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New Psychoactive Substances and receding COVID-19 pandemic: really going back to "normal"?

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To the Editor,

The ongoing rise of New Psychoactive Substances (NPS), i.e. psychotropic molecules devised and synthesized to replicate the effects of traditional drugs of abuse in order to circumvent banned substances schedules, has been posing a challenge of enormous magnitude to substance detection systems and law enforcement worldwide. Still, it would be remiss to ignore the role played by the unprecedented public health emergency relating to the COVID-19 pandemic in the exacerbation of the NPS crisis. The diversion of resources has in fact hindered conventional approaches to drug monitoring, surveillance, control, and public health responses. The dangerous path ahead in our struggle against NPS abuse is best exemplified by the rather recent emergence of isotonitazene, an analogue of a benzimidazole class of analgesic compounds, powerful synthetic opioid and full mu-opioid receptor agonist belonging to the 2-benzylbenzimidazole group of compounds, which comprises the structurally different clonitazene, metonitazene and etonitazene (1).

Isonitazene has reportedly been detected on European markets in at least five different forms and could even supplant fentanyl derivatives (2).

Currently available data on isonitazene-related abuse and fatalities seem to be emblematic of the volatile, elusive nature of NPS: deaths in which isotonitazene was involved in fact presented substantial differences from casualties arising from synthetic opioids abuse. Case reports have highlighted how flualprazolam was detected in most fatalities associated with isotonitazene whereas flualprazolam was involved in only 8% of other synthetic opioid overdose deaths (3). Rather than rising background use, such a finding seems to suggest likely co-use or co-distribution of flualprazolam and isotonitazene.

The key element of polysubstance involvement is rife in synthetic opioid overdose deaths. That being said, significantly more substances were implicated in isotonitazene-related deaths than fatalities linked to other synthetic opioid overdose (4, 5). Such dynamics and mortality patterns further stress the urgency of expanding health services for those suffering from opioid addiction disorders. Fine-tuned and standardized detection mechanisms relying on specialized assays based on sensitive instrumentation are essential for the timely and accurate characterization of such novel synthetic opioids (6-8). Isotonitazene in fact cannot be detected by common fentanyl testing strips (9). Hence, the essential nature of clinical and toxicological cannot be overstated, if we are to effectively deal with the public health risks arising from new substances or classes, along with the healthcare and social costs thereof (10). As new substances appear on illicit markets and are detected, their distinctive traits can only be identified by user experience, in the early stages (11-13).

Nonetheless, the pandemic scenario has brought about a profound alteration of substance abuse patterns, and opened up new avenues of supply and demand for which our surveillance/detection systems may not be fully prepared or well-suited. As the

pandemic appears to recede and hopefully turn into an endemic context based on coexistence with the SARS-CoV-2 and its less harmful variants, it would be a mistake to take for granted that drug abuse/trafficking dynamics will also get back to where they were before the pandemic. Putting in place policies aimed at monitoring web-based platforms and social media can potentially constitute a valuable tool in terms of keeping in check emerging substances, given how during the COVID-19 pandemic many interactions between traffickers and buyers have moved online (14). After all, social media have been playing an increasingly relevant role as interacting platforms, which users and drug dealers can take advantage of in order to discuss drug prices, substance purity, distinctive traits of the "high" (i.e. desired drug effects) they are seeking, ways of taking the substances, dosages, and characteristics of any new NPS becoming available on such back-alley marketing channels (15). Softwares designed and specifically programmed to sift through and analyze all detectable online information in that regard may prove valuable to figure out evolving dynamics of trafficking, purchases and use. Probing social media users has proven effective tool for public health concerns, e.g. drug checking services which have been harnessed due to their harm reduction potential in places estimated to be at risk, with large crowds gathering (concerts, clubs and the like). Nonetheless, research efforts need to be directed towards the new realm of criminality, the "Dark Web", in which all sorts of illegal exchanges and interactions are known to take place. A 2020 study has highlighted the appalling risks for drug users who choose to pursue that option in order to buy drugs (16). Three dealers were selected on a specific "Dark Web" marketplace, and NPS were ordered through such a channel.

All these exchanges were thoroughly documented, and an analysis was undertaken of all the substances thus bought, totaling nine samples, by NMR, HRMS, LC-UV, and two also by x-ray diffraction. It was ultimately concluded that four out of five substances bought had been labeled with NPS names that did not match the actual substance, and two out of three samples of substances sold as new (i.e. unscheduled) NPS were instead found to be already documented substances, mislabeled and peddled under false pretenses.

Drug dealers were therefore either deceiving their clients or were unaware as to the actual substances which they were selling. In light of such extremely worrisome findings, it is not hard to understand the implications and the major public health risks that such new trends of trafficking and abuse may entail. It is therefore incumbent upon the scientific community and law enforcement agencies to adapt and strive to meet the new challenges brought by the new criminal ecosystems in terms of drug enforcement, first and foremost the impervious environment known as "Dark Web" relying on untraceable cryptocurrencies for illegal transactions.

