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Polysubstance Use and Overdose Visualized via Maps: Amphetamines and Cocaine

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Abstract

Abuse of drug substances and resultant overdose deaths are no longer very straightforward—*viz.*, attributable to a single chemical entity of known purity. The reality is that most overdose deaths involve polysubstance use (*i.e.*, the use of combinations of substances). Further, the combinations are often of unknown purity, and even of unknown composition. Overdose deaths are at all-time highs. The depressing statistics are monitored and reported by several international and governmental organizations such as the WHO (World Health Organization), CDC (Centers for Disease Control and Prevention), several Institutes of the NIH (National Institutes of Health), Regulators, and Enforcement Agencies (*e.g.*, DEA). The information is disseminated for free for review and use. But it is our observation that although numeric presentation is helpful and adequate for professionals, the non-expert and the visual learner often find a visual representation clearer and compelling. With this in mind, we present the "gestalt" of polysubstance use and overdose using available maps of the data. The previous article in the series considered the opioids. This one considers amphetamines and cocaine, and places the rise in opioid-associated overdose deaths in the context of other abused drugs.

Keywords

Polysubstance Use/Abuse, Use Disorder, Overdose, Maps, Amphetamine, Cocaine

1. Introduction

As we pointed out in our recent first publication in this series [1], there is an in-

creasing trend in drug-overdose deaths—they involve more than one drug (*i.e.*, they are polysubstance use and overdose) [2] [3]. In fact, although many/most drug overdose deaths involve an opioid (in particular illicit fentanyl or fentanyl analog), it is estimated that more than half of current drug overdose deaths now result from combination (polysubstance) use and/or abuse [4]. The real or perceived advantages of polysubstance use are many and individualized, but include enhancing the pharmacodynamic effect, extending the duration of the desired effect, mitigation of adverse effects, and amelioration of withdrawal symptoms. Whatever the logical or naive reason, however, the added danger of polysubstance versus mono-substance use is the potential for additive or even synergistic (greater-than-additive) negative interaction between the pharmacologic/toxicologic effects of the individual drugs alone [5]. Such deleterious interactions are known for combinations of opioids and benzodiazepines [5] [6] [7], amphetamines [8], cocaine [9], alcohol [10], muscle relaxants [11] [12], and others.

A series of open-access graphs (maps) that provide illustrative and instructive visual guides to the extent and the temporal progression of substance use/abuse and overdose deaths have recently been provided by Ritchie & Roser (2018) [13]. Since the majority of polysubstance overdose deaths involve the opioids—intentionally or unknowingly—we considered them first in our prior publication [1]. The aim of the present manuscript is to try to see if there is something special about the opioids *per se*, or whether their use parallels the use of other abused drugs such as amphetamines and cocaine.

2. Amphetamines and Cocaine

2.1. Magnitude of the Problem

Methamphetamine is the 3rd most commonly used illicit stimulant drug in the United States, used by an estimated nearly two million persons aged 12 and older during the previous year; and cocaine is the 2nd most commonly used illicit stimulant drug in the United States, used by an estimated more than 5.5 million persons aged 12 and older during the previous year [14].

2.2. Molecular Pharmacology

The amphetamines—and related substances such as MDMA (aka, ecstasy, molly), mephedrone, and khat—have multiple, related mechanisms of action. The most prominent effect is thought to result from an increased extracellular concentration of the monoamine neurotransmitters dopamine (DA) and norepinephrine (NE, NA) within their respective synapses [15] [16] [17]. The increased synaptic concentration results in magnified binding to the postsynaptic DA and NE receptors and hence amplifies the effects of the neurotransmitters. The details of the mechanism involve inhibition of the neuronal reuptake transporters for DA (DAT) and NE (NET, NAT), which reduces the clearance of DA and NE from their synapses, inhibition of the vesicular monoamine transporter-2 (VMAT-2), and others.

Whereas the amphetamines and similar substances compete with DA and NE for DAT and NET and also displace monoamine neurotransmitter molecules from vesicles by action at VMAT-2, cocaine acts more mono-mechanistically to block neurotransmitter reuptake at DAT and NET [18] [19]. Cocaine has other actions on neurons, such as local anesthetic [20].

