

TO THE ISSUE OF MEDICATION THERAPY OF CHRONIC PAIN SYNDROME IN PATIENTS WITH TERMINAL RENAL INSUFFICIENCY RECEIVING THERAPY FOR CHRONIC HAEMODIALYSIS

Javokhir Khalmukhamedov, Botir Daminov, Yorqin Rasulev
e-mail: abzalova71@mail.ru
Tashkent Pediatric Medical Institute, Republic of Uzbekistan

Abstract : *A growing number of publications in the literature show that chronic pain is also characteristic of patients with terminal renal failure (TRF). The disease tends to be moderate or severe and affects virtually all aspects of health and quality of life. Unfortunately, there is a lack of clinical and research focus in nephrology, and TAPN pain is poorly understood. The article reflects the main aspects of the problem of pain medication therapy for patients with terminal renal insufficiency receiving chronic hemodialysis. The main pathophysiological mechanisms of medication influence on kidney structures are described.*

Keywords: *renal insufficiency, pain, hemodialysis, non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants in pain treatment.*

Dialysis is a successful life-supporting therapy for patients with end-stage renal failure (ESRF), its effectiveness is largely judged by the survival of patients. However, the dialysis patient population is aging and suffering from various concomitant diseases, and in the future it will become increasingly difficult to maintain a reasonable level of health-related quality of life (HRQL) for these patients. A growing body of literature has shown that pain is the most common symptom for patients with ESRF, affecting almost every aspect of HRQL, and is also the first symptom of greatest anxiety towards the end of patients' lives. The range of chronic pain varies from moderate to severe, as well as insufficiently stopped. For these reasons, it is very important for nephrologists and family doctors to master the principles of pain assessment and management. Despite this, clinical and research directions in this area are absent or insufficiently studied. This article will examine the epidemiology of chronic pain in ESRF, as well as discuss the basic principles for assessing and treating pain, and highlight some problems in the treatment of pain in ESRF, with the hope of further recommendations by medical professionals in the effective management of pain in patients with ESRF.

Pain of various localization and intensity is one of the main complaints of patients with end-stage renal failure in conditions of dialysis centers. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." [1] The epidemiological evidence of pain in ESRF is extremely limited, but nevertheless, recent

studies have shown that moderate to severe chronic pain is often found in ESRF. The literature suggests that between 37% and 50% of hemodialysis patients experience chronic pain and that for 82% of these patients, pain in intensity is moderate to severe. [2-4] Even in the last days of life, pain is present in 42% of patients leaving dialysis. It is unambiguous that it represents an important sensation that allows one to appropriately perceive the damaging effects and avoid factors causing danger to the body as a whole, but very often in this category of patients the pain syndrome is chronic and becomes an independent disease, reducing not only the quality of life of patients, but and worsens their condition for the next dialysis sessions. In addition, any pain always has an emotional aspect, which leaves its mark on the affective status of the patient and on his attitude not only to the disease, but also to the treatment as a whole. Adequate analgesic therapy is one of the most important tasks of everyday clinical practice, as it is important from an ethical and economic point of view and is an indispensable component of successful treatment and rehabilitation of such patients. Currently, for the choice of methods of drug therapy for pain, the most important is the understanding of the pathogenetic mechanisms underlying it, the so-called mechanism-based therapy. Allocate acute and chronic pain. It must be remembered that pain can be nociceptive, neuropathic, dysfunctional and mixed, therefore, approaches to drug therapy will differ. With nociceptive pain, the use of non-steroidal anti-inflammatory drugs (NSAID), analgesics is indicated, in some cases with severe nociceptive pain and opioid analgesics. With neuropathic pain, antidepressants, anticonvulsants, opioids, local anesthetics, or a combination of the listed groups of drugs are indicated [1]. Patients with end-stage renal failure receiving therapy with programmed hemodialysis are a special cohort of patients whose approaches to the treatment of pain should also be special. In this article, we consider the characteristics of each group of drugs used for analgesic therapy in patients with the studied pathology. In 1986, WHO recommended a research-based three-step approach to pain pharmacotherapy (Fig. 1).

