

Review article

The Influence of Psychoactive Substances on Nephrotoxicity of the Kidneys

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SUMMARY

Background/Aim. The metabolism and effects of the abuse of psychoactive substances are not yet fully understood, but it is evident that they represent a tremendous risk to the health of individuals. This paper aims to present a review of published results on the impact of psychoactive substance abuse on kidney function.

Methodology. PubMed and MEDLINE databases were used to search the literature related to drug abuse and its effects on renal function.

Results. For this study, we found 79 human studies that aimed to present a summary of published results on the impact of psychoactive substance abuse on kidney function. Renal manifestations of specific illicit drug abuse were included in this review.

Conclusion. Understanding the nephrotoxicological profile caused by the use of psychoactive substances is the basis for adequate risk assessment and improvement of the treatment of consequential kidney disorders.

Keywords: abuse, psychoactive substances, kidney disease, nephrotoxicity, complications

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INTRODUCTION

Prevalence of the use of psychoactive substances worldwide and their impact on health

Over the last 30 years, the number of recreational drug users appears to have increased. In 1997, an average of 25% of the world's population stated that they had used illegal drugs at some point in their lives, and 10% in the last year (1, 2). The growing number of drug users worldwide (about 269 million in 2018) represents a global public health problem. This number is predicted to reach close to 300 million by 2030. Therefore, controlling drug abuse has become a challenge for researchers and public health policymakers (3, 4). Tobacco, alcohol, and illicit drugs are among the top 20 risk factors for ill health identified by the World Health Organization. It is estimated that tobacco is responsible for 8.8% of all deaths and for 4.1% of the global burden of all diseases, which is measured as the number of years spent living with a disease, while alcohol is responsible for 3.2% of deaths and 4% of disability-adjusted life years (5, 6).

Drug abuse primarily damages the brain and has psychotropic effects (impairment of memory and cognition, psychosis, anxiety). The toxic effects of psychoactive substances are also manifested in other organs, including the kidneys, which are responsible for the filtration, concentration, and partial metabolism of these substances, creating potentially toxic metabolites. Since most psychoactive substances are excreted through the kidneys, the metabolites of these substances have a direct nephrotoxic effect (3, 4).

METHODOLOGY

At the beginning of 2023, research was carried out in databases PubMed and Web of Science (Medline), from January 1, 2004 to September 30, 2022, to search for publications related to drug abuse and its effects on renal function. We employed database-specific search strategies with multiple keywords: abuse, psychoactive substances, kidney disease, nephrotoxicity, and complications.

SEARCH STRATEGY

After the initial search, all articles were retrieved and reviewed by the first author, where ini-

tial duplicate screening and removal were done. Publications that report on the effect on kidney function about the keywords were selected. The results were summarized descriptively and organized within each category of psychoactive substances; a general description of the study characteristics of findings organized by sub-themes inductively derived from the data. The sub-themes within each category are as follows: the influence of psychoactive substances on kidney function, description of the individual effects of the most commonly used psychoactive substances on kidney function, heroin, morphine, cocaine, ecstasy, mushrooms, cannabis, marijuana, methamphetamine, smoking cigarettes, solvents, glues, varnishes, alcohol, anabolic androgenic steroids, new psychoactive substances. Of the selected publications that we used for literature, the largest number were reviews and original papers, books, case reports, case series, systematic reviews, recommendations, and editorial comments, which correlated with our search. Publications that were written in English and Serbian language, that reported renal injury due to illicit drug use, were selected.

RESULTS

After excluding ineligible manuscripts, we found 76 human studies that aimed to present a summary of published results on the impact of psychoactive substance abuse on kidney function. Out of 76 papers, there were: 10 case reports, 4 case series, 18 original papers, 35 review papers, 1 book, 2 recommendations, 4 systematic views, and 2 editorial comments. Renal manifestations of specific illicit drug abuse were included in this review.

