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RESEARCH PROGRESS ON FENTANYL-LIKE SUBSTANCES

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Abstract: Fentanyl-like substances are a class of synthetically powerful anesthetics represented by fentanyl. In recent years, the abuse and trafficking situation has been severe in many countries around the world, posing a great threat to people's health and social stability. By reviewing the abuse, pharmacological and toxicological effects, detection methods and control conditions of fentanyl-like substances, we can improve people's understanding of their basic properties, research status and control conditions, and provide reference for future research.
Keywords: Fentanyl; Fentanyl-like substances; Drug abuse; Pharmacological and toxicological effects; Detection methods; Drug control

1 ABUSE OF FENTANYL-LIKE SUBSTANCES

In recent years, problems such as the manufacture and abuse of new psychoactive substances have become increasingly serious around the world, bringing serious challenges to international anti-drug work. challenges, especially the high fatality rate caused by fentanyl-like substances. It has attracted widespread attention from anti-drug authorities around the world. Fentanyl was first designed and synthesized by Dr. Paul Janssen of Belgium in 1960, and was introduced into European clinical practice as an analgesic in 1963. Its analgesic effect is about 75 to 100 times that of morphine. It is a powerful narcotic analgesic and is included in the World Health Organization and my country's essential medicine list[1]. In our country, the definition of "fentanyl-like substances" Meaning means that the chemical structure is consistent with one of the following or Substances with multiple conditions: (1) Use other acyl groups to replace propionyl groups; (2) Use any substituted or unsubstituted monocyclic aromatic groups to replace A phenyl group directly connected to a nitrogen atom; (3) There is an alkane group on the piperidine ring Base, alkenyl, alkoxy, ester, ether, hydroxyl, halogen, alkyl halide substituents such as base, amino and nitro; (4) Use other arbitrary groups (Except hydrogen atoms) to replace phenethyl[2].
Fentanyl-like substances belong to the pharmacological category of new psychoactive substances Opioid substances in the class, which have potent analgesic and It has addictive effects, is simple to prepare and easy to derive. In recent years, criminals have continuously synthesized various new fentanyl chemicals through underground processing plants. Titanyl-like substances and evade legal supervision through chemical modification. department Newly synthesized non-medicinal fentanyl substances have more pharmacological effects than fentanyl Titanyl is even more powerful, such as fentanyl derivative 3-methylfentanyl The pharmacological effect of 3-methylfentanyl is 1 000 stronger than that of heroin times[3]; the analgesic effect of carfentanil is about that of morphine It is 10,000 times the most powerful opioid in the world. It is stipulated that it can only be used for the anesthesia of large animals and cannot be used for humans[4]. These fentanyl-like substances flowing into the drug market cause varying degrees of The abuse has brought huge harm to people's health and social stability. threaten.
The first reported abuse of fentanyl-type substances was the emergence of alpha-methylfentanyl in the street drug market in the United States between 1979 and 1988. The substance was classified as a Schedule I controlled drug by the United States in 1981. Narcotic drugs[5].
In recent years, fentanyl-like substances have been rampant in many countries around the world, and their abuse is more serious in North America. According to the United Nations on Drugs and Crime Issues Office (United Nations Office of Drugs and The World Drug Report 2019 published by Crime, UNODC According to the report, in 2017, the number of opioid overdose deaths recorded in the United States was More than 47,000 people, an increase of 13% from 2016. these deaths In large part due to synthetic compounds such as fentanyl and its analogs deaths caused by opioids compared to 2016 The number of deaths increased by nearly 50%. The U. S. Government and the U. S. Drug Enforcement Administration, etc. Anti-drug law enforcement agencies attach great importance to the abuse of fentanyl-like substances issue, the United States is said to be experiencing unprecedented levels of opioid abuse A serious public health crisis resulting in death from chemicals, the main reason of which is because of the use of fentanyl-like substances, and they used "non-"common, very dangerous drugs" to describe fentanyl-like substances[6]. In Canada, nearly 4,000 opioid-related deaths were reported in 2017, an increase from the 3,000 overdose deaths reported in 2016. 33% of deaths involved fentanyl or fentanyl analogues in 69% of deaths, compared with 50% in 2016.
In other countries, the abuse and trafficking of fentanyl-like substances The situation is also relatively common. In Estonia, fentanyl is the most abused There are a lot of opioids; according to Australian wastewater analysis data, the local per capita fentanyl use doubled in April 2018 compared with 2017. more than doubled; in Japan, where opioid abuse is relatively low, in recent years There have been many cases of abuse of fentanyl-like substances. Spanish teeth in many European countries from June 2014 to April 2018 (such as France, Spain and the United Kingdom, etc.) seized from underground trading markets After analysis of the heroin, it was found that the sample was adulterated with a variety of fentanyl Nepalese substances; India seized in December 2018 about to be shipped to North Korea Fentanyl 100 kg in America[7]. Report