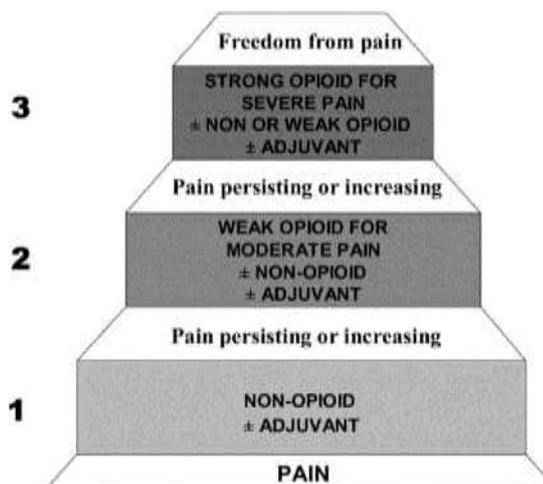


Figure 1. World Health Organization staircase.

However, this concept is not always applicable in dialysis patients. Let us dwell on some important points. The functional unit of the kidney is nephron. In its structure there is not a single component in which there would be no cyclooxygenase receptors (COX) -1 or COX-2. COX-1 receptors are responsible for controlling intrarenal hemodynamics and glomerular filtration rate, COX-2 receptors for salt and water excretion. It is COX-2 that is a protector from renoprivalent arterial hypertension [11]. The negative effect of NSAID on the kidneys is manifested by damage to interstitium, decreased glomerular filtration, increased blood pressure (BP) and decreased effectiveness of most antihypertensive drugs (beta-blockers, diuretics, angiotensin converting enzyme antagonists).

The etiology of pain can be caused by numerous causes. Pain can be caused by comorbidity despite the fact that dialysis supports life, systemic diseases and pain syndromes, such as limb ischemia and various neuropathies persist. Given the physiological aging of dialysis patients and the increasing prevalence of comorbidity, including diabetes and hypertension, it is not surprising that chronic pain is a particular problem for patients with ESRF. However, pain can also be caused by ESRF itself. There are numerous pain syndromes unique to ESRF, such as calciphylaxis and renal osteodystrophy, which can develop during dialysis. Pain may be the result of a primary kidney disease (for example, polycystic kidney disease) or the result of treatment with ESRF. Painful chronic infections such as osteomyelitis and discitis are complications from central catheters, and arteriovenous fistulas can lead to painful ischemic neuropathies. Periodic pain caused by the introduction of a needle, muscle cramps and headaches during dialysis is perceived by some patients as chronic pain. [2]

Despite limited data, it seems that pain in the musculoskeletal system is the most common of chronic pain syndromes in both ESRF and the general population. [2] However, unlike the general population, musculoskeletal pain in ESRF is on average in severity equal to neuropathic and ischemic pain. The synergistic effect of hyperparathyroidism and osteoarthritis in the development of bone pain can contribute to the high prevalence and severity of musculoskeletal pain in this population.

However, the relative roles of osteoarthritis and renal osteodystrophy in these chronic pains in patients with ESRF are unclear. Given the various causes of pain in this population, it is not surprising that pain during dialysis in patients is often multifactorial. The ability to distinguish between potential causes of pain is necessary in determining the optimal pain management strategy. For example, neuropathic pain is often difficult to control because it is less sensitive to strong opioids and usually requires adjuvants such as antidepressants and anticonvulsants. The synergistic interaction of these drugs with opioids is usually required for adequate pain control. Chronic pain is associated with a psychological disorder; as well as the problem of interpersonal relationships; excessive use of medical care; a significant limitation of activity at work, in the family and social life; and most importantly, the adoption of the role of the chronic patient. [6,7] Recent studies in the field of ESRF suggest that the patient's perception of physical symptoms, especially pain associated with depression and insomnia, may be more important than objective assessments in the determination of HRQL of patients with ESRF. [2,8,9] The term "total" pain [10] refers to any unmet needs of the patient that can aggravate the pain and capture the importance of all of the following interactions: physical, emotional (anxiety and depression), social (isolation and abandonment), spiritual (search for meaning and purpose), and financial (fear of burdening the family). [11] The pain threshold and response to pain therapy is largely dependent on these patient-related factors, rather than the effectiveness of the analgesics. These psychosocial and spiritual problems enter into a vicious circle of interaction and prolong the manifestation of the patient's physical symptoms and suffering. This emphasizes the need to solve psychosocial and spiritual problems, as well as the physical management of pain.

Pain in ESRF is not amenable to adequate treatment, and despite the fact that there is an increasing prevalence of chronic pain, the use of analgesics has decreased over the past few years.