The pathophysiological mechanism of the influence of psychoactive substances on kidney function

The majority of psychoactive substances are excreted through the kidneys and renal complications of drug abuse that include a wide range of glomerular, interstitial, and vascular diseases are very common. The damage may be acute and reversible or chronic and can lead to end-stage renal failure. The involvement of the kidney due to drug abuse is either attributed to their elimination through the kidney or a direct nephrotoxic effect. Opioids produce physiological changes in the kid-

ney; endorphins along with other opioid peptides participate in the development of uremic syndrome. Exogenous opioids like morphine and heroin produce renal injuries and can cause progressive chronic renal failure and tubular epithelial cell degeneration. Overdose of morphine increases the oxidative stress in the renal epithelium which leads to renal injury. Heroin abuse is also responsible for several renal complications. Cocaine abuse may cause interstitial fibrosis, renal atherogenesis, glomerulosclerosis, renal infarction, electrolyte imbalance, acute renal failure, and urinary tract infections. Chronic exposure to nicotine increases the severity of acute renal ischemia-reperfusion injury, which may be due to increased oxidative stress in renal cells or due to the involvement of angiotensin II type 1b receptor found in kidneys. Both acute and chronic

alcohol consumption can compromise kidney function and its consumption has been shown to reduce renal function. Alcohol consumption is a probable risk factor for end-stage renal disease (7). Rhabdomyolysis and tubulopathy occur as a result of the abuse of cocaine, heroin, amphetamines and derivatives, synthetic cannabinoids, and cathinone, which can lead to exceeding the capacity of tubular reabsorption and acute tubular necrosis. Cases of acute interstitial nephritis have been described in people who consume ecstasy (8 - 10) (Table 1).

We can conclude that kidney diseases, under the influence of psychoactive substances, can be classified according to the damaged kidney compartment and are manifested by glomerular, tubular, and vascular lesions, with serious clinical manifestations concerning kidney functions (Table 2) (3).

Table 1. *Nephrotoxicity of psychoactive substance abuse*

Heroin	Nephrotic syndrome, amyloidosis, urinary abnormalities, acute kidney disease (rhabdomyolysis), and various degrees of chronic kidney disease.
Cocaine	Acute and chronic kidney damage, kidney infarction, aneurysm dissection and rupture, electrolyte imbalance, and urinary tract infection in infants exposed to cocaine <i>in utero</i> . Acute kidney disease in pregnancy due to placental abruption and pre-eclampsia.
Ecstasy	Rhabdomyolysis, disseminated intravascular coagulopathy, hyponatremia, a wide range of urinary disorders, acute tubular necrosis and acute interstitial nephritis, and acute kidney disease (nontraumatic rhabdomyolysis).
Mushrooms	Acute kidney failure, progression of chronic renal failure.
Morphine	Acute kidney disease (rhabdomyolysis), increased the risk of progression of chronic renal failure.
Cannabis and marijuana	Acute kidney injury, development and progression of chronic renal failure.
Methamphetamine	Prerenal acute renal failure, progression of chronic kidney disease.
Smoking cigarettes	Cancer and kidney damage.
Solvents, glues, Varnishes etc.	Microhematuria, pyuria, proteinuria, distal tubular acidosis, and various forms of tubulointerstitial changes.
Alcohol	Increased risk of acute and chronic renal failure, renal papillary necrosis, and IgA nephropathy.
Anabolic androgenic steroids	Increase in serum creatinine, proteinuria, glomerular damage, acute and chronic interstitial nephritis.
New psychoactive substances	Acute kidney disease, reduction of renal perfusion, acute tubular necrosis, glomerular damage.

Table 2. Classification of psychoactive substances according to the site of renal compartment damage and their clinical manifestations (revised by reference 3)

Location of the change	Psychoactive substance	Clinical manifestations
Renal vessels (perfusion)	Cocaine	Atherosclerosis, malignant hypertension, renal artery dissection and thrombosis, necrotizing vasculopathy
	Synthetic cannabinoids	Decrease in renal blood flow
Glomerulus	Heroin Anabolic androgenic steroids Non - heroin abuse (Oxymorphone) Amphetamines Cocaine with levamisole	MPGN, FSGN, minimal change disease, sclerosing glomerulonephritis, secondary amyloidosis FSGS Thrombotic microangiopathy Focal or segmental necrotizing glomerulonephritis Pauci-immune crescentic glomerulonephritis
Tubulointerstitium	Anabolic steroids Synthetic cannabinoids	ATN, rhabdomyolysis, bile casts, AIN ATN, tubulointerstitial nephritis, and uveitis syndrome
	Cocaine Heroin LSD, PCP	ATN, rhabdomyolysis Rhabdomyolysis, acute tubular necrosis Rhabdomyolysis
	Amphetamines Bath salts	Rhabdomyolysis, AIN, hyponatremia Rhabdomyolysis, hyperuricemia
	Magic mushrooms Toluene	Rhabdomyolysis, AIN Non-anion gap metabolic acidosis, AIN

