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REVIEW ARTICLE

U-47700. An old opioid becomes a recent danger

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Abstract U-47700 is a synthetic opioid analgesic and a potent, short acting structural isomer of the earlier opioid AH-7921 that has recently invaded the drug arena in Europe and the Unites States. Although the drug was synthesized and patented in the 1970s, it was first identified in October 2014, as a powder sample that was seized by Swedish Customs. Sweden formally notified the European Union Early Warning System in January 2015. Animal studies proved that U-47700 is a strong μ-opioid receptor agonist and has a morphine-like analgesic action, being 7.5 times higher than morphine. The drug has a much lower affinity for the κ-opioid receptor. This newly appearing psychoactive substance has already led to more than 25 confirmed fatalities associated with U-47700 in Europe and the United States and to six non-fatal intoxications reported in the United States. The aim of this review is to summarize the current knowledge about this drug, regarding its chemistry, synthesis, pharmacology, toxicology and metabolism, as well as its international legal status. The existing analytical methods for the determination of U-47700 in biological samples are also presented. Published or reported U-47700 related cases, fatalities or intoxications, and self reports from drug users are reviewed.

Keywords U-47700 · New psychoactive substance · μ-Opioid receptor agonist · Recent trend of abuse · Pharmacology and toxicology · Legal status

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Introduction

During the last decade, new psychoactive substances (NPSs), which are mainly synthesized by substitution of already controlled compounds, are commonly used worldwide by drug addicts or recreational users. These substances are often identified during the toxicological investigation of relative intoxication or fatal cases [1, 2]. Due to the chemical alterations of the parent compounds, NPSs are not initially scheduled as controlled substances and sometimes there is a time lag for their scheduling [3]. They are usually produced in China or other Asian countries and purchased via Internet retailers, as "designer drugs", "legal highs" or "research chemicals" [3–7].

NPSs are mainly synthetic phenethylamines, piperazines, cathinones and cannabinoids, but some new synthetic opioids have also emerged on the recreational and illicit drug market [1]. This is the case of U-47700 (3,4-dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide), which is a synthetic opioid, derived from the earlier opioid analgesic AH-7921 (3,4-dichloro-*N*-{[1-(dimethylamino)-cyclohexyl]methyl}benzamide). This opioid is openly ordered via the Internet mainly from China or Eastern Europe, and it is characterized as "legal high", "research chemical" or "designer drug" [3, 4, 8, 9].

U-47700 is used or abused for its morphine-like properties, as it is a strong μ-opioid agonist, whereas it has much lower affinity for the κ-opioid receptor. It was developed and patented in 1978 by Jacob Szmuszkovicz, a chemist at the Upjohn Company, as a potential analgesic medicinal drug. The "U" of its name refers to Upjohn [10]. U-47700 has been studied only in animals, and it was found to be 7.5 times more potent than morphine, but about 10 times less potent than fentanyl [2, 11]. Pharmacological and toxicological data for U-47700 are limited or

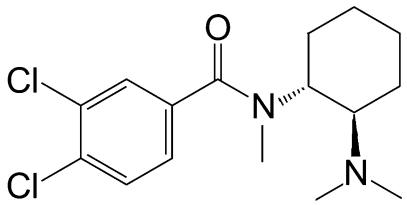
unavailable, as it was never studied in humans or marketed as a pharmaceutical and medicinal drug for human use. It is expected to produce effects similar to those of other potent opioid agonists, like analgesia, sedation, pronounced euphoria, constipation, itching, hypothermia, respiratory depression and miosis. Prolonged use of the drug shows addictive behavior and very high doses could result in coma and death [2, 12]. Many intoxication or fatal cases associated with the use of U-47700 alone or along with other opioids, like fentanyl, furanyl and butyryl fentanyl, have been reported in 2016 [1–6, 8, 13, 14]. These reports indicate that U-47700 poses an imminent hazard to the public safety [15].

Seizures of U-47700 have been reported in eleven member states of the European Union (Austria, Belgium, Denmark, Estonia, France, Germany, Lithuania, Slovenia, Spain, Sweden and United Kingdom,) and in the United States; severe intoxication cases or deaths have also been reported during the last two years. Thus, U-47700 is already controlled in three European countries (Sweden, Finland and United Kingdom) and in the United States for 2016 [15, 16].