fentanyl seizures to UNODC The number of countries using nicotine substances also increased from 4 in 2013 to 2017. In 16 countries, the trafficking of fentanyl-like substances has expanded to world.

The "World Drug Report 2019" describes synthetic opioids as "despite their adverse health consequences, the market is booming", which mainly refers to fentanyl-like substances. According to its report, the number of new psychoactive substances (mainly fentanyl analogues) belonging to synthetic opioids on the market is growing at an unprecedented rate, indicating the global manufacturing and abuse situation of fentanyl-like substances in the short term. It is quite serious. This phenomenon should attract great attention and sufficient attention from anti-drug law enforcement agencies and relevant researchers in various countries.

2 PHARMACOLOGICAL AND TOXICOLOGICAL EFFECTS OF FENTANYL-LIKE SUBSTANCES

Unlike cathinones and other psychostimulant substances, fentanyls will not cause the user to hallucinate and cause violent behaviors that endanger others. It will put the user in a relaxed and euphoric state, but overdose Fentanyl-like substances can have a depressive effect on the brain and can easily cause depression of the respiratory center and lead to death.

2.1 Pharmacological Effects

2.1.1 General Pharmacological Effects

Fentanyl-like substances are synthetic It is a strong opioid with pharmacological effects mostly similar to fentanyl. The relative molecular mass of fentanyl is small, 336. 47, and the oil-water distribution The coefficient is 4. 28 , it has strong fat solubility, can quickly combine with plasma, and has Large distribution volume, and can quickly pass through the blood-brain barrier and enter the body central nervous system[8]. It mainly binds to mu opioid receptors to produce It has an agonistic effect and has high affinity. The binding affinity (Ki) in the recombinant human mu opioid receptor is 1. 35 nmol/L, and the intrinsic activity is strong[9]. The half-life of fentanyl in the body is about 2 to 4 hours. It has a short action time and can be rapidly metabolized by the liver. It is mainly N-dealkylated by CYP3A4 into inactive norfentanyl and thus inactivated. It is also effective when taken orally. Strong liver first pass effect[5]. Fentanyl substances are mainly metabolized through this pathway, and a few are metabolized through other pathways. For example, remifentanil is mainly metabolized outside the liver and is mainly metabolized and degraded into remifentanil acid by non-specific esterases in red blood cells and tissues. 10]. Fentanyl is widely used in clinical practice due to its advantages of fast onset, strong efficacy, short action time, and no accumulation during continuous infusion, and is often used to treat cancer pain and chronic pain[11]. There are three main fentanyl substances currently used clinically in my country: fentanyl, remifentanil and sufentanil.