MPGN: Mesangioproliferative glomerulonephritis

FSGN: Focal segmental glomerulosclerosis

ATN: Acute tubular necrosis

AIN: Acute interstitial nephritis

LSD: D-lysergic acid diethylamide

PCP: Drugs like phencyclidine

DESCRIPTION OF THE INDIVIDUAL EFFECTS OF THE MOST COMMONLY USED PSYCHOACTIVE SUBSTANCES ON KIDNEY FUNCTION

Heroin

Diacetylmorphine, diamorphine (heroin), the most commonly abused psychoactive substance, may result in several renal complications. A spectrum of glomerular abnormalities including focal segmental glomerulosclerosis, amyloidosis, focal glomerular sclerosis, minimal change disease, mesangial proliferation, and membranoproliferative

glomerulonephritis were reported in heroin users with renal disease (11).

Heroin use has been known to cause nephropathy, a term known as heroin-associated nephropathy. It was postulated that chronic use of heroin or its vehicle incites an undefined response which leads to focal glomerulosclerosis with glomerular IgM deposition, resulting in nephrotic syndrome (12).

A recent case series from San Francisco reported 24 patients with biopsy-proven kidney amyloid A amyloidosis; all were chronic heroin users and many had recurrent skin infections (13). On the other hand, the plurality of case series describing amyloid A amyloidosis in the kidneys has reported an exceedingly low frequency of heroin use. Among

374 patients referred to the United Kingdom National Amyloidosis Center from 1990 to 2005, the prevalence of injection drug use was only 4% (14).

Proliferative glomerulonephritis with immune complex deposition is also described in heroin users. Patients present with hematuria, proteinuria, and kidney failure. Low complement levels are typically present, and most often it is presented as a membranoproliferative glomerulonephritis, most likely as a result of chronic viral or bacterial infections due to contamination in a heroin user (15).

It is estimated that the risk of developing kidney dysfunction is three times higher in heroin users compared to non-users. It is estimated that the development of hypertension and renal insufficiency of varying degrees, proteinuria, glomerulosclerosis, and urinary abnormalities occurs within a period of several months to 15 years from the start of heroin use. Heroin overdose causes rhabdomyolysis, myoglobinemia renal failure and consequent acidosis, systemic hypoxia, muscle compression, and direct toxic and immunological effects. The same effect has been reported in overdose-induced coma leading to pressure-induced muscle damage and rhabdomyolysis with consequent hypotension, hypoxia, acidosis, and dehydration. Renal complications associated with heroin may be due to both immune hypersensitivity reaction or a direct myotoxic effect (15).

Morphine

Clinical studies suggest that morphine addicts have an increased risk of progressive chronic renal failure due to urinary excretion of its metabolites. Morphine overdose causes rhabdomyolysis which causes acute renal failure. Chronic administration of morphine causes an increase in the level of urea, uric acid, and creatinine in the serum. Consequently, increased levels of these end products of nitrogen metabolism cause kidney damage with long-term morphine intake (7, 16).

Cocaine

Cocaine abuse results in both acute and chronic kidney damage, including acute kidney disease, renal infarction, electrolyte imbalance, and urinary tract infection in infants exposed to cocaine *in utero*. Acute tubular necrosis caused by cocaine can be a consequence of acute rhabdomyolysis. The pathophysiology of cocaine-induced rhabdomyolysis may

include ischemia, hyperthermia, direct cocaine toxicity to muscle cells, and disseminated intravascular coagulation. Cocaine abuse causes acute kidney disease by precipitating/accelerating malignant hypertension and acute interstitial nephritis caused by cocaine intoxication. Cocaine-induced activation of the renin-angiotensin system may be responsible for fibrosis in mesangial tissue, increased platelet aggregation, thromboxane synthesis, whereas endothelial and vasospastic injury may contribute to renal infarction. Results from experimental studies as well as autopsy findings indicate that cocaine leads to the acceleration of atherogenesis. Endothelin and other vasoconstrictive factors also contribute to the development of changes in blood vessels. Clinically, cardiovascular symptoms with elevated blood pressure are common findings in patients with acute cocaine intoxication (17).