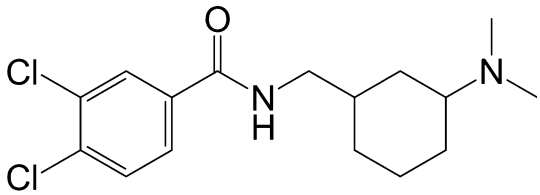
The aim of this review is to summarize the current knowledge about U-47700, regarding its chemistry, synthesis, pharmacology, toxicology and metabolism, as well as its legal status. The existing analytical methodology for the determination of U-47700 in biological samples is also presented. Published or reported U-47700 related cases, fatalities, intoxications, and self reports from drug users are reviewed.

Chemistry

U-47700 is a structural isomer of the opioid AH-7921 and an atypical opioid of the benzamine class that is selective for the μ-opioid receptors (Fig. 1). Similarly to its isomer, U-47700 is a derivative of dimethylaminocyclohexane to which the 3,4-dichlorobenzamide moiety is appended [15, 17, 18]. It was designed, synthesized and patented in the late 1970s among a series of (2-aminocycloaliphatic) benzamides and naphthamides [10]. Its IUPAC name is 2-(3,4-dichlorophenyl)-*N*-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]-*N*-methylacetamide, while 3,4-dichloro-*N*-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide and *trans*-3,4-dichloro-*N*-[(2-(dimethylamino)cyclohexyl]-*N*-methyl-benzamide are also used as alternative chemical names. U-47700 and U-47,700 are used as common names [15, 17]. U-47700 has the molecular formula $C_{16}H_{22}Cl_2N_2O$, a molecular weight of 329.27 g/mol and a melting point of 97–98.5 °C. Its free base CAS number is 121348-98-9, while its hydrochloric acid salt has the CAS number 82657-23-6 [12, 15, 17].



U-47700



AH-7921

Fig. 1 Chemical structures of U-47700 and AH-7921

U-47700 possesses two chiral centers; thus, it can occur as two geometric diastereomers (*cis* and *trans*) that show different pharmacological properties [6, 15]. Particularly, the *trans* isomer has been the target of specific in vivo pharmacology studies [11, 19]. As mentioned above, U-47700 and AH-7921 are isobaric compounds, as they have the same molecular formula, but they have different molecular structure. This can be a problem during the differentiation of these two drugs. Pure reference standards should always be used to detect and differentiate U-47700 from AH-7921 [6].

Synthesis

The synthesis of U-47700 was first described by Szmuszkovicz, who owned the relative patent in 1978 and later by Cheney et al. [11] who synthesized it among a series of *trans*-*N*-[2-(methylamino)cyclohexyl]benzamides that possess morphine-like pharmacological properties. The synthetic procedure included an initial reaction of *N*-methyl-azabicyclo[4.1.0]heptanes with dimethylamine followed by a refluxed reaction of the resulting *trans*-1,2-diaminocyclohexane with 3,4-dichlorophenylacetyl chloride to yield 3,4-dichloro-*N*-[(1*R*,2*R*)-2-(dimethylamino)-cyclohexyl]-*N*-methylbenzamide [10, 11].

Prevalence and use

U-47700 firstly appeared on the European drug market in October 2014, when the Swedish Customs in Arlanda airport (Sweden) seized 5.3 g of white powder, which was analytically confirmed as U-47700 [16]. In October 2015, another seizure of 0.80 g white powder, sent from the

United Kingdom and labeled as "U-47700", was made by the Estonian Customs at Tallinn (Estonia). A parcel sent from China to France was seized in the Roissy airport of Paris (France) in December 2015 and was found to contain 10 g of U-47700 as a white powder and 10 g of a fentanyl pentanamide analogue. During 2016, several seizures of powder, liquid samples and tablets were made all over Europe. More specifically, seizures took place in Spain (1054 g white powder, sent from China), Belgium (10 g white powder, en route to Germany), Slovenia (1 g white powder), Denmark (2 g white powder, sent from Belgium), Sweden (1 g powder and 261 mL liquid), the United Kingdom (three seizures for a total 2629 tablets), Germany (49.9 g white powder, the country of destination was Poland), Lithuania (1.6677 g white powder, sent from China) and Austria (783.6 g white powder). The three different types of seized tablets in the United Kingdom featured three separate designs of counterfeit diazepam that bore logos like "MA" (854 white tablets), "5" (1014 yellow tablets), "COX" and "DC" (761 yellow tablets), whereas all of them were opposite-unmarked [16, 20]. In the United States, seizures of U-47700 have been made for counterfeit tablets that also mimic pharmaceutical opioids and those in powder form [15]. In Central California, beige pills, street-purchased as "Norco", bore the "Watson" imprint and contained U-47700 according to the toxicological analysis of the biological fluids of an intoxicated user of them [3]. A European Union Early Warning System Alert (EU-EWS-RCS-AL-2016-0003) for "U-47,700 in Europe" was issued in June 2016 by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), after three deaths occurred in the first two months of 2016 in three member states, Belgium, the United Kingdom, and Sweden. Two more deaths were recorded in Finland in April and July of 2016 [16, 20].

