (approximately 70 to 85%), immunity to Covid 19 develops in the community.

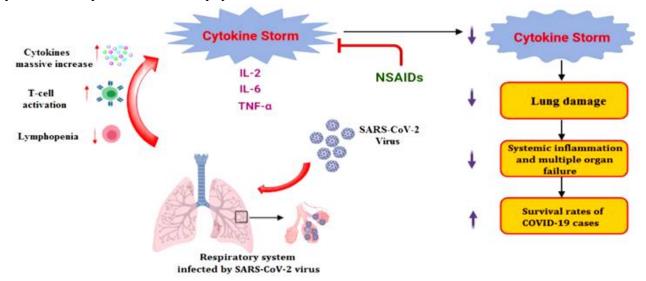


Figure 4: Molecules Computational Insights on the Potential of Some NSAIDs [5]

To prevent gastrointestinal ulcers in high-risk patients, PPIs such as pantoprazole are preferred to H2-blocker drugs such as ranitidine in patients receiving NSAIDs. Still. Direct hepatic complications are not common with NSAIDs. However, diclofenac and solindac are the most commonly associated among these drugs. Ibuprofen may be used with caution in patients with mild liver problems and no cirrhosis; In patients with cirrhosis, the use of NSAIDs is generally considered due to various underlying problems and increased risk of bleeding contraindicated and other drugs are preferred in these conditions. Some people may experience hypersensitivity reactions to NSAIDs, patients may report symptoms of shortness of breath. Patients with asthma, in the background, are at higher risk for hypersensitivity reactions to NSAIDs. People with a history of a severe hypersensitivity reaction to an NSAID are more likely to have a similar reaction when exposed to other drugs in this class. It is generally recommended to routinely use NSAIDs in patients with renal insufficiency and glomerular filtration rate (GFR) less than 30 ml/min or increase serum creatinine by more than 30% of baseline hyperkalemia (higher potassium). 5.5 mEq/mL or an increase in potassium above 5 mEq/mL during treatment, in patients with

hemodynamic conditions, patients unstable receiving antiplatelet or anticoagulants therapeutic doses, patients with a history of CABG, uncontrolled hypertension, and patients with heart failure as well as patients with a history of gastrointestinal ulcers should be avoided. It is recommended to avoid concomitant use of NSAIDs with each other, as there is no evidence or clinical experience that indicates an increase in efficacy, analgesic, and antiinflammatory action with this action. On the other hand, concomitant use of two or more NSAIDs may be associated with increased incidence of side effects of these drugs [16].

Antidepressants

Pain-reducing effects of antidepressants can be divided into two categories: direct analgesic effects. affecting neurotransmission descending pathways independent of the observed effects on mood, and indirect effects, possibly affecting the cerebral cortex and limbic. The direct analgesic effects of antidepressants have been shown to reduce pain by examining these effects in patients without neurological problems and reducing pain in depressed patients over 2 weeks. This indicates that the onset of analgesic effects of the drug occurs faster and at a lower dose than its antidepressant

effects. Drugs in this class are able to change the perception of pain sent from the spinal cord to the brain and reduce anxiety and sleep regulation, thus helping to control chronic pain. It has also been shown a significant correlation between different pain conditions. Chronic and psychiatric disorders such as depression, physical symptoms, and related disorders. Mood disorders can affect pain processing and act as an emotional and cognitive enhancer, leading to increased pain intensity or poor coping with stress. Low doses of antidepressants are often used to relieve chronic pain. Especially in patients with mood disorders, neuropathic pain due to diabetes, migraine and tension headaches. osteoarthritis, and fibromyalgia may be helpful. The most effective antidepressants in treating neuropathic pain appear to be TCAs, type III amines, such as amitriptyline, doxepin, imipramine, venlafaxine, bupropion, and duloxetine. These drugs have common side effects such as drowsiness or insomnia, dizziness, changes in blood pressure, blurred vision, and more critical side effects such as conduction disorders of the heart, headache, peripheral neuropathy, tremor, hallucinations, nausea, and vomiting. Stomach irritation, breast enlargement in men, sexual dysfunction, changes in blood sugar, changes in appetite and weight may also occur.

Anticonvulsant Drugs

Anticonvulsants such as gabapentin, pregabalin, carbamazepine, x-carbazepine, and phenytoin can also be used as analgesics and are used in cases such as pain caused by triple neuralgia or diabetic neuropathy. Anticonvulsant drugs may help manage pain through several mechanisms, but the exact mechanism of their analgesic effect is still unknown. These drugs are thought to work by stimulating sodium and calcium ion channels and stimulating receptors for glutamate and N-methyl D-aspartate and inhibiting GABA and glycine receptors.

