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SPECIAL ARTICLE

Abuse of tropicamide eye drops: review of clinical data

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Over the past 15 years, the increasing nonmedical use of tropicamide ophthalmic drops has been reported in Europe, coinciding with an increase in opioid addiction and drug-related mortality. Although tropicamide is generally known as a cheap alternative to heroin in Eastern Europe, it still appears to be a relatively new phenomenon that has arisen over the last decade. A narrative review was conducted of all the relevant sources published in more than five countries between January 1, 1975 and January 10, 2021. For bibliographic accuracy, the materials published in Russian and Italian were professionally translated to English. During the preparation of this report, we were able to interview five Russian-speaking patients who injected tropicamide in the past and we discuss another case of intravenous tropicamide use. This review was acknowledged by the institutional review board of the University of Missouri-Kansas City. All patients interviewed at the Unica Medical Center consented for their clinical information to be reported in a medical publication. We analyzed data from 50+ various sources and covered a variety of drug-related issues, including information on the extent, patterns, and trends in tropicamide use, its health consequences, and other clinical findings. The information provided in this article may help providers better detect tropicamide abuse and incorporate new rehabilitation strategies into the management of these patients.

Keywords: Tropicamide; eye drops; abuse; addiction; opiate

Introduction

Tropicamide is a topical anticholinergic antagonist that is used in ophthalmic practice in the same way as many cycloplegic agents. For example, it is used for diagnostics in fundus examination, during surgical procedures, and as direct therapy for some inflammatory eye conditions. Tropicamide is also known as a "seven-monther" – the amount of time it takes to kill a young person without significant pre-existing conditions.[1,2] Over the past several years, the misuse of eye drops with anticholinergic effects, such as cyclopentolate and tropicamide, has sharply increased.[3] Previously, this anticholinergic drug epidemic was believed to be limited to the former Soviet Union, but recent studies have since shown that the epidemic extends well beyond Eastern Europe.[4] Over the past 10 years, a number of cases of tropicamide abuse via intravenous injection have been reported in several countries,[4] including Turkey,[5] Italy,[6] France,[1] Tajikistan,[7] and Kazakhstan.[8]

It has been hypothesized that the rise of tropicamide use in Russia is related to increased enforcement of policies targeting illicit drug use.[4] Over a three-year period, sales of tropicamide in Eastern Europe increased from 2 million to 11 million units,[9] with no established connection to any increase in diagnosed eye conditions.[10] Access to tropicamide-containing medications in Russia was originally restricted, but lobbying by pharmaceutical companies in the early 2010s eased these restrictions, and pharmacist guidance was routinely ignored at the point of purchase.

The number of Western European tropicamide addicts has soared over the past decade. New scientific reviews of the research that fueled the trend suggest that drugs like tropicamide have been oversold in Italy[3] and France.[11] The availability of data on tropicamide sales in the European Union has increased in recent years, but is still quite limited. European governments restricted access to tropicamide-containing medications, but local media reports suggest these bans didn't stop tropicamide abuse. For example, at least 17 falsified tropicamide prescriptions were identified in France in 2014-2015.[1] There is no central European Union policy addressing drug abuse, and some controlled substances could easily enter the legal supply chain.

This report examines 1) the clinical aspects of tropicamide abuse in various countries and the characteristics

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of affected individuals, and 2) what is known about different therapies used during treatment to help those who are using tropicamide.

Methods: clinical cases

In the spring of 2021, during data collection for a review on tropicamide, we attempted to obtain information from former tropicamide users. The theoretical part of this study was acknowledged by the institutional review board of the University of Missouri-Kansas City. Before collecting data, administrative approval was granted by Unica Medical Center (Moscow, Russia). After obtaining informed consent and formal approval, we conducted five diagnostic semi-structured psychiatric interviews with a pre-designed blend of closed- and open-ended questions to ensure that each of the participants participated in a consistent and reliable interview session. The interview consisted of questions regarding 1) demographic variables, 2) screening for major psychiatric disorders and substance use, 3) a review of past psychiatric issues (main behavioral aspects, tropicamide abuse pattern, social history, self-identified aggravating/alleviating factors related to tropicamide addiction), 4) overview of physical and behavioral impairments and psychosocial limitations. The responses were analyzed accordingly. Limited retrospective reviews of medical records were conducted to clarify certain aspects of the patients' presentation, medical history and treatment.