The pharmacological effects of fentanyl are similar to those of morphine. It is analgesic, sedation and anesthesia, and can reduce endocrine and metabolic stress. Exciting reaction[12]. Fentanyls and opioids in general Similarly, mainly in the central nervous system (CNS) of the brain and mu opioid receptors Produces analgesic effects by binding to opioids on neuron cells Receptor binding modulates presynaptic and postsynaptic sensory neurons, altering signal transduction and ion conduction to reduce pain transmission[13-14], and can Putting the person in a "conscious sedation" state without pain and anxiety. remove In addition to producing analgesia and sedation, fentanyl-like substances can also be used Used in anesthesia and reduce stress response. Research by Xu Lu et al. [15] showed that Shufen Titanyl has a strong inhibitory effect on stress response, mainly through affecting Hypothalamic-pituitary-adrenal axis and sympathoadrenal medullary axis excitability, lowering plasma catecholamines, beta-endorphins, and antidiuretic hormone and blood sugar levels. In addition, when fentanyl-like substances are used for anesthesia, they It has a series of advantages, such as remifentanil and sufentanil, which are commonly used clinically It has rapid onset of action, short elimination time, no obvious tissue accumulation effect, and small respiratory depression[16-17].

Fentanyl-like substances are associated with acute tolerance. Dumas et al. [18] have shown that tolerance is related to the efflux of P-glycoprotein, and the upregulation of this barrier transporter may further limit the central nervous system penetration and anti-nociceptive effects of some opioids. Comer et al. [9] have shown that fentanyl tolerance occurs through the G protein-coupled receptor kinase 3 (GRK3) mechanism. Sutou et al. [19] found that large doses or long-term use of fentanyl led to a decrease in the activity of protein phosphatase 2A, resulting in a decrease in phosphorylated receptors and the inhibition of the G protein activation process after interacting with β-endorphin. Multiple effects desensitize mu-opioid receptors and prevent them from binding to the drug, leading to the development of tolerance. In addition, Neunhoeffer et al. [20] have shown that the development of tolerance may be related to the upregulation of the cyclic adenosine monophosphate (cAMP) pathway. 2. 1. 2 Addictive effects

Fentanyl-like substances have strong of addiction. Long-term use of fentanyl substances can cause physical physical dependence and mental dependence. Physical dependence of fentanyl-like substances Dependence is mainly manifested as withdrawal reactions. Physical dependence can lead to The body seeks fentanyl-like substances in an attempt to avoid withdrawal symptoms, by Persistence of repeated exposure leads to addiction[21-22]. There is research Acetylfentanyl (0. 5 mg/kg), butyrylfentanyl (0. 1 or 0. 5 mg/kg) can quickly inhibit or reduce morphine (3 mg/kg) in rhesus monkeys. kg) withdrawal symptoms and morphine substitution effect[23]. Fentanyl analogues Substantial mental dependence mainly refers to the ingestion of fentanyl substances that lead to childbirth. The reward effect of life. Studies show that fentanyl-like substances cause depression The mechanism of reward effect is that after they bind to mu opioid receptors, they And inhibit gamma-aminobutyric acid neurons and increase the number of ventral tegmental area pamine neuron activity, and increase

dopamine release in the nucleus accumbens[21]. Pan Lishan et al. [24] found that remifentanil (5. 0 μg/kg) can make rats Rats developed an obvious place preference effect, and at a dose of 20. 0 At μg/kg, it can completely replace rats' discrimination of 2. 5 μg/kg morphine. Effect, showing obvious mental dependence.

The addictive mechanism of fentanyl-like substances is relatively complex. In addition to the mechanisms mentioned above, there are many mechanisms that may cause it Related to addiction. Bekhit et al. [25] have shown that glutamate is an important An important excitatory neurotransmitter, activation of mu opioid receptors can promote Intracellular protein kinase C removes magnesium ions and channels NMDA receptors channel blocking effect, and then increase NMDA receptor-mediated glutamate Acid response; subsequent increase in intracellular Ca2+ concentration further stimulates Protein kinase C activity leads to the continuous enhancement of glutamate synaptic efficiency, creating a positive feedback loop. Lucai et al. [26] found that the Glial cells are also involved in opioid addictive behaviors, and opioids can activate Toll -like Receptor 4 (TLR4), activates microglia and secretes a large number of inflammatory factors It regulates reward signaling pathways, increases neuron excitability, and participates in the formation and performance of addictive behaviors.