2.3. Toxicity of Overdose

As expected, at low doses stimulants such as the amphetamines and cocaine produce an increase in the respiratory drive (the increase in synaptic NE in essence mimicking the "fight-or-flight" response) [21]. But at high doses, stimulants can directly produce respiratory depression (possibly synergistically) in animal models [22] [23] [24] and human overdose [25] [26] [27].

3. Opioid-Associated Overdose Death Rates

Death rates due to overdose involving opioids have risen over the past decades worldwide, but particularly in the United States, and the trend continues upward [28]. A variety of explanations have been offered by a variety of qualified experts: psychosocial, economic, financial, over-prescription and/or over-promotion of opioids for pain, the pandemic, etc. [29].

A plausible suggestion is that the rise in opioid-associated overdose deaths has paralleled an increase in opioid prescribing and use. But, in fact, dispensing of opioids in the United States peaked between about 2008 and 2012, then actually declined substantially through 2020 [1].

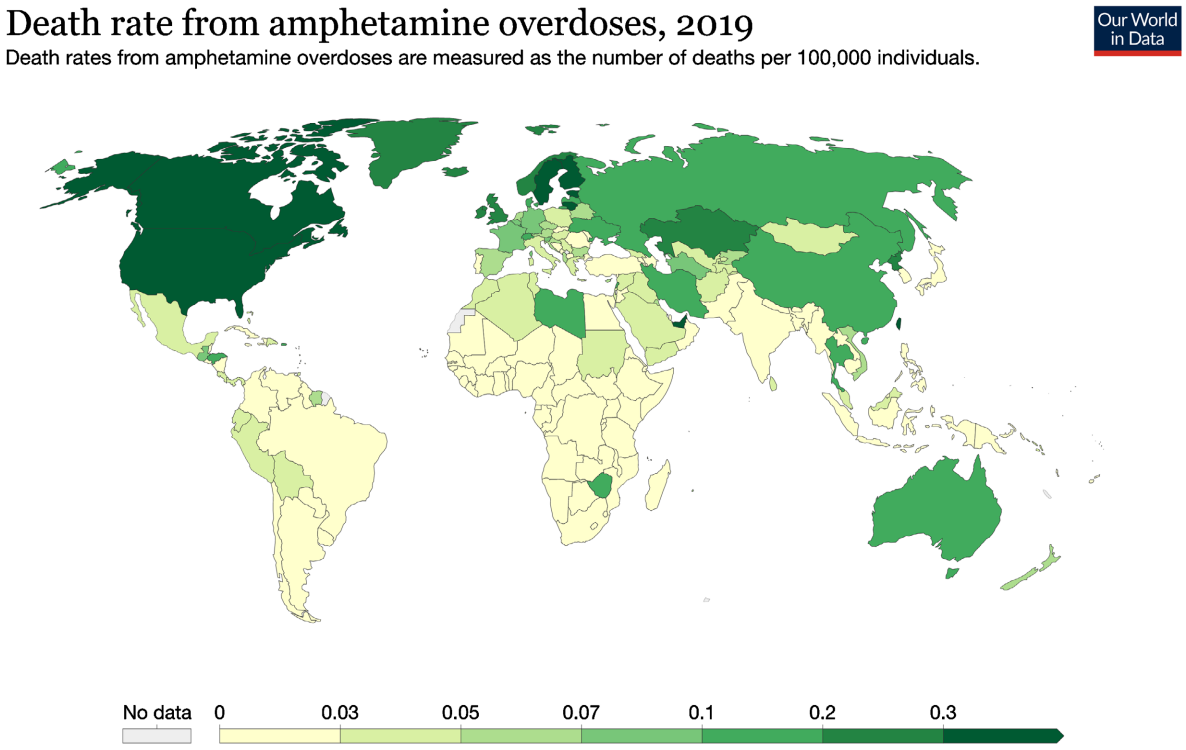
4. Amphetamine and Cocaine Overdose Death Rates

Possible insight into "opioid"-associated drug overdose deaths might be obtained by referral to overdose death rates from other abused substances. For the purpose of comparison, we chose amphetamine and cocaine, the reportedly 2nd and 3rd most commonly used illicit substances. It turns out that the overdose death rates for these drugs increased dramatically in the same places and over the same time period as it did for the opioids (**Figures 1-3**) [13].

