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## THE MANIFESTATION OF FEATURES OF OPIOIDS AND NARCOTICS USING BY DRUG ADDICTED PEOPLE AND THE ROLE OF REPLACEMENT PHARMACOTHERAPY IN TREATMENT AND RECOVERY OF THE PATIENT

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*Aim of the research* was to study and analyze the features of opioids and narcotics using by drug addicted people and the role of replacement drugs in treatment and recovery of the patient.

*Materials and methods:* We conducted a systematic review and meta-analysis of studies. Were used Systematic literature reviews and meta-analyses. The material of the article was data from the scientific literature, processed and analyzed by generalization and systematization. The scientific research ensues the fundamentals of assessment development of significant reviews. The ensuing databases were used: (for searching considerable literature to study and analyze the features of opioids and narcotics using by drug addiction people and the role of replacement drugs in treatment and recovery of the patient) Pub Med, Web of Science, Clinical key, Tomson Routers, Google Scholar, Cochrane Library, and Elsevier bases. Additionally studied national and international policy and guidelines and also grey literature.

*Results:* Addiction is well known to be associated with its high level of physical and mental disorders. Most chronic chemical dependencies of drug addiction are also associated with its very high mortality rates, estimated to be several times those of the non-clinical population. Since addictive substances are known to disrupt cell growth and cell division, it can be assumed, that they particularly affect dividing cells, such as stem cell pools and progenitor cells. It is also known, that they either individually or in combination potentiate apoptosis, i.e., contribute to this effect. The medicine of aging in recent times has become an independent scientific discipline. The cellular aging hypothesis suggests the aging phenotype. The organism is associated with cellular correlates of age associated changes including cell loss, reduced cell velocity, renewal and more aging, negligible functional and non-replicating cells in tissues. So, the anti-growth effects of drug addiction can reasonably occur throughout the body. Expect signs of accelerated aging to be evident. One would expect such a putative progeroid effect to occur subject to increased morbidity and mortality rates, clinically observed almost identically in drug addicts as is the case in the geriatric population. In this connection there are various changes, consideration of all clinical aspects' expression of this general toxicology hypothesis of opioids is needed.

*Conclusion:* Pharmacological management of drug use should be only one component of treatment for drug needs, tailored to a comprehensive needs assessment of the child or young person, carried out in conjunction with appropriate psychological therapy and mental health interventions, and in the context of a clear and applied approach to the clinical management system. Caution is required when leaving these establishments due to the risk of overdose and in the transition to adult services. Physicians should carefully consider the degree of dependence on any substance, especially when alcohol and other substances, such as opiates, are used together. The full implementation of treatment, rehabilitation and harm reduction services will reduce the negative health, social and economic consequences of drug use for individuals, communities and society as a whole. The number of drug users will increase, those involved in counseling, treatment, rehabilitation and harm reduction programs

*Keywords:* Opioid, dependent, drug, addiction, patients, methadone, replacement therapy

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### 1. Introduction

In modern medicine, opioid dependence or opioid addiction is regarded as a chronic disease that goes through cycles of remission (temporary diminution) and relapse (acute exacerbation). There are different treatment approaches for this disease that fall into two major groups: drug-free lifestyle-oriented therapy and agonist maintenance therapy, i.e., substitution therapy. For the society, especially for the family members and next of kin of drug-

dependent individuals the most desirable treatment method is the one that is oriented on cessation of drug use from the very outset. However, the years-long international experience shows that it hasn't been proved to be a highly effective treatment.

The situation clearly proves the need for the development of institutional mechanisms for universal, selective and targeted prevention of psychoactive drugs in Georgia. Currently, prevention activities are not based on evidence

and relevant international standards, and are mostly limited to fragmented campaigns and public lectures. In Georgia, drug addiction is treated in private and state institutions, as well as by the non-governmental sector. Types of treatment are: Abstinence-oriented outpatient and inpatient treatment (detoxification), combined with short-term, primary rehabilitation and short-term, psychosocial rehabilitation, and substitution therapy [1, 2].

Clinical guidelines address psychosocial and pharmacological approaches, as well as the social context, in which people cope with their problems and receive help in treatment and recovery. Pharmacological approaches remain extremely important and have clearly proven effective and efficient for those who have problems with the use of heroin or other opiates. However, this approach is of limited use in treating people with problems, associated with the use of other types of drugs. It is also important, that many of those who come into contact with care services seek ways to cope with their mental health problems and the effects of past trauma, as well as support to find decent work, stable housing, as well as family and other social support. There have been positive developments in increasing the availability of community-based psychosocial interventions, as well as peer support and mutual assistance for people in treatment for drug addiction. However, there are also areas with obvious shortcomings, including the lack of effective support for social inclusion, including employment and housing, which remain underprovided for this group. Significant progress has been made, including on some associated health complications, such as significant improvement in the treatment of chronic hepatitis C infection. We are honored to provide updated guidance on these new treatments, and it is our shared responsibility to do so to ensure new treatments that are used to achieve health benefits. The systems and services to meet these needs can vary widely. Previous versions of the manual were written when the system was largely split between prescribing secondary health care and providing advice and support to the voluntary sector. Today the situation is quite different, as the number of specialized health workers has been drastically reduced and large independent or third sector organizations are the main providers of health care under various cooperation arrangements. Regardless of the composition of the launch and implementation, the principles underlying the clinical guidelines remain fundamental and must be carefully considered to ensure better coverage, better quality and adequate monitoring of the benefits of various treatment-based therapies, as the evidence is that they should be put into service in order to meet the clinical needs of the population with health problems. Despite advances in reducing the number of young people currently developing heroin addiction, the morbidity, mortality and long-term needs of a cohort of elderly patients with long-term heroin addiction problems mean that treatment is becoming increasingly complex, and coordination between services is essential. This includes greater integration into general, physical and mental health care. Furthermore, a large number of new psychoactive substances with little-known long-term effects pose new challenges for doctors [3, 4].