A comparative study of dialysis results and practical models of the use of analgesics from 1997 to 2000 was conducted for 3749 patients in 142 US institutions. The percentage of patients using any kind of analgesics decreased from 30% to 24%. Drug use decreased from 18% to less than 15% and acetaminophen use decreased from 11% to 6%. In this study, 74% of patients with pain that interfered with their work did not have an analgesic prescription. These data are consistent with other sources in which 35% of hemodialysis patients with

chronic pain did not receive analgesics, despite the vast majority experiencing moderate or severe pain and only less than 10% were prescribed strong opioids.

Inadequate pain management is not a unique condition for nephrology. Despite the existence of effective interventions for pain management [13] and published clinical guidelines [14] for the management of malignant and non-malignant pain, many patients continue to be in a state of inadequate analgesia. [15] Factors associated with patients are a serious problem. Patients do not seek medical attention until the pain becomes unbearable. They think they need analgesics, especially the powerful opioids "When It Is Absolutely Necessary." Fear of developing addiction is also popular. Some patients stop taking opioids because side effects such as nausea and vomiting are mistaken for an allergic reaction. Inadequate pain assessment and lack of time and staff training on the basic principles of pain management were also identified as barriers to adequate pain management in cancer patients. [16] These barriers are also applicable to patients with ESRF. The lack of recognition by the community of nephrologists of the relative severity of the problem, and hence the lack of clinical and research focus in this area. This led to the lack of discrete medical literature that synthesizes pain management and nephrology. Probably one of the biggest obstacles is the damaging pharmacokinetics and pharmacodynamics of analgesics in ESR. The high level of comorbidity, polypharmacy, as well as the elderly patients complicate the management of pain due to the increased risk of toxicity and adverse effects of analgesics. In addition, the adverse effects of analgesics can be mimicked by uremic symptoms, which leads to the removal of analgesia. Finally, there is a clear lack of training programs in nephrology for assessing and managing pain. [12]

The effect of NSAIDs on the kidneys of healthy people is negligible. So, the risk of developing NSAID-associated complications such as increased blood pressure, hyperkalemia, fluid retention and heart failure is small and is 3%. The risk of increasing creatinine levels to 1.3 from the norm is 1%. Long-term (more than a year) and short-term (up to 15 days) administration of any NSAIDs in therapeutic doses from a nephrological point of view is relatively safe. COX-2 - selective NSAIDs do not have advantages over non-selective ones in relation to the development of renal complications. However, it should be noted that drugs that primarily affect COX-2 have a greater potential for fluid, sodium and potassium retention than non-selective ones [2]. The recommendations of national nephrology communities (Europe, USA) state that in patients with stage III chronic kidney disease (CKD) (glomerular filtration rate [GFR] = 30–59 ml per minute), NSAIDs should be avoided at doses higher than recommended, especially coxibs, in patients with CKD IV (GFR = 15–29 ml per minute) and V (less than 15 ml per minute or dialysis) stages, the use of any NSAIDs is contraindicated [2]. However, in real clinical practice the situation is different, CKD of various stages is relatively high in patients, while the frequency of prescribing NSAIDs to such patients corresponds to the same frequency of prescribing these drugs in people without CKD. This is due to objective reasons (relief of postoperative pain, limited use of opioid analgesics, lack of knowledge of the medical staff of the departments of nephrology and dialysis, the requirement for the correction of concomitant diseases) and subjective factors (self-administration of anti-inflammatory drugs, incorrect doses or joint use of several NSAIDs, failure to comply with recommendations doctor). According to the recommendations of the International Association of Nephrologists (NKF, 2011), the path to minimizing possible adverse renal reactions lies through the selection of a safe drug. Based on this, we can distinguish the features of the drug, which can be considered safe, for patients with impaired renal function:

1. the drug should inhibit COX-1 and COX-2 (but mainly COX-2), approaching selective NSAIDs;
2. it should have a short half-life;

3. the preparation should not be cumulated after repeated administration;
4. Preferably, there should be no need for dose correction in elderly patients;
5. in combination with diuretics the drug should not cause changes in BP and osmolality of urine / sodium excretion;
6. there should be no need for dose adjustment in patients with mild forms of renal failure;
7. the drug must meet the requirements of general safety, including the safety of damage to the gastrointestinal tract.

