Journal of Pain Research

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EDITORIAL

The Polysubstance Overdose-Death Crisis

This article was published in the following Dove Press journal:
Journal of Pain Research

John F Peppin[1]
Robert B Raffa[2–5]
Michael E Schatman[6,7]

[1]Department of Internal Medicine, Marian University College of Osteopathic Medicine, Indianapolis, IN, USA; [2]Temple University School of Pharmacy, Philadelphia, PA, USA; [3]University of Arizona College of Pharmacy, Tucson, AZ, USA; [4]Neumentum, Inc., Morristown, NJ, USA; [5]Enalare Therapeutics, Naples, FL, USA; [6]Department of Diagnostic Sciences, Tufts University School of Dental Medicine, Boston, MA, USA; [7]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

In the late 1990s and early 2000s, it was recognized that an increasing number of people were dying from opioid overdose, and regulatory agencies, professional societies, and legislative bodies actively adopted and promulgated efforts to reduce the "epidemic". Yet, despite multiple guidelines, legislative enactions (often draconian), and attempts at legal and financial-penalty remedies, death rates continue to climb. The literature is now replete with the terms "opioid-induced respiratory depression" and "opioid overdose death" to describe the cause of death in many of these cases. Unfortunately, this terminology is too simplistic and now woefully outdated. It understates the complexities of these deaths, and the fact that the majority of overdose deaths currently involve multiple substances – that is, it is now a polysubstance-overdose death crisis.

The older terminology belies the complexity of both the victims and the difficulty in treating them. Individuals who use multiple substances in combination do so based on a number of internal genetic and external experiential influences, and for different reasons and purposes. The rationale behind the abuse is a salient factor: is it pharmacologic – ie, is the individual's choice of a drug combination based on its psychoactive effects, to self-medicate, to magnify the effects of another drug, or counteract specific side effects of that drug? Or is it mainly situational – ie, due to circumstance or happenstance? In such a case, simple availability is often an important factor. Supply-chain issues, price, and other factors influence, or even dictate, what substances will be used at a given time.[1]

Prior to the DSM-5, "Polysubstance Abuse" was a listed diagnosis with specified criteria.[2] The term was eliminated from DSM-5 and, instead, "Substance Abuse" was intended to be more consistent for various abusable substances and situations.[3,4] However, the elimination has raised an issue regarding treatment:

> There is currently limited evidence to assess whether treating multiple substance problems concurrently is more effective than treating them individually and sequentially.[3] (p. 273)

Although drug overdose deaths amount to only a small fraction (about 2%) of all deaths in the US each year, they account for more than a third (38%) of all accidental deaths caused by unintentional and preventable injuries.[5] A majority of these deaths involve polysubstance abuse and are polysubstance overdose deaths. Signals of polysubstance overdose death can be traced back for decades. In a study on heroin overdose deaths from San Francisco in the 1970s, 47% of victims were positive for ethanol and 28% for "other drugs".[6] In a study published in 1996, only 19% of the overdose victims had taken only one substance related to the overdose.[7] More recently, a 2017 study by Hannah and colleagues found that the average

Correspondence: Michael E Schatman
Tel +1 425 647-4880
Email Michael.Schatman@tufts.edu

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DovePress
http://doi.org/10.2147/JPR.S295715

number of drugs (most commonly alcohol, amphetamines, and multiple opioids) found in so-called prescription opioid overdose decedents' toxicology reports was six.[8]