U-47700 has not been approved by the Food and Drug Administration (FDA) for human consumption and has no established or acknowledged industrial, agrochemical, cosmetic, human or veterinary medical value or use; there is no marketing authorization for this substance worldwide. The drug is legitimately used as an analytical reference standard and can be ordered online from suppliers of chemicals. These licit products are, of course, not intended for human consumption. However, this opioid is openly sold on the Internet at various websites as "U-47700" or "U4" and "hot melt powder", for as little as $ 40 per gram of powder with discounts if larger quantities are purchased. A 15 mL bottle of liquid containing 20 mg/mL of U-47700 is sold for $ 35.99. All products are labeled as "research chemical", "not for human consumption" or "for research purposes only", in order to pretend that they have licitness [4, 5, 13, 15].

Information about the dosage and the route of administration of U-47700 or its concomitant use with other drugs of abuse, such as medicinal drugs and alcohol was collected from published papers concerning intoxication and lethal cases, or was extracted from self-reported experiences in drug forums and other related websites. U-47700 is used by oral consumption, inhalation, snorting, intravenous injection and intrarectal administration or by combinations of these routes, and in the forms of tablet, powder and liquid at doses ranging from 1 to 50 mg [1–4, 14, 21, 22]. A threshold dosage is considered to be 1–4 mg, a light one 4–6 mg, a common dose 6–8 mg, a strong dose 8–10 mg and a heavy dose higher than 10 mg [22].

In some published case reports of deaths or intoxication cases, alcohol, medicinal, controlled drugs and/or other NPSs were also detected in biological samples along with U-47700, because many drug addicts or recreational users take it in combination with other substances, especially fentanyl or its analogues, like furanyl and butyryl fentanyl [2–4].

Pharmacology and toxicology

To our knowledge, the pharmacological and toxicological data of U-47700 based on animal studies is limited [11, 19]. Cheney et al. [11] accomplished a comparison study, and they concluded that the drug showed morphine-like behavioral effects. The drug proved to be a strong μ-opioid receptor agonist ($K_d = 5.3$ nM) that also exhibited some κ-opioid receptor agonism ($K_d = 910$ nM) [11]. Corresponding results were obtained later by Loew et al. [19]. The drug possessed significant analgesic properties ($ED_{50} = 0.2$ mg/kg), while it did not antagonize morphine at dosages as high as 100 mg/kg of body weight ($ED_{50} > 100$ mg/kg) [11]. The analgesic action of U-47700 proved to be 7.5 times stronger than that of morphine in the animal models tested [11, 23].

There are no published studies concerning the pharmacological or toxicological action of U-47700 in humans. The drug has not been approved by the FDA for human consumption [15]. The scarce information on its pharmacology and toxicology originates from drug addicts or recreational users, who report their experiences in drug forums or related websites, and from recently published intoxication or fatal cases. The drug when used at common doses produces euphoria, relaxation, anxiety suppression, pain relief, respiratory depression, itch, irritability, sedation, fatigue, constipation, cough suppression, urination difficulty, miosis, nausea, drowsiness and decreased libido. Some users mentioned that some of its effects are similar to those of oxycodone. The onset of the effects takes place

after 5–10 min, the come up after 15–20 min and the peak after 1–2 h. The total duration lasts 2–3 h, whereas after-effects can be observed after 2–4 h. When used at high doses, U-47700 induces respiratory depression that can result in a shortness of breath, abnormal breathing, cyanosis, semi-consciousness or unconsciousness, coma, pulmonary edema and death [1, 2, 5, 14, 22]. Snorting of U-47700 can cause epistaxis for users [13]. Drug users report a "comedown" or "crash" during the retreat stage of the drug effect, whereas its desired (positive) effects, described as "a very pleasant opiate glow" or "the radiant glow of euphoria", generally occur during its peak [13, 21, 22]. A U-47700 user mentioned that he "intranasally ingested 6 mg of U-47700 over a span of maybe 30 min. It kicks in slowly, but I feel fantastic euphoria and happiness" [21]. Another female user after snorting of the drug felt "cool and relaxed" and described a euphoric state similar to that of heroin use [5].