A good therapeutic alliance is essential to any therapeutic intervention, whether medical or psychosocial. As stronger supportive relationships are formed, service users

are more likely to complete treatment, actively investigate problems, experience less stress and feel more comfortable, abstain from alcohol and drugs during treatment, and have better outcomes with long-term drug use. Key competencies of clinicians or practitioners in building the therapeutic alliance that underpins the effective delivery of any psychosocial intervention include: the ability to appropriately involve the patient with a satisfactory level of kindness and attention; the ability to inspire trust and to do so, namely, adopting a personal style that matches the patient's style; the ability to adjust the type and intensity of intervention to the patient's abilities; the ability to understand and work with the patient's emotional context, including the patient's motivation. Studies of general attitudes or beliefs among therapists show that more flexible orientations and the ability to use different approaches lead to better outcomes. The most effective way for services to ensure such a positive therapeutic relationship is established through regular clinical monitoring by appropriately qualified professionals [5, 6].

**Aim of the research** was to study and analyze the features of opioids and narcotics using by drug addiction people and the role of replacement drugs in treatment and recovery of the patient.

## 2. Materials and methods

We conducted a systematic review and meta-analysis of studies. Systematic literature reviews and meta-analyses were used. The material of the article was data from the scientific literature, processed and analyzed by generalization and systematization. The scientific research ensures the fundamentals of assessment development of significant reviews. Were used the ensuing databases: (for searching considerable literature to study and analyze the features of opioids and narcotics using by drug addiction people and the role of replacement drugs in treatment and recovery of the patient) Pub Med, Web of Science, Clinical key, Tomson Reuters, Google Scholar, Cochrane Library, and Elsevier bases. Additionally studied national and international policy and guidelines and also grey literature.

## 3. Results and discussion

The role of drugs in treatment and recovery depends on the type of substance and the individual needs of the patient. There are no medications, recommended to treat stimulant or cannabis addiction, and not all opiate addicts need opiate replacement therapy. Thus, psychosocial interventions will be the basis of treatment for these problems. Substitution medications, administered to opioid users, can be effective in supporting treatment participation, thus providing a platform for psychosocial interventions to drive change. However, access to medication should not depend on participation in a mental health program. Rather the services must provide a program, in which users of the services are willing to voluntarily participate. An integrated approach using psychosocial skills and interventions, as well as prescriptions, helps plan care to stimulate recovery, motivate and support harm reduction and relapse prevention.

Alcohol and other drugs have long been used for recreational purposes. The so-called illegal drugs are substances whose non-medical use is prohibited by international control systems. Illicit drugs include, but are not limited to,

opioids such as heroin, morphine, opium and other pharmaceutical opioids: cannabis, amphetamines and cocaine. Addiction to illicit and prescription drugs can develop in people who take them regularly over a long period of time and is characterized by loss of control over and overuse and increased awareness of substances use in human life.

The importance of preventing and treating drug use problems in the elderly is becoming increasingly important as the Georgian population grows and ages. Two separated but sometimes overlapping groups of older people with problem of drug use have been described and may be useful in clinical practice to meet a range of needs. Older adults with a long history of substance use that continues into adulthood, including long-term users of heroin, crack, tobacco or alcohol, may be called "early adopters" to distinguish them from the sometimes quite diverse group of older adults. "Late adherents". Early users may already have experienced significant drug or alcohol-related complications that may affect their life expectancy and need for treatment (eg, need for treatment for hepatitis C). Many older drug users, especially heroin drug users, may have a long history, including negative experiences with services, such as day care, the criminal justice system, and health care, that have shaken their faith in the services as a result of stressful life events or lifestyle changes that typically occur later in life (for example, the latter group tends to be a larger but less visible population of drug addicts' older people) who typically use prescription or over-the-counter medications (such as benzodiazepines and opioid pain relievers) or consume problematic amounts of alcohol, users undergoing treatment for physical or mental health problems, with suspicions or attitudes of simply having a self-inflicted disorder, attitudes that may conflict with expectations or affect the confidence of older dependents. Even within specialist drug treatment services, some drug users may receive suboptimal care or be excluded from services for inconclusive reasons, due to changes in the professional approach over time, or simply due to changes in medical staff. Tobacco and alcohol use is more harmful at the population level in the older age group, and these issues need to be addressed in those undergoing treatment for other addictions. Currently, there are an increasing number of users of addiction treatment services who continue to receive opioid substitution therapy aged 50 and over. Nearly half of people who seek addiction treatment services for opiate-related problems are now 40 years of age or older. The number of people seeking treatment in this age group has increased in recent years, although the total number of people seeking treatment has declined significantly. This reflects a declining trend in the incidence of heroin addiction, along with an aging cohort of lifelong addicts. In recent years, there has also been an increase in the number of people over the age of 40 seeking treatment for alcohol dependence. The median age of drug-related deaths (primarily opioid-related) has also increased over the past decade. Continued injection drug use remains a key factor in overdose mortality [7, 8].

Prescriptions for people over 65 often include multiple drugs with high potential for interactions and side effects. People over 65 are particularly vulnerable to the effects of drugs and alcohol due to the reduced body fat-to-water ratio, decreased ability to metabolize drugs, potential for comorbidities, and likelihood of increased drug interactions. Comorbidity may be a key factor, as age in-

creases risk of chronic pain, insomnia, grief, loneliness, and mood disorders. In addition, memory disorders, immobility, urinary incontinence, sensory disturbances and iatrogenic problems can develop. These physiological and medical changes mean that older people, particularly those over the age of 65, may be at greater risk of consuming even small amounts of alcohol, drugs or other substances. Falls in particular can have serious consequences in adulthood. When prescribing psychiatric drugs for this age group, the general recommendation is to "start slowly and gradually". First. A family doctor can be made aware of a substance use disorder in an older person by studying a suspected substance use disorder, writing prescriptions for certain medications, or contacting an affected family member. Older people may experience the same or better results than younger people when beginning addiction treatment. It is important, that they have access to effective health services where they are cared for with dignity and compassion [9, 10].