All respondents were in sustained remission at the time of the interview, having devoted months of their life to sobriety:

- Patient 1, in remission for four years, seven-year history of tropicamide consumption with stimulants.
- Patient 2, in remission for five years, four-year history of tropicamide consumption with opiates and pregabalin.
- Patient 3, in remission for six years, two-year history of tropicamide consumption with opiates and stimulants.
- Patient 4, in remission for six years, six-year history of tropicamide consumption with opiates and stimulants.
- Patient 5, in remission for nine years, five-year history of tropicamide consumption with opiates.

Table 1 provides additional information regarding the patients included in this study.

Intoxication after taking tropicamide together with opiates is stronger and lasts longer – "The lamest rush gets stronger." There is a strong sedative effect, lethargy: "The brain is paralyzed, memory disappears," and vision decreases. After withdrawal, the urge to resume consumption is many times stronger than that of opiates alone. The urge is especially strong on an emotional level; it causes severe suffering. Taking tropicamide in its pure form without opiates is described by patients as a "severe" condition similar to a "severe hangover," often accompanied by nausea, "stomach convulsions," a soapy taste in the mouth, heavy breathing, apathy, anxiety, sharp depression, and drowsiness. The urge at such moments is even stronger, "incomparable with any other."

When taken together with stimulants, tropicamide also enhances their effect. Patients have described a feeling of persecution and striking perceptive distortion: "devils are creeping around, and you can't tell them from reality." Surrounding objects "become distorted, as if they have a very realistic, visually clear face and essence; they do not speak, but I can read their thoughts, as if they transmit information to me in this way," and "you get a fix – and it's like all riddles of the universe are revealed." The intensity of the post-withdrawal urge is comparable to the urge for stimulants. The respondents reported that perceptive distortion stopped immediately after intoxication ended. One patient reported that when regularly consuming tropicamide without other stimulants an extremely severe emotional state developed as the drug's effects terminated, which he described as a "grave comedown:" "I had a harder time than with any other drug." Thoughts of "the meaninglessness of life" and suicide would often arise. There is a physically unpleasant feeling of stretched skin, and users reported that their urine smells of "rotten eggs." When taking tropicamide with alcohol, there was an almost "instantaneous" onset of intoxication to an "unconscious state." All respondents reported that with prolonged tropicamide use, they stopped remembering everything that happened during intoxication.

Despite long-term sobriety, 2 of the 5 respondents reported that their urge continued on a physical level during the conversation: "I'm speaking – and my palms are sweating," "I'm drooling," "Fear, nausea, pressure in my eyes, it scares and attracts me at the same time," and "So far, for me it's the strongest example of compulsion." One of the five people said, "Now, the compulsion does not arise for no reason; if you talk about consumption for a long time, anxiety and discomposure can develop."

Literature review

Tropicamide is an anticholinergic ophthalmic solution that causes mydriasis and cycloplegia.[12] One bottle contains 10 mL of a 1 or 0.5% nasal solution, which is a clear and colorless liquid.[13] The cycloplegic effect appears 15-30 minutes after instillation and lasts for four to six hours, which distinguishes it favorably from atropine, whose effects last up to 14 days.[14] Tropicamide rapidly expands the pupil and paralyzes accommodation for a short time. For adults, the dosage is one drop of 1% or two drops of 0.5% solution.[13] When instilled in the eyes, tropicamide is well distributed both locally and systemically, and the eye drops rapidly penetrate into the nasal cavity through the nasolacrimal duct. Regarding the vasculature, the inhibition of M3 in vascular endothelial cells causes a decreased synthesis of nitric oxide and limits vascular smooth muscle cell relaxation, which explains tropicamide's effect on vascular tone.[15,16]

When taken in large doses, however, tropicamide can produce stimulant, euphoric, and hallucinogenic effects.[16] Although its mechanism of action is not completely understood, tropicamide is believed to bind to and block the muscarinic receptor M4.[15] What is known, however, is that the addictive properties of tropicamide seem to originate from interaction between the cholinergic system and opioids.[6] Antagonism of M1 receptors produces a central anticholinergic syndrome, which manifests as