There was a dramatic increase in the worldwide death rates attributed to amphetamine overdoses over the period 1990 to 2019. The rise was clearly more prominent (more than an order of magnitude increase for both drugs) in the United States than it was in other countries of the world. It also shows no sign of abating. And any future near-term decreases, albeit welcome, would take several decades to return to 1990 levels. The situation was similar for overdose deaths that were attributed to cocaine. Interestingly, the continuous upward trend hit a sort of plateau for both substances during the same period, *i.e.*, between about 2005 and about 2011.

5. Conclusions

The data maps provided by Ritchie & Roser (2018) provide food for thought,



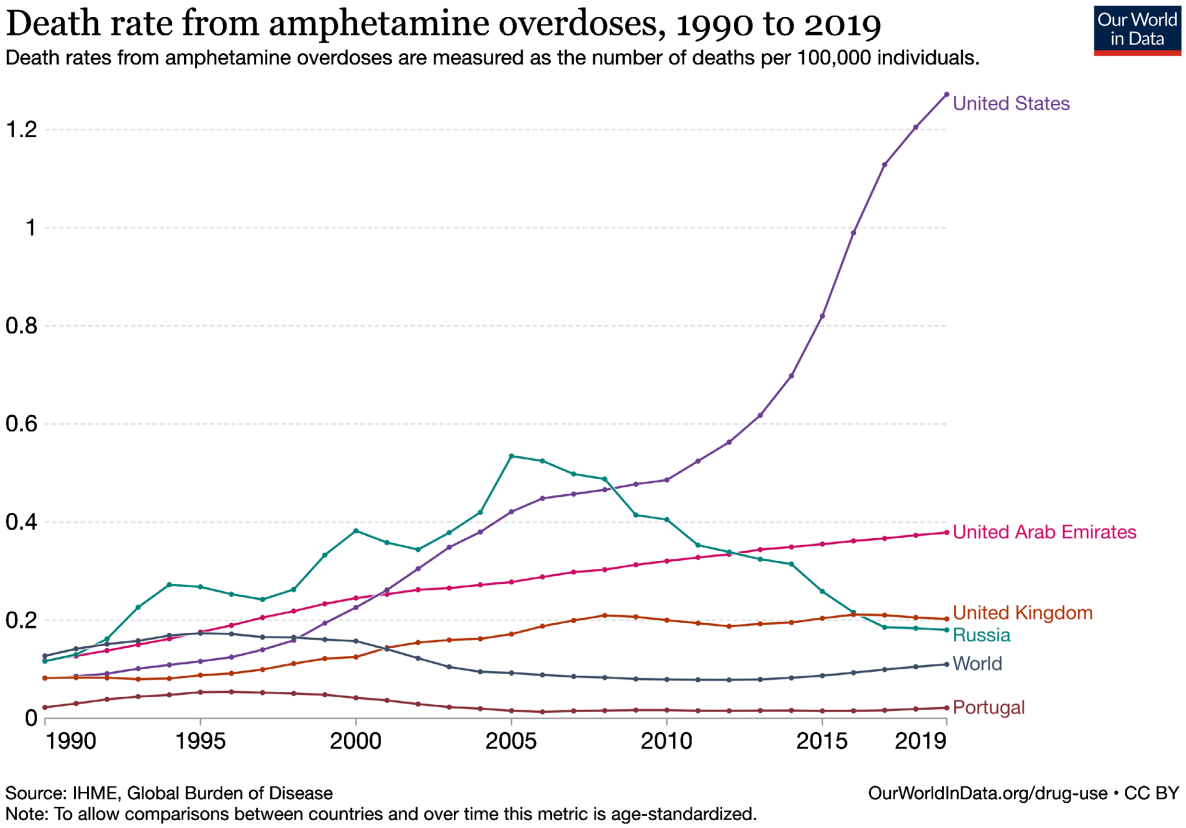
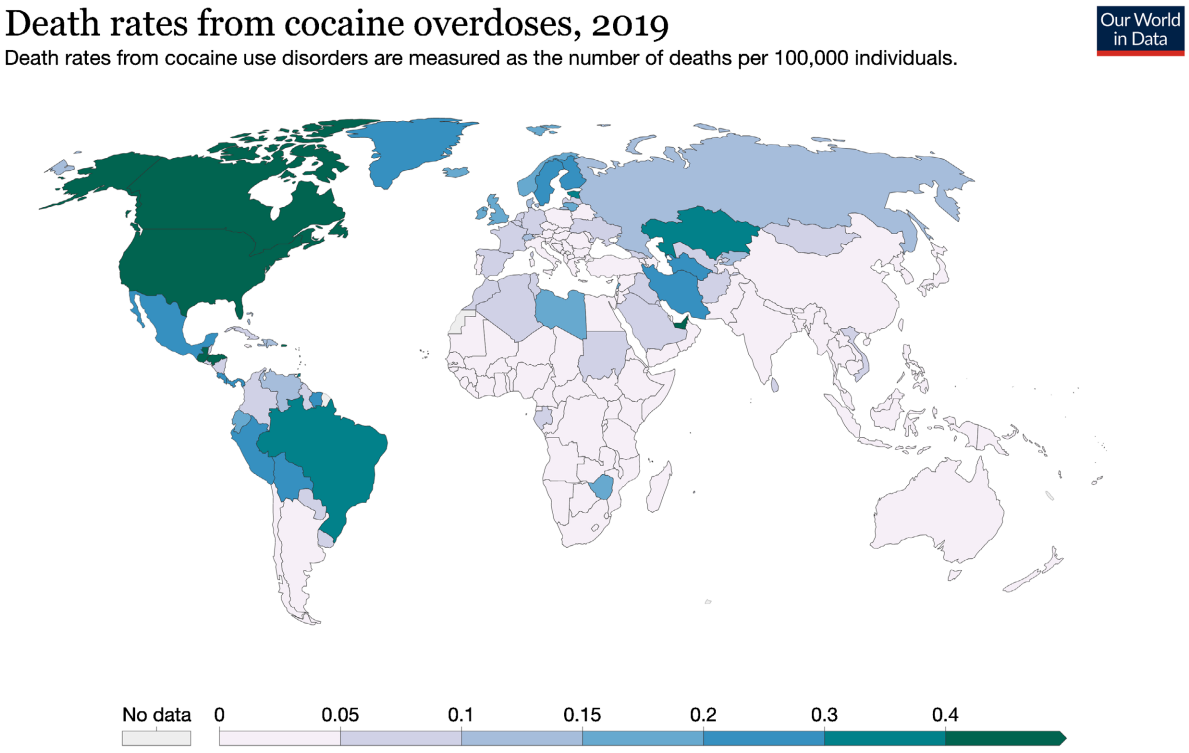