The main drugs, used to treat opiate addiction in adolescents, are similar to those used in adults, mainly methadone and buprenorphine. Both drugs can be used to support abstinence lasting several weeks or months. They can also be used for long-term stabilization and for maintenance and inspection times. The conditions for dose induction and titration can be at home or in a day clinic. This depends on the age of the child/teen, the severity of the addiction and other factors, such as the impact of mental health issues, other medications used, and family/social support. All of these drugs must be administered under supervision. As with adults, thorough assessment of addiction by competent groups, including toxicologists, is required. Attention should be paid to the initial tolerance, as it is not always so pronounced in young people. Dose induction and titration are similar to adults, but care should be taken to start with the daily loading dose and initial escalation, usually beginning with a lower dose (eg, less than 30 mg methadone per day or less), taking into account the age and physique of the child/adolescent, but also knowledge of signs of tolerance and intoxication or continued drug withdrawal. Caution is advised, but introducing too little methadone too slowly can also lead to further illicit heroin use, for example with additional risks. These problems can be solved by providing the young person with very thorough information, with the guarantee of frequent examinations in order to adjust the treatment if necessary. For people, addicted to prescription opioids, such as tramadol or over-the-counter opioids, there is little evidence to guide drug selection. Clinical practice includes the use of buprenorphine replacement therapy or the use of the originally prescribed drug at reduced doses. Clinical consensus suggests that stabilization with a long-acting replacement drug, such as buprenorphine, may be more beneficial, when appropriate, to allow time to assess all other needs, fully involve young persons and their family, and develop and implement a plan of care. However, this can be addressed on a case-by-case basis by monitoring stabilization (avoiding ups and kickbacks). The length of the stabilization phase and duration of detoxification depend on clinical risk, severity of addiction, use/dependence on other drugs or alcohol, social functioning, mental health issues, marital status, and criminal behavior [11, 12].

Substance use also carries the risk of other negative health outcomes. For example, injecting drug use is risky

when non-sterile injection devices are used, i.e., potential exposure to HIV and viral hepatitis, other infections, and other injection-related injuries and diseases, such as sepsis, thrombosis, and endocarditis. Alcohol consumption increases the risk of both intentional and unintentional harm, and both are non-transferable (e.g., cancer, gastrointestinal and cardiovascular systems) and infectious (e.g., tuberculosis and pneumonia). Alcohol and drug use can harm others.

Addiction is well known to be associated with its high level of physical and mental disorders. Most chronic chemical dependencies of drug addiction are also associated with its very high mortality rates, estimated to be several times those of the non-clinical population. Since addictive substances are known to disrupt cell growth and cell division, it can be assumed, that they particularly affect dividing cells, such as stem cell pools and progenitor cells. It is also known, that they either individually or in combination potentiate apoptosis, i.e., contribute to this effect. The medicine of aging in recent times has become an independent scientific discipline. The cellular aging hypothesis suggests the aging phenotype. The organism is associated with cellular correlates of age associated changes including cell loss, reduced cell velocity, renewal and more aging, negligible functional and non-replicating cells in tissues. So, the anti-growth effects of drug addiction can reasonably occur throughout the body. Expect signs of accelerated aging to be evident. One would expect such a putative progeroid effect to occur subject to increased morbidity and mortality rates, clinically observed almost identically in drug addicts as is the case in the geriatric population. In this connection there are various changes, consideration of all clinical aspects' expression of this general toxicology hypothesis of opioids is needed [13, 14].

Various complications of heroin intoxication have been described in the literature, including pulmonary edema, shock, myocardial injury, acute renal failure, rhabdomyolysis, and leukoencephalopathy. To date, not a single case of heroin intoxication with damage and dysfunction of six organs has been registered. There are several hypotheses regarding the pathogenesis of complications of heroin intoxication, including the primary toxic role of heroin, hypoxia, ischemia-reperfusion injury, anaphylactic reactions, and the toxic role of impurities. However, recent investigators have not found sufficient evidence to support the hypotheses of anaphylactic reactions and the toxic role of contaminants [15, 16].

The injection of opiates, particularly heroin and subutex (buprenorphine), poses a particular problem. It has been established, that the main route of transmission of infection among registered HIV-infected persons is through injection drug use. Although HIV prevalence among IDUs (injecting drug users) is only 1–3 %, the large number of IDUs and the high prevalence of hepatitis C in this population pose a high risk of high spread of HIV in Georgia. Since late 2005, the GFATM (Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria) has been supporting methadone substitution therapy programs in Georgia. Three programs are currently underway. Studies, conducted by the Institute for the Study of Addictions to monitor the effectiveness of pilot programs, have shown a significant improvement in the psychophysical state of patients with a very high level of rehabilitation and decriminalization and a significant reduction in problems related to

drugs, such as risky behavior. The results show that methadone substitution treatment programs in Georgia are highly effective as an important tool for both opioid dependence treatment and harm reduction. To have a greater impact on public health, further expansion of substitution therapy programs is needed.

Recently, opioid  $\delta$ -receptor agonists have been proposed as interesting targets for the development of new antidepressants. Several studies have shown that single treatment with  $\delta$ -opioid receptor agonists has antidepressant effects in the forced swim test, which is one of the most popular animal models for antidepressant screening. In addition, subchronic treatment with  $\delta$ -opioid receptor agonists has been shown to completely attenuate the hyperemotional responses, found in olfactory bulbectomy rats. This animal model exhibits hyperemotional behavior that may mimic the anxiety, aggression, and irritability, seen in depressed patients, suggesting that  $\delta$ -opioid receptor agonists may be effective in treating these symptoms in depression. On the other hand, the prototype opioid  $\delta$  receptor agonists cause convulsive effects that limit their therapeutic potential and clinical development. In this review, we present current knowledge of the antidepressant-like effects of  $\delta$ -opioid receptor agonists, including some recently developed non-convulsant drugs [17, 18].

The biological effects of endogenous opioid peptides are mediated through three classes of naloxone-sensitive opioid receptors: mu ( $\mu$ ), kappa ( $\kappa$ ), and delta ( $\delta$ ). Several lines of evidence suggest a role for opioid receptor systems in depression, including early studies examining the potential of antidepressant therapy with endogenous opioid peptides in humans. For example, it has been shown, that serum levels of  $\beta$ -endorphin (an endogenous opioid peptide that binds to  $\mu$  and  $\delta$  opioid receptors) are significantly increased in depressed patients after treatment with antidepressants. Elevated plasma levels of  $\beta$ -endorphin in patients following electroconvulsive shock (ECS) treatment for depression have also been reported, suggesting that endogenous  $\mu$ - and/or  $\delta$ -opioid receptors were at least partially involved in the mechanisms of the antidepressant action of electroconvulsive shock (ECS). In fact,  $\beta$ -endorphin has been reported to rapidly exert antidepressant effects in depressed patients. Clinical trials have also demonstrated the efficacy of the  $\mu$ -opioid receptor agonists oxycodone, oxymorphone and buprenorphine in patients with refractory major depression. In contrast, the nonselective opioid receptor antagonist naltrexone was shown to cause psychiatric depression in self-reported volunteers in an open-label, placebo-controlled study. Taken together, these data suggest that endogenous opioid systems play an important role in the pathogenesis of depression [3, 4, 8].

