Journal of Pain Research

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EDITORIAL

Fentalogues

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

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The ongoing media maelstrom regarding opioids and classification of an "opioid crisis" during the initial decade of this millennium has stirred awareness, outrage and action among regulatory and other government agencies, professional clinician organizations, community pharmacy policies, legislators, patient advocacy groups, anti-opioid advocate groups, and others. However, mass media reports often skew or misdirect the aggregate facts in a possible effort to abridge or sensationalize stories.[1] Discernable distinctions, for example, are rarely drawn between licit pharmaceutical fentanyl, illicit fentanyl analogues, and certain highly potent analogues approved only for ungulates. The omission of this information has resulted in distorted public information that has far reaching consequences in medicine and policy development, as it leads to misunderstanding and misinterpretation of the facts by politicians, lay people and many clinicians.[2] It is particularly relevant today, as pharmaceutical fentanyl is often an essential drug for intubation regularly required for ventilation procedures in declining patients that may succumb to novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These distinctions are critical in the shifting landscape of the opioid crisis as prescriptions for opioids decrease yet overdose deaths remain alarmingly prevalent and continue to rise.

Licit fentanyl was first synthesized in the 1950s via manipulation of another phenylpiperidine, meperidine, in an effort to develop a novel analgesic agent and laying the groundwork for pharmaceutical fentanyl and multiple analogues. Only a small percentage of those analogues are actually approved for medical use.[2] The remainder are dangerously potent with high binding affinity to opioid receptors and rapid entry to the CNS. These characteristics make them particularly hazardous when added to other illicit substances such as heroin, unbeknownst to the end-user with potentially deadly consequences.[3]

Illicit fentanyl has had a dramatically increasing impact on opioid overdose deaths in the US over the past decade. According to provisional data from the 2018 Centers for Disease Control and Prevention, over half of the opioid-related overdose deaths in 2018 involved non-methadone synthetic opioids; the most common of which was illicitly manufactured fentanyl.[4] Perhaps more telling are the annual data released by the New Hampshire Department of Justice, with the most recent of which indicating that less than 7% of 2019 opioid overdose deaths in the state were due to prescription opioids.[5] These illicit opioids have affected the landscape of opioid abuse to the extent that the Drug Enforcement Agency (DEA) chose to emergently schedule all fentanyl-related substances (FRS) to schedule I as of February 2018.

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DovePress
http://doi.org/10.2147/JPR.S265901

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The implication of this rescheduling is to mitigate circumvention of regulatory controls by those who manufacture illicit FRS and streamline prosecution of those who synthesize clandestine FRS without reliance on the Analogue Act.[6] Established in 1988, the Analogue Act provides that all analogues of schedule I substances be treated as schedule I substances themselves, a key consideration with over 20 illicit fentanyl analogues identified as of June 2018 and new compounds frequently being synthesized.[7] The DEA identified illicit fentanyl and other synthetic opioids as the most lethal category of opioids used in the US in the 2018 national threat assessment.[8]

In fact, the very limited diversion of pharmaceutical (licit) fentanyl that occurs is noted to mostly be for small-scale personal use and street sales while illicit fentanyl analogues are trafficked into the US from China and Mexico and are considered to be the primary cause of the high rate of fentanyl-associated overdose deaths in the US, often due to central nervous system depression secondary to additive pharmacologic activity when combined with heroin with which these FRSs are frequently laced.[8] Non-pharmaceutical fentanyl products that have been chemically altered into new products are often created in unregulated, clandestine laboratories and can be tainted with toxic adulterants.[8,9] Alarmingly, some legitimate laboratories have been found to also be manufacturing illicit fentanyl analogues in addition to their legitimate manufacture of pharmaceutical grade medication.[3] Often, these products have been manipulated to increase potency, some hundreds to thousands of times more potent than licit fentanyl, resulting in more addicting and potentially lethal substances.[7]

These fentanyl analogues are DEA Schedule I substances, deemed not to have any therapeutic indication while also presenting the strongest potential for abuse and associated morbidity and mortality.[8] Further, they have not been studied in humans, and potency data is generally lacking.[7,8] Given the specific qualities and extreme hazard associated with non-pharmaceutical, illicit fentanyl analogues, we propose that specific terminology be used going forward in reference to these chemicals, ie "fentalogues". Notably, while preparing this editorial, consideration was given to multiple spellings of "fentalogue" including "fentanylogue", "fentylogue", and "fentanilogue". However, reference to "fentalogues" was identified in a recent publication by Sofalvi et al in reference to novel fentanyl analogues, and it therefore was decided to select this spelling to maintain consistency in the literature.[10]

As Bettinger et al noted, the distinction between licit and illicit fentanyl is an essential public health interest due to its potential to stigmatize legitimate patients.[7] Use of the term "fentalogue" to differentiate illicit, non-pharmaceutical fentanyl analogues from licit prescription fentanyl can also allow for precise documentation and increased accuracy in reporting of an often "murky" distinction. The stigmatization of the roughly 20 million Americans reliant upon prescription opioids in order to maintain some semblance of quality of life has been brutal and highly unnecessary. The lives of these unfortunate patients are difficult enough, and conflating licit and illicit opioids only serves to make their plight worse. Although our recommendation to begin referring to illicit fentanyl products as "fentalogues" is highly symbolic, our hope is that it will serve as a reminder to the media, legislators, and the general public that iatrogenic addiction among legitimate chronic pain sufferers is estimated at 2–8% with a tendency towards the lower end—this needs to be clearly and strongly delineated from those suffering from opioid use disorders.[11]

Disclosure

Dr Jeffrey Fudin is speaker for Abbott Laboratories, Acutis Diagnostics, Inc.; advisory board, speakers bureau, and/or consulting for AcelRx Pharmaceuticals, BioDelivery Sciences International, Daiichi Sankyo, Firstox Laboratories, GlaxoSmithKline (GSK), Human Half-Cell, Inc., Quest Diagnostics, Scilex Pharmaceuticals, and Salix Pharmaceuticals, outside the submitted work. Dr Erica Wegrzyn reports personal fees from Remitigate LLC, outside the submitted work. Dr Amelia L Persico is currently affiliated to Valor Healthcare, Kingston, NY, USA. The authors report no other conflicts of interest in this work.

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