A woman with chronic back pain who tried orally three counterfeit "Norco" pills felt sleepy within 30 min and was found unresponsive later [3]. Another woman felt asleep for 3 h after snorting of U-47700 powder for recreational reasons [5]. A user who took 17 mg U-47700 intrarectally stated that "I can only stay awake for 20 min…I fall into a deep and pleasant sleep…I wake up and feel no effects". According to users of U-47700, the duration of effects after intrarectal use is longer (about 2 h) than that after intranasal use (about 1 h) [21].

The probability of toxic effects associated with the use of unknown compounds, especially those with opioid activity, is extremely high [4]. Due to its high potency as an opioid, the toxicity of U-47700 is high and dose dependent. The drug shows high potential for abuse as its chronic use can cause psychological dependence, tolerance or cross-tolerance with other opioids and withdrawal symptoms when suddenly stopped [15, 22]. It is a common practice that opioids are co-abused with benzodiazepines, as this increases the level of euphoria [24]. In reported cases, U-47700 has been detected along with benzodiazepines like alprazolam, diazepam, nordiazepam, oxazepam, temazepam, lorazepam and phenazepam [2, 8, 14]. The combination of U-47700 with other substances can provoke harmful interactions, like dangerous or even fatal respiratory depression, increased risk of vomiting during unconsciousness and death from the resulting suffocation when it is consumed with sedatives (1,4-butanediol, alcohol, barbiturates, benzodiazepines, and GHB/GBL) and dissociatives (arylcyclohexamines, morphinans or piperidine derivatives). Furthermore, combined with stimulants, the sedative effect of U-47700 decreases, but these effects significantly increased again after the action of stimulant retreats [22].

Metabolism of U-47700

To our knowledge, there is limited data about U-47700 metabolism that is mainly derived from reported cases and not from animal or human metabolic studies [6, 13]. It is suggested that the phase I metabolic steps include *N*-demethylation of the tertiary amine group followed by hydroxylation of the cyclohexane ring (Fig. 2), but there is no information whether these metabolites are pharmacologically active or not. The prominent phase I metabolites of U-47700 were identified mainly in urine based upon the intact molecular weight, molecular fragmentation patterns and chromatographic characteristics. The four metabolites of the drug that were totally identified in drug users' biological samples were desmethyl-U-47700, *N,N*-bisdesmethyl-U-47700, desmethyl hydroxyl-U-47700 and *N,N*-bisdesmethyl hydroxyl-U-47700. The main metabolite was found to be desmethyl-U-47700. Two primary and two minor isomers for each hydroxylated metabolite were further identified. Phase II glucuronide metabolites were not detected in urine [13].

Intoxication and fatal cases related to U-47700 use

The growing recreational use of U-47700 has led to an increasing number of confirmed cases of severe intoxications and fatalities associated with its consumption in Europe and the United States [15, 16]. During 2016, a significant number of U-47700 intoxication cases that occurred in the United States were reported in the scientific literature. The clinical symptoms described in these case reports included miosis, respiratory depression, cyanosis, depressed level of consciousness, drowsiness, tachycardia, anxiety, nausea, abdominal pain and epistaxis [1, 3, 5, 13, 14]. In most of these cases, the toxicity symptoms were reversed after administration of naloxone, and this is consistent with the known in vitro and in vivo opioid-receptor agonism of U-47700. Furthermore, the short length of time that its opioid toxicity lasted suggests a relatively short half-life of the drug [1].

A 41-year-old woman with chronic back pain illicitly purchased pills that were thought to be "Norco" (a combination of acetaminophen and hydrocodone) in the United States (California). After ingestion of three pills, she felt sleepy within 30 min and later she was admitted to hospital practically unresponsive with remarkable miosis. The patient woke up in the resuscitation room after intravenous administration of naloxone. Lorazepam and diphenhydramine were further administered. She had no desire to remain at hospital for a long time and was discharged 4 h later completely recovered. U-47700 and fentanyl were