There is growing concern about illicit drug use and its complications. Health risks in many countries. The non-medical use of various classes of prescription drugs (opioid analgesics, benzodiazepines, anxiolytics, and sedative-hypnotics) should be considered because of serious health risks. The increase in non-medical use of legal and illegal drugs has led to increased medical needs, poisoning and deaths. The use of prescription opioids along with illicit drugs and alcohol, as seen in the polydrug model, has contributed to deaths in many countries. The administration of illegal drugs and unsterile crushed tablets introduces many

pathogens and other harmful substances into the body. In addition, many impurities of drugs are injected into the blood on the street. In addition to the risk of overdose, toxicity and death, illicit drug users have a high incidence of acute and chronic illness and organ failure. There are many classes of drugs used around the world, but their use varies in extent, patterns and trends across countries and societies. Each class of drugs and their impurities have their own side effects in the body [19, 20].

Impaired lung function due to COVID-19 can also put people with opioid use disorder, methamphetamine, and other stimulant use disorders at risk. Chronic respiratory disease increases the risk of fatal overdose in users of opioid therapeutics. In addition, the slowing of breathing due to opioids causes hypoxemia, which can lead to cardiac, pulmonary, and brain complications and, in severe cases, overdose and death. Methamphetamine is a highly toxic drug that causes lung damage, pulmonary hypertension and cardiomyopathy, and its use has increased dramatically. Physicians should be alert to the possibility of an increased risk of side effects from COVID-19 in methamphetamine users [21, 22].

People with opioid use disorder may have difficulty getting medication or receiving services through needle exchange programs. Social distancing will make opioid overdoses more likely when there are no bystanders giving naloxone to reverse them, and therefore more likely to be fatal. Physicians in the emergency department with increased workloads are less likely to initiate buprenorphine treatment for patients with opioid use disorder, which is an important part of opioid crisis relief. In response to these concerns, the substance abuse and mental health administration has recommended that opioid treatment programs should be more flexible in dispensing drugs into homes during the pandemic and the drug enforcement administration has issued guidelines to facilitate prescribing [8, 14, 19].

Opioid use disorder is a chronic brain disorder that occurs due to the effects of long-term opioid use on the brain structure and function. These brain changes and the resulting addiction can be treated with life-saving drugs, but these drugs are out of reach for most people who need them. Methadone, buprenorphine, and long-acting naltrexone are safe and highly effective drugs, already approved in many countries to treat opioid use disorder. By alleviating withdrawal symptoms, reducing opioid cravings, or reducing future responses to drug use, these drugs reduce the likelihood that people with opioid use disorder will relapse into drug use and risk a fatal overdose. These drugs also help people regain their ability to function, improve their quality of life, and reintegrate into their families and communities. These drugs save lives, but most people with opioid use disorder in the United States go untreated [23, 24].

As with any other condition, people with opioid use disorder should not be denied medication without proper medical justification. To refuse them for ideological or other unproven reasons is to deny people the medical care they need. However, some drug treatment facilities that prohibit drugs are still supported by funding streams, linked to the criminal justice system or housing authorities, creating strong incentives to refer patients to non-drug treatments.

As the number of people with opioid use disorder increases, the need for treatment far exceeds current ca-

pacities. Many systemic barriers prevent people from accessing these drugs. For example, when facilities offering opioid use disorder treatments are segregated from the rest of healthcare, the associated regulatory and legal requirements can create significant barriers to accessing opioid use disorder drugs. The current opioid use disorder treatment system is fragmented and unfair, requiring coordinated action to overcome the inertia that has escalated the crisis to this point. Containing the epidemic requires a practical strategy across all sectors – healthcare, criminal justice, patients and families and beyond – because no one sector can solve the crisis alone. Making access to medicines much wider and more equitable is the first priority for making significant progress in saving the lives of people with opioid use disorder [25, 26].

Addiction is a chronic illness, associated with the compulsive or uncontrolled use of one or more substances, despite adverse consequences. As with other chronic diseases, a combination of genetic, environmental, and social factors determines a person's susceptibility to addiction and ease of recovery from it. These factors determine a person's propensity to use and continue using drugs, as well as a person's susceptibility to certain types of neurobiological changes in the brain that characterize addiction progression. Based on decades of research, the scientific community has rallied around the brain disease addiction model. In people with opioid use disorder and other substance use disorders, long-term and repeated drug use has long-lasting effects on the brain structure and function over time. Prescription and illicit opioids have powerful and lasting effects on the brain's opioid system; repeated use can deregulate the system and lead to tolerance, physical addiction and dependency. The data shows that these brain changes can be effectively treated with preparations that help people avoid drug use, significantly reducing the risk of overdose and death. By relieving opioid cravings and withdrawal symptoms, medications may also offer ways to address the behavioral and social components of addiction that are critical to both the development of the disorder and its treatment [27, 28].

This scientific understanding of opioid use disorder is at odds with the prevailing public perception of the disorder, which is shaped by misconceptions about addiction as a mere moral failure. This widespread belief has been spread through generations by socially stigmatizing people who use drugs; this misplaced stigma has extended to medications, used to treat opioid use disorder as well. In fact, people with opioid use disorder have a chronic condition that, like many others, requires long-term care beyond occasional emergencies.

Opioid use disorder is caused by changes in brain circuits that can be treated with medication to restore healthy brain function, resulting in improved addictive behaviors. The drugs, currently approved by the FDA for the treatment of opioid use disorder, are evidence-based, safe, and highly effective. The opioid use disorder medications aim first to control withdrawal symptoms and then to control or eliminate the patient's compulsive opioid use, most commonly with methadone or buprenorphine agonists. Large systematic reviews and randomized controlled trials show that patients with opioid use disorder who receive these drugs are less likely to die from overdose or other causes related to their addiction. Patients taking medica-

tion have longer treatment durations, better long-term treatment outcomes, and better social functioning; they are also less likely to inject drugs or transmit infectious diseases. For patients who have been in opioid withdrawal long enough, extended-release naltrexone can be used for maintenance therapy. The available evidence clearly supports drug use and the need to improve drug access to reduce or eliminate compulsive opioid use, reduce the risk of premature death, and improve the quality of life for people with opioid use disorder and their families [29, 30].

