

Commentary: “Ockham’s Razor” Doesn’t Apply to “Opioid” Overdose Death

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Abstract

Polysubstance Abuse (PSA) greatly complicates an attempt to implicate a single drug as sole cause of an overdose death. Since PSA now occurs in the majority of cases of drug overdoses, many or most overdose deaths are polysubstance overdose deaths. And since many of the substances involved in a polysubstance Overdose Death (POD) are Central Nervous System (CNS) depressants, many of which can cause overdose death themselves, or synergistically with opioids, it is somewhat puzzling that prescription opioids have been singled out as the cause of these deaths—without reference to PSA. This is particularly puzzling in light of the fact that the issues of PSA and POD have been recognized and discussed in the literature since at least the 1960’s and before. We therefore here consider the question: are we facing an “opioid” crisis or, instead, a “polysubstance crisis”? And we wonder if the issue has been over-simplified, to the detriment of the individuals affected, and to society more broadly. There is a need for an “agnostic” respiratory stimulant that can reverse polysubstance-induced respiratory depression.

Keywords

Opioid, Overdose, Polysubstance Use, Polysubstance Overdose, Treatment

1. Introduction

“Ockham’s razor” is the principle of parsimony attributed to William of Ockham in the 14th century that “Entities should not be multiplied without necessity.”

ty” [1]. It has been repeated by numerous philosophers down through the centuries, and is a backbone of the scientific endeavor [2]. Unfortunately, when it comes to medicine many medical issues are much more complex, and we must “multiply with necessity”, since trying to fit the issue into a simple box only leads to confusion and error [3]. This seems certainly true with the issue of “opioid” overdose deaths.

The inverse of Ockham’s razor is evident in the issues surrounding the “opioid” crisis. Data collected on overdose deaths has appropriately led to great concern among stakeholders. The concern was propagated in media, government, and professional organizations decrying the over-prescription of, and extensive access to, prescription opioid medications as the source of this crisis [4]. Articles abounded about the evils of prescription opioids, and overdose deaths were ascribed to prescription opioid medications [5]. Local, County, State and Federal agencies developed regulations to “stem the tide” of prescription medication overdose [6]. Guidelines were developed by agencies as well as professional societies formed to specifically combat the issue, e.g., CDC Guidelines and PROP (Physicians for Responsible Opioid Prescribing) [7] [8]. Unfortunately, although the concern was well placed, it pushed Ockham’s razor to the extreme. It was contended that all we needed to do was reduce physician’s opioid prescribing for pain. After restrictive and sometimes draconian legislative measures, the prescription of opioids has been dramatically reduced [9]. Unfortunately, overdose deaths involving opioids continued to rise; with recent increased spikes during the COVID-19 pandemic (**Figure 1**) [10].

2. “Opioid” Overdose

The issue of “opioid” overdose death, turns out not to be one of a single drug or even a single class of drugs [11]. It is an example of why we should understand fully the clinical situation and not accept data without understanding the much more complex issues with which they are associated. The issue of overdose deaths is actually one of polypharmacy and has been for decades. Certainly opioids, licit and illicit, play a role, but the combination of multiple drugs, *i.e.*, poly-substances, in a given patient greatly contributes to the overdose death problem. This problem is more accurately viewed as a poly-substance issue, rather than a single drug or single drug-class issue. This is true even of illicit “fentanoids” (highly potent fentanyl analogs such as alfentanil, carfentanil, and sufentanil). Although the action of fentanoids on the respiratory system is very fast, overdose individuals routinely have polysubstances involved, which may interact together to produce a fatal outcome.

3. The Data

Although criticized on a number of levels, the National Survey on Drug Use and Health is a major database concerning substance abuse in the United States [12]. Established in 1971, its data has been used to establish policy concerning substance