Table 1 Summary of the patients' clinical profile

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Male	Male	Male
Age	43	35	47	35	37
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
History of substance use	Tropicamide stimulants	Tropicamide opiates pregabalin	Tropicamide opiates stimulants	Tropicamide opiates stimulants	Tropicamide opiates
Previous inpatient & outpatient treatment	1 inpatient hospitalization 1 IOP	10 inpatient psychiatric admissions 4 IOPs/rehab	7 - inpatient psychiatric admissions 1 - IOP/ rehab	9 - inpatient psychiatric admissions 2 - IOPs/ rehab	1 - IOP/ rehab
Remission duration	4 years	5 years	6 years	6 years	9 years
History of relapses	None	Multiple relapses shortly after inpatient/IOPs No relapses after rehab	Multiple relapses shortly after inpatient hospitalizations No relapses after rehab	Multiple relapses shortly after inpatient hospitalizations No relapses after 2 rehabs	None
Psychiatric comorbidities	None	None	None	None	None
Medical comorbidities	Hepatitis C	None	Hepatitis C	Hepatitis C	None
Family history of psychiatric problems and/or SUD	None	None	Alcohol use disorder, father's side	Alcohol use disorder, father's side	Alcohol use disorder, both sides of the family
Education level	Some college	Secondary and/or higher education	Secondary and/or higher education	High school	High school
Legal problems related to substance use	None	None	Yes	Yes	Yes
Health insurance coverage	OMI + self-pay	OMI + self-pay	OMI + self-pay	OMI + self-pay	OMI + self-pay

IOP = intensive outpatient program; OMI = obligatory medical insurance; SUD = substance use disorder;.

agitation, often with pressured speech, delirium, and visual and/or auditory hallucinations. Some patients have been seen picking at nonexistent objects on their bedsheets and/or clothes, which is likely because of visual perceptual disturbances during delirium.[17] More serious effects of anticholinergic toxicity include coma, seizures, tachycardia, and cardiac arrhythmias due to QRS prolongation.[17] Furthermore, a decrease in the adverse symptoms associated with a discontinuation of opioid use may be associated with a blockade of M5 receptors.[18]

Tropicamide is misused because of its stimulating and euphoric properties, which are explained by the high affinity tropicamide has for cholinergic receptors. As a result, acetylcholine accumulates in the synaptic cleft – which means a significant part of the parasympathetic effect is blocked – and central nervous system activity shifts toward adrenergic system overactivity and various psychotomimetic and hallucinogenic effects. Muscarinic receptor activation in the cerebral cortex is involved in limiting discrete events in the stream of consciousness. In the absence of cortical acetylcholine, temporarily inadequate information from internal and external stimuli, which is always present on a parallel subconscious level, invades conscious processes. This partially explains the misuse of antimuscarinic drugs such as tropicamide, which can cause visual hallucinations.[19]

Older age, a scarcity of sensory impressions, and a noticeable weakening of cognitive function may contribute to the development of anticholinergic hallucinations with low doses of the drug.[20] The symptoms produced by this substance are reversible upon discontinuation.[21] Figure 1 provides additional information regarding the "pharmacological effects" of tropicamide.

Epidemiology of tropicamide abuse

The prevalence rates of drug abuse in Eastern Europe, although decreasing according to official statistics, appear to be higher than those in Central and Western Europe. For example, the rate of heroin-related events in Eastern Europe has increased almost twofold, whereas the rate of tropicamide abuse remains unclear.[22] No confirmed tropicamide abuse cases have yet been reported in the United States and its territories.

Since 2009, tropicamide use has steadily increased among individuals with substance use disorders. The first reported cases of recreational intravenous use of tropicamide eye drops were published in 2012-2013 after large quantities of eye drop bottles began appearing around pharmacies. In the initial attempts to analyze this phenomenon, researchers had to turn to unofficial primary sources, such as thematic forums, social media