Methadone, buprenorphine and long-acting naltrexone act on mu-opioid receptors of the opioid system. Because each drug has a different mechanism of action, the most appropriate drug and dosage will vary from patient to patient and may vary in the same patient over the course of treatment. Existing drugs are very effective, but not perfect; For example, data gaps remain on how to select the most effective drug for a given patient and how to maintain treatment, which in itself is a major challenge. Because opioid use disorder has complex behavioral and social causes and consequences, it remains to be seen which behavioral interventions are most appropriate to restore patients to full functioning. So, while urgent action is needed to improve access to existing medicines, innovation must not stagnate. Research should remain focused on developing new and better drugs to treat opioid use disorder, identifying the most effective behavioral therapies for maximum results, and improving the most appropriate protocols for their effective use.

Methadone (methadone hydrochloride) is a long-acting, potent synthetic opioid agonist. Its main target is mu opioid receptors. In people who have not taken opioids, methadone has qualitatively the same effects as morphine and other opioids; however, in opioid-dependent patients, the right dose of methadone prevents the development of both withdrawal and intoxication symptoms, leaving patients feeling "normal".

Methadone has a high (85 %) bioavailability (that is, the amount of a therapeutically active drug that reaches the systemic circulation and acts after oral administration). The maximum concentration in the blood is reached 2–4 hours after taking the dose. Methadone is distributed in tissues and 60–90 % binds to proteins of methadone. It is demethylated by liver cytochrome P450 3A4 and 2D6 (CYP2D6) enzymes to its main metabolite – 2-ethylidine-1.5-dimethyl-3.3-diphenylpyrrolidine. This inactive metabolite is excreted in feces and urine along with unchanged methadone. Simultaneous use of other drugs acting on these enzymes may cause clinically significant interactions.

Methadone dose should be adjusted accordingly. During methadone replacement therapy, a decrease in its serum concentration has been described, indicating the development of liver tolerance due to auto-induction of microsomal enzymes [31, 32].

Usually, patients tolerate methadone well, but in some cases, the following side effects may be noted: asthenia, edema, constipation, sweating, dry mouth, sleep disturbances, decreased libido, weight gain, etc. Especially noteworthy is the increase in the QT interval on the electrocardiogram and, accordingly, the increase in the risk of arrhythmias when receiving high doses of methadone, which is why regular monitoring of the patient's condition

is desirable. The risk of overdose is high when methadone is administered to an opioid-intolerant person, so care must be taken in diagnosis, patient assessment, and initial dosing to avoid overdose and respiratory depression. Since methadone is mainly metabolized in the liver, it should be administered with caution to patients with severe liver dysfunction. In particular, drugs that are metabolized by the cytochrome P450 enzyme system should be avoided while receiving methadone, since potentiation of toxic effects may occur.

Regarding the implementation of opioid substitution treatment with methadone indications for methadone-supported substitution therapy, methadone is the most commonly used substitution drug in the world today, although the medical use of buprenorphine and naloxone is becoming increasingly widespread. Although other drugs are used for supportive replacement therapy today, the effectiveness of these two substances – methadone and buprenorphine - has been sufficiently evaluated. Due to the high effectiveness of substitution therapy, supported by these drugs, in 2005 the World Health Organization included methadone and buprenorphine in the main list of drugs, recommended for countries. Methadone-supported substitution treatment is indicated for all opioid-dependent patients who are able to give informed consent and for whom there are no specific contraindications. Given that treatment is long and there is a potential risk of toxicity in the first two weeks, a high-confidence diagnosis should be made before starting replacement therapy with opioid agonists. Staff should also be careful when refusing a patient in opioid agonist replacement therapy, as such patients have a poor clinical outcome if left untreated [33, 34].

Diagnosing opioid dependence and assessing the patient opioid dependence is primarily based on the history, provided by the patient. Sometimes the patient may be motivated to exaggerate or understate his/her drug use; therefore, it is usually necessary to corroborate the patient's history with the results of a physical examination and diagnostic tests. Sometimes the anamnesis, collected from relatives, helps us to make the correct diagnosis. In order to successfully conduct the evaluation process, it is necessary to establish a relationship between the patient and the medical staff, focused on the free exchange of information. In the beginning, the patient may only be trusted to provide the information, needed to begin the treatment process. However, once trust is established between patient and staff, more information can be shared. This will allow the medical staff to better tailor the treatment to the individual patient. The patient's physical, psychological, and social needs are an important part of the assessment. The assessment should also include factors that may influence drug use. These include past treatment experiences, living conditions, legal issues, professional situation, social and cultural factors. The clinician should collect a substance use history to assess the following: Which psychoactive substances have been used in the past and which are currently used; The type of use of each substance, including information on amount and frequency of use, level of neuroadaptation to each substance; Drug-related health and social problems; Outcome of previous treatment and other interventions; Whether the patient meets criteria for abuse or dependence. How the patient views his/her drug use; Factors that contributed and cur-

rently contribute to the patient's use of psychoactive substances; Short-term, medium-term and long-term goals, set by the patient; What brought the patient to the treatment facility this time. Clinicians must distinguish between drug dependence and drug use without dependence, as the correct selection of treatment strategies depends on the diagnosis [11, 15, 28].

Intensity of Opioid Intoxication and Opioid Withdrawal (ie, withdrawal and intoxication) are very important syndromes from a diagnostic point of view. However, we must always remember that the presence of only one of these conditions does not allow us to make a diagnosis of addiction, if they are not confirmed by the presence of other criteria. This is especially true in the state of intoxication, since there may be single or irregular consumption without dependence. When examining a patient, the degree of intoxication and withdrawal should be interpreted based on when the patient last took the drug. The signs of opioid intoxication are mainly the following: euphoric mood, analgesia, narrowing of the pupils, drooping of the eyelids, itching, sedation, somnolence, decreased blood pressure, slowing of the pulse, decreased breathing rate, characteristic speech disorders, etc. The state of opioid withdrawal is a combination of symptoms of different types and severity, which is observed when the psychoactive substance is completely or partially stopped. The onset and duration of withdrawal symptoms is limited to a certain time and depends on the psychoactive substance and its dose, which was taken before stopping or reducing the drug [35, 36].