Prescription opioid deaths also commonly involve multiple other substances, such as alcohol, sedatives, illicit drugs, and benzodiazepines (BZDs).[9,10] BZDs are among the most commonly prescribed drugs.[11] They are commonly prescribed or abused in conjunction with prescription or illicit opioids.[12] The majority, up to 80% or more, of heroin users also use cocaine or BZDs.[13,14] Polysubstance users also frequently use cocaine and amphetamines, and 74% of cocaine and 80% of methamphetamine users also use other substances.[15] However, reports of the true extent of use are highly variable; for example, the range of those using cocaine and alcohol is reported to be 37% to 96%.[15] This large variability illustrates the complexity in polysubstance abuse and overdose patterns. Those who abuse "fentalogues" (illicit fentanyl and its analogs, eg, alfentanil, carfentanil, and sufentanil)[16] tend to have even greater incidence of polysubstance abuse than do abusers of other substances, albeit many victims of overdoses due to fentalogues are unaware of taking this class of drugs.[17,18] Cannabis and binge drinkers are also more likely to use other substances.[19,20]

- The practice of combining an opioid + psychostimulant ("speedball") and its potential lethal consequences were reported in the literature at least as early as the 1950s.[21] The practice persists; it was responsible for 12,676 (18.8%) of the 67,367 drug overdose deaths in 2018.[22]
- A study of polysubstance overdose deaths in New York City from 1990 to 1998 found 57.8% of them were attributed to polysubstance combinations.[23]
- A 1999 study conducted in San Francisco reported 48% of all overdose deaths occurred with drug combinations.[24]
- Cone's postmortem reviews in 2003 and 2004 of 1243 cases of opioid overdose involving oxycodone found that 96.6% had "at least one other plausible contributory drug".[25,26]
- In a study in 2008 from New Mexico, 47.2% of unintentional drug overdose deaths were "caused by the use of two or more substances".[27]
- A study from New York in 2010 reported that 98% of the overdose cases involved more than one substance.[28]
- Studies from Switzerland, Austria, Australia, Spain and Scotland yield similar data.[29–33]

Importantly, these are probably underestimates, as early studies had limited validated assays to detect the variety of substances potentially involved in an overdose.[34] Further, survey data were frequently used in older studies, and are still used, despite the limitations of this type of study design.

It is time to take the blinders off. It is time for everyone – clinicians, legislators, insurers, media, family members, and all others, including the general public – to recognize the complexities of the issues surrounding the crisis of polysubstance overdose deaths. The terms "opioid-induced respiratory depression" and "opioid-overdose death" are outdated, as they fail to reflect current realities and only further continue the errant notion of simplicity. They should be abandoned for the more accurate and clinically-helpful terms "polysubstance-induced respiratory depression" (PIRD) and polysubstance-overdose death" (POD). Furthermore, healthcare professionals need to not only better understand the issues surrounding polysubstance-use disorders, but also to recognize that treatment of this type of overdose is considerably more complicated than is single-substance opioid overdose, and significantly more challenging than – and unresponsive to – the interventions that they likely were taught. Finally, a uniform system for distinguishing between opioid-alone overdose deaths and those due to polypharmacy is sorely needed. Schatman and Ziegler noted in 2017 that the United States Centers for Disease Control and Prevention (CDC) fails to do so, inflating figures.[35] Despite their warning, to the best of our knowledge, only New Hampshire and Massachusetts actually break down opioid overdose deaths adequately, resulting in their reported mortality numbers being the only ones that reflect reality.

There is no way to "end" the polysubstance abuse crisis, but there is certainly a path to reduce its incidence and the fatalities that result from it. A first step is an understanding that we are dealing with polysubstance abuse and overdose deaths. This clearly changes the diagnostic and therapeutic approach. Further, screening for these disorders needs to be a regular occurrence in healthcare professional's offices; and there need to be a good referral-base and timely referrals. Appropriate reimbursement is needed for evaluation, screening, and treating these persons. Finally, more effective options for treating polysubstance-induced respiratory failure need to be investigated and applied when possible. Approaches that would reverse respiratory depression independent of the causative substance would potentially save myriad lives.

Disclosure

Professor Robert B Raffa reports personal fees from Enalare Therapeutics, during the conduct of the study; is the co-founder for Enalare Therapeutics and the CSO for Neumentum Inc, outside the submitted work. Dr Michael E Schatman serves as a research consultant for Firstox and Modoscript, outside the submitted work. The authors report no other conflicts of interest in this work.

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