Letter

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The health threat of new synthetic opioids as adulterants of classic drugs of abuse

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Abstract

Extensive scientific evidence shows that there is a broad spectrum of substances used as adulterants, whose effects on the user's health may be extremely harmful. The degree of purity of the drugs most commonly abused is highly variable depending on the region or epidemiological context. Practices of drug adulteration have been substantially evolving over the years: a significant trend has been observed in the last decade indicating a decline in the average purity of most drugs. Although the most frequent adulterants of common street drugs have long been well known, the rise of synthetic opioids has inevitably entailed gaps in knowledge in terms of the substances being used and their composition, which constitutes an even greater threat to public health. ***Clin Ter 2020; 171 (2):e107-109. doi: 10.7417/CT.2020.2198***

Key words: *New Synthetic Opioids, adulterants; drugs of abuse*

Dear Editor,

The proliferation of dangerous adulterated drugs has reached alarming proportions. Deaths from unintentional overdose are almost globally endemic, and not limited to impoverished countries and communities. Overdoses from adulterated heroin, cocaine, prescription opioids or ecstasy have been recorded throughout demographics and socioeconomic segments, and the incidence is not biased by race, income or geographical location. In this letter, the authors will be briefly describing the dangers posed by new synthetic opioids used as adulterants and the process and trends involved.

Illicit drugs are often found, at the point of purchase, to contain substances in addition to the active ingredient (or named drug); these adulterants can have serious, sometimes fatal, health consequences. Substances may be added as bulking agents (i.e. to increase volume) or for the purpose of diluting the drug, to enhance the effects of the active ingredient, or to make drug administration easier, for instance in powdery drugs such as heroin and cocaine (1, 2). Lidocaine, caffeine (3) and dextromethorphan are well known adulterants that have been associated with synergistic or additive effects with illicit drugs on the central nervous system and cardiovascular system (4). In addition, foreign substances or contaminants may be created through a chemical reaction during processing, or added though accidental contamination during storage. The term "adulterant" generally refers to the addition of substances with some psychoactive effects, such as caffeine or ephedra. Such adulterants are cheaper than the main substance, but may produce similar or complementary effects when added, thus helping to conceal the fact that the desired substance has been cut or diluted (5). Substances without psychoactive properties such as lactose, other sugars, or talc, are added to a drug primarily to increase the volume or weight of the illicit substance, or for aesthetic purposes in order to deceive the user. The most commonly adulterated illicit drugs are heroin, cocaine, methamphetamine, ecstasy and cannabis. Heroin is sometimes cut with phenobarbital, quinine, clenbuterol, scopolamine, caffeine, procaine, paracetamol, strychnine. Cocaine has been found to be adulterated with lidocaine, hydroxyzine, antihistamine, phenactin, levamisole, caffeine, procaine, strychnine. Methamphetamine may be cut with Methylsulfonyl, caffeine, or be contaminated by lead, possibly a manufacturing residue. Ecstasy could be added with dextromethorphan, amphetamine and/or methamphetamine, paramethoxymethamphetamine and/or paramethoxyamphetamine, caffeine. Recently, even GHB has been adulterated with sildefanil (6) or more commonly substituted with its precursor GBL (7). Furthermore, GHB/GBL, mephedrone, ketamine and other synthetic cathinones are at times used in conjunction with illicit opioids in high-risk "chemsex" practices (8). The "cutting" or "adulteration" of street drugs is common practice at the manufacturing, distribution, and selling stages; the main purpose is undoubtedly to maximize profits. Some adulterants, on the other hand, are simply the by-product of the particular drug manufacturing process. For example, illicitly manufactured methamphetamine is frequently contaminated by non-stimulant impurities such as lead or mercury (extremely toxic heavy metals), or by carcinogenic solvents used in the synthesis. The local anesthetic lidocaine is often added to cocaine, since both drugs are fast-acting local anesthetics.