Symptoms of an opioid withdrawal state include: dilated pupils, rhinorrhea, lacrimation, drooling, goosebumps, headache, agitation, irritability, restlessness, insomnia, muscle and joint pain, myoclonus, abdominal cramps, vomiting, diarrhea, rapid breathing, increased blood pressure. and pulse delirium. Sometimes there may be room for change of consciousness and heartbreak. Visual inspection: in the initial assessment (which may sometimes be time-poor), the visual inspection is very important. If intravenous administration is noted in the anamnesis, nanemars should be visible and consistent with the anamnesis (as a rule, both new and old nanemars are visible). Inspection of the injection site can provide useful information about the timing and duration of injection drug use. The last injection site is small and red, sometimes inflamed, or bordered by a small bruise. The old injection site is usually not inflamed, but sometimes it is characterized by a change in pigmentation (darker or lighter), the skin may be atrophic – it looks like a dropped area. In a given period, a patient with neuroadaptation usually has new and old memories. Many sites can be used for injection, but the axillary fossa, the inner surface of the elbow joint, and the groin are the most common injection sites. The presence of trophic ulcers on the skin gives us some information. The effects of local burns, often the result of cigarette smoking during opioid sedation, may be encountered. Also, attention should be paid to tattooing at the injection sites, burns and post-incision skin damage, which may be the result of the patient's attempt to cover the injection marks [37, 38].

At drug screening of biological fluids if available and financially feasible for the organization, urine (or other biological fluids, eg saliva or blood) should be

routinely analyzed for drugs and psychotropic substances prior to treatment. In order to be considered eligible for treatment, this test must confirm recent opioid use. When the cost of urinalysis is an issue, it should still be performed when recent opioid use cannot be confirmed otherwise (eg, opioid withdrawal or intoxication). A negative response to an urine drug screening test and the absence of withdrawal symptoms rule out the presence of neuroadaptation to opioids at this stage; However, this does not exclude opioid dependence in the past 12 months. Thus, the diagnosis of addiction should not be made solely on the basis of the result of a urinalysis, but a negative test for the presence of drugs in the urine and the absence of withdrawal symptoms question the use of opioids and other sedative drugs. Urinalysis, along with history, is also useful in identifying other recent substance abuse. In order to start the appropriate treatment, one should not wait for the result of the urine test, if other already available data strongly indicate the diagnosis. Routine use of the naloxone test to confirm neuroadaptation is not appropriate because it can induce a strong inhibitory state effect. Usually, the same information can be obtained by taking the patient's history, examining the patient, and interpreting the urinalysis. Before starting the treatment, the patient should undergo the following tests: general blood analysis, determination of glucose in the blood, determination of narcotic/psychotropic substances in urine (or other biological fluid), electrocardiography. It is also recommended, although in standard cases it is not mandatory to conduct the following examinations: general analysis of urine; determination of transferases in the blood; determination of bilirubin in the blood, determination of prothrombin time in blood; immunoserological examinations of viruses (HIV, hepatitis B, hepatitis C). At the doctor's discretion, the patient may be assigned additional examinations or specialist consultations. It is desirable, that the institution has the possibility to conduct the mentioned examinations. Otherwise, he/she should be required to conduct the above-mentioned examinations in a competent institution and present the results to the substitution therapy unit. A pregnancy test should be offered to all women, so that in case of a positive answer, appropriate treatment tactics can be selected. It is recommended, that all patients be counseled and, if necessary, tested for HIV infection and hepatitis B and C.

Neurobiological Aspects of Opioid Addiction are that regular use of opioids causes neuroadaptive reactions in various brain neurons, involved in motivation, memory, behavior control and disinhibition processes. Over the past decade, knowledge about the neurobiological aspects of drug addiction has grown significantly. Certain brain structures are known to play an important role in regulating pleasure-related behaviors. Neuronal pathways leading to and from these areas form the so-called "Circles of feedback". They are located in the mesocorticolimbic dopamine systems that originate in the ventral tegmental areas and project into the nucleus accumbens, the amygdala, and the prefrontal cortex. The different opioid receptors emerged, and further pharmacological studies identified three classes of opioid receptors, namely the mu, delta, and kappa receptors. Opioid receptors belong to the G protein-coupled receptors, and each receptor class includes several subtypes. Opioid effects of

analgesia, euphoria and sedation are predominantly mediated by mu receptors. Opioids indirectly induce dopamine release by reducing gamma-aminobutyric acid (GABA) inhibition via mu receptors in the ventral tegmental area. They also directly induce dopamine release by interacting with opioid receptors in the nucleus accumbens. The effects of chronic opioid exposure on human opioid receptors are not well understood. Tolerance develops through multiple mechanisms, including acute desensitization of the opioid receptor (which develops within minutes of opioid use and resolves within hours of use) and long-term opioid receptor desensitization (which persists for several days after opioid agonist withdrawal). Changes are also observed in the number of opioid receptors – in particular, there is a compensatory up-regulation of cyclic adenosine monophosphate (cAMP). When an opioid is withdrawn, the cAMP cascade is hyperactivated, leading to a “noradrenergic storm” that manifests clinically as a state of opioid withdrawal and thus creates a motivation to resume taking the drug. Long-term changes in neuronal circuitry similar to those seen in learning and memory are observed with regular opioid use. This effect leads to a high risk of relapse to opioid use, even after a long-term abstinence state [39, 40].

Ethical principles in accordance with the right to self-determination and the attainment of the highest possible standard of health as defined in Article 12 of the International Covenant on Economic, Social and Cultural Rights, a person should have the right to freely choose whether or not to participate in treatment. WHO's Mental Health, Human Rights and Law Resource Book states that for consent to be valid, it must meet the following criteria: The person/patient giving consent must be competent to do so; Competence is assumed unless otherwise stated; Consent must be obtained independently, without threats or undue pressure; It is necessary to provide information accordingly and adequately. We must provide information about the purpose, method, expected duration and expected benefits of the proposed treatment; About the possible pain and discomfort and the risk of the proposed treatment, as well as the side effects. This information should be discussed with the patient; According to good clinical practice, if possible, the patient should be offered a choice of alternative treatment methods, especially less invasive ones; Information should be provided in a language that is understandable to the patient; The patient must have the right to refuse treatment or stop treatment; Consequences of refusing treatment should be explained to the patient, which may include discharge from the hospital; Consent must be documented in the patient's medical records; The right to consent to treatment implies that there is also the right to refuse treatment. If we believe that the patient has the capacity to give consent, we must respect his/her decision even if he/she does not give consent [21, 35].

