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Commentary
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Buprenorphine and Drug Overdose Deaths

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Abstract

In the clinical practice of Medication Assisted Treatment (MAT) buprenorphine as a Medication to treat Opioid Use Disorder (MOUD) has an excellent efficacy and safety profile. As a result of such safety and efficacy, the US National Institute on Drug Abuse has identified the medication as a first line treatment for opioid dependence.

However, a recent study and others, have questioned such safety, which may have created confusion among legislators and even medical practitioners who are not knowledgeable about the pharmacology of buprenorphine.

This article is a review/commentary on the safety of buprenorphine as a MOUD.

Keywords: Buprenorphine; Opioid; MAT; MOUD; OUD

Commentary

Opioid Use Disorder (OUD) is the official US diagnostic term for "a problematic pattern of opioid use leading to clinically significant impairment or distress", as defined in the current edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1].

OUD is both a medical and societal problem that has exacted a heavy toll on the United States and, indeed, the world [2]. According to the most recent statistics from the US Centers for Disease Control, "… there were an estimated 100,306 drug overdose deaths in the United States during 12-month period ending in April 2021, an increase of 28.5% from the 78,056 deaths during the same period the year before." The estimated overdose deaths from opioids alone increased to 75,673 in that 12-month period, up from 56,064 the year before [3]. Worldwide, according to the World Health Organization, about 0.5 million deaths annually are attributable to drug use [4].

Reducing the death toll requires a multi-focal approach involving government, law enforcement, and the medical community. The latter group is equipped with highly effective pharmacologic tools for treating OUD, denoted as Medications for Opioid Use Disorder (MOUD), viz. methadone, buprenorphine, and naltrexone [5,6]. But naltrexone is useful only to aid individuals who are already abstaining from opioids, and methadone is a full agonist opioid with all the inherent problems and risks [7,8].

Buprenorphine, a thebaine derivative, is one of the natural alkaloids present in opium; it is a Schedule III drug, with a high binding affinity for the mu opioid receptors in the CNS, which enables it to displace full agonists from opioid receptor sites [9-11]. Once bound to the opioid receptor it prevents full agonists (such as heroin) from binding to the receptor sites thus causing "opioid blockade." The blockade acts as a deterrent to patients abusing full opioid agonists while on buprenorphine maintenance. Since buprenorphine has low intrinsic activity for the opioid receptor it causes only limited subjective and physiologic agonist effects, thus further lowering its potential for abuse. Its maximal opioid effects, such as respiratory depression, also reach a ceiling, which confers a higher safety profile, compared to full mu agonists like methadone or heroin. These properties make it a much safer MOUD than methadone and misuse is much less frequent than full agonist opioids.

However, there is still some misunderstanding about the safety of buprenorphine, as evidenced by numerous publications associating buprenorphine as the primary cause of death in adult drug overdoses [12-14]. Such reports, without careful analysis, may convince some state authorities (medical and legislative) involved in the regulation of opioids and MAT to put buprenorphine in the same category as full antagonists, such as methadone and heroin, or to impose regulations that

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exceed the requirements of Federal law, which could reduce already limited access to treatment [15-17].

For example, one recent paper by Bishop-Freeman et al. [18], stated directly in the Abstract that "…BUP was detected in peripheral blood and considered a primary Cause of Death (COD)…" in accidental drug overdose deaths, although in other parts of the paper the phrase "buprenorphine-related", rather than primary cause, is used. The authors also mention the addition of naloxone to deter the misuse of buprenorphine, e.g. snorting or IV administration. The addition of naloxone was an early claim to deter such misuse, even though there is little evidence of such benefit, and indeed there is some evidence to the contrary [19,20]. The paper also repeats the often stated, but disproven [21,22], claim that naloxone is poorly absorbed SL, "…rendering it essentially inactive when a combination product is taken as prescribed." But the repetition of such erroneous information has often prejudiced reports from patients about the side effects of taking the combo-product, i.e. with naloxone. Bishop Freeman reported buprenorphine concentrations ranging from 0.84 ng/ml to 22 ng/ml with a mean of 4.1 ng/ml, and that all postmortem blood concentrations "overlap antemortem therapeutic concentrations in plasma reported in the literature for opioid dependent subjects receiving sublingual maintenance therapy". In no case were other opioids detected (although only brief, non-specific mention was made of "designer" opioids). Furthermore, a study of buprenorphine administered as a single dose IV in humans reported that 10 min after a dose of 16 mg resulted in maximum plasma concentrations of 137.7 ± 18.8 ng/ml with no adverse effects [23].

