Received: 11 November 2020 | Revised: 15 November 2020 | Accepted: 16 November 2020

DOI: 10.1111/jcpt.13320

COMMENTARY

Journal of Clinical Pharmacy and Therapeutics WILEY

Are opioid receptor antagonists adequate for "Opioid" overdose in a changing reality?

John F. Peppin DO, FACP[1,2] | Joseph V. Pergolizzi Jr. MD[3,4,5] | Albert Dahan MD, PhD[6] | Robert B. Raffa PhD[3,4,7,8]

[1]Marian University College of Osteopathic Medicine (Clinical Adjunct Professor), Indianapolis, IN, USA

[2]Clinical Professor Internal Medicine, Pikeville University, College of Osteopathic Medicine, Pikeville, USA

[3]Enalare Therapeutics Inc, Naples, FL, USA

[4]Neumentum Inc., Summit, NJ, USA

[5]NEMA Research Inc., Naples, FL, USA

[6]Leiden University Medical Center, Leiden, The Netherlands

[7]University of Arizona College of Pharmacy (Adjunct Professor), Tucson, AZ, USA

[8]Temple University School of Pharmacy (Professor emeritus), Philadelphia, PA, USA

Correspondence
John F. Peppin, DO, FACP, Marian Clinical Professor Internal Medicine, Pikeville University, College of Osteopathic Medicine, Pikeville, USA
Email: johnpeppin@msn.com

Abstract

What is known and Objective: Deaths due to opioid-induced respiratory depression (OIRD) continue to rise despite intense regulatory and professional actions. COVID-19 has only worsened this situation.[1] An opioid receptor antagonist (ORA) such as naloxone is the most common intervention for OIRD. However, with increasing overdose from highly potent illicit opioids and polysubstance abuse, appraisal of the adequacy of ORA seems warranted and timely.

Comment: OIRD results from the binding of an excess number of agonist molecules to opioid receptors. Mechanistically, it makes sense to reverse this by displacing agonist molecules by administering an ORA. But realistically, the trend to higher-potency agonists and polysubstance abuse diminishes the effectiveness of this approach. We are left facing a crisis without a solution.

What is new and Conclusion: For the increasingly common OIRD from highly potent illicit agonists and polysubstance overdose, ORAs are correspondingly less effective. Alternatives are needed—soon.

KEYWORDS
adverse effect, naloxone, opioid antagonist, opioid overdose, polysubstance use

1 | WHAT IS KNOWN AND OBJECTIVE

The "opioid crisis" has had a profound impact internationally. Death rates continue to climb, with an alarming spike during, and possibly attributable to, stresses of the COVID-19 pandemic.[1,2] Despite numerous attempts to reduce these deaths through federal and state regulations, federal and professional recommendations (eg CDC Guidelines), and the issuance of stricter medical board oversight, deaths have not abated.

The treatment of choice (both mechanistically and practically) for an opioid overdose is an opioid receptor antagonist (ORA). Naloxone is the most commonly used opioid receptor antagonist, and it has become a focused treatment option at multiple points during the interaction with healthcare providers. Delivery systems have been developed to make it easier to administer, even by members of the lay public. And it is now relatively common that a naloxone prescription is added to a prescription for an opioid to have readily available at home. The US Federal Government has even fast-tracked naloxone nasal delivery products to address the crisis.

Unfortunately, a focus on prescription opioid overdose, perhaps initially appropriate, is a bit dated. Illicitly manufactured fentanyl (IMF) and analogs (alfentanil, carfentanil, sufentanil, etc) have been introduced and are responsible for an increase in opioid deaths; deaths from prescription opioids have fallen to low levels. It also misses the more common misuse of multiple substances together (polysubstance abuse). Most drug overdoses involve multiple substances, which greatly complicates treatment and makes antagonists such as naloxone less effective.