2.2 Toxicological Effects

Fentanyl-like substances are highly toxic. In the acute toxicity experiment of fentanyl, the median lethal dose (LD50) was 3. 1 mg/kg in rats and 0. 03 mg/kg in rhesus monkeys[8]. The acute toxicity of acryloylfentanyl is not as strong as that of fentanyl, and its LD50 in rat experiments is about 25~50 mg/kg[27].

2.2.1 Nervous system toxicity

There is substantial evidence that long-term opioid use or abuse can impair cognitive function. The pyramidal cell layer of the hippocampus is one of the regions with higher expression levels of μ-opioid receptor protein and μ-opioid receptor mRNA. Pyramidal neurons are glutamatergic neurons with many dendritic spines that contain AMPA receptors. and NMDA receptors. Fentanyl will have certain effects on dendritic spines and synaptic AMPA receptors in hippocampal neurons by internalizing μ opioid receptors[28].

Opioid-induced hyperalgesia (OIH) caused by the use of fentanyl-like substances has also been associated with nerve damage. Hyperalgesia caused by fentanyl-like substances usually produces diffuse pain that extends from preexisting pain to other distribution areas and worsens with increasing dose[19]. Wei et al. [29] found that OIH and neuropathic pain share a common pathophysiological mechanism, and the potential mechanisms involve excitatory neurotransmitters, intracellular messenger phosphokinase C (PKC) and N-methyl-D-aspartate. (NMDA) receptor activation, etc.

2.2.2 Respiratory toxicity

Fentanyl-like substances can cause respiratory depression, mostly transient, and may also lead to pulmonary edema. The respiratory depression caused by fentanyl substances is a comprehensive effect at multiple sites, such as stimulating μ2 receptors in the brainstem respiratory center and acting on respiratory neurons located in the medulla, resulting in suppression of respiratory frequency and respiratory drive. It also affects peripheral chemoreceptors located in the carotid sinus and aortic body; it can also inhibit the ventilatory response of the lungs, leading to hypoxemia and hypercapnia, inhibiting the brain arousal system and arousal, and producing a sedative effect[30]. Studies have shown that fentanyl can weaken the response of the respiratory center and cause dose-dependent suppression of ventilatory function. In large doses, it can even cause apnea in awake patients[31].

2.2.3 Cardiovascular system toxicity

Use of fentanyl-like substances can May cause symptoms of bradycardia or hypotension. Research has shown that Remifentanil inhibits sympathetic nerves, excites vagus nerves, and Inhibits the cardiac conduction system and interferes with the refractory period to slow down the heart rate[32]; when fentanyl is combined with tranquilizers such as midazolam, it Even small amounts may cause cardiac output, blood pressure, and peripheral vascular resistance. decrease in strength[31].

2.2.4 Other systemic toxicity

Fentanyl overdose It can also cause muscle rigidity and muscle tone clonus throughout the body, which can Can be related to stimulating central receptors. Such substances can also act on The emetic chemoreceptor area of the hypothalamus area postrema causes nausea and vomiting and other reactions[33-34]. The most common adverse reactions during intraspinal application are malignant palpitations, itchy skin, sedation, dizziness and chills, and occasionally urinary retention and hair Health, and pupil constriction etc. [12]. There are also reports of using Sufen Tanil may also cause acute vocal cord closure[30]. Opioid receptor antagonist The antagonist naloxone is often used to relieve poisoning caused by overdose[8].

At present, systematic research on the pharmacology and toxicology of fentanyl-like substances, especially non-medicinal fentanyl-like substances, is extremely scarce at home and abroad. There is an urgent need to carry out multiple studies, such as the development and verification of fentanyl-like substances. Research on key diagnosis and treatment technologies for addiction, forensic toxicokinetic research on fentanyl-like substances, and the establishment of different technical quantitative evaluation standards for the addictiveness and toxicity intensity of such substances.

