Strategies of intervention to limit the novel synthetic opioids (NSO) escalation in Europe

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Abstract

October 9th 2018 marked the entry into force of the EU-funded project JUSTSO (Analysis, knowledge dissemination, JUstice implementation and Special Testing of novel Synthetic Opioids) (1). The JUSTSO Project involves 10 European partners from Italy, Spain, Greece, Latvia, Germany. The project is aimed at studying Novel Synthetic Opioids (NSO), a class of psychoactive substances that mimic heroin and can be up to 10000 times more potent than heroin, being the cause of thousands of deaths in the US and Canada. NSO have been used to adulterate heroin, often taken by subjects made dependent on opioid pain killers. Given the growing use of opioid pain killers and NSO in Europe, the project intends to collect data on their diffusion and to develop effective intervention strategies to prevent their spread and to inform and educate the public in order to acquire a social awareness of their addiction liability and lethality.

KEY WORDS:synthetic opioids, nso, nps, fentanyl.

Introduction

Novel synthetic opioids (NSO) are a class of novel psychoactive substances (NPS) that mimic morphine and heroin but, in contrast to them, may be fully effective by the intranasal and oral route and many times more potent than morphine in producing acute toxicity. Their use is likely to become the primary source of NPS-associated deaths in Europe, given its increasing prevalence, opposite to that of other NPS classes, that is decreasing. This trend calls for action and better knowledge of the profile, setting and effects of these substances in order to devise strategies of intervention from the legal, epidemiological, diagnostic, clinical, emergency treatment and public awareness viewpoints. The objective of the JUSTSO project is to evaluate, test, profile, and feedback into education and prevention knowledge relating to new NSO emerging or re-emerging in Europe, their properties and potential harm.

Context of the action

Novel psychoactive substances (NPS) are drugs not controlled by current legislation but that may produce effects similar to those of illegal psychoactive drugs (2, 3). As current NPS are made illegal by governments, they are replaced by new analogues not yet subjected to legal control. The first wave of NPS came from Europe around 2004, as synthetic cannabinoids; around 2010 synthetic cathinones, drugs with cocaine-like effects, became available (4). The more recent and most dangerous NPS are novel synthetic opioids (NSO). In Europe two such drugs, MT-45 and AH-7921, have been associated to respectively 28 and 15 deaths and have been made illegal by the EU Council in 2015 and 2016 respectively (5). In USA, U-47700, a structural isomer of AH-7921, has ben associated to 46 deaths and placed under Schedule 1 in 2016 (5). These NSO are a few times (<10 times) more potent than morphine *in vivo* but, in contrast to morphine, are fully active by the oral route. However, by far the most dangerous NSO are fentanyl and its derivatives (F&D). In the USA, F&D have been associated to as many as 15000 deaths in the past 2 years. As to Europe, up to 2011, 650 deaths have been associated to F&D in Estonia, 160 in Germany, 50 in UK and 40 in Finland. Recently, carfentanyl has been suspected to be responsible of 53 overdoses in the USA (5). This opioid is about 10000 times more potent than morphine, 20 micrograms of it being lethal. Two fentanyl derivatives, 4-

fluoroisobutyrylfentanyl and tetrahydrofuranylfentanyl, have been associated to 30 deaths in Sweden and are under risk assessment by EMCDDA. F&D may be sold as counterfeit heroin for intravenous administration.

European dimension of the action

Europe has been the first area where outbreaks of NSO have taken place and from where they have spread in the US. Now NSO are back to Europe in a new chemical outfit that of fentanyl derivatives. In spite of the fact that Europe has been the seminal market of these compounds (Estonia and Germany in particular), they have been, among the NPS utilized in Europe, the least studied. This in turn contrasts with their high toxicity and in particular with the possibility that they are included in preparations sold as heroin. The importance of these compounds in terms of the possible harm associated to their diffusion in Europe is demonstrated by the fact that 2 fentanyl derivatives are at the top of the list of NPS whose risk is to be assessed by the EMCDDA commission. The partners of the JUSTSO are from a range of European countries (Spain, Italy, Germany, Greece, Latvia) that are representative of the EU as a whole. The project incorporates diverse data from a wide range of EWS-type sources examined by a central EU hub, together with innovative and integrated technical approaches to profile individual molecules. Information collated will be accessible to a range of stakeholders, especially law enforcement agencies and EU health professionals and educators. It is predicted that the results of this project will have a long lasting impact on EU population. Thus, diffusion of knowledge among the public about the health risk associated with NSO will arguably be associated with a reduction of NSO consumption and related toxicity.