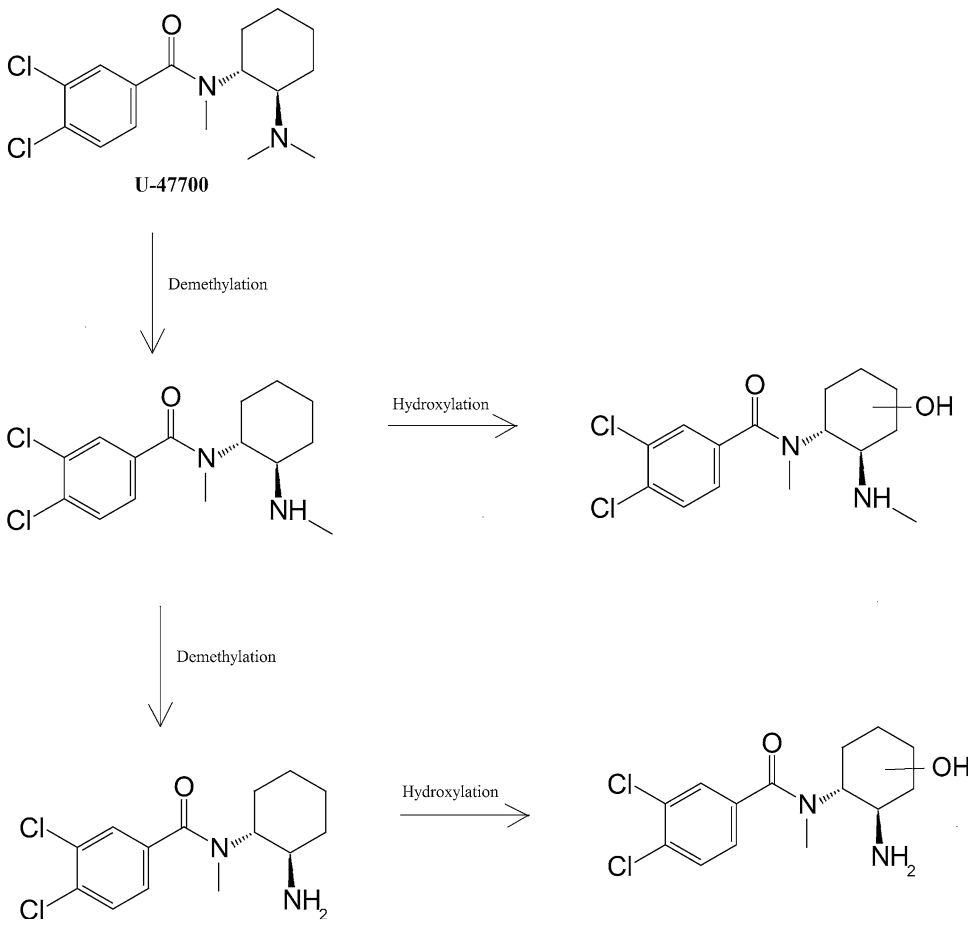


Fig. 2 Proposed metabolites of U-47700 by Jones et al. [13]

found in her serum at concentrations of 7.6 and 15.2 ng/mL, respectively [3].

A young couple in the United States (Texas) purchased on the Internet a powder named U-47700, thinking it was "synthetic cocaine", and they snorted it after the consumption of alcohol and alprazolam. The woman (24-year-old) felt "cool and relaxed" and slept for about 3 h. When she woke up, she found the man (26-year-old) unresponsive with tachycardia, agonal breathing and cyanosis, and called for an ambulance. The man was admitted to the intensive care unit, and he was discharged after three days without any further problems. The woman remained at the hospital for 24 h observation as she was only complaining of anxiety, nausea and abdominal pain. U-47700 was detected in urine samples of both patients by liquid chromatography (LC)–quadrupole (Q) time-of-flight (TOF)–mass spectrometry (MS), but was quantitated only in the man's urine at a concentration of 0.1 ng/mL by LC-tandem mass spectrometry (MS/MS). The drug concentration in the woman's urine was below the detection threshold of the analytical method used, as she possibly used a smaller dose of the drug. Due to this, she suffered a milder opioid toxidrome that was restored prior to her hospital admission. Alprazolam was not detected in the patients' urine, while ketorolac was detected in both samples. Domanski et al. [5] suspected that ketorolac was sold to the patients as alprazolam.