3 DETECTION OF FENTANYL-LIKE SUBSTANCES

The detection of fentanyl-like substances is conducive to their monitoring and control, and more in-depth analysis (such as the analysis of its precursor ions using mass spectrometry technology) can also help determine whether it is a new derivative of this type of substance[35]. In addition to the detection and analysis of seized samples, the detection of such substances

can also detect the prototypes and metabolites of drug addicts' plasma, urine, vitreous fluid, bile and other matrices[36]. Common detection methods are as follows.

3.1 Chromatography

Commonly used chromatography methods mainly include high performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), ultra-high performance liquid chromatography-tandem quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF MS), liquid Chromatography-high resolution mass spectrometry (LC-HRMS), liquid chromatography-secondary mass spectrometry (LC-MS/MS), gas chromatography-secondary mass spectrometry (GC -MS/MS), etc. [37-39]. Misailidi et al. [39] used GC-MS to detect four substances, furofentanyl, orfentanyl, acetylfentanyl and butyrylfentanyl, in whole blood. The detection of furofentanyl and orfentanil The detection limit and quantitation limit of acetylfentanyl and butyrylfentanyl are 0. 15 and 0. 50 ng/mL respectively. These four kinds of fentanyl The recovery rates are all greater than 85%, the systematic error of accuracy is less than 6%, and the relative standard deviation of precision is less than 8%, showing higher sensitivity than LC-MS/MS.

3.2 Spectroscopy

Spectroscopic detection mainly includes infrared spectrum detection and Raman spectrum detection. Infrared spectroscopy can be used for rapid qualitative analysis, can distinguish positional isomers, and can establish an infrared spectrum library. It has rapid screening capabilities, but it can only detect high-content samples[40-41]. Raman spectroscopy detection has the ability to detect samples It is non-destructive, fast, small in volume and does not require preparation. It can also be used for large-scale screening and is often used for on-site testing[42]. Kong Lingce et al. [43] used surface-enhanced Raman spectroscopy to detect fentanyl in water. Under optimized conditions, the detection limit of fentanyl could reach the level of 0. 1 μg/mL.

3. 3 Immunoassay

The immunological detection method uses the specific binding reaction between antigens and antibodies to detect the preliminary content of substances in the sample. It is mostly used for the preliminary screening of drugs in drug detection, and can also be used for on-site rapid detection. Measurement. Immunological detection methods include enzyme-linked immunosorbent assay (ELISA)[44], radioimmunoassay (RIA)[45] and colloidal gold immunochromatography. (GICT)[46-47] etc. The ELISA method is more sensitive, Nicholas[44] used fentanyl ELISA kit to detect fentanyl in whole blood and urine. The lowest detection limits of Ni detection are 0. 25 and 0. 5 ng/mL respectively. Smith et al. [45] used RIA method to detect fentanyl and its metabolites in calf plasma. Metabolite content. Immunological assays can be used on large batches of samples Preliminary screening can even be used to infer the last time an abuser took drugs. The test results are more intuitive, but the sensitivity is susceptible to temperature and other factors.
Impact[44-47].

3.4 Ion Mobility Spectrometry

Ion mobility spectrometry can be used to detect the presence of fentanyl-related substances in the field, providing near real-time results without the need for sample preparation. However, there are still some shortcomings. For example, Zaknoun et al. [48] found that although this method can successfully detect the presence of fentanyl-like substances in all samples, it is difficult to distinguish substances with similar ion mobility, such as fentanyl and Tetrahydrocannabinol, acetylfentanyl and benzylfentanyl, etc. ; and cannot distinguish between the citrate and hydrochloride forms of fentanyl, as well as the positive mode furylfentanyl; and although this method can detect Unprogrammed fentanyl-related substances, but alarms cannot be generated for them, and information about them is only available through advanced user mode, etc.
Methods recommended by the United Nations Office on Drugs and Crime (UNODC) for the identification and analysis of fentanyl-like substances in biological samples include immunoassays, GC-MS, LC-HRMS, HPLC/UV and LC/MS/MS. Since immunoassays are prone to cross-reactivity between substances, they are often used for preliminary screening of biological samples to presumptively identify the presence of drugs. GC-MS and LC-HRMS can be used to determine the type of substance contained in the sample, and these two methods can also be used for further confirmation and quantitative analysis of the substance when combined with HPLC/UV, LC/MS/MS[49] .
The detection methods introduced above are all for one or several fentanyl-like substances alone. In view of the fact that my country has already listed the entire category of fentanyl-like substances, and considering that many unknown new fentanyl-like substances may appear in the future, it is recommended that timely research and development of in vitro high-efficiency and sensitive substances be carried out based on the core structure of fentanyl-like substances. On-site rapid detection and early warning technology and related equipment to help relevant departments further strengthen the identification and control of unknown fentanyl-like substances that have been discovered and may appear in the future.