As the kidneys require a rich blood supply for optimal functioning, vasoconstriction is one of the main mechanisms underlying cocaine-induced kidney injury (17). Because of this, cocaine users are about 19 times more likely to develop kidney disease and 9 to 10 times more likely to develop end-stage renal disease as a result of hypertension (18). However, the overall exact mechanism of cocaine-induced injury and the resulting pathology remains unclear (19).

Ecstasy

The clinical picture of ecstasy (methylenedioxymethamphetamine-MDMA) abuse, in addition to symptoms of psycho-neurological manifestations (euphoria, alertness, increased energy and endurance with reduced fatigue, muscle tension, restlessness, headache, nausea, anorexia, insomnia, hallucinations, anxiety, and possible psychosis) also leads to hyperpyrexia. An increase in temperature is the basis of systemic manifestations of MDMA use, including rhabdomyolysis, disseminated intravascular coagulopathy, and hepatotoxicity, very often hyponatremia with life-threatening complications (20).

Likewise, abuse of ecstasy is manifested by nausea, vomiting, pain in the stomach or back, diarrhea, and in the urinary system with a wide range of changes in urinalysis, acute tubular necrosis, and acute interstitial nephritis in the form of acute kidney disease. Acute tubular necrosis caused by isch-

emia resulting from hypovolemia is considered a probable mechanism. Ecstasy is associated with a spectrum of nephrotoxic effects, including acute kidney disease and hyponatremia (21).

Mushrooms

Kidney failure caused by mushrooms can result from severe dehydration or directly from specific damage caused by the mushroom's toxin. Early syndromes that develop in less than 6 hours in the form of nausea and vomiting are usually associated with good prognosis. Delayed syndromes carry a greater risk of health damage due to organ failure, with the liver and kidneys being the most commonly affected (22, 23).

Mushrooms, in their composition, contain the nephrotoxic substance orellanine, which can delay their effect, so oliguria can develop only 5 - 12 days after taking them (22). Orellanines show a high renal tropism, inhibiting protein synthesis in tubular cells. Orellanine degradation produces oxygen free radicals and glutathione depletion. Orellanines remain in renal tissue for up to 6 months after intake. In humans, symptoms gradually develop over 2 – 20 days after ingestion. Clinical presentation starts with digestive symptoms (nausea, vomiting, and diarrhea) and headache, anorexia, and chills within 24 – 36 hours after the mushroom ingestion. Orellanine inhibits protein synthesis and generates free oxygen radicals, leading to tubulo-interstitial nephritis (22).

Hemodialysis is not effective in eliminating mycotoxins and is indicated only in cases of severe acute kidney injury (22).

Cannabis, marijuana

The word "cannabis" refers to all products obtained from the Cannabis sativa plant. There remains limited information on the specific effects of endocannabinoids on renal hemodynamics, including the control of blood flow parameters and its direct effect on blood pressure (19, 24).

The cannabinoid hyperemesis syndrome is rare (25, 26) and can lead to the complications like metabolic alkalosis, hypokalemia, acute kidney injury, or injuries of the esophagus. Major features for diagnosis of cannabinoid hyperemesis syndrome are severe cyclic nausea and vomiting, resolution with cannabis cessation, relief of symptoms with hot showers or baths, and abdominal pain (27, 28).

Several cases of acute kidney injury are associated with the use of synthetic cannabinoids that can be nephrotoxic, causing nausea, vomiting, and flank pain. Cannabis dependence or abuse in the year before kidney transplantation was not shown to be associated with death or transplant failure in the year after transplantation. On the other hand, cannabis abuse is associated with an approximately two-fold increased risk of death-censored graft failure, all-cause graft loss, and death within two years of initiation of use. Nevertheless, it must be emphasized that cannabis use by kidney donors has not shown any negative effects on donor or recipient glomerular filtration rate after transplantation (29).