Basics of pain management:

1. The assessment of pain and its response to treatment should be recorded daily until the pain has stabilized. Basics of pain assessment:
 - a. Believe the words of the patient complaining of pain.
 - b. Assess the localization, nature, intensity, degree of pain, as well as facilitating and aggravating factors.
 - c. Use a simple rating tool such as a numerical scale of 0-10
 - e. Teach patients or their relatives at home pain assessment and mapping.
2. Patients may experience more than one type of pain; each pain syndrome should be independently diagnosed and stopped.
3. Strive to achieve control at a level acceptable to the patient. Sometimes it may not be necessary or possible to make the patient completely anesthetized.
4. Pain can be related and aggravated by other symptoms, including psychological symptoms. The psychological state of the patient should be evaluated and treated accordingly with equal attention.
5. Use an interdisciplinary team to manage "total pain". This may require consultation with a palliative care team or a chronic pain clinic.
6. Know the opioids and adjuvants for opioids.
7. Recognize that misconceptions about pain and opioid therapy are still a stumbling block in adequate pain control.
8. If necessary, seek non-medication interventions such as physiotherapy (eg, percutaneous nerve stimulation, hot and cold therapy, exercise, and neuromuscular massage).
9. Educate patients and caregivers on the goals of therapy, management plan, and potential complications. This will help minimize the consequences.

Rules to be followed when using opioids

1. Use a specific opioid for a specific type of pain.
2. Use adjuvants wisely to provide additive analgesia and minimize side effects.
3. Five main opioid (analgesic) dosages
 - a. "By mouth": whenever possible, medications should be administered orally.
 - b. Hourly: Dose more than 24 hours on a regular basis. Additional breakthrough drugs should be available as needed (PRN).
 - w. "On the stairs": take painkillers "step by step" according to the WHO analgesic stairs
 - e. "For humans": no standard dose of strong opioids. A "right" dose is a dose that relieves pain without causing unacceptable side effects.
 - e. Attention to detail: pain changes over time, so there is a need for ongoing evaluation and reassessment.
4. Know how to prevent and manage the side effects of opioids: nausea, sedation, constipation, cognitive impairment.

Opioid dependence facts

1. The frequency of addiction in patients receiving opioid therapy for pain relief does not differ from the general population with less than 1%. [10]
2. Patients will become physically dependent if they take opioids for a while, and therefore will have a withdrawal effect if the opioid suddenly stops.
3. Physical dependence is easily controlled by the slow reduction of the opioid when the pain has subsided.
4. Physical dependence is not synonymous with dependence.
5. Dependence is a psychological problem, not a physical one, and is characterized by the fact that patients engage in manipulative behavior to get a drug.
6. People with addiction use opioids for reasons other than pain. Taking drugs to relieve pain is not taking them for pleasure.

The choice of anti-inflammatory agent in assessing renal risks should be based on these safety requirements for NSAIDs [3]. If it is necessary to use drugs from this group, it is possible to prescribe acetylsalicylic acid or aceclofenac, which have the least pronounced side effect on glomerular filtration. It is recommended to increase the interval between doses to six hours, to avoid the use of long-acting drugs with a half-life of more than 12 hours, in order to prevent a persistent and clinically significant decrease in ESRF associated with the inhibition of vasodilator renal prostaglandins. Avoid the joint use of x-ray contrast drugs, agents that can have a nephrotoxic effect or worsen renal hemodynamics [4]. Also, for the period of taking NSAIDs in dialysis patients, it is necessary to exclude the appointment of inhibitors of the renin-angiotensin-aldosterone system and diuretics, as well as to conduct careful, if necessary daily, monitoring of the patient's condition for the timely detection of volume overload [5, 8]. Acetaminophen, as a monotherapy or in combination with weak opiates, is considered one of the safest non-narcotic analgesics for patients with terminal renal failure (ESRF) who are receiving chronic hemodialysis therapy, but it may have nephrotoxic effects with prolonged use at high doses.

Tramadol as a representative of weak opioids is usually used for moderate pain in patients with chronic kidney disease, since it does not have a direct nephrotoxic effect. However, with ESRF, drug excretion is reduced. The half-life of tramadol metabolites is five hours, and it can double in patients with nephrological pathology. With the accumulation of these metabolites in the blood, patients may develop respiratory depression and lower the seizure threshold. In addition, the drug can provoke the development of malignant serotonin syndrome in patients receiving therapy with selective serotonin reuptake inhibitors (SSRIs). The maximum dose of tramadol in patients with ESRF should not exceed 50 mg twice a day in tablet form. Such a dose does not require its correction after hemodialysis sessions, since tramadol is not excreted by dialysis and hemofiltration. The prescription of other opioid analgesics in the preparation of chrono-hemodialysis is limited by their pharmacodynamic characteristics. The accumulation of active and toxic metabolites of drugs from this group can lead to severe inhibition of brain activity and respiratory depression, which is extremely characteristic of morphine, oxycodone, propoxyphene. However, the use of methadone and fentanyl is allowed due to the fact that the main metabolite of methadone is excreted through the gastrointestinal tract, and in ESRF with feces (compensatory excretion route) it does not accumulate significantly in the body of patients with renal failure. Fentanyl metabolites are pharmacologically inactive and have no toxic effect. The use of fentanyl transdermal system is a backup method for patients with good tolerance of opiates, if other methods have been ineffective.