2 | COMMENT

2.1 | Traditional opioids and opioid receptors

The binding of an endogenous or exogenous opioid to a seven-transmembrane G coupled–protein opioid receptor (7-TM GPCR) elicits the characteristic opioid actions (analgesia, constipation, euphoria, etc). The mu (MOP), delta (DOP) and kappa (KOP) opioid receptor (OR) subtypes are naloxone-sensitive. The non-classic nociceptin/orphan-FQ receptor is naloxone-insensitive.[3] Opioid receptor densities vary in different areas of the body and under different conditions.[4] ORs couple to G_i/G_o proteins and enhance the efflux of potassium, hyperpolarizing postsynaptic neurons. Binding to opioid receptors also closes voltage-gated Ca^{2+} channels, which reduces release of presynaptic neurotransmitters that transmit pain signalling.[3] Newer research has elucidated a role for ß-arrestin[3] and interaction among receptors both in a physical sense (as heterodimers) and at a systems level.[3] Heterodimers can be combinations of OR subtypes or form with non-opioid receptors,[5] and have different response profiles than the individual receptors of which they are composed. The endogenous opioid families[6,7] play important roles in physiologic processes[8] and have targeted actions and short half-lives. In contrast, exogenously administered opioids are (too) widely distributed and have long half-lives. Their effects (good and bad) are thus exaggerated. Tolerance (diminished response to the same dose of drug) develops when receptors have a reduced ability to propagate a signal after overexposure.[4] This physiologic compensatory mechanism can be blunted by excess drug use,[4] as can mechanisms to remove a drug from the body.[4] Once this occurs, even small increases in drug intake can result in disproportionate increases in adverse effects.[4] Much drug-discovery effort has been directed at attempts to try to mitigate these problems.[9]

2.2 | The complications introduced by the "Fentanoids"

Fentanyl is used for legitimate medical purposes in both IV and transdermal formulations. It is metabolized by the cytochrome P450-3A4 isozyme[10]; thus, CYP-3A4 inhibitors (as might be encountered in polysubstance use) can increase toxicity.[11] The recent influx of illicitly manufactured fentanyl (IMF) has greatly complicated treatment of "opioid" overdoses.[12,13] Fentanyl and analogs ("fentanoids") enter into the brain rapidly,[12] due to high lipid-solubility and other factors.[14] As a consequence, there has been: "increasing awareness that respiratory depression by fentanoids is harder to reverse with naloxone than that by other opioids such as heroin, and may require multiple and/or higher doses of naloxone."[13]

For non-IMF opioid overdose, it was possible to keep the naloxone dose low to prevent serious withdrawal problems. However, in today's IMF environment, much higher doses of naloxone can be required. In addition, fentanoids may affect how naloxone acts at MOP,[13] reducing naloxone's ability to displace fentanyl.[13] Masquerading as other drugs further complicates matters.[15]

The abuse of fentanoids can set up a potential "double whammy": chest-wall rigidity along with respiratory depression.[13] The incidence has been estimated anywhere between 8% and 100%.[16] A fairly recent review suggests that it may be an even more significant contributor to death than previously thought,[16] and a clear treatment paradigm has not yet been developed.[17] Carfentanil has an even higher potency than fentanyl[12] and is relatively easy to make. It also has a potential for "re-narcotization" that requires larger and repeat dosing of an ORA.[12]

2.3 | Opioid receptor antagonists

The development of opioid receptor antagonist (ORA) agents was founded on the concept that minor changes in chemical structure could convert an opioid agonist into an opioid antagonist. The first published report of an ORA, nalodeine (*N*-allylnorcodeine), appeared in 1915,[18,19] but it was not marketed. In the 1940s, nalorphine (*N*-allylnormorphine) was synthesized.[20] Both compounds had significant negative effects on mood. To overcome this problem, naloxone, *N*-allylnoroxymorphone, was developed in the 1960s.[21] Naloxone has a short-lasing action compared with the opioids that are commonly encountered in overdose, so there was a need to develop a longer-acting agent; naltrexone came onto the market in the 1980s.[18,22] Naloxone and naltrexone were designed using oxymorphone, a thebaine derivative, as a base.[18] Nalmefene (originally nalmetrene) is a derivative of naltrexone and is equipotent to naloxone, but longer-acting,[22] and reported higher affinity for MOP.[23] Nalmefene was withdrawn from the US market due to low sales in 2008,[23] but is available internationally. Naloxone, naltrexone and nalmefene bind to MOP, DOP and KOP[24]; however, the binding affinity for MOP is much higher than for DOP or KOP. They are competitive reversible antagonists.[25]

Naloxone can be administered by multiple routes: IV, IM, SC, intranasal, inhalational [26] and endotracheal tube in intubated patients.[27] Highly lipophilic, it undergoes rapid hepatic metabolism and most is excreted through the kidneys as conjugated metabolites.[28] It is usually not administered orally since it undergoes extensive 1st-pass metabolism.[29] However, sublingual absorption of naloxone might be greater than originally thought.[30] There is no apparent evidence that either naltrexone or naloxone is transported by p-glycoprotein,[31] but it has been suggested that naloxone and fentanyl may share a cellular membrane transporter.[28] This transporter may become saturated at high doses and plasma concentrations of fentanyl, reducing the blood-brain barrier transport of naloxone.[28]

The plasma half-life of naloxone is about 8.3 hours, that of nalmefene 1.3 h, but the brain residency time of nalmefene might be significantly longer than that of naloxone.[32] Naltrexone has a plasma half-life of approximately 3.5 h,[31] but brain residency 72 to 108 h.[32] This suggests that naltrexone might be a better option for opioid

overdose, although to date little data have been generated to prove this point.