Based on the evidence detailing the physiological and pathophysiological effects of cannabis use, it is likely that individuals who use these substances may develop acute and chronic renal failure. Unfortunately, there is still a lack of epidemiologic observations from cohort studies regarding the potential renal effects of cannabis use. Biopsy reports indicate acute tubular necrosis, and less commonly acute interstitial nephritis has been observed. A systematic review that included the majority of randomized controlled trials showed that the use of cannabis for an average of two weeks did not lead to serious side effects, and no cases of acute kidney injury were recorded. Information on the effects of cannabis and cannabinoid use on the development and progression of chronic renal failure is also very limited. In a cohort of 647 patients interviewed about illicit drug use, those who consumed any type of illicit substance were found to have a significantly higher risk of mild decline in kidney function over a seven-year follow-up period, while the same association was not demonstrated individually for marijuana (30).

Methamphetamine

More serious complications of methamphetamine use, except aggression, paranoia, hallucinations, tachycardia, hypertension, headaches, tremors, and gastrointestinal irritation, include myocardial infarction, epileptic seizures, acute liver failure, disseminated intravascular coagulation, and hyperthermia. Hemodynamic instability can lead to pre-renal acute renal failure due to fluid volume depletion and ischemic acute tubular necrosis. Rhabdomyolysis, which is the most common cause of acute renal failure in users of psychoactive substances,

occurs as a consequence of pigmented nephropathy (31).

The effects of methamphetamine on the kidneys can be divided into three groups: vascular effects, non-traumatic rhabdomyolysis, and direct nephrotoxicity. In addition, research has shown that methamphetamine directly stimulates the release of endothelin-1. Endothelin-1 stimulates vasoconstriction, inflammation, and fibrosis, causing hypertension, arteriosclerosis, and chronic kidney disease. Often, the effect of methamphetamine on the kidney is indirect through vascular, prerenal effects, and rhabdomyolysis. A direct effect of methamphetamine on the kidneys, such as acute tubular necrosis, rarely occurs. Donor kidneys from methamphetamine abusers should be carefully evaluated before transplantation (31, 32).

Smoking cigarettes

The specific mechanism by which smoking damages kidney function is still unknown. It is assumed that the basis of the damage is increased blood pressure and changes in glomerular pressure, as well as chronic injuries such as endothelial cell dysfunction. These mechanisms can affect glomerular filtration function and kidney microvessel damage (33).

Sufficient clinical research evidence indicates that smoking is a risk factor for kidney damage. These damages are especially pronounced in people with hypertension and type 2 diabetes where it has a synergistic effect (34).

Some studies indicate that avoiding smoking can effectively prevent the development of kidney cancer (35), and recent studies have shown that the success rate of kidney transplantation was significantly lower in smokers (36 - 38). Exposure to secondhand smoke is associated with reducing kidney function (39), however, there was no significant evidence of a greater impact of active smoking on kidney function (40). The association of secondhand smoke exposure with chronic kidney disease is still questionable (41). Smoking can cause chronic endothelial dysfunction, oxidative stress, and glomerular hardening which impairs renal function (42, 43). It is not well known whether reducing or quitting smoking can slow the progression of chronic kidney disease.

Adverse effects of smoking on kidney function have been demonstrated among the general popu-

lation and the population with chronic kidney disease. In the Cardiovascular Health Study, a dose-dependent association of smoking with serum creatinine was demonstrated. Namely, for every 5 cigarettes smoked per day, the level of serum creatinine increases by 0.3 mg/dl (44). In patients with type 1 diabetes, the rate of decline in glomerular filtration rate was observed to be 4.3 times higher in smokers compared to non-smokers (45).

Solvents, glues, varnishes

The nephrotoxic effects of volatile adhesives seem to be a consequence of the effect, above all, of toluene. Numerous kidney lesions have been identified as a consequence of its misuse: microhematuria, pyuria, proteinuria, distal tubular acidosis and Fanconi syndrome, calculus, glomerulonephritis, Goodpasture syndrome, acute tubular necrosis, hepatorenal syndrome, and acute and chronic interstitial nephritis. It is assumed that toluene achieves a nephrotoxic effect by affecting the tubulointerstitial feedback loop. Consecutive tubular acidosis mobilizes calcium from the bones, hypercalciuria, and consequent calculus of the urinary tract (46).