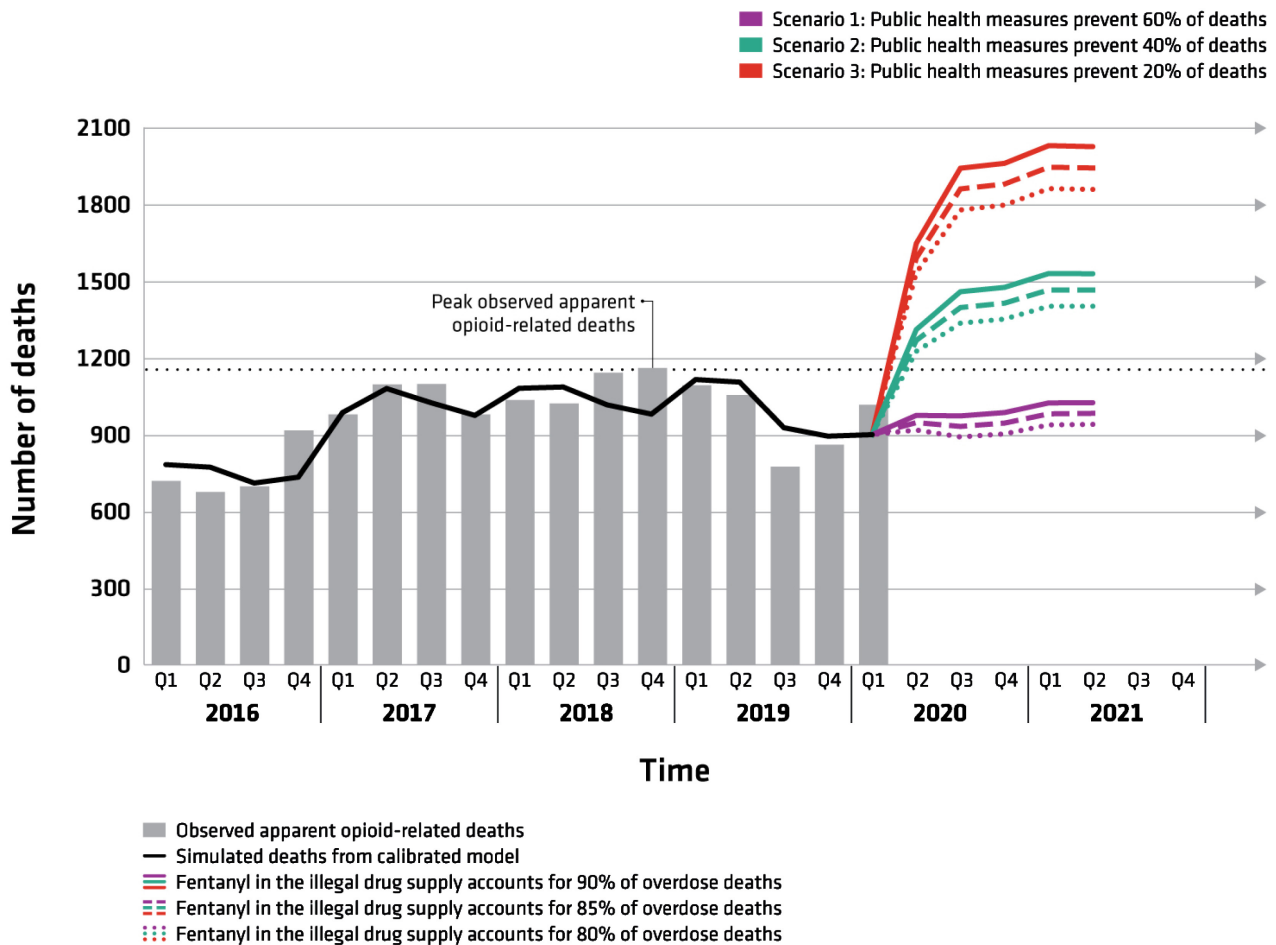


Figure 1. Example: the current and projected COVID-related increase in opioid-related deaths in Canada. <https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/data-surveillance-research/modelling-opioid-overdose-deaths-covid-19.html>.

use, and has been used by the media and others to describe the opioid crisis [13].

Overdose-death data start with the death certificate. Although beyond the scope of the current article, it is critical to understand the limitations of our current system of death-data collection. The high error rates in recording cause of death (CoD) in a death certificate are significant. The CDC estimates that one in three death certificates are in error [14]. Other studies suggest even higher error rates, especially when dealing with opioid overdose deaths [15]. Death certificates require a single cause of death, but allow for secondary causes. In a polysubstance overdose death, a single drug must be entered as the “cause of death”. This can be misleading as to the actual cause the death, because the multiple substances taken concurrently can have combined or even synergistic effects on depression of respiration and CNS function. Limitations and misinterpretation of forensic toxicological evaluations further contribute to confusion on CoD in polysubstance cases. This led Miron in 2018 to state “With fatal toxic concentration levels being so broad and overlapping, with ranges that many addicts live with, a toxicology report is of little help with determining the cause of death.”

[16].