Jones et al. [13] reported an overdose case of a 23-year-old female in the United States (Minnesota), who was found unresponsive after snorting and injection of a substance that she called "U4". The woman admitted to the hospital with respiratory depression and cyanosis and her chest X-ray revealed patchy infiltrates and mild congestion consistent with pulmonary edema. She was given intravenously naloxone and placed on a bilevel positive airway pressure device, which restored her oxygen saturation and respiratory rate. The patient was discharged the following day after her pulmonary status was improved. She confessed that she had injected the drug after snorting it for the last three days; something had caused her epistaxis. U-47700 was found in serum and urine samples of the patient at concentrations 394 and 228 ng/mL, respectively. The desmethyl (1964 ng/mL), *N,N*-bisdesmethyl (618 ng/mL), desmethyl hydroxy (447 ng/mL) and *N,N*-bisdesmethyl hydroxy (247 ng/mL) metabolites of U-47700 were detected in appreciable amounts in urine. In serum, only desmethyl U-47700 (27 ng/mL) was found. The concentrations of all metabolites were approximate and

based on the assumption that the molecular response of the metabolites corresponds to the response of the parent drug. The concentrations of the hydroxy metabolites were estimated as the total of the four detected hydroxylated isomers [13].

Schneir et al. [1] presented a case of a 22-year-old male found unconscious, apneic and cyanotic by his mother. The young man had a history of heroin abuse, and his mother performed cardiopulmonary resuscitation according to the instructions of emergency medical services for about 5 min until paramedics arrived. An oral pharyngeal airway was placed with a bag-valve mask and naloxone was given intravenously. The oxygen saturation was improved, and his coma and bradypnea were completely reversed. He was discharged home after approximately five hours from the emergency department. The patient stated that he purchased 250 mg of U-47700 in powder form via the Internet and divided it into five separate doses. It was the third time that he used the drug after placing the dose in a syringe, mixing it with water and applying it to his nostrils. U-47700 was detected in the powder supplied by the patient and in his urine sample [1].

Another intoxication case presented by Vo et al. [14] dealt with a 29-year-old male who showed mild symptoms after intravenous injection of U-47700. He was found unresponsive, but spontaneously regained consciousness before his arrival at hospital. The patient was presenting hypertension, tachycardia and a slightly increased creatinine value. He remained at the emergency department for observation only for 3 h, where his vital signs improved without any pharmaceutical treatment. The man admitted that he had purchased U-47700 over the "darknet" and injected it intravenously. He had also taken phenazepam some days ago. U-47700 and phenazepam were detected in serum and urine samples. The serum concentrations of the two drugs detected were found to be 240 and 1400 ng/mL, respectively [14].

The pilot exercise on collection of toxicology data of the United Nations on Drugs and Crime (UNODC) that took place in July and August 2016 reported that U-47700 was the most frequent NPS implicated in fatal cases [25]. This indicates that this drug is a harmful substance worldwide that can be an imminent hazard to the public safety. According to EMCDDA, five U-47700 related deaths have been reported during 2016 in Belgium (1), the United Kingdom (1), Sweden (1) and Finland (2). The presence of U-47700 was analytically confirmed in all these cases [4, 6, 16]. In the two fatal cases that occurred in Finland, the concentration of the drug in femoral postmortem blood was 190 and 220 ng/mL, respectively [16]. In a recent Drug Enforcement Administration (DEA) report, at least 15 overdose fatalities involving U-47700 have been confirmed during the last 2 years in New Hampshire (1), North Carolina (10), Ohio (1), Texas (2) and Wisconsin (1) [15].

Data from some of the abovementioned reported fatal cases are included in some recently published papers. Spargo [8] reported two fatal cases that occurred in 2015 in Dallas, Texas and were analytically confirmed in February 2016. A 27-year-old white male with a history of depression, pill abuse, suicidal thoughts, hypertension and possible illegal drug use was found dead in a kneeling position with his face on the floor and a bloody exudate drained from his airways. At the scene of death, two bags of unknown white powder were found. According to his father, they were purchased from China via the Internet. During autopsy, cardiomegaly and pulmonary edema were observed. U-47700 was identified in one of the powder samples, as well as in his femoral blood, whereas etizolam was detected in the other powder but not in his biological samples. Ibuprofen, diazepam, nordiazepam, oxazepam and temazepam were also found in his blood. The second case concerned a 20-year-old white male with a known history of cocaine and marihuana abuse who was found unresponsive and died few minutes later. His friends stated that he had used "opiate-like substances [purchased] over the Internet that wouldn't show up on a drug test". During autopsy, cardiomegaly, hepatosplenomegaly, gross pulmonary congestion and edema were observed. The only drug detected in his biological fluids during toxicological analysis was U-47700 [8].