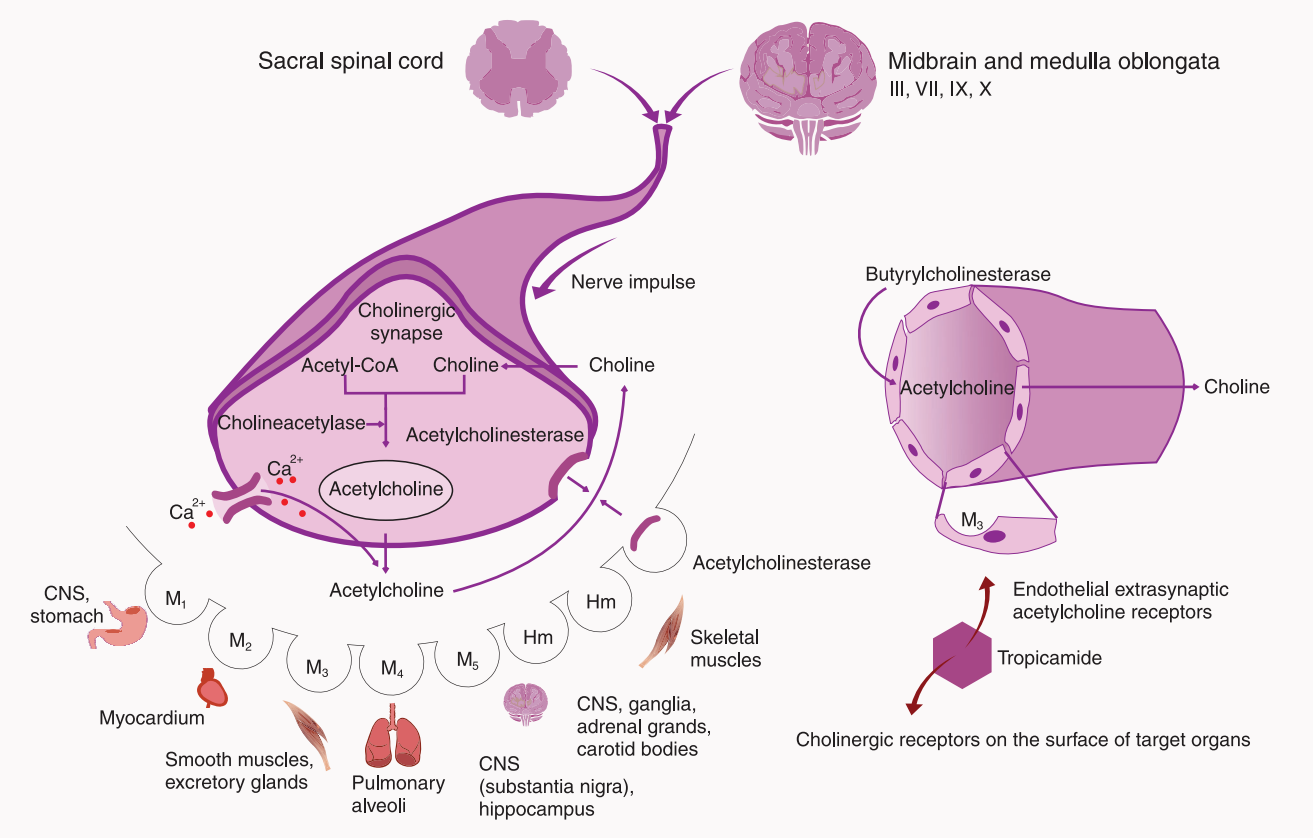

Figure 1 Pharmacological effects of tropicamide: the dashed red arrow indicates the proposed inhibition of M3 receptors on vascular endothelial cells; the continuous red arrow indicates excessive inhibition.

communities, and news reports. One such report was an infamous article in the British edition of the *Independent* entitled "The Miserable and Lonely Death of Ivan Kanev."[23] This 25-year-old man had injected tropicamide eye drops directly into the femoral artery of his groin for several months.

Two other observational studies have described 118 patients in Kazakhstan who were addicted to several psychoactive substances, 10 of whom were classified as addicted to tropicamide.[8,24] Interestingly, 1 out of 100 male participants reported using tropicamide to relieve opiate withdrawals in a focus group study.[7] One prospective cross-sectional observational study was conducted between November 2016 and January 2017 at 16 different community pharmacies in Amman, Jordan. Of the 140 ophthalmic product requests by 130 observed customers, 1 in 6 requests for ophthalmic products were associated with suspected abuse.[25]

Based on data obtained from France in 2014, the average consumption level was more than 13 mL/day per patient, which remained similar in 2015. From 2014 until July 2016, 65 pharmacies reported more than 90 suspicious but unsuccessful attempts to obtain tropicamide eye drops.[1] This study provides a baseline for assessing the general significance of the prevalence of ophthalmic cycloplegic drug abuse.[26] In addition, a thorough review of the literature suggested that tropicamide is a significant drug of abuse among the heroin-using population; however, large-scale studies are needed to assess its true prevalence.[27]

Clinical aspects of tropicamide abuse

The misuse of anticholinergic eye drops has become widespread among people with intellectual disabilities and mental disorders. Tropicamide misuse should be suspected in patients who develop an unusual array of symptoms. Specifically, the reported effects of intravenous tropicamide use include excitability, tachycardia, hallucinations, delirium, dysphoria, unconsciousness, and "open eye" dreams.[12] Cases of acute psychosis after topical tropicamide administration have also been recorded, although withdrawal contributes to rapid recovery.[14]