The treatment of ESRF patients receiving hemodialysis program therapy, suffering from neuropathic pain, is a much more difficult task than the treatment of patients with other variants of the pain syndrome. The main method of dealing with neuropathic pain is

pharmacotherapy. Recent EFNS recommendations confirm the high efficacy of tricyclic antidepressants (TCAs) in a daily dose of 25–150 mg, in addition, the importance of anticonvulsants, gabapentin (1,200–3,600 mg per day) and pregabalin in (150–600 mg per day) are emphasized. first-line drugs (level of evidence A) in the treatment of various types of pain associated with damage to the nervous system. The therapeutic choice in favor of a class of drugs from those recommended as the first line should be based on an assessment of the ratio of efficacy and safety and the clinical condition of the patient (comorbid conditions, contraindications, concomitant therapy).

A cross-sectional clinical trial conducted in Turkey compared the efficacy of gabapentin and pregabalin in the treatment of patients with neuropathic pain undergoing hemodialysis, as well as the effects of these drugs on the quality of life associated with health. Despite the high prevalence of neuropathic pain in dialysis patients, studies to evaluate the effectiveness of modern anticonvulsants in this cohort of patients have not been previously conducted. Single publications reflect studies of the use of gabapentin and pregabalin, which patients received after each hemodialysis session at a dose of 300 and 75 mg, respectively, for six weeks, followed by a two-week washout period. All studies demonstrated the high effectiveness of the above anticonvulsants in the treatment of neuropathic pain syndrome in dialysis patients, as well as a significant improvement in the quality of life of patients with both drugs (Atalay H. et al., 2013).

A review of studies of different levels on the effectiveness and safety of antidepressant drugs in patients with ESRF undergoing hemodialysis, including the Cochrane review, also showed a lack of knowledge of this issue. Almost all publications talk about the benefits of using antidepressants in chronic pain, however, many patients with ESRF had side effects of their use, although they were rated as mild and did not require discontinuation of therapy [6, 7, 10]. Due to the high connection with tissue and plasma proteins and the large volume of distribution, antidepressants are poorly dialysis, therefore hemodialysis is excluded as a treatment for overdose. This is an important condition for the use of this group of medicines in patients with severe renal pathology who are on programmed hemodialysis. It is recommended to use antidepressants with a mild psychostimulating effect, reduced doses of amitriptyline, venlafaxine, duloxetine, reboxetine. As first-line drugs, drugs from the SSRI group are recommended [6, 9]. The only exception is fluoxetine, since with severe renal impairment, the excretion of the drug slows down, and hemodialysis does not completely excrete its metabolites due to the high degree of binding to plasma proteins and a large volume of distribution, which is fraught with overdose even when using low doses. A very important part of working with patients with dialysis centers suffering from pain is the explanation of the meaning, principles and rules of therapy, which allows achieving optimal compliance and trust for the patient and doctor in solving the problem of combating pain. The patient must understand why he was prescribed certain drugs, be informed about their features and the effect on kidney function, be able to ask questions of interest and discuss to express their doubts [1].

Thus, despite significant limitations in the use of drugs for the treatment of pain in patients with ESRF receiving hemodialysis, a practitioner who knows the features of the use of a particular group of medicines can draw up an adequate and effective program for combating pain. This will improve the quality of life of this category of patients, achieve a high degree of trust in the doctor during dialysis sessions and, thereby, increase the effectiveness of complex therapy, as well as reduce the number of refusals to continue dialysis therapy.

