Opioid induced respiration is a major problem.

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Introduction

Opioid use disorder has emerged as a major American public health crisis, and the majority of the half-million American drug overdose deaths from 2000 to 2015 were opioid related [1]. Opioid overdose fatalities are typically caused by respiratory depression which occurs as a result of an opioid-induced decrease in respiratory drive combined with a decrease in the supraglottic airway tone [2,3]. The risk of potentially fatal respiratory depression may increase with certain comorbid conditions, such as obstructive sleep apnea or with high doses of opioids or certain drug combinations [2]. Naloxone can reverse opioid toxicity by competing with the ingested opioid for mu-opioid-receptors; naloxone can effectively reverse respiratory depression in moments. Naloxone dosing is empirical and emergency responders increasingly find that multiple doses are necessary for street users [4,5]. This is due in part to the fact that the use of very potent illicit fentanyl is increasing among those who take street opioids [6]. However, even in the home or hospital setting where opioids are taken appropriately under medical supervision, opioid-induced respiratory depression may still occur, particularly in deeply sedated patients [7].

A murine study of seven opioid agents found that no two had the same profile in terms of antinociception, rates of constipation or respiratory depression [8]. Indeed, the "ceiling effect" of buprenorphine for respiratory depression is well described in the literature [9-11]. Buprenorphine does not exhibit a ceiling effect for analgesia [9,10,12].

The opioid crisis in America is complex and involves the overprescribing or mis-prescribing of prescription opioids (and the concomitant lack of physician education in terms of opioid prescribing), recreational use of opioids, lack of patient and consumer education about opioids, and a sudden abundance of cheap heroin and illicit fentanyl. The healthcare system can only control a few of these factors, namely physician/patient education and appropriate opioid prescribing. The "ideal opioid" analgesic product for prescribers would likely possess certain attributes. It would have to be a safe, effective pain reliever with a low potential for abuse. This describes buprenorphine with its ceiling effect for respiratory depression, its potency as an analgesic (it may be effective at low doses in treating pain) [13-15] and its abuse potential. In the United States, buprenorphine is categorized as a Schedule III controlled substance, unlike morphine and oxycodone and other opioids (Schedule II) [16]. In studies of individuals with opioid use disorder, buprenorphine is less "likeable" than other opioids, such as oxycodone, where likeability is related to how often the drug is abused [17,18]. This is not to say that buprenorphine cannot be abused — that is not true — but it is among the least likely opioids to be taken inappropriately [19].

This stands in direct contrast to the better "liked" opioid of oxycodone, which is among the most frequently abused opioids in America [20]. Efforts have been made in developing abuse-deterrent formulations of oxycodone (and other opioids, such as morphine) in an effort to deter tampering with the tablets for use by alternate routes of administration, for example, by inhalation or injection [21].

Unfortunately, insurance companies in the U.S. as well as the Centers for Medicare and Medicaid Services (CMS) encourage the use of the least expensive opioid analgesics, which often means reimbursing for generic oral formulations of Schedule II opioids (such as morphine, oxycodone) rather than an effective Schedule III opioid such as buprenorphine or an abuse-deterrent oral opioid product. Reimbursement can often mandate that a patient get a riskier Schedule II opioid, even though products with lower abuse potential are readily available.

Transdermal and buccal buprenorphine is in many ways the closest thing to an "ideal opioid pain reliever" on the market. It is a Schedule III controlled substance, meaning it has a lower potential for abuse than most other opioids. It is a potent opioid — much more potent than morphine — meaning that in some cases pain control can be achieved with relatively low doses [22]. It has been clinically evaluated and shown to be safe and effective in studies with patients suffering from chronic cancer and non-cancer pain [14,23-25]. Furthermore, the unique pharmacology of buprenorphine allows it to be used with dosing adjustments in geriatric patients and patients with renal dysfunction [26]. The transdermal delivery system and the buccal formulation are convenient for patients and may enhance compliance because it does not increase the pill burden. They both allow for easy administration of the dose and may be particularly suitable for patients with dysphagia. The role of buprenorphine should be expanded in light of the opioid public health crisis and the need for safer but effective analgesics.

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