Coopman et al. [4] presented a fatal case due to combined use of fentanyl and U-47700. This death occurred in Belgium in January 2016 and concerned a 30-year-old man who was found dead after possibly inhaling fumes of a powder burnt on aluminium foil. Fentanyl and U-47700 were determined in his blood at concentrations of 10.9 and 13.8 ng/mL, respectively. Sertraline was also determined at a therapeutic blood concentration (180 ng/mL). All three substances were also detected in his urine. The urine concentration of U-47700 was found to be 71.0 ng/mL. Drug paraphenarlia, a recently delivered envelope from China and a powder labeled "hot melt powder" were also found at the scene of death. The victim was a known drug abuser who often experimented with substances purchased from different websites. The cause of this accidental death was judged to be overdose with fentanyl and U-47700 [4]. Although, it is to be noted that a more recently published paper [26] commented on this case that the concentrations of U-47700 found in blood and urine are not compatible with U-47700 overdose, because blood concentration was much lower than urine concentration and metabolites of U-47700 were not determined in urine or were determined by mistake as the parent compound. The finding of pulmonary edema was also questioned.

Elliott et al. [6] presented another fatal case that happened in January 2016 in the United Kingdom. The victim was a 27-year-old man, who was found dead at home, and he was a known user of cannabis, ketamine, mirtazapine, cathinones and other "legal highs". The toxicological analysis performed in biological fluids revealed the presence of U-47700 and its metabolites (desmethyl U-47700 and *N,N*-bisdesmethyl U-47700) with greater abundance in blood compared to urine. The blood concentration of the parent compound was found to be as high as 1460 ng/mL. Powder found in his nasal area was also analyzed and U-47700 was also determined [6].

Mohr et al. [2] reported 16 U-47700 related deaths that occurred in the United States between October 2015 and March 2016. In six of these cases, U-47700 was determined along with fentanyl analogues, such as furanyl fentanyl ($n = 5$) and butyryl fentanyl ($n = 1$). The blood concentration of U-47700 in all these cases ranged from 17 to 490 ng/mL. Other opiates or opioids like morphine, 6-monoacetylmorphine, oxycodone, tramadol and *O*-desmethyltramadol were also identified in postmortem blood. In some of the above cases, ethanol and drugs of abuse or medicinal drugs like amphetamine, mephedrone, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol, alprazolam, lorazepam, etizolam, 3-methoxyphencyclidine, 4-aminophenyl-1-phenethylpiperidine, diphenhydramine, chlorpheniramine, citalopram,venlafaxine, *O*-desmethylvenlafaxine and quinine were also determined. All victims were males aged from 18 to 40 years; most of them had a history of drug use or abuse, and a significant number of them were regularly ordering designer drugs from the Internet [2].

Analysis of U-47700 in seized materials and biological samples

The analytical data for U-47700 are limited, and this often makes its detection, monitoring and control more difficult. The developed methods are mainly based on LC combined with MS/MS or TOF-MS, and they have been mostly applied in biological samples for clinical and forensic purposes. Due to its chemically basic nature and structure, its extraction from biological samples is usually by simple liquid–liquid techniques.

Some analytical data of U-47700 coincide with those of AH-7921, as they have the same molecular formula ($C_{16}H_{22}Cl_2N_2O$), but different structure. Schneir et al. [1] confirmed the presence of a compound with the above molecular formula in a powder seized material and a urine sample using LC–TOF-MS. They reasonably concluded that it was U-47700 and not AH-7921, as the two substances had different retention times and spectra [1]. Armenian et al. [3] also confirmed the presence of U-47700 and fentanyl in patient's serum by LC–QTOF-MS.

Specific immunoassays for U-47700 are not commercially available. Nevertheless, the drug or an unknown metabolite of it gave a false positive result by immunoassay using Roche ONLINE DAT Plus performed on a Cobas 6000 analyzer (Roche Diagnostics International Ltd., Switzerland) for benzodiazepines in a patient's urine. Further study indicated that either a very high concentration of U-47700 (>10 mg/mL) or an unknown metabolite of the drug possibly cross-reacted with the specific immunoassay [1]. The use of a benzodiazepine, not tested for, cannot be excluded [1, 14].