References

- [1] Prilepskaya OA, Durova MV, Lebedev I.A. Features of drug therapy for pain in patients with end-stage renal failure receiving chrono-hemodialysis therapy. *Medical alphabet*. 2017; 1 (2): 9-12.
- [2] Danilov An.B., Danilov A.B. Management of pain: a biosocial approach. AMM Press. - Moscow, 2014, 592 p.
- [3] Gordeev A. Century. Nonsteroidal anti-inflammatory drugs and kidneys. // *Consilium medicum*. Extra issue. Materials of the II Eurasian Congress of Rheumatologists, scientific symposium "Pain in patients with rheumatic diseases: from the beginning of development to treatment", p. 11-15.
- [4] Karateev A.E., Nasonov E.L., Yakhno N.N. et al. Clinical recommendations "Rational use of non-steroidal anti-inflammatory drugs (NSAIDs) in clinical practice." *Modern rheumatology*. 2015; 1: 4–24.
- [5] Griffin M. R., Yared A., Ray W. A. Nonsteroidal anti-inflammatory drugs and acute failure in elderly persons // *Am. J. Epidemiol.*, 2000, Vol. 151, P. 488–496.
- [6] Lafrance J. P. et al. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. // *Pharmacoepidemiol. Drugs Saf.*, 2009, Vol. 18, P. 923–931.
- [7] Mor M., Sevick M. A., Shields A. M. et al. Associations of depressive symptoms and pain with Dialysis Adherence, Health resource utilization and mortality in patients receiving chronic hemodialysis. // *Clinical Journal of the American Society of Nephrology* — 2014.
- [8] Phuong-Chi T. Pharm, Edgar Toscano, Phuong-Mai T. Pharm et al. Pain management in patients with chronic kidney disease // *NDT Plus*. Volume 2, N 2, 2009.
- [9] Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American College of Rheumatology white paper/ // *Arthritis Rheum.*, 2008, Vol. 59, P. 1058–1073.
- [10] Rossat J. et al. Renal effects of selective cyclooxygenase- 2 inhibition in normotensive salt-depleted subjects.
- [11] Saarto T., Wiffen P. Antidepressants for neuropathic pain. *Cochrane Database of Systemic Reviews* 2005; 20: CD 005454.
- [12] Swan S. K. et al. Effect of cyclooxygenase- 2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. // *Ann. Intern. Med.*, 2000, Vol. 133, P. 1–9.
- [13] Halmukhamedov Zh. A., Sharipov A. M., Shukurov B. I., To The Question Of Objective Assessment Of Acute Pain // *Bulletin of emergency medicine*. - 2019.- T. 12. - No. 2.
- [14] McQuay H, Moore A: An Evidence Based Resource for Pain Relief. Oxford, Oxford University Press, 1988
- [15] Zech DFJ, Ground S, Lynch J, et al: Validation for World Health Organization Guidelines for cancer pain relief: A 10-year prospective study. *Pain* 63:65-76, 1995
- [16] Cleeland C, Gonin R, Hatfield AK, et al: Pain and its treatment in outpatients with metastatic cancer. *New Eng J Med* 330:592-596, 1994
- [17] Anderson KO, Mendoza TR, Valero V, et al: Minority cancer patients and their providers: Pain management attitudes and practice. *Cancer* 88:1929-1938, 2000
- [18] Nematilla Aralov, Dildora Nosirova, & Feruz Akhmedov Efficiency Of Inclusion Immunomodulating Drugs In Complex Therapy Of Community-Acquired Pneumonia *Journal Of Biomedicine And Practice* 2018-1 9-12 <http://dx.doi.org/10.26739/2181-9300-2018-1-2>

- [19] Fayziyev Shokhrud Farmonovich Medical law and features of legal relations arising in the provision of medical services. International journal of pharmaceutical research Volume 11, Issue 3, July - Sept, 2019 P. 1197-1200 doi:10.31838/ijpr/2019.11.03.088
- [20] Bryanskaya Elena, Fayziev Shokhrud, Altunina Anna, Matiukha Alena Topical Issues of an Expert Report in the Process of Proving in a Criminal Examination. International Journal of Engineering and Advanced Technology (IJEAT) ISSN: 2249 – 8958, Volume-9 Issue-1, October 2019 5345-5349 DOI: 10.35940/ijeat.A2946.109119
- [21] Fayziev Shokhrud (2019) Legal Aspects of Transplantology in the Republic of Uzbekistan. Systematic Reviews in Pharmacy, ISSN: 0976-2779, Vol: 10, Issue: 2, Page: 44-47 doi:10.5530/srp.2019.2.08
- [22] Shokhrud F. Fayziev The problem of social stigma during a pandemic caused by COVID-19 International Journal of Advanced Science and Technology Vol. 29, No. 7, (2020), pp. 660-664