In addition to the pathological risk of allergy to heart failure patients, extremely risky behavior may put them at even greater risk during a pandemic. Accidental deaths, associated with substance use disorders, are significantly higher compared to the general population across all categories, including age, gender, income, and education, and the relative risk of occurrence is notable among women. People with multiple alcohol, drug and tobacco use disorders appear to be at particularly high risk of developing them. The people with substance use disorders are susceptible to serious health complications, including chronic infections, a compromised immune system, vari-

ous respiratory, cardiovascular and metabolic diseases as well as a number of secondary diseases comorbidities. Although they experience stigma and marginalization due to limited access to health care, the difference in perceived danger and risky prescription can result in a higher mortality rate for people with substance use disorders. Due to the particular nature of substance use disorders and COVID-19 research, the group is also seeking guidance for large companies and policymakers regarding the comorbidity of COVID-19 infections [41, 42].

An adverse drug reaction is defined as an obviously harmful or unpleasant reaction resulting from a drug-related intervention that predicts risk for future use and requires discontinuation of a specific treatment, change in dosing regimen, or product discontinuation. Currently, such reactions are reported using WHO adverse reaction terminology, which will eventually become part of the International Classification of Diseases. Adverse drug reactions are classified into six types (with mnemonics): dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Illness, test results, and how they are retrieved can help establish a causal relationship with a suspected adverse drug reaction. Treatment includes stopping the drug when possible and specifically healing its effects. Any suspected adverse drug reaction should be reported.

In this regard, a different treatment approach has been developed - the so-called agonist maintenance therapy, or substitution therapy, which implies application of substitute narcotic substances for a relatively long period of time. It is recommended, that such therapy be combined with psychosocial support activities. Today, agonist maintenance therapy is regarded by international experts as the most effective means to treat opioid-dependent persons, to ensure their decriminalization, social integration, as well as to reduce harmful effects, associated with the use of ‘street drugs’.

The substitution therapy is nowadays widely applied across the globe. The expansion of these programs was triggered by HIV/AIDS epidemic, as the aforesaid treatment is basically the only means to prevent the spread of HIV/AIDS and Hepatitis C among injection drug users. *Buprenorphine and methadone hydrochloride, or a buprenorphine/naloxone combination, are mostly applied in the agonist maintenance therapy nowadays because of their specific therapeutic properties.*

Methadone is a long-acting (lasting 24–36 hours per dose) synthetic narcotic substance. It is an opioid agonist, which implies that it has the same effect as morphine or similar narcotic substances. If applied in doses relevant to the maintenance therapy, it considerably reduces the need for drug without producing narcotic effect (so-called ‘high’) and eliminates withdrawal symptoms. Patients who undergo methadone therapy under medical supervision usually feel themselves well, they are adequate and able-bodied. Such treatment allows an opioid-dependent person to improve his/her physical and mental health, to give up on criminal life, to learn and work effectively, to become a full-fledged member of his/her family or community. The agonist maintenance program helps some patients to completely give up drugs, including substitutes, and start a drug-free life.



Methadone hydrochloride syrup, oral solution or tablets are applied in the maintenance therapy. It is recommended, that they should be taken in a specialized institution or unit, under direct supervision of healthcare personnel, in order to maximally prevent outflow of methadone from a medical institution to the 'black' market. To avoid the use of illegal drugs (so-called 'street drugs') the patients are regularly subjected to urine chemical and toxicological testing for detection of narcotic/psychotropic substances. In case of patient's failure to comply with the appropriate treatment regime, including the use of drugs, not prescribed by the doctor, he/she may be required to quit the program [17, 26].

In case the drugs are taken without a doctor's relevant prescription, the involvement in agonist maintenance therapy program in no way exempts a patient from legal liability.

Agonist maintenance therapy for opioid dependence has been recommended by the World Health Organization (WHO). This very organization has put methadone hydrochloride on the List of Essential Medicines.

Opioid substitution therapy (OST) is the most effective treatment for opioid dependence. Opioid substitution therapy programs are an effective way to significantly reduce illicit opioid drug use, HIV-related risk behaviors, overdose deaths, criminal activity, and financial and other stress, experienced by drug users and their families. In addition, OST programs attract injecting drug users who would otherwise never come into contact with treatment facilities. Act as a gateway to access health care, HIV testing, antiretroviral therapy, tuberculosis, hepatitis C and other treatment services. These four programs are supported by the World Health Organization, the Joint United Nations Program on HIV/AIDS and the United Nations Office on Drugs and Crime. Methadone and buprenorphine are on the World Health Organization's list of essential medicines.

Regular use of opioids causes neuroadaptive reactions in various neurons of the brain, which are involved in the processes of motivation, memory, behavior control and disinhibition. Over the past decade, knowledge about the neurobiological aspects of drug addiction has grown significantly. Certain brain structures are known to play an important role in regulating pleasure-related behaviors. Neuronal pathways leading to and from these areas form the so-called "Circles of feedback". They are located in the mesocorticolimbic dopamine systems that originate in the ventral tegmental areas and project into the nucleus accumbens, the amygdala, and the prefrontal cortex.

The signs of opioid intoxication are mainly as follows: euphoric mood, analgesia, constriction of the pupils, drooping of the eyelids, itching, sedation, somnolence, decrease in blood pressure, slowing of the pulse, decrease in the frequency of breathing, characteristic speech disorder, etc. The condition of opioid withdrawal is a combination of symptoms of different types and severity, marked by complete or partial withdrawal of the psychoactive substance. The onset and duration of withdrawal symptoms is limited to a certain time and depends on the psychoactive substance and its dose, which was taken before stopping or reducing the opioid drug.

The goal of the program is to reduce the harm, associated with drug use and to treat patients suffering from drug addiction. The program services include: Inpatient detoxification and primary rehabilitation; Implemen-

tation of replacement therapy and provision of replacement pharmaceutical product delivery (transportation, escort), providing psycho-social rehabilitation in Tbilisi and regions, including provision of short-term and long-term detoxification with a substitute pharmaceutical product in penitentiary institutions.

The goals and objectives of substitution therapy are: Improvement of the somatic and mental condition of persons suffering from opioids addiction, social adaptation, reintegration into society; Prevention of the spread of HIV-infection/AIDS, hepatitis and other blood-borne diseases; Achieving a state of remission in patients through replacement treatment and medical-social rehabilitation; Cessation/reduction of injecting drug use by opioid-addicted persons, Cessation/reduction of illegal drug/psychoactive substance use and improvement of their psychosomatic condition; Reducing the risk of public danger for persons, involved in the substitution treatment program.