4. Polysubstance Use, Overuse, and Death

The understanding of the nature and extent of POD is hindered by inaccuracies in the data collected and used to describe these deaths. For example, studies on Substance Use Disorder (SUD) frequently exclude those with a history of multiple drug use [17]. Many of the studies use surveys and patient questionnaires to ascertain patterns of drug use. However, these have shortcomings, especially when dealing with polysubstance abuse, where there are significant issues with recall bias. This places extra reliance on cause of death data, and their use as basis to develop public policies and regulations intended to prevent premature and accidental mortality [18]. It is thus important that CoD data be accurate, timely, and sufficiently detailed. Unfortunately, the error rate in CoD designations in death certificates approaches 20% - 30%, and drug overdose cases are no exception [18] [19] [20].

Multiple studies in the U.S. and Europe have reported that death certificate errors are especially common in drug overdose cases where preliminary death certificates have been issued before laboratory results of toxicology tests are known [18] [21] [22] [23] [24] [25]. When multiple substances are identified in postmortem toxicology screens, certifiers frequently record imprecise causes of death that have little epidemiological value, such as “mixed drug intoxication” or “polypharmacy” [26]. The death certificate often will contain an incomplete or ambiguous CoD based solely on an immunoassay of the decedent’s urine. Unfortunately, the use of postmortem toxicology testing requires expertise rarely found in coroners, medical examiners, and others who draw the samples used. The chief of the Mortality Statistics Branch of the NVSS (National Vital Statistics System), recently was quoted as saying that before the current coronavirus pandemic, one in every three death certificates was “wrong,” and that things were about to get worse [18]. In an editorial, four CDC analysts acknowledged that it was inaccurate to include IMF (illicitly prescribed fentanyl) the same ICD (International Classification of Diseases) coding for prescribed fentanyl [27]. This mistake greatly overstates the impact of prescription fentanyl, and reduces the impact of the newer fentanoids. Similar undisclosed error in the CDC’s methodology for calculating annual prescription opioid overdose deaths may occur with the agency’s coding of methadone-involved overdose deaths. Methadone is a Schedule II opioid agonist indicated for the management of severe chronic pain. In fairness, it must be noted that the ICD was neither originally established nor intended to be a database for describing the indication of drug-related morbidity and mortality. Attempting to use it for this purpose has produced errors, as admirably admitted by the CDC itself.

5. Discussion

This article is meant to illustrate the complexities surrounding the issue of “opioid

overdose death”. Unfortunately, there is no simplifying “Ockham’s razor” answer. It is an inherently complicated issue that cannot be simplified. Efforts to improve the evaluation of patients’ pain, the design of a personalized treatment approach that may or may not use opioids or indeed employ non-pharmacologic as well as pharmacologic treatments, and the goal of fewer and lower doses of opioids is laudable, and we support such measures. But although evaluating for substance use disorder should be a more common occurrence in all practices, unfortunately this is not the current norm [28]. The old adage of “throwing the baby out with the bathwater” may apply. The pendulum has now swung very far, and chronic pain patients are suffering as a result. They should benefit if we realize that the issue is not opioid use disorder *per se*, but rather polysubstance use disorder. For example, benzodiazepines rarely are demonized, although recent data and FDA guidance suggest that they have much more dire long term outcomes than were previously appreciated [29].

Due to intense governmental and professional efforts that focused on prescription opioids, prescriptions for opioids have decreased, but deaths have increased [30]. Obviously the current approach has been less than successful. Research needs to be generated in the area of polysubstance use disorder rather than continuing to focus on individual use disorders as though the parts will explain the whole. Other authors already have suggested that tracking single agents is insufficient to help with medical and public health interventions [31].

A serious implication of polysubstance overdose is that a single treatment, such as an opioid receptor antagonist, may not be effective [32].

Perhaps we can summarize by quoting Wardrop (2008): “As clinicians, we should consider all possible causes for a given presentation and seek the fewest, but we must not allow ourselves to be distracted by trying to find a unifying diagnosis when it simply may not be present. As the great 20th century physicist Albert Einstein once said, ‘Keep things as simple as possible, but no simpler’” [33].

There is a great and growing need for understanding the issues, patterns, and treatment of polypharmacy overdose deaths. And there is a need for other treatments, in addition to receptor antagonists, that can reverse polysubstance-induced respiratory depression. An example might be recent work in the area of respiratory stimulants as a potential addition to the treatment regimen in these cases [34].

Conflicts of Interest

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

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