In addition, the autopsy findings on most of the patients, combined with the other toxicology findings, provide ample support for a COD unrelated to their ingestion of buprenorphine. Indeed, although there is not equivalent human data, in rats the LD50 is greater than 140 mg/kg and all animals receiving up to 90 mg/kg survived [24]! In another study, buprenorphine hydrochloride in 5% dextrose was given to dogs IM in doses up to 2.5 mg/kg/day for 3 months, and rats were given 5 mg/kg/day SC per day, all with no mortality [25]. Again, those are doses that would never be achieved accidentally in humans and would be difficult to achieve even with volition. On the other hand, Bishop-Freeman et al. do provide a brief discussion of P-glycoprotein in order to support their contention that toxic CNS levels of the metabolite norbuprenorphine might be present even in the presence of therapeutic blood levels of the precursor molecule, but invoking that mechanism to explain how buprenorphine could cause death is a big stretch, especially since the series involves only 131 cases of buprenorphine-related deaths in 9 years (2010-2018). If norbuprenorphine toxicity were really an issue there should have many more such cases, not just in NC, but nationwide.

All such similar reports suffer from the same problem, i.e. often conflating association with causation, a serious mistake in medical science, or any science for that matter. In most drug overdose deaths, there are typically confounding factors, such as polypharmacy use and medical comorbidities. Even those that restrict analyses to cases in which no other opioids were detected do not always report specific testing for the newer and much more potent "designer" opioids such as carfentanil, para-fluorofentanyl, and opioid analogs called "nitazines" such as isotonitazine, metonitazene, and etometonitazene [26-32].

In the clinical practice of Medication Assisted Treatment (MAT) buprenorphine has an excellent safety profile. For instance, in Tennessee, the state Department of Health data reported that in only 10 cases, between the years 2013 and 2016, individuals had buprenorphine alone present when they died [33]. Yet in 2016 alone, the same state reported 1,186 overdose deaths associated with opioid use. Mariottini [34] on the other hand, found no death cases with buprenorphine as the only toxicological finding, and Paone [35] likewise reported that buprenorphine was infrequently found in fatal overdose in New York City. Most diverted buprenorphine regardless of formulation is used on the street by persons already addicted to a μ-opioid agonist to self-treat withdrawal and as a substitute for more dangerous opioids [36-39]. Hammersley [40] in reporting a 4-fold increase in overdose deaths in Glasgow in 91-92 compared to 90-91, even speculated that the use of buprenorphine by drug injectors during the prior period had kept the number of overdoses relatively low, i.e. even gross misuse of buprenorphine is safer than the use of full agonists.

As a result of such safety and efficacy, the US National Institute on Drug Abuse has identified the medication as a first line treatment for opioid dependence [41].

However, there is evidence that the respiratory depressant ceiling effect (plateau) of buprenorphine may be attenuated by concomitant ingestion of CNS depressant drugs such as benzodiazepines and alcohol [42-46]. As Tracqui noted [12], "Fatalities involving BUP alone seem very unusual: in our series; all cases but one involved a concomitant intake of psychotropics." Benzodiazepines ranked first in that study, being present in 18 of 20 observations.

So, it is important clinically, when evaluating safety of buprenorphine for MOUD to understand the confounding problems of pre-existing comorbidities and concomitant ingestion of depressant drugs, rather than perpetuating the prejudice against this important tool in the fight against OUD and overdose mortality.

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