Justso general objectives

The JUSTSO project deals with the detection, effects in animal models and humans, abuse liability and epidemiology, social context of use, risk assessment and scheduling as illegal substances of NSO. The project is articulated into 4 main lines of activity for a 24 months of duration. The first line involves collection of information from providers in several countries related to individuals who have been intoxicated by NSO or who died from their use. These data will indicate the specific classes of compounds towards which to orient the second line of activity, involving the development of new rapid analytical methods of NSO present in biological specimens. The third line of activity consists in the study of selected NSO *vis* a *vis* their potency and intrinsic activity *in vitro* as opiate agonists and their behavioral and neurochemical effects *in vivo*. In order to develop effective interventions against NSO overdosing and lethality, known (e.g. naloxone, naltrexone) or *ad hoc* synthesized antagonists of μ receptors (MOR) with higher affinity and efficacy will be tested in animal models and humans. In the fourth line of activity, existing information and that generated by the project will be made available to the public in order to provide awareness of the toxic liability of these compounds and with tools to reduce their use and to treat their emergencies. It is hoped that this action will contribute to invert the current growing trend of NSO use and mortality. The action consists of 5 integrated work packages (WP): WP1, general action management and coordination; WP2, collection of information from providers in several countries relating to individuals reported to have utilized NSO or who died from such use. These data will indicate which compounds to investigate in WP3 and WP4, and will be disseminated by WP5. WP3 will focus on the development of rapid and innovative analytical methods of NSO in biological specimens; WP4 will investigate NSO pharmacological effects in vitro on their biological target (μ opioid receptor, MOR) and behavioural and neurochemical effects *in vivo*. In addition, to develop new therapies for counteracting NSO overdose (lethality), known (e.g. naloxone, naltrexone) or *ad hoc* synthesized antagonists of μ receptors with higher affinity and efficacy will be tested. Finally, WP5 will integrate 'real-time' NSO data to understand the new trends in the field of drug addiction and to provide Governments, scientific community and civil society with reliable data regarding these compounds. This will be achieved by a range of resources, including online teaching and e-learning for integrated spiral curricula on the health risks of NSO for use in inter-professional medical, pharmacy and health education settings.

Peculiarity of the justso project

The main advantages of the JUSTSO project over previous and current EU projects, existing drug surveillance systems, and EWSs include: I. A multilingual approach, better suited to track relevant information on emerging NSO; II. A wider range of datasources from recreational, urban-metropolitan, clinical, detoxification unit, methadone maintenance clinics, self-injection facilities; III. A wider range of collected biological specimens from emergency departments and intensive care units, drug addiction services, fit to drive medical examinations, recreational, urban-metropolitan settings; IV. Collaboration with National Regulatory Organizations (Sistema di allerta precoce-Early Warning System-Italy; National Organization for Medicine-Greece, DBDD Deutsche Beobachtungsstelle für Drogen und Drogensucht, Sistema Español de alerta temprana, Centre for Disease Prevention and Control of the Republic of Latvia); V. Development and validation of rapid and novel analytical method for detection of NSO in biological specimens, and its distribution to hospital, forensic and law enforcement analytical laboratories,

and possible use across the EU; VI. Pharmacological profiling, abuse liability, behavioral effects of NSO compared with reference compounds (fentanyl and heroin) producing a wider knowledge that allows a prevention of health damage and update relevant professionals; VII. Development of new therapeutic agents and effective emergency treatments; VIII. Capacity-building in terms of monitoring, analysis and profiling of NSO, via exchange of study visits between labs in 5 countries, hence improved exchange of information; IX. Use of up-to-date communication tools in a range of European languages to inform health professionals, educators and other stakeholders, disseminated via pan-European seminars and an international conference.

Perspective and remarks

Fentanyl and derivatives are the ideal heroin substitutes, due to their low price, high potency and central bioavailability. This is in fact the main source of threat for public health. Thus, due to the high potency and purity of these compounds overdose is likely to be more common. On the other hand, their high affinity for the opiate receptors and high penetration of the blood brain barrier makes the currently used antagonist, naloxone, inadequate, due to its low affinity and short duration of action, to provide reversal of their effects. Closely related to the possibility of an effective intervention in overdoses is the availability of a rapid method of detection of NSO in the biological fluids. On a later stage, more sophisticated procedures allowing the unambiguous identification of the substance would be applied. A second aspect that needs to be clarified is the relative dose and schedule of naloxone to be administered in order to reverse respiratory depression in overdoses. This in turn might be the basis for selecting a more appropriate, higher potency and longer lasting antagonist. Another aspect that will require a specific investigation is a register and analysis of all the overdoses and death cases observed in Europe and to define prevalence rates and trends of NSO diffusion and use. These studies should be complemented by in loco studies of the individual trends of NSO use across Europe. A final goal to be pursued is that of increasing the awareness on NSO by the professionals (physicians, nurses, psychologists, psychiatrists) working in the presidia dedicated to the treatment of heroin addiction. To this end, courses specifically dedicated to NSO will be organized. Separate courses should be dedicated to the personnel in charge of law enforcement. In line with EU drugs strategy (2013-20) and action plan (2013-16; Perspective on drugs), this project intends to evaluate, test, profile, and feedback into education and prevention, knowledge related to the NSO currently utilized in Europe, their nature, effects and associated harm. This project contributes to an effective and coherent application of EU law and support development of new approaches in the area of drugs within the specific priority “Support activities in the area of identification and epidemiology of use of new psychoactive substances”, intended to reduce adverse consequences and death.

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Competing interest

The Authors have declared that no competing interests exist.

References

1. JUST-2017-AG-DRUG (GRANT AGREEMENT NUMBER - 806996 - JUSTSO).
2. UNODOC, World Drug Report 2017.
3. European Drug Report 2016: Trends and Developments EMCDDA, Lisbon, May. 2016.
4. Miliano C, Serpelloni G, Rimondo C, Mereu M, Marti M, De Luca MA. Neuropharmacology of New Psychoactive Substances (NPS): Focus on the Rewarding and Reinforcing Properties of Cannabimimetics and Amphetamine-Like Stimulants. Front Neurosci. 2016 Apr 19;10:153.
5. Prekupec MP, Mansky PA, Baumann MH. Misuse of Novel Synthetic Opioids: A Deadly New Trend. J Addict Med. 2017 Jul/Aug;11(4):256-265.