Figure 1. Death rates worldwide from amphetamine overdoses 1990 to 2019.



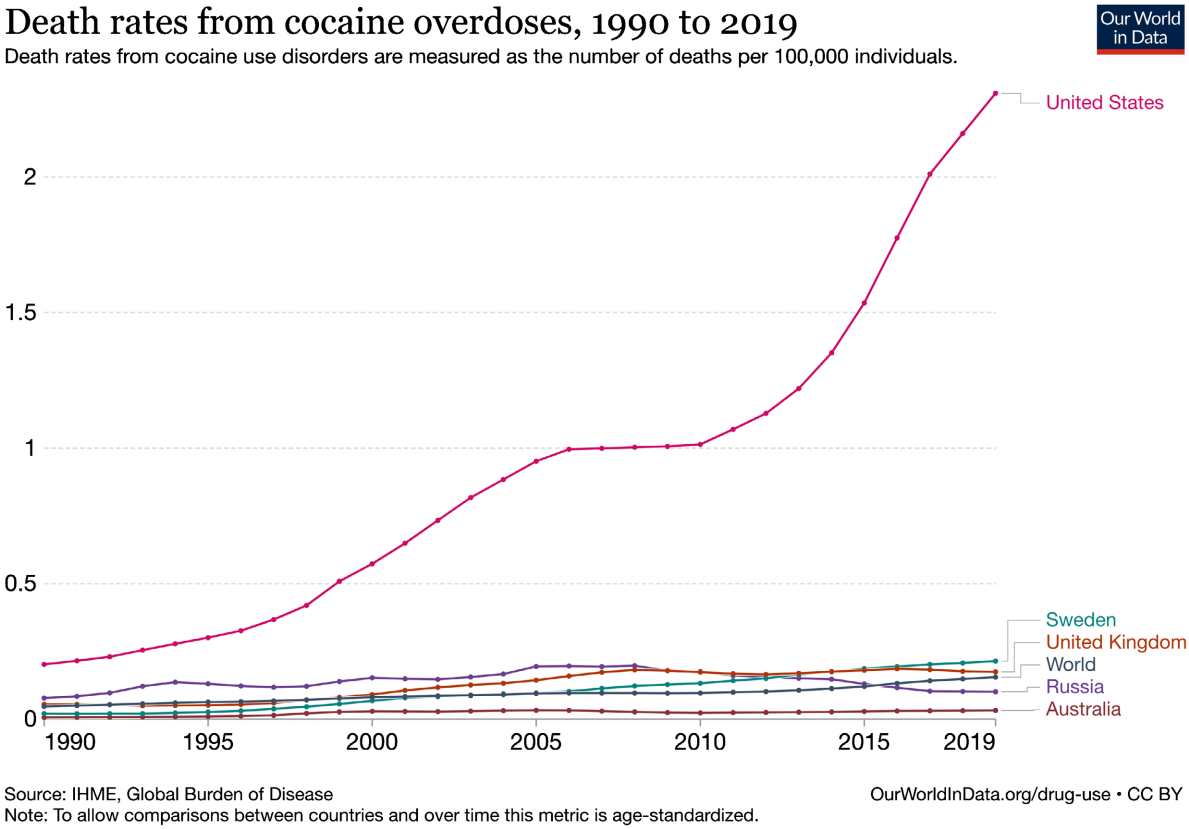
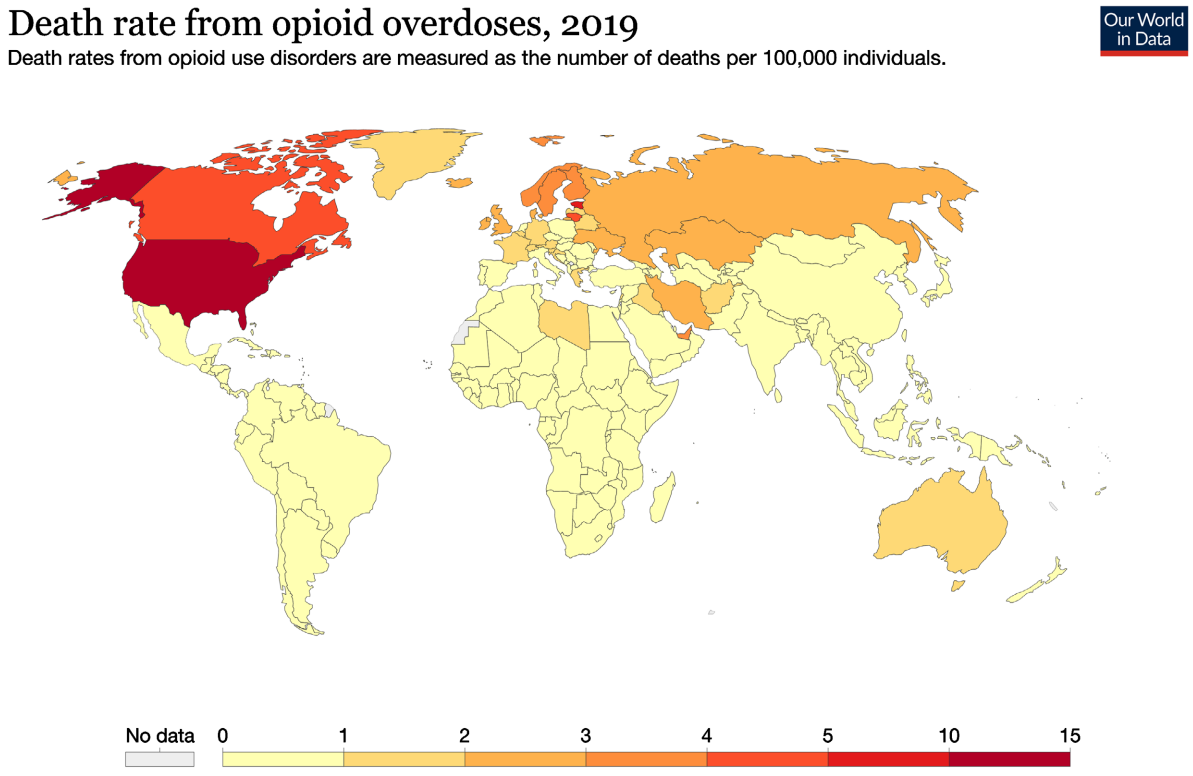


Figure 2. Death rates worldwide from cocaine overdoses 1990 to 2019.