One of the earliest cases of tropicamide solution misuse was reported in 1975.[28] A 25-year-old man with emotional instability developed an addiction following medical treatment that he initially sought for severe infectious blepharokeratoconjunctivitis. Tropicamide was prescribed, along with antimicrobial agents and cyclopentolate. After two years, the patient returned to the clinic with complaints of drug-induced keratitis. The patient was observed for four days, while all other medications were withdrawn. However, at the next visit, all symptoms remained, including mydriasis. The patient admitted that he continued instilling 100-200 drops of tropicamide and cyclopentolate. Collateral information obtained from the patient's mother revealed that for the last nine months, he had slept most of the day, did not leave his room, and had lost 14 kg.[28] Interestingly, a very similar presentation was reported by Russian researchers,[23] who noted rapid deterioration in patients. These patients lost 5-8 kg of weight two to three months after initiating tropicamide as part of their established heroin routines. Similar to other substances, such as arsenic, tropicamide accumulates in various organs, tissues, and body fluids, causing hepatic and renal failure.[4,29]

Tropicamide-abusing patients suffer from many psychiatric difficulties, leading some researchers to suggest that polysubstance use may be a syndrome associated with a pre-existing psychiatric disorder and with certain personality traits.[30,31] Only a few studies have explored the connection between tropicamide abuse and psychopathology. For example, Mahmadnazarov & Guliamov screened 40 patients for prescription opioid and heroin use as part of an overall health evaluation; their work offered evidence that the nonmedical use of tropicamide may precipitate the development and recurrence of psychopathology in opiate-tropicamide users.[32] Some plateau effects persist after a tropicamide dose or when the number of injections is increased to 10-15 per day.[32] With an average single dose of 3-5 mL and a maximum single dose of 10 mL of 1% solution, the daily dose could be 50 mL.[23]

Effects of tropicamide abuse in patients with opiate use disorder

In recent years, analysis of clinical cases published in the literature shows that the use of both pure tropicamide and its combination with opioids may be more common than originally thought. By blocking muscarinic receptors, tropicamide produces dilatation of the pupil, preventing the eye from accommodating for near vision.[33] This mechanism allows individuals to hide the symptoms of opiate use (e.g., opiate miosis) and deflect questions when asked about it. Bersani et al. found that patients reported that the combination of tropicamide with heroin enhances the effects of intoxication.[27] Patients with opioid use disorder started using tropicamide, on average, four and a half years after starting heroin use. All patients injected tropicamide and heroin in the same syringe. The starting dose was 1-5 mL of a 1% solution. In most cases, immediate systematic combined use of heroin and tropicamide ensued. At one to three minutes after the injection, users reported that the pronounced effect of heroin was followed by a "second wave." Patients noted an increase in the effect of heroin, which included tactile and paresthesia-like sensations. These individuals noted the following: "stronger and more intense onset," "it was funny," "warmth spreading throughout the body," "a jolt in the back of the head," "a feeling of being in another place," a feeling of "deterioration of vision," and "could not see anything close" (although vision was later restored). In addition, tropicamide was specifically credited with increasing the length of a heroin high, which resulted in a dramatic increase in the frequency of injections. In the early stages of tropicamide abuse, the dosage was 0.5 g, which progressively increased to 1 g and even 1.5 g. These are extremely aggressive doses; for comparison, one drop contains 150 μg of tropicamide.[4,27]

According to Mokhnachev et al., in five of their 21 cases, after the simultaneous use of heroin with tropicamide, patients experienced various visual and auditory

hallucinations, which occurred as the dosage of tropicamide increased.[23] For example, according to their observations, during intoxication, a patient "collected something off the floor and the walls" and "could stand on all fours, with his head bowed, on the floor, or in another awkward position for 20 minutes."[23] Other authors also noted that patients with hallucinatory disorders did not remember the hallucinations and were only aware of then due to the reports of others who observed their behavior while intoxicated.[34]

Withdrawal syndromes following the discontinuation of opiates and tropicamide

Ostler reported that discontinuing the eye drops led to a pronounced withdrawal syndrome characterized by anxiety, sweating, nausea and vomiting, muscle stiffness, and tremors.[28] Some symptoms were managed with prochlorperazine; however, on the seventh day, anxiety and agitation reached a critical level, with manifestations of aggression toward the mother, who refused to give the drops.