Alcohol

Alcohol use reduces kidney function by promoting interstitial edema and kidney hypertrophy. Chronic alcohol abuse increases the risk of acute renal failure and leads to the development of renal papillary necrosis. Alcohol consumption may increase the risk of kidney failure by initiating and/or promoting atherogenic risk factors, such as high blood pressure, hyperuricemia, insulin resistance, and diabetes. Alcohol plays an important role in the development of rhabdomyolysis. Electrolyte abnormalities caused by alcohol intake are also important for muscle damage. Ethanol intoxication involves water-electrolyte and acid-base imbalance with excessive excretion of calcium, magnesium, and phosphate in the urine, which leads to the development of metabolic acidosis, hypomagnesemia, hypocalcemia, and hypophosphatemia (3, 47).

Anabolic androgenic steroids

Damage from years of high androgen intake, often 50 - 100 times the physiological level, is a sig-

nificant cause of chronic kidney disease. With the abuse of anabolic androgenic steroids, a variable increase in serum creatinine and significant proteinuria were registered. The mechanism of kidney damage is probably multifactorial. Hyperfiltration injury is an important factor. Patients with markedly elevated lean body mass require an increase in glomerular filtration rate in one nephron, similar to patients with obesity-related glomerulopathy. The most commonly reported renal adverse events in patients using anabolic androgenic steroids are focal

segmental glomerulosclerosis, nephroangiosclerosis, chronic interstitial nephritis, and acute interstitial nephritis (3).

New psychoactive substances

New psychoactive substances, or designer drugs, are produced with the intent that they will elicit feelings of euphoria similar to those experienced with the use of controlled substances (Table 3) (48, 49).

Table 3. Nephrotoxicity of designer drugs and their systemic effect (revised by reference 3)

A type of designer drug	Compound	Nephrotoxic effect	Systemic effects
Amphetamine derivatives	Methamphetamine	Prerenal AKI, ATN Rhabdomyolysis	Hyperpyrexia and fibrinolysis (disseminated intravascular coagulation), microvascular obstruction, myoglobinuria, systemic hypotension or hyperpyrexia, acute renal failure
	MDMA	Prerenal AKI, ATN Rhabdomyolysis Hepatorenal syndrome Malignant hypertension Necrotizing vasculitis Acute tubular injury Hyponatraemia	
	251-NBOMe	Prerenal AKI, ATN	
Phenylpiperazine derivatives	BZP and TFMPP	Prerenal AKI, ATN Rhabdomyolysis Acute interstitial nephritis Glomerulopathy Hyponatraemia	Hyperthermia, renal failure, disseminated intravascular coagulation
Synthetic cathinone	MDPV and mephedrone	Prerenal AKI, ATN Rhabdomyolysis	Hyperthermia, renal failure, disseminated intravascular coagulation
Synthetic cannabinoids	δ9-THC derivatives	Prerenal AKI, ATN Acute interstitial nephritis	Hyperthermia, dehydration, muscle damage, renal failure
NMDA receptor antagonists	PCP	Rhabdomyolysis	Acute and chronic renal diseases, fibrogenesis
	Ketamine	Uric acid nephropathy Lower genitourinary pathology Obstructive nephropathy Papillary necrosis	
Synthetic opioids	Oxymorphone	Thrombotic thrombocytopenic purpura	Dehydration, hypotension, rhabdomyolysis, urinary retention, chronic kidney disease, amyloidosis

δ⁹-THC, δ 9-tetrahydrocannabinol, 251-NBOMe, 4 iodo 2,5-dimethoxy N-(2-methoxybenzyl) phenethylamine, AKI: acute kidney injury, ATN, acute tubular necrosis, BZP: N benzylpiperazine, DMA: 3,4-methylenedioxymethamphetamine, MDPV: 3,4-methylenedioxypyrovalerone; mephedrone, 4 methylcathinone, NMDA: N methyl-d aspartate, PCP,: phencyclidine, TFMPP: trifluoromethylphenylpiperazine