4 CONTROL OF FENTANYL-LIKE SUBSTANCES

Fentanyl was first synthesized in 1960. Due to its potent effects and potential for abuse, it was included in the 1961 Single Convention on Narcotic Drugs by the United Nations as a Class I drug for control in 1964. Later, sufentanil and other fentanyls were Titanyl-like substances have been synthesized and listed one after another. Most of the new fentanyl-like substances that have appeared in recent years are to evade control and be used for illegal purposes[4]. Currently, the United Nations controls a total of 25 fentanyl-like substances and 2 fentanyl precursors[50].

In response to the first large-scale abuse of fentanyl-like substances in 1988, New Zealand enacted a bill to control the entire class of fentanyl-like substances and defined the chemical structure of fentanyl-like substances. The UK has also classified fentanyl-like substances as the most dangerous substances and classified them as Class A drugs for control. The U. S. Drug Enforcement Administration (DEA) listed the entire class of fentanyl-like substances as Class I drugs on February 6, 2018 and placed them under temporary control for two years[51]. Other countries such as the Netherlands have listed some fentanyl-like substances. The European Monitoring Center for Drugs and Drug Addiction (EMCDDA) also issued early warnings on fentanyl-like substances to encourage European countries to increase their attention and control of fentanyl-like substances[52] .

Our country has always attached great importance to the control of fentanyl-like substances. In the 1996 version of the "Catalogue of Narcotic Drugs", 12 fentanyl-like substances were included in the national controlled list[53], and other fentanyl-like substances were subsequently added. For example, carfentanil was added to the list in 2017. Four fentanyl-like substances, including fentanyl, furanylfentanyl, acryloylfentanyl and valerylfentanyl, were included in the "Supplementary Catalog of Controlled Varieties of Non-Medicinal Narcotic Drugs and Psychotropic Substances"[54]. By the end of 2018, my country 25 fentanyl-like substances and 2 fentanyl precursors have been listed and controlled, and since May 1, 2019, the entire category of fentanyl-like substances has been included in the "Control of Non-Medicinal Narcotic Drugs and Psychotropic Substances" "Supplementary Catalog of Varieties" provides sufficient legal protection to further strengthen the crackdown and control of fentanyl-like substances.

Although many countries have controlled fentanyl-like substances to varying degrees, the current global abuse and black market trafficking of fentanyl-like substances is still severe. In addition to controlling fentanyl-like substances and their precursors in terms of policies, countries can also take measures in other aspects, such as further strengthening the general public's knowledge of fentanyl-like substances and strengthening the understanding of medicinal fentanyl-like substances. Monitor the non-medical use of fentanyl-like substances, increase law enforcement, and at the same time strengthen international cooperation to better combat and control fentanyl-like substances in all aspects of manufacturing, trafficking, abuse, monitoring, and testing.

5 CONCLUSION

At present, in addition to the three fentanyl substances used clinically, the country There is a lack of systematic in-depth study of other types of fentanyl-like substances both internally and externally. understanding, and research in some areas is still blank, resulting in the inability to provide Provide more powerful technical support for the control of titanyl substances. Therefore, it is necessary to strengthen systematic scientific research on fentanyl-like substances and at the same time Balance control with prevention, combat, rational medical use, industry (or civil The relationship between use and use is an important issue facing the current anti-drug work. Big challenge.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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