Opioid withdrawal symptoms were less pronounced in those who used them combined with tropicamide (ie, these patients reported an improvement in opiate withdrawal symptoms).[23] Patients combining heroin with tropicamide were more likely to display vegetative manifestations and reported less severe pain than those who only used heroin. This is consistent with the findings on the benefits of atropine as a possible means of withdrawal treatment.[5,23] Psychological withdrawal symptoms can include frequent mood swings, such as extremely low mood with severe dysphoric and parasuicidal reactions, as well as episodes of psychomotor agitation and exaltation. Patients were burdened by their hospital stay, demanded immediate discharge, were rude, and expressed a conscious cravings for tropicamide.[23] Notably, to relieve these symptoms, the doses of psychotropic drugs were higher than those usually prescribed to patients with opioid use disorder.[23,35] The withdrawal symptoms lasted, on average, 5 to 7 days, but pronounced cravings for tropicamide persisted in the post-withdrawal period. These cravings remained relevant for 20-30 days after opioid withdrawal.[23]

In patients who used opiates with or without tropicamide, Kuliev found a significantly higher rate of psychopathological symptoms among those who used tropicamide, concluding that they appear to be a vulnerable population.[35] The risk of asthenic symptoms tends to be 26.1% higher in individuals with combined opiate-tropicamide use.[35] Finally, among people with substance use disorders, tropicamide coadministration may be both a driver of substance use and contributor to worse treatment prognosis.[35,36] Table 2 shows the wide range of symptoms displayed by different groups of the patients enrolled in Kuliev's study.

Combined use of tropicamide and psychostimulants

Although polysubstance abuse often refers to the abuse of multiple illicit agents, it is also includes the use of prescription medications in nonmedical circumstances. Studies published from 2000 to 2015 reported that tropicamide was used in combination with various psychostimulants.[4,37,38] Research has suggested that patients with polysubstance use are often diagnosed with complex conditions, while monodependent users tend to present with poor impulse control and attention-seeking behavior specific to stimulant use.[38] Patients with a history of using tropicamide in combination with amphetamines usually take tropicamide during the second or third year of drug use. Those who were admitted to the hospital also reported enhanced onset following amphetamine use.[23] Some patients have reported switching to tropicamide only, which increased autostimulation to such an extent that they continued to inject the drug while intoxicated. Many developed acute paranoia and persecutory delusions. The authors suggested that tropicamide antagonizes muscarinic receptors, thereby causing the onset of hallucinations and reducing the level of consciousness.[14,39] In some cases, they refused to eat, feared poisoning, and believed that their phone conversations were being recorded.[23] Furthermore, other perceptual disturbances came to the fore, mainly in the form of visual hallucinations.[23] Reportedly, patients continued using tropicamide, gradually increasing the dose, mainly by increasing the frequency of administration (up to 30 injections per day), although without amphetamines.[23,32] Additionally, some patients could not specify the dose of tropicamide they used because they continued taking the drug while intoxicated.[36]

Patients who used tropicamide alone described a feeling of extraordinary lightness, with difficulty staying on their feet. After assuming a horizontal position, they felt "warm and light." At the same time, they felt growing anxiety, dry mouth, changes in sensitivity, and a feeling that "the skin becomes rough and dry and the hair on the hands is soft and thin." After about 10 minutes, they felt a strong desire to sleep, "but not like from sleeping pills," as if "the control of the eyelids is being transferred to another person." At the same time, hallucinations were described by the patients as "insignificant." For example, "the drawings become voluminous," and "the noise becomes

Table 2 Opiates vs. opiate-tropicamide Clinical Opiate Withdrawal Scale scores

Clinical signs and symptoms of withdrawal	Patients with opiate use disorder (n=30)	Patients with opiate-tropicamide use (n=30)
Typical opiate withdrawal symptoms	2.3±0.1	2.9±0.1*
Pain-like symptoms	2.6±0.2	2.9±0.1
Psychopathological symptoms	2.4±0.1	2.8±0.1*
Duration of opiate withdrawal symptoms (in days)	5.2±0.3	9.9±0.4*

Adapted from Kuliev.[35]
* $p < 0.05$.

controllable.'' After 30 minutes, the drowsiness disappeared, which was replaced by a feeling of warmth throughout the body that was often accompanied by frequent urination. This was followed by manifestation of psychopathological symptoms, such as aggression, obsession with various meaningless nonspecific requests, frequent mood swings from an elevated ''euphoric'' mood to pronounced dysphoric reactions, including excitement, aggression, and blurred vision.[23]