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Invited Commentary

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New Psychoactive Substances and evolving criminal dynamics against the backdrop of the fourth industrial revolution

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The letter by Dr. Napoletano and colleagues offers us a glimpse as to where drug trafficking, and overall criminal activity dynamics, may be headed as the sea-change transformation of our lives unfold. Digital and web-based technologies and applications have dramatically and profoundly changed the way human beings function and interact, and such a revolution has been thoroughly explored and researched from the legal, ethical, moral and anthropological perspectives. Daily activities and interactions in which we routinely engage rely more and more on softwares, devices and applications for an ever more extensive range of tasks: from financial transactions and banking services to research, from information and to travel planning, from entertainment to telemedicine, which has been greatly developed and brought major benefits during the SARS-CoV-2 pandemic, and will be valuable as we strive to manage the new phase of the pandemic as well. The Fourth Industrial Revolution is poised change healthcare at its very core as well. As technology advances, it will enable greater medical breakthroughs and the faster development of innovative treatments and medications. Nonetheless, as Dr. Napoletano and colleagues insightfully point out, the criminal element has found fertile ground as the web has evolved and new avenues have become

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available to circumvent surveillance and rely on anonymity in the furtherance of a crime. Cybercrime has been coined to indicate any of the countless criminal acts thus perpetrated. The Dark Net is constituted by overlay networks utilizing the Internet, for which specific software or credentials are necessary to access. It is impervious to outside surveillance and constitutes an almost ideal ecosystem for illegal transactions and services to be exchanged. Some may be surprised to learn that the Internet we all use multiple times every day, which we could refer to as "surface web", only accounts for 5% of the World Wide Web (1). By far the largest share is constituted by the so-called "Deep Web", which does not necessarily coincide with illegal activities, but rather encompasses websites that are not indexed in the search engines we all use, including medical records, legal documents, subscription information and the like, and requires special software or credentials to access.

The third level, the Dark Web (i.e websites that exist on the Dark Net, an overlay that 'covers' the internet and enables anonymity), which Dr. Napoletano and colleagues mention in connection with new psychoactive substances trafficking, is beyond unindexed sites, and accounts for a small fraction of the Deep Web (rough estimates place its share at 1-4%, although an accurate quantification is impossible) (1). While merely accessing the Dark Web is not illegal, much of the activities and exchanges that take place on it are indeed illegal. Anonymity while using Dark Web sites is guaranteed through encryption, which is definitely a priority to those pursuing criminal activities. One of the main legal, and even valuable, uses of the Dark Web is by political dissidents living under dictatorial regimes which constrain freedom of information and speech by strict control over internet communications, and by whistleblowers, who would otherwise risk retaliation after divulging sensitive information usually linked to crimes committed by their governments or superiors. Websites on the Dark Web are most commonly encrypted (and thus difficult to track) using the Tor (acronym of The Onion Router, a metaphor for the multiple layers of encryption that make it extremely difficult to control) browser, which most Dark Web users access those sites, though there are other encryption tools and browsers, such as I2P (2). Another key peculiarity in such dark corners of the cybersphere is there are no search engines, since any such kind of indexing would provide a "breadcrumb trail" for investigators . For the illegal substances supply chain and transactions, anonymity is key, both in seeking the drugs and in terms of paying for them. In that respect, cryptocurrencies add a further layer of anonymity. The development over the years of large scale "cybercriminal communities" which thrive on the Dark Web is extremely worrisome, considering that drug trafficking is the single most important illegal activity performed via the dark net. Interventions by law enforcement agencies have been reported as mixed in terms of results (3). As of 2020, 38 identified active dark marketplaces for illegal drugs were identified. When law enforcement agencies successfully shut down marketplaces, a sudden increase in drug listings in coexisting marketplaces has been observed (4). All the complexities herein briefly elaborated on have to be contextualized by taking into the equation the distinguishing traits of new psychoactive substances (NPS). While NPS are extremely dangerous and deadly, due to their elusiveness and unpredictable effects, dark marketplaces do not offer any protection to customers or vendors, hence the danger for users is magnified. Such compounds are extremely attractive to drug dealers and smugglers due to their potency and because a high "street value" can be achieved with relatively small amounts, minimizing the risks involved in transit and trafficking compared with equipotent quantities of drugs such as heroin, especially on Dark Web marketplaces. The high level of potency is the main reason for their lethal potential and their catastrophic impact on public health (5). The new, almost untraceable means of trafficking have given rise to small, independent criminal networks that are not tied to traditional drug trafficking organizations, which makes them considerably harder for law enforcement to monitor (6). In light of the major ongoing evolution of

illicit drugs supply-and-demand avenues and ecosystems, it is of utmost importance to fine-tune our responses for fighting crime while upholding public health. New toxicological and forensic approaches need to take into account in the global challenge to health risks caused by new psychoactive substances and how the changing routes of trafficking require new sets of skills and a broad-ranging, truly multidisciplinary effort (7, 8). The impact that cybercrime can generate on public health is daunting, and represents an existential threat for the very fabric of our societies and the lives of millions. As the enemies and threats to our social peace and well-being now lurk in the ether, almost invisible and untraceable, an extraordinary effort needs to be undertaken to adapt, integrate our skills and take global cooperation and exchange to a whole new level, if we are to prevail.

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