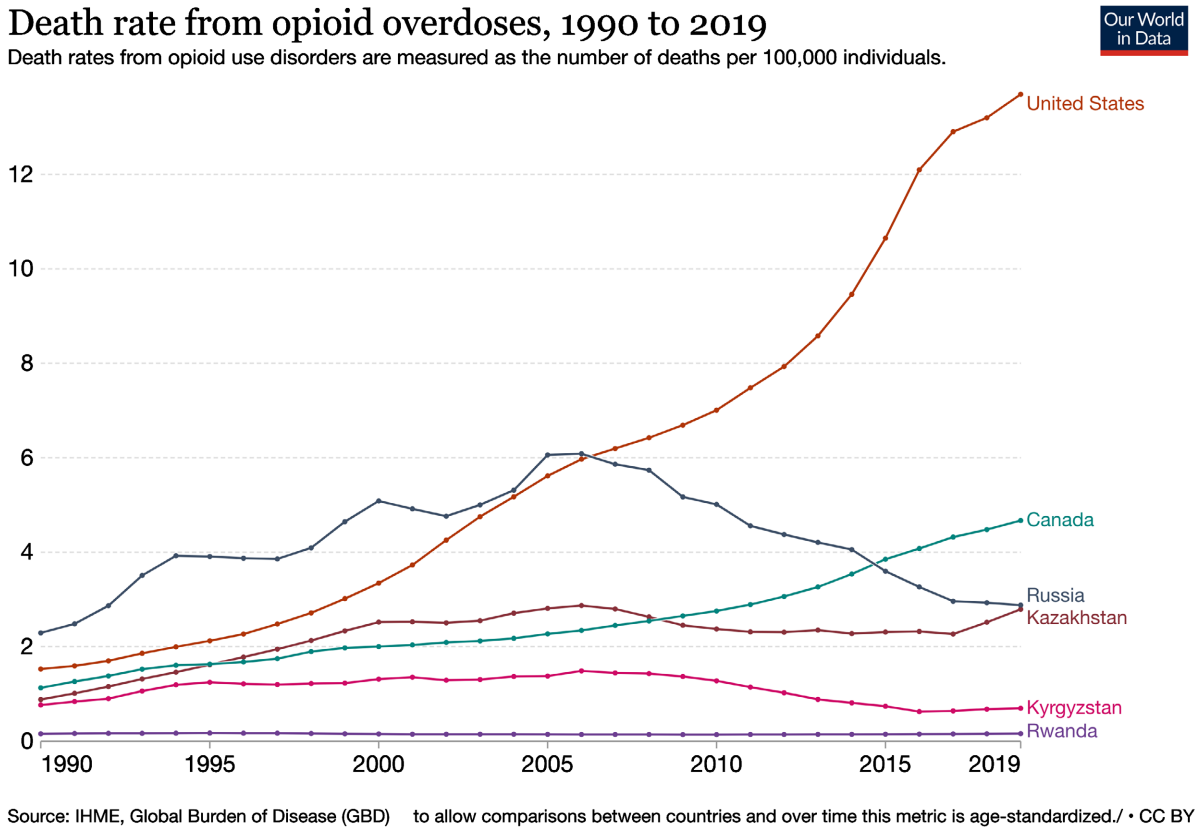


Figure 3. Death rates worldwide from opioid overdoses 1990 to 2019.

and are revealing in many ways [13]. They seem to suggest that attributing opioid-associated overdose deaths to something unique about the opioids themselves (that is, either their pharmacology or their dispensing and availability) might not be as fruitful as some might think. It might necessitate some broader thinking about substance use disorder, something more nuanced and fundamental to the biology, psyche, or experience of the users (nature and nurture). In this regard, modern psychology theories of drug use and overdose are more comprehensive; in these theories, the properties of the drug(s) used are just one factor among many [30].