Coopman et al. [4] reported the determination of U-47700 in postmortem blood and urine samples by ultra performance liquid chromatography (UPLC)–MS/MS after alkalization of the biological samples and liquid–liquid extraction with a mixture of *n*-hexane/ethyl acetate (7:3, v/v). The drug was also identified by UPLC–MS/MS in a powder labeled as "hot melt powder" found at the scene of death after extraction with methanol [4]. Domanski et al. [5] detected U-47700 in urine samples after dilution with pure water and direct injection to LC–QTOF-MS and quantitated the drug by LC–MS/MS after hydrolysis with β-glucuronidase and extraction by solid-phase extraction (SPE) using PSCX cartridges [5].

There are only two published case reports that included the determination of U-47700 metabolites in biological samples [6, 13]. Elliott et al. [6] used their previously developed methodology [27] for the determination of U-47700 and its metabolites (*N*-desmethyl U-47700 and *N,N*-bisdesmethyl U-47700) in biological samples. Their methodology included high-performance liquid chromatography with diode-array detection, LC–MS/MS, and ultra high-performance liquid chromatography (UHPLC)–QTOF-MS methods. The samples were liquid–liquid extracted with 1-chlorobutane after alkalinization [6]. Jones et al. [13] determined U-47700 in serum and urine during the investigation of an intoxication case. The sample pretreatment procedure included only extraction with methanol followed by dilution with water prior to UHPLC–MS/MS analysis. The developed method was also used to study metabolites of the drug that were identified in the urine sample, like desmethyl U-47700, *N,N*-bisdesmethyl U-47700, desmethyl hydroxy U-47700 and *N,N*-bisdesmethyl hydroxy U-47700 [13]. Further metabolic studies and certified reference standards will verify the above detected substances as metabolites.

Mohr et al. [2] developed and validated a method for the determination of U-47700, U-50488 and furanyl fentanyl in blood using LC–MS/MS for the toxicological investigation of opioid-related overdoses. Sample preparation included SPE using Clean Screen DAU 130 mg columns (UCT, Bristol, PA, USA) and elution of the analytes with ethyl

acetate/acetonitrile/ammonium hydroxide (78:20:2, v/v/v) [2].

Nuclear magnetic resonance, Fourier transform infrared spectra and mass spectrum of U-47700 are available at the European Information System and Database on New Drugs and can be used for the identification of the drug in seized materials [16].

Legal status

U-47700 is currently controlled in only three European countries, Finland, Sweden and the United Kingdom. Particularly, in Finland the drug was included in a list of 65 NPSs, and according to a government decree, their production, import, storage, sale and handling are prohibited since 28 September 2015 [28]. In Sweden, U-47700 is controlled as a narcotic since 26 January 2016 after the proposal of the Public Health Agency on 17 November 2015 [29]. In the United Kingdom, this substance is illegal to produce, supply or import under the Psychoactive Substances Act since 26 May 2016 [22, 30].

In May 2016, the Governor of Ohio of the United States urgently issued an executive order to add U-47700 to Schedule I as a controlled substance opium derivative [31]. In September 2016, the Deputy Administrator of the DEA decided to temporarily classify U-47700 as a Schedule I controlled substance under the US Federal Controlled Substances Act on the manufacture, distribution, possession, importation, exportation, research, and conduct of, instructional activities of this synthetic opioid in order to avoid an imminent hazard to the public safety. Any subsequent final order for temporarily scheduling of this substance will be effective on the date of publication in the Federal Register and will be in effect for a period of two years, with possible extension of one additional year, pending completion of the permanent or regular scheduling process [15].

Conclusions

U-47700 is a newly appearing psychoactive substance that is available online and constitutes a public health danger in many countries worldwide. It was first synthesized in the late 1970s, but it was recently (in 2014) indentified in drug seizures (powder and tablets). U-47700 is a potential analgesic drug with addictive properties that mimics the effects of morphine, while at the same time it outsmarts the drug laws like other synthetic opioids. The drug was never approved for human medical use, and the knowledge about its pharmacological or toxicological action is limited as it has not been studied in humans. Its pharmacological properties and the potential side effects after its use are expected to be similar to those of morphine. The use of U-47700 has been expanded during the last two years, and it has so far killed several people worldwide or caused a number of non-fatal intoxication cases. The drug is currently controlled in only three European countries, and it is only temporarily scheduled in the United States. Similar actions are expected to be taken worldwide. Clinical and forensic toxicologists must remain vigilant as various new synthetic opioids, like U-47700, continuously appear. New analytical methods for the identification and determination of such substances and their metabolites are needed to be developed in terms of emergency and forensic toxicology. Better international collaboration, continuous community alertness and effective legislation are needed to tackle the current growing problem of U-47700 use and abuse.

Compliance with ethical standards

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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