Today, evidence-based medicine offers the following main methods for treating opioid addiction; Opioid withdrawal; Opioid withdrawal with subsequent antagonist supportive therapy; Opioid supportive replacement therapy (agonist supportive therapy); In addition to the above, there are other methods of treatment, but today their effectiveness is not sufficiently evaluated or is considered less.

Substitution treatment of opioid addiction: Opioid substitution treatment is the treatment of an opioid-dependent person with a substitution drug, to which the patient's cross-dependence and cross-tolerance have been established. Agonist replacement therapy usually involves taking an opioid agonist (eg., methadone) or taking a partial agonist (eg., buprenorphine) every day. The stable level of opioid effect obtained is perceived by the addicted user as not intoxication or withdrawal, but as a "normal" state.

Types of opioid replacement therapy: Short-term detoxification with a replacement drug – treatment with decreasing doses of a replacement drug for no more than one month. Long-term detoxification with a replacement drug – treatment with decreasing doses of a replacement drug for more than one month. Short-term supportive, i.e., maintenance treatment – treatment with stable doses of a replacement drug for a period of up to 6 months; Long-term supportive, i.e., maintenance treatment – treatment with stable doses of a replacement drug for more than 6 months.

Current drug legislation focuses only on punitive measures and is aimed at restricting supply. The amount of human and financial resources, allocated to the repressive component of the policy and forceful measures, leads to a sharp imbalance between the punitive and care/help vectors of the anti-drug policy. Strict drug policy complicates the implementation of treatment-rehabilitation and prevention programs. Added to this is the country's insufficient efforts in the direction of prevention and treatment-rehabilitation. In addition, the socio-economic situation of the families of drug users is aggravated by fines, imposed by the state, plea agreements, etc.

The abuse of opioids is a topical issue for our country and neighboring countries. This is because the non-medical use of opioid agonists comes with a lot of problems for both the user and society. These problems can be conditionally divided into medical and social. Medical include: direct mortality, the formation of dependence syndrome, an

increased risk of contracting blood-borne infections (viral hepatitis, HIV), an increased likelihood of other diseases, associated with the route of drug administration (thrombophlebitis, infective endocarditis), diseases, associated with a decrease in immunity (tuberculosis and etc.). Social problems can be called ones that are not directly related to the medical consequences of use. These include increased criminal activity (directly drug trafficking itself, as well as acquisitive crimes in order to obtain funds for the purchase of drugs), violations in family and social interaction. All these phenomena lead to significant financial costs for various state and non-state organizations.

The traditional approach to treatment has long been proven to be effective and bring positive results in terms of reduced frequency of drug use, improved employment and fewer crimes committed. However, a common problem in inpatient detoxification and rehabilitation is the high rate of early termination of treatment.

The method of substitution therapy differs significantly from the methods of treatment of opioid dependence described above, the main difference of which is the absence of a requirement for the drug user to completely stop using psychoactive substances, as well as the need to experience the withdrawal syndrome, associated with drug withdrawal.

Methadone – one of the first synthetic opioids (the second after meperidine) was synthesized in Germany in 1944 in the process of searching for analgesics that do not have narcoleptic properties. According to its chemical structure, methadone belongs to diphenylheptane derivatives and is a full agonist of opioid receptors. Methadone has a pronounced  $\mu$ -receptor agonist activity and has a pharmacological profile almost identical to that of morphine. However, the hypnotic effect of methadone is less pronounced than that of heroin and morphine.

Methadone is the first drug to be used in substitution therapy for opioid dependence syndrome. This choice was due to a number of unique properties of methadone. These include: high bioavailability (up to 90 %) when taken orally, which avoids injections and delayed elimination (the half-life of methadone is 14–30 hours, and with systematic use, on average, 22 hours). At the same time, the half-life for morphine fluctuates around 1.9 hours, and for heroin – 30 minutes. This makes it possible to prescribe methadone once a day. It is important to note, that oral methadone has almost no euphoric effect.

The effectiveness of opioid substitution therapy has been confirmed by numerous studies and at the moment there is no doubt among specialists in the treatment of addictions. The effect includes a decrease in the prevalence of blood-borne infections and HIV infection among drug users, a decrease in criminal activity and a decrease in unemployment. In our opinion, it is also important to note, that participation in methadone substitution therapy, in addition to economic indicators, improves the quality of life of people suffering from opioid dependence syndrome. This has been shown in numerous studies both in our

country and in other countries where substitution therapy for opioid dependence is being implemented.

In addition to methadone, other countries use buprenorphine, codeine/dehydrocodeine, slow-release morphine, diamorphine, and other drugs for substitution therapy. Each of them has its own advantages and disadvantages for different groups of patients, however, in most studies, significant differences in effectiveness (both positive and negative) compared with methadone were not found.

A large number of publications confirm that the use of methadone substitution therapy is associated with an increase in patients' adherence to treatment for other diseases they have, a decrease in their use of street opioids, a decrease in cravings for psychoactive substances, and an improvement in their social functioning. There is also a well-documented reduction in the use of other drugs among patients on methadone substitution therapy.

#### 4. Conclusions

Pharmacological management of drug use should be only one component of treatment for drug needs, tailored to a comprehensive needs assessment of the child or young person, carried out in conjunction with appropriate psychological therapy and mental health interventions, and in the context of a clear and applied approach to the clinical management system. When medications are used, prescribing protocols and best practice guidelines are followed: the prescription should be carefully monitored and regularly reviewed by competent staff, with the involvement of family and parents, as appropriate. Age-appropriate pharmacological interventions for substance abuse require the involvement of specialist services, such as pediatricians, educators, medical staff and psychiatric narcologists. In settings, such as gated communities, housing units, acute care or psychiatric hospitals, special care is needed to ensure that withdrawal treatments, such as alcohol and opiates, are available if needed. Caution is required when leaving these establishments due to the risk of overdose and in the transition to adult services. Physicians should carefully consider the degree of dependence on any substance, especially when alcohol and other substances, such as opiates, are used together. The full implementation of treatment, rehabilitation and harm reduction services will reduce the negative health, social and economic consequences of drug use for individuals, communities and society as a whole. The number of drug users will increase, those involved in counseling, treatment, rehabilitation and harm reduction programs.

#### Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results, presented in this article.

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#### Data availability

Manuscript has no associated data.

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