Other clinical features of tropicamide abuse

Other systemic symptoms of tropicamide use include hyperthermia, tremors, paralytic ileus, persistent mydriasis,[40] cardiovascular effects[41,42] and anaphylaxis.[43] Prolonged systemic administration of tropicamide is associated with toxic cardiomyopathy, urinary retention with dysuria, severe anemia, angiopathy, toxic hepatitis, and cirrhosis.[5,23] People with a history of intravenous tropicamide use are at risk of venous disease and leg ulcers, especially if they inject or used to inject it into the femoral and/or other superficial veins.[44] Regarding the other effects, tropicamide can cause seizures in children[45] and adults.[46] Another case report described a 62-year-old patient who developed a generalized convulsive seizure with respiratory arrest 30 minutes after fundoscopy and required emergency treatment.[47] An acute anticholinergic reaction was reported in a 2-month-old boy after instillation of tropicamide.[48]

In theory, any anticholinergic drug use may result in cognitive impairment, but reports regarding the cognitive effect of tropicamide are limited. Tropicamide is a non-selective muscarinic antagonist that binds to all main subtypes of muscarinic receptors.[49] Its long-term interaction with M1 receptors could cause cognitive impairment in certain patients. Fortunately, it rarely causes systemic neurocognitive effects when used topically.[50-52] Finally, magnetic resonance imaging of the brain of a patient with a 4-year history of tropicamide use revealed multiple foci of demyelination.[34] This clinical example demonstrated acute isoniazid poisoning from a background of tropicamide use. Later, this patient developed acute psychosis and was admitted to a psychiatric ward.[34] Figure 2 summarizes the potential negative outcomes of tropicamide abuse.

Discussion

This review of the existing data shows that the abuse of ophthalmic drops is still under-researched worldwide. Early impulsive behaviors, a genetic predisposition, a dysfunctional family, parents or siblings/peers with problem drug use, excessive use of alcohol, unemployment with potential social deprivation, undiagnosed mental health problems, legal issues and crime, and drug availability (e.g., online pharmacies) and system-based issues are risk factors associated with increased likelihood of tropicamide abuse. Our observations also confirm that risk factors occurring during early childhood further increase the risk of substance abuse. Moreover, these risk factors are common across multiple substance use disorders.

Although tropicamide abuse is not common in the USA, optometrists and ophthalmologists may encounter many other illegal drugs. We believe that optometrists could be the first clinicians to become aware of a patient's drug use problem. Although some ophthalmologists are aware of the addictive potential of tropicamide because of its

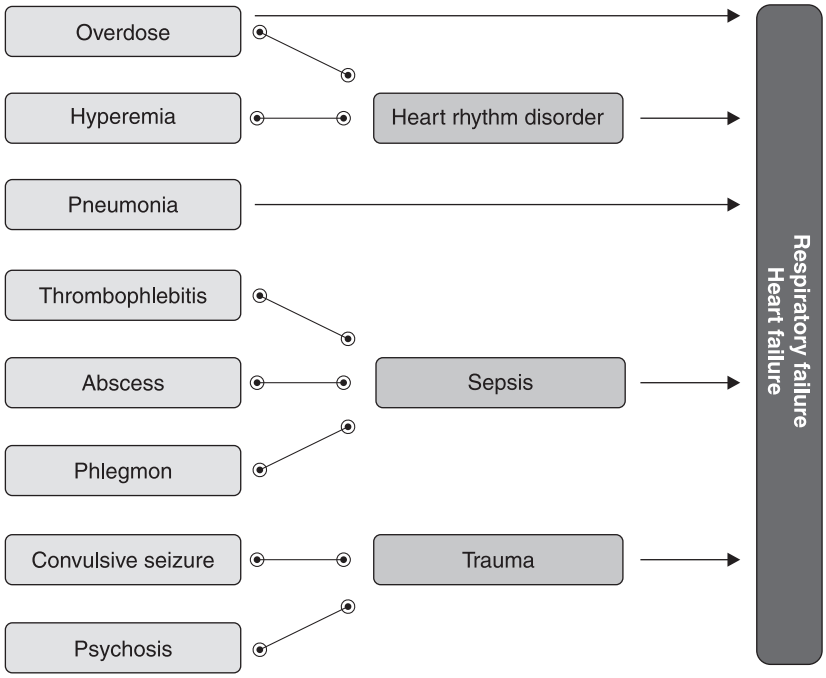

Figure 2 Negative clinical consequences of tropicamide abuse.