Just as we concluded in the first publication in this series, the multiplicity of disparate sources that provide information about drug overdose deaths can be perplexing, rather than elucidating. That is why references to the maps supplied in Ritchie & Roser [13] provide such a valuable resource, and opportunity to visualize at a glance the extent, distribution, and temporal relationship of the problem. They also help to support, or discount, undocumented notions of trends, and proposed theories of causality.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Raffa, R., Pergolizzi, J.J. and Cukier, H. (In Press) Polysubstance Use and Overdose Visualized via Maps: Opioids. *Pharmacology & Pharmacy*, **13**, 107-118. https://doi.org/10.4236/pp.2022.134008

[2] Compton, W.M., Valentino, R.J. and DuPont, R.L. (2021) Polysubstance Use in the U.S. Opioid Crisis. *Molecular Psychiatry*, **26**, 41-50. https://doi.org/10.1038/s41380-020-00949-3

[3] Tori, M.E., Larochelle, M.R. and Naimi, T.S. (2020) Alcohol or Benzodiazepine Co-Involvement with Opioid Overdose Deaths in the United States, 1999-2017. *JAMA Network Open*, **3**, Article ID: e202361. https://doi.org/10.1001/jamanetworkopen.2020.2361

[4] Kandel, D.B., Hu, M.C., Griesler, P. and Wall, M. (2017) Increases from 2002 to 2015 in Prescription Opioid Overdose Deaths in Combination with Other Substances. *Drug and Alcohol Dependence*, **178**, 501-511. https://doi.org/10.1016/j.drugalcdep.2017.05.047

[5] Xu, L., Chockalingam, A., Stewart, S., Shea, K., Matta, M.K., Narayanasamy, S., *et al.* (2020) Developing an Animal Model to Detect Drug-Drug Interactions Impacting Drug-Induced Respiratory Depression. *Toxicology Reports*, **7**, 188-197. https://doi.org/10.1016/j.toxrep.2020.01.008

[6] Jones, C.M. and McAninch, J.K. (2015) Emergency Department Visits and Overdose Deaths from Combined Use of Opioids and Benzodiazepines. *American Journal of Preventive Medicine*, **49**, 493-501. https://doi.org/10.1016/j.amepre.2015.03.040

[7] Boon, M., Van Dorp, E., Broens, S. and Overdyk, F. (2020) Combining Opioids and Benzodiazepines: Effects on Mortality and Severe Adverse Respiratory Events. *An-*

nals of Palliative Medicine, **9**, 542-557. https://doi.org/10.21037/apm.2019.12.09

[8] Uemura, K., Sorimachi, Y., Yashiki, M. and Yoshida, K. (2003) Two Fatal Cases Involving Concurrent Use of Methamphetamine and Morphine. *Journal of Forensic Sciences*, **48**, 1179-1181. https://doi.org/10.1520/JFS2002293

[9] Pennings, E.J., Leccese, A.P. and Wolff, F.A. (2002) Effects of Concurrent Use of Alcohol and Cocaine. *Addiction*, **97**, 773-783. https://doi.org/10.1046/j.1360-0443.2002.00158.x

[10] Jones, C.M., Paulozzi, L.J., Mack, K.A. and Centers for Disease Control and Prevention (2014) Alcohol Involvement in Opioid Pain Reliever and Benzodiazepine Drug Abuse-Related Emergency Department Visits and Drug-Related Deaths—United States, 2010. *Morbidity and Mortality Weekly Report*, **63**, 881-885.

[11] Li, Y., Delcher, C., Wei, Y.-J.J., Reisfield, G.M., Brown, J.D., Tighe, P., *et al.* (2020) Risk of Opioid Overdose Associated with Concomitant Use of Opioids and Skeletal Muscle Relaxants: A Population-Based Cohort Study. *Clinical Pharmacology & Therapeutics*, **108**, 81-89. https://doi.org/10.1002/cpt.1807

[12] Horsfall, J.T. and Sprague, J.E. (2017) The Pharmacology and Toxicology of the 'Holy Trinity'. *Basic Basic & Clinical Pharmacology & Toxicology*, **120**, 115-119. https://doi.org/10.1111/bcpt.12655

[13] Ritchie, H. and Roser, M. (2018) Opioids, Cocaine, Cannabis and Illicit Drugs. https://ourworldindata.org/illicit-drug-use

[14] Substance Abuse and Mental Health Services Administration (2019) Section 1 PE Tables - Results from the 2019 National Survey on Drug Use and Health: Detailed Tables. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf

[15] Faraone, S.V. (2018) the Pharmacology of Amphetamine and Methylphenidate: Relevance to the Neurobiology of Attention-Deficit/Hyperactivity Disorder and Other Psychiatric Comorbidities. *Neuroscience & Biobehavioral Reviews*, **87**, 255-270. https://doi.org/10.1016/j.neubiorev.2018.02.001

