

SECTION 1: DEFINING THE PROBLEM

Introduction

Ending Unnecessary Opioid-Related Deaths: A National Priority

Deaths related to prescription opioids have brought intense official scrutiny to the pain medicine field from regulators, legislators, and health care policy-makers. Most notably, the Food and Drug Administration (FDA) responded with a complex process aimed at developing class-wide risk evaluation and mitigation strategies to address the heightened risks long-acting opioids pose to patients and the public. Preventing unnecessary deaths should be a central focus of everyone working in the field of pain medicine. If we work to reverse the trend of opioid-related deaths, we can also expect improvement in adverse outcomes related to the nonmedical use of opioids, whether that misuse takes the form of recreation or misguided patient overconsumption. This has been described as the Hawthorne effect, whereby focusing attention on the worst of several related outcomes should improve all outcomes [1].

Corrective actions that do not impede access to appropriate and indicated pain therapy will likely come only when health care professionals, patient advocates, and all other stakeholders better understand the root causes of opioid-related deaths in legitimately treated patients. This supplement aims to discuss the available, albeit limited, data on the major risk factors for these deaths and to suggest possible ways to mitigate the harm associated with treating patients with potentially lethal analgesics. In pursuit of these same goals, an expert panel met in Salt Lake City, Utah, in 2009, resulting in the publication titled “An Analysis of the Root Causes for Opioid-Related Overdose Deaths in the United States” [2]. Although the data reviewed by the panel revealed regional differences in risk factors and prevalence of overdose deaths, common characteristics do emerge in decedent profiles and prescriber behaviors.

A striking finding is the frequency with which respiratory depression leading to an opioid-related death is exacerbated by the presence of additional substances, including alcohol, illicit drugs, and other prescription medications, particularly benzodiazepines. Combining benzodiazepines with opioid therapy raises a number of serious concerns. Benzodiazepine use has been found to contribute to life-threatening sleep-disordered breathing [3]. Furthermore, data from the West Virginia Office of the Chief Medical Examiner found benzodiazepines involved in more than a

third of prescription drug deaths in 2006, with the analysis suggesting nonmedical rather than psychotherapeutic use [4].

Medical examiner reports and associated clinical records reveal that a significant proportion of people who died from opioid-related overdose had histories that included risky behaviors, psychiatric disorders, and/or substance use disorders. In this supplement, Passik and Lowery address behaviors, some stemming from psychiatric or personality disorders, that can threaten effective opioid therapy and that many clinicians recognize but often lack language to describe [5]. Cheatle goes on to explore the links between chronic pain, depression, and suicidality, positing that some deaths due to opioids may be unrecognized suicides [6]. Unrelenting physical pain no doubt contributes to the despair that leads to some fatalities, whether suicide is consciously intended or the patient—past tolerating the agony and often combining opioids with other mood-altering respiratory-depressant drugs or alcohol—simply no longer heeds the potential consequences of medication overuse. The Joint Commission, which accredits many U.S. hospitals, recently issued an alert advising hospital and emergency department clinicians to watch for attempted suicides among patients without psychiatric histories but who, instead, may be motivated by chronic pain and other debilitating factors [7]. In doing so, the commission cited evidence that 25% of 827 in-hospital suicides reported since 1995 occurred in nonpsychiatric settings.

Some evidence suggests that even when pain is the principal complaint at the time of the first opioid prescription, many patients who eventually enter detoxification treatment for controlled substance dependence had prior detoxifications and early first use of alcohol or illicit drugs [8]. Chronically low hedonic tone is strongly implicated as illustrated by methadone-maintenance patients who declared they had always needed “some substance” to feel normal [9]. Gourlay and Heit made a similar point in a recent letter to the editor of the *Journal of Pain* in which they aver that substance abuse is not about “the molecule” but principally about the patient [10]. Clearly, these complex interactions indicate that formal evaluation of patients’ psychological and social circumstances should

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figure in clinicians' well-reasoned therapeutic decisions to predict and reduce risks of overdose.

Physician error also propagates patient harm. Methadone presents special challenges, and its misprescribing has contributed to many deaths as supported by the monograph, "A Review of Forensic Implications of Opioid Prescribing with Examples from Malpractice Cases Involving Opioid-Related Overdose" [11]. Errors can be unwitting but potentially fatal as evidenced by recently discovered methadone metabolic pathways and their variously expressed genes [12]. Additional causes of errors include insufficient education, carelessness, and system failures. Knowledge deficits on the part of practitioners require an educational remedy, an example of which can be viewed in the supplement article by Cochella and Bateman [13].

Several of this supplement's contributions are more narrative and descriptive than quantitative. The purpose is to highlight new thinking and programs with some documented success but whose final outcomes are still undergoing analysis. A central message is that analysis of death causation is extraordinarily complicated, and simplistic conclusions can be misleading [14,15]. Sound methodology must be applied to all public health initiatives intended to improve patient outcomes. The state of Washington recently enacted guidelines to counteract opioid misuse, diversion, and overdose in part by creating an arbitrary ceiling dose (120 mg oral morphine equivalents per day) that calls for specialist consultation [16,17]. The consequences of what appear to be economically or politically driven "solutions" in the absence of empirically driven science are unknown but worrisome.

It is indisputable that some patients sustain more harm than help from long-term opioid therapy. Several subsets of patients may be harmed by opioids in various ways and for various reasons. Similarly, patients who are helped, whose lives may be saved by the analgesia and consequent improvement in function and quality of life conferred by opioids, also likely occupy a subset. Genomic studies can be expected to identify certain at-risk subsets in the future. For now, our best screening methods and clinical judgment must suffice; furthermore, we must apply these imperfect tools knowing that many patients' lives may hinge on the treatment they receive, and that treating too little may prove as risky as treating too much.

Constructive solutions founded upon sound analysis can minimize serious harm while allowing the majority of patients who derive benefit from opioid therapy to retain access. Finding a balance between treating pain and preventing harm is daunting because the patients who are at greatest risk of overdose often appear to be those with the greatest need for strong analgesics. The challenge will require cooperative and collaborative efforts of all stakeholders.

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Disclosures

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