Box 1 Ocular manifestations of illicit drug use

Substance	Ocular changes and findings
Alcohol	Horizontal gaze-evoked nystagmus. Increased risk of cataracts, macular degeneration, optic neuropathy, impaired visual quality, and retinal vascular disease.
Nicotine and nicotinic acetylcholine agonists	Smoke-related dryness, poor corneal healing/laceration, increased risk of cataract, age-related macular degeneration.
Cannabis	Decreased intraocular pressure, ''red eye syndrome,'' decreased saccadic accuracy, diminished smooth pursuit eye movements, decreased acuity, and increased photophobia.
Cocaine	Pupillary dilation, conjunctival blanching, decreased corneal sensation, ''crack cornea,'' bilateral keratitis if snorted, secondary infectious keratopathy.
Heroin	Pupillary changes, talc retinopathy, endogenous infectious endophthalmitis and toxoplasmic chorioretinitis (in intravenous users).
Methamphetamine and other stimulants	Pupillary dilation, decreased accommodation with blurry vision, intra-retinal hemorrhage or a non-ischemic optic neuropathy, episcleritis, scleritis and retinal vasculitis, cornea ulceration, and exposure keratopathy.

relaxing properties, in one study, less than 50% of practicing ophthalmologists were able to correctly identify the pattern and correct definition of abuse.[25] Physicians and optometrists who treat patients with substance use disorder have limited data to guide treatment decisions. Familiarity with the local healthcare network is important for improving patient outcomes. Fortunately, ''eye doctors'' can recognize drug-related damage or dysfunction to eye structures and counsel those patients accordingly. Box 1 summarizes how abusing specific drugs can affect various ocular structures.

While the tropicamide abuse epidemic is still predominantly fueled by intravenous drug users from the former Soviet Union, there are clear signs that the epidemic continues to spread around the world. Furthermore, the lack of effective coordination between law enforcement, state government and public health agencies has led to inadequate interagency preparation and response to drug-related threats, as well as other public health emergencies. In response to the addiction crisis, Russia and other countries should focus their efforts on improving access to treatment and recovery services. Yet, despite abundant evidence that addiction is a treatable medical condition, drug addiction continues to be criminalized.[53] Thankfully, in Switzerland and France, public health officials realized they couldn't force drug users into treatment.[11] Additionally, forced abstinence through imprisonment isn't treatment, and it doesn't cure addiction. European data show that individuals with substance use disorders benefit more from a supportive approach than punishment.[11,54] Between 1991 and 2010, overdose deaths in Switzerland decreased by 50 percent, HIV infections decreased by 65 percent, and new heroin users decreased by 80 percent.[55,56] Unfortunately, opioid agonist therapy has not yet been implemented in Russia and some post-Soviet countries (e.g., Uzbekistan, Turkmenistan). This system still limits access to evidence-based drug dependence treatment for injection drug users (including tropicamide users). Clearly, foundational changes are needed in the health system to serve the best interests of tropicamide and/or drug users and to achieve health care and evidence-based treatment that are adequate and affordable for everyone.

In the past, ''designer drugs'' were produced in illegal laboratories and sold directly on the black market. Today these chemicals are legally sourced and then sold as ''legal'' replacements for controlled substances. Moreover, some countries have encountered serious problems due to the use of prescription drugs with psychotropic effects for non-medical purposes. Today, anyone can buy agents like tropicamide online without ever showing proof of age or a prescription.[2,57]

We reviewed multiple protocols and treatment strategies available online but could not identify a unified approach in the treatment of these patients. Although neurotoxicity and behavioral changes can be caused by numerous anticholinergic agents, the main treatment for poisoning due to tropicamide abuse is terminating exposure to the substance. Some cholinergic agents, such as pilocarpine, are used off label to counter the effects of cycloplegics like tropicamide and diminish the other effects of anticholinergics, but their systemic use is questionable. Similarly, other adrenergic antagonists, such as dapiprazole or moxisylyte, can be used topically,[58] but no approved methods exist for reversing tropicamide-induced systemic effects. According to Bozkurt et al., combined therapy with buprenorphine/naloxone, mitrazapine, trazodone, and sometimes atypical antipsychotics may be helpful in inpatient settings[5]; however, no data yet support this regimen for long-term management of tropicamide users.

In conclusion, several factors have been proposed for the increasing misuse of tropicamide, including its enhancement of the positive effects of heroin (''intensifies the high''), its decrease and delay of opiate withdrawal symptoms, its quick and potent effects after administration, its availability as an over-the-counter drug in many parts of the world, its relatively low cost, and anecdotes about it on the Internet and in popular media sources. Furthermore, the lack of effective coordination between

law enforcement and social agencies and the lack of complex and multidisciplinary approaches, especially to drug demand reduction, treatment, and rehabilitation, must still be addressed in most countries. Finally, more high-quality, large-scale studies are needed to accurately characterize tropicamide misuse globally.

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