Designer drugs have substantial potential to induce adverse effects or overdose in users. Neurological, psychiatric, and cardiovascular abnormalities associated with these substances have been reported as well as renal and electrolyte disturbances. There is a wide spectrum of nephrotoxic effects of designer drugs and their systemic effect: prerenal acute renal failure, acute tubular necrosis, rhabdomyolysis, malignant hypertension, necrotizing vasculitis, acute tubule injury, acute interstitial nephritis, hyponatremia, uric acid nephropathy, obstructive nephropathy, papillary necrosis, thrombotic thrombocytopenic purpura, hepatorenal syndrome, glomerulopathy (Table 3) (3, 50). Prerenal and post-renal forms of kidney injury are the result of extrarenal disorders such as hypovolemia, hypoperfusion, or obstruction of the urinary tract. New psychoactive substances are known for their negative inotropic effects, which can cause a decrease in renal blood flow. Intrinsic causes of acute renal failure are related to tubular, glomerular, interstitial, or vascular damage. Acute tubular necrosis is a leading cause of acute renal failure and may be associated with rhabdomyolysis. However, the exact mechanisms of kidney damage due to abuse of new psychoactive substances remain unknown even today (51, 52).

The increasing use of designer drugs means that clinicians must be aware of the clinical presentation and associated end-organ toxicity. Nephrotoxicity from designer drug use should be considered in the differential diagnosis of any patient with acute kidney injury of unknown or unclear etiology whether or not there is direct nephrotoxicity due to the drug, an adulterant, or a systemic complication. As new drugs are developed and classes of designer drugs and their derivatives expand, clinicians and other healthcare providers need to recognize the potential for kidney injury with the use of designer drugs (3).

CONCLUSION

Abuse of psychoactive substances is a growing global problem. It is, therefore, a challenge for researchers and social policymakers to design multi-sectoral responses to prevent or reduce harm from their misuse. Even though previous studies have somewhat clarified the specific mechanism of renal function impairment caused by the use of psychoactive substances, significant dilemmas remain. They primarily relate to the effects of abuse of multiple psychoactive substances and the use of psychoactive substances in persons with certain comorbidities or infections, especially infections with hepatotropic viruses. That is why constant education and research are necessary to fully understand the mechanism of kidney damage caused by the abuse of psychoactive substances. It is extremely important to understand the nephrotoxicological profile of psychoactive substances, which is the basis for improving the risk assessment as well as the treatment of substance use disorders. Given that clinicians are not always sufficiently aware of the risks associated with the use of psychoactive substances, there is an untimely identification of potential users and damage to their health. That is why it is necessary to timely and adequately inform health and social workers about the harmfulness of psychoactive substances, possible psychopathological risks, the modalities of taking and the effect of these substances, their impact on psychosomatic health, as well as different treatment protocols.

Disclosure statement

The authors declare that there is no conflict of interest.

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Nefrotoksični uticaj psihoaktivnih supstanci

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SAŽETAK

Uvod/Cilj. Iako metabolizam i efekti zloupotrebe psihoaktivnih supstanci još nisu u potpunosti shvaćeni, očigledno je da predstavljaju ogroman rizik po zdravlje pojedinca. Cilj ovog rada bio je da predstavi pregled objavljenih rezultata o uticaju zloupotrebe psihoaktivnih supstanci na funkciju bubrega.

Metodologija. Za pretragu literature o zloupotrebi droga i njihovom uticaju na funkciju bubrega korišćene su baze podataka *PubMed* i *MEDLINE*.

Rezultati. Za potrebe ovog rada nađeno je 79 studija čiji je cilj bio da prikažu pregled objavljenih rezultata o uticaju zloupotrebe psihoaktivnih supstanci na funkciju bubrega kod ljudi. Manifestacije specifične zloupotrebe nedozvoljenih droga na bubrezima bile su uključene u ovaj pregled.

Zaključak. Razumevanje nefrotoksičnog profila izazvanog upotrebom psihoaktivnih supstanci predstavlja osnovu za adekvatnu procenu rizika i unapređenje lečenja oboljenja bubrega koja su nastala kao posledica.

Ključne reči: zloupotreba, psihoaktivne supstance, bolest bubrega, nefrotoksičnost, komplikacije