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The case of antiparasitic medication levamisole appears to be particularly significant in that regard: according to the United States Drug Enforcement Administration (DEA), 60%-89% of seized street cocaine contains levamisole (9). Levamisole appears to be partly metabolized into an amphetamine-like compound, which could increase dopamine concentration in the mesolimbic pathway,thus activating endogenous opioids: it can replicate the effects of cocaine at a much lower cost. Levamisole has been linked to various types of severe blood disorders, including leukopenia, agranulocytosis, multifocal inflammatory leukoencephalopathy, and neutropenia; pulmonary vasculitis has also been observed in abusers of levamisole-adulterated cocaine (10); a common presentation is vasculitis resulting in loss of limbs. Thus, a real danger in adulterants such as levamisole is their toxicity beyond those of the drug to which they are added, causing numerous medical consequences – including death. To further complicate the overall scenario, new synthetic opioids such as fentanyl have emerged: such adulterants are certainly a new trend in the landscape and pose a serious threat to public health (11), and can be extremely harmful even in very small amounts (12). In March 2015, the DEA issued a nationwide alert on fentanyl as a threat to health and public safety in the United States (13, 14). Fentanyl analogues are commonly abused, posing major health concerns, in addition to other opioid sub-categories of novel psychoactive substances (NPS) such as desomorphine, mitragynine, tramadol, tapentadol, salvinorin A and its analogue herkinorin (15). Given the elusive nature of such substances, progressively coordinated reporting systems focused on pharmacovigilance would be vital in order to identify new trends of NPS adulteration (16). In fact, over the last 3 years, the availability of illicitly manufactured fentanyl, often used as a heroin adulterant (17), has caused an unprecedented rise in overdoses and deaths (18). In 2016, 75% of overdose-related fatalities in the state of Massachusetts had fentanyl in their system, a significant rise from 57 percent in 2015 (19). The DEA has also warned that the Mexican cartels have increased production of the fentanyl analogue acetyl fentanyl, which can be easily made in clandestine labs, and has much lower production costs. According to the DEA, acetyl fentanyl may be slightly less potent than fentanyl, but is still potentially deadly and difficult to identify, because it is not yet included in most toxicology assays for drugs identification in urine or blood (20-22). Acetyl fentanyl-laced heroin is more expensive than regular heroin, yet it is in high demand, because users believe its extreme potency to produce a more intense "high", which justifies the higher cost. Opioid addicts have in fact a strong tendency to seek more and more intense experiences, even if it means putting their lives at risk in doing so. Moreover, ocfentanil (23) and carfentanil, two potent synthetic opioids and fentanyl analogues synthesized in 1986 and 1974 respectively, have come to play a significant role in the recent fentanyl crisis (24). The emergency is made even worse by the fact that most toxicological analyses currently available can only identify a rather limited amount of adulterants in illicit drug samples (25). That in turn allows adulterants to often go undetected; therefore, their presence and incidence is probably underreported. The worsening synthetic opioid crisis and the issue of drug adulterants has gained growing attention in the United States, which led to the authorities focusing on the potential role of such factors when assessing and treating patients with addiction issues, involved in drug abuse, or overdose deaths (26). In conclusion, new synthetic opioids certainly represent a daunting threat to public health. Given the large number of casualties caused by such compounds, it is essential to improve the identification and detection processes involving biologic matrices in order to implement adequate therapies and tackle severe complications such as respiratory depression and cardiovascular and neurological fallout caused by opioid-related adulterants. It is important for specialists treating fentanyl intoxicated patients to consider the possibility of fentanyl-analogue adulteration as well. Hence, synthetic opioids ought to be covered by toxicological screening methodologies, along with analysis of alternative matrices, whenever available; that would be greatly helpful in detecting poly-drug use and possible opioid tolerance. In order to effectively address such a pressing public health issue, it is necessary to build broader and more comprehensive international collaboration, targeted legislation, reliable investigative procedures, and a closely-focused oversight of online forums and markets, particularly those operating in the "deep web", underground version; furthermore, in light of the issue's social pervasiveness, all communities need to get involved with raising awareness and spreading knowledge throughout societies. Doctors should make sure at all times that the resources available are effectively harnessed, while ensuring that the evolving right to health is upheld with no discrimination (27).

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