Opioid Drugs

Opioid drugs can control all types of pain with any underlying cause such as somatic, visceral, or neuropathic pain. The variety of drug forms in this category is vast, and the appropriate drug delivery route may be selected according to the patient's condition. The maximum dose that can be used for this class of drugs is determined according to the patient's clinical condition and experience in receiving these drugs and the occurrence of side effects in each particular patient, and a fixed amount that applies to all patients cannot be determined in this regard. Opioid drugs stimulate various receptors, including mu, kappa, and delta receptors in the central nervous system and spinal cord, which stimulate mu receptors to produce an analgesic effect in the patient. Low-potency opioids, such as codeine, act on the upper centers of the brain and spinal cord, and by binding to opioid receptors, they alter pain perception and help control some types of chronic pain. When using oral narcotic analgesics, side effects such as respiratory weakness, nausea, vomiting, constipation, and changes in mental processes in the patient should be monitored and controlled if necessary. Following pain treatment, low-potency oral drugs such as methadone are substituted for lowpotency drugs if the response is not adequate. Morphine and morphine-like drugs such as oxycodone, fentanyl, and buprenorphine are high-potency sedatives.

Injectable Drugs

The use of injectable drugs is a relatively safe, effective, and efficient method and provides more prolonged therapeutic effects than oral medicine and is less invasive than various surgical techniques. This procedure may be used for various neuropathic or orthopedic pain. Injection of anesthetics for a nerve block is an example of this method used to manage chronic pain. Injections are given to cut off nerve signals before they reach the brain. This treatment is also to diagnose the source of pain ortreat pain caused by inflamed nerves. Injections of corticosteroids into the epidural space are also used to control pain in some types of chronic low back pain or inflammatory diseases of the joints and relieve pain and improve the inflammatory process in these patients. Pain and reactions at the injection site, including infection, are complications of this treatment technique.

Other drugs

Surgery in cases such as removing a tumor or disc herniation in the vicinity of the tissue by removing the leading cause of pain leads to its improvement. Topical pain relievers, such as the lidocaine skin patch, which is FDA-approved in doses of 1.8% or 5% for the treatment of neuralgia after herpes virus infection and is recommended for other types of peripheral neuropathies, such as capsaicin cream and lotion. Sprays or sprays used to relieve pain and inflammation in muscles and joints may help control localized pain; however, it should be noted that some people may experience hypersensitivity reactions to these drugs.

Corticosteroids may also be helpful in the management of some types of pain due to their

anti-inflammatory effects, dexamethasone due to its longer half-life and more minor mineralocorticoid side effects, and the availability of oral and injections are primarily used. Due to its relaxing effects on the muscle, diazepam may help reduce pain in some patients in the short term by reducing spasms and hypnotic effects and anxiety.

Other measures that may be considered to control persistent pain include neural network injection, neural block, neuraxial infusion techniques, and implanted nerve stimulation. Peripheral neuropathy, which results from damage to your peripheral nerves, often causes weakness, numbness, and pain, usually in the arms and legs. This damage can affect other parts of the body, as well (Figure 5).

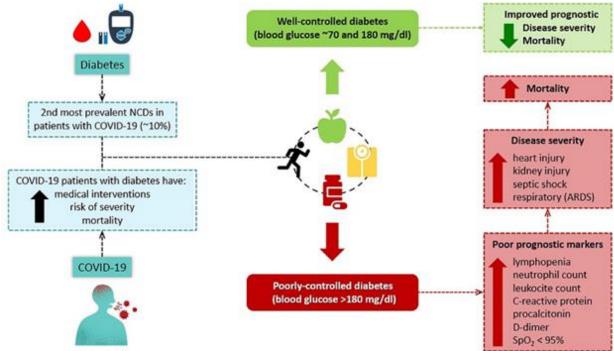


Figure 5: The Urgent Need for Recommending Physical Activity for the Management of Diabetes

Conclusions

The course of Covid disease is slower than the flu. The flu is an acute fever and respiratory illness that peaks within four to five days; however, in Covid we expect lung tissue involvement to begin on the sixth or seventh day, so the flu process is faster. But the difference between the flu and Covid is not discernible in the clinic. "It is difficult for the medical staff of a medical center to distinguish between these two respiratory diseases, so in cases where there are symptoms, they must include the flu test in the medical

centers from the second half of the year." The flu epidemic is not like Covid. The flu rate is lower, but it is a disease that consistently challenges the country's health system in the second half of the year. Therefore, as in previous years, people at high risk for the flu virus should be vaccinated. Including pregnant women, the elderly, people with defective immune systems and certain professionals. diseases, and health care Therefore, since all of these groups are high-risk individuals, as in the past, arrangements have been made to receive a new flu vaccine this year.

Research has shown that strength training can improve muscle function in average people with Peripheral Neuropathy (PN). Regular exercise can also help reduce the pain of neuropathy and control blood sugar. Diabetics should closely monitor their blood sugar during exercise to prevent significant fluctuations. This may include educating the patient and monitoring their blood ideally through a multidisciplinary approach to rehabilitation. Specific exercise programs should include flexibility. Pain can be a problem for some people with peripheral neuropathy and is challenging to treat. Several medications may help you. These include medications commonly used to treat epilepsy (anticonvulsants) such as pregabalin, gabapentin, and carbamazepine. A group of antidepressants called tricyclic antidepressants may also be helpful. Amitriptyline is commonly used. In addition to having antidepressant effects, these drugs are also helpful in controlling pain. Treating the symptoms of autonomic nerve problems may be more difficult. Sometimes stockings or elastic stockings, or a drug called flavodocortisone (or other similar medications) may be helpful if you have low blood pressure. If you have problems with various medications, it may help with digestion. Eating small, frequent meals, sleeping on your bed, or other activities may help.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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