[16] Heal, D.J., Smith, S.L., Gosden, J. and Nutt, D.J. (2013) Amphetamine, Past and Present—A Pharmacological and Clinical Perspective. *Journal of Psychopharmacology*, **27**, 479-496. https://doi.org/10.1177/0269881113482532

[17] Hutson, P.H., Tarazi, F.I., Madhoo, M., Slawecki, C. and Patkar, A.A. (2014) Preclinical Pharmacology of Amphetamine: Implications for the Treatment of Neuropsychiatric Disorders. *Pharmacology & Therapeutics*, **143**, 253-264. https://doi.org/10.1016/j.pharmthera.2014.03.005

[18] Docherty, J.R. and Alsufyani, H.A. (2021) Pharmacology of Drugs Used as Stimulants. *The Journal of Clinical Pharmacology*, **61**, S53-S69. https://doi.org/10.1002/jcph.1918

[19] Cheng, M.H., Block, E., Hu, F., Cobanoglu, M.C., Sorkin, A. and Bahar, I. (2015) Insights into the Modulation of Dopamine Transporter Function by Amphetamine, Orphenadrine, and Cocaine Binding. *Frontiers in Neurology*, **6**, Article No. 134. https://doi.org/10.3389/fneur.2015.00134

[20] Taylor, A. and McLeod, G. (2020) Basic Pharmacology of Local Anaesthetics. *BJA Education*, **20**, 34-41. https://doi.org/10.1016/j.bjae.2019.10.002

[21] Tseng, W., Sutter, M.E. and Albertson, T.E. (2014) Stimulants and the Lung: Review of Literature. *Clinical Reviews in Allergy & Immunology*, **46**, 82-100. https://doi.org/10.1007/s12016-013-8376-9

[22] Trippenbach, T. and Kelly, G. (1994) Effects of Acute and Chronic Cocaine on Breathing and Chemosensitivity in Awake Rats. *American Journal of Physiology*, **266**, R696-R701. https://doi.org/10.1152/ajpregu.1994.266.3.R696

[23] Tseng, C.C., Derlet, R.W. and Albertson, T.E. (1992) Cocaine-Induced Respiratory Depression and Seizures Are Synergistic Mechanisms of Cocaine-Induced Death in Rats. *Annals of Emergency Medicine*, **21**, 486-493. https://doi.org/10.1016/S0196-0644(05)82511-9

[24] Tseng, C.C., Derlet, R.W., Stark, L.G. and Albertson, T.E. (1991) Cocaine-Induced Respiratory Depression in Urethane-Anesthetized Rats: A Possible Mechanism of Cocaine-Induced Death. *Pharmacology Biochemistry and Behavior*, **39**, 625-633. https://doi.org/10.1016/0091-3057(91)90138-R

[25] Richard, C.A., Harper, R.K., Schechtman, V.L., Ni, H. and Harper, R.M. (1993) Respiratory Patterning Following Cerebral Ventricular Administration of Cocaine. *Pharmacology Biochemistry and Behavior*, **45**, 849-856. https://doi.org/10.1016/0091-3057(93)90131-C

[26] Di Maio, V.J. and Garriott, J.C. (1978) Four Deaths Due to Intravenous Injection of Cocaine. *Forensic Science International*, **12**, 119-125. https://doi.org/10.1016/0379-0738(78)90019-1

[27] Erzouki, H.K., Allen, A.C., Newman, A.H., Goldberg, S.R. and Schindler, C.W. (1995) Effects of Cocaine, Cocaine Metabolites and Cocaine Pyrolysis Products on the Hindbrain Cardiac and Respiratory Centers of the Rabbit. *Life Sciences*, **57**, 1861-1868. https://doi.org/10.1016/0024-3205(95)02166-G

[28] Friedman, J.R. and Hansen, H. (2022) Evaluation of Increases in Drug Overdose Mortality Rates in the US by Race and Ethnicity Before and During the COVID-19 Pandemic. *JAMA Psychiatry*, **79**, 379-381. https://doi.org/10.1001/jamapsychiatry.2022.0004

[29] De Weerdt, S. (2019) Tracing the US Opioid Crisis to Its Roots. *Nature*, **573**, S10-S12. https://doi.org/10.1038/d41586-019-02686-2

[30] West, R. and Brown, J.D. (2013) Theory of Addiction. 2nd Edition, Wiley Blackwell, Hoboken, 1-263. https://doi.org/10.1002/9781118484890