Prior to IMF, naloxone was reported to be almost 100% effective in reversing respiratory depression.[33] However, as the opioid crisis has progressed, reports of a need for increasing doses and repeated doses have emerged. In 2017, Sommerville reported that 83% of patients required more than 2 mg naloxone doses before there was a clinical response.[34] In that same study, 36% of fatal deaths had a drug overdose within seconds to minutes after drug use and 90% were pulseless by the time of arrival of emergency responders. Faul and colleagues, also in 2017, suggested that: "the increase in multiple dose naloxone indicates the prevalence of higher potency opioids."[35] They reported an increased use of multiple naloxone treatments from 14.5% in 2012 to 18.2% in 2015.

2.4 | Naloxone side effects

The relative safety of naloxone is believed to be well established. For example, one package insert states that "in the absence of narcotics, naloxone exhibits essentially no pharmacologic activity." In a 2006 study of 164 patients treated with primarily IV, but also IM and intranasal naloxone, agitation and combativeness were noted to occur at a rate of 15%, and vomiting at 4%.[36] Buajordet reported in 2004 that the side effects attributed to naloxone increased with the severity of the opioid toxicity, 22% for mild cases and 49% for severe.[37] With the injectable form, dizziness and injection-site erythema have been reported.[38] However, the major "side effects" of naloxone are the consequence of abrupt precipitated opioid withdrawal.

Although there are multiple reports of pulmonary oedema with the use of naloxone in the setting of opioid overdose and toxicity, whether or not naloxone is the cause is still unclear. Pulmonary oedema is common in opioid overdoses even in the absence of naloxone; the reported incidence is around 48% of hospitalized overdose cases.[28] Interestingly, the incidence of pulmonary oedema seen in opioid overdose cases has decreased, possibly due to pre-hospital administration of naloxone and aggressive pre- and intra-hospital treatments.[28] Rzasa states: "overall the incidence of naloxone-induced pulmonary oedema appears to be rare and primarily encountered within the peri-operative arena."[28]

2.5 | Opioid overdose and treatment

Clinical findings in opioid overdose include the "classic toxidrome," including apnoea, stupor and miosis. [4] The *sine qua non* of opioid overdose is respiratory depression. Opioid intoxication is suggested when the respiratory rate is 12 breaths per minute or less, the individual is not asleep and has miosis. Individuals who are somnolent and who are difficult to awaken are at urgent risk.[4] A person with respiratory rate <12 and is somnolent is at risk of rapid decompensation of respiratory function. In a monitored setting, reversal by titrated IV infusion of an ORA should be considered (IV infusion may be safer and more efficacious than IV push).[39] A patient history is critical in establishing the diagnosis; also helpful is knowledge of the drug-abuse patterns for a given locale.[40] In all cases, patients need to be monitored closely, since the half-life of naloxone is often less than that of the opioid.

Physicians frequently overlook acetaminophen hepatotoxicity in the context of an opioid overdose.[4] Opioid substance abusers frequently use combination opioid products that contain acetaminophen, and early hepatotoxicity can go unrecognized. In a suspected overdose situation, acetaminophen levels should be obtained and the potential for acetaminophen toxicity be addressed.

Opioid overdose is cared for over 5 distinct periods: 1) the patient's family, friends and loved ones, 2) emergency medical teams, 3) emergency department, 4) hospital and 5) post-discharge. Since most overdoses occur in the home, early intervention with nasal or IM naloxone by an individual's friends and loved ones should be a goal, especially in the era of IMF.[41] Families should be instructed on the use of these products. Close monitoring till the emergency response team arrives is critical, so there should be a low threshold for administering additional doses of naloxone. Unfortunately, studies have shown significant gaps in "knowledge, access, and use" of naloxone by patients, their families and even some healthcare providers.[42,43] Once the emergency response team arrives, further naloxone can be given, either IV, if access is obtained, or IM. In the emergency department once the patient is hospitalized, more in-depth evaluations and support can be continued.

Although the effect of naloxone through IV delivery is very quick, obtaining IV access can be challenging for numerous reasons.[28] The IM and SC routes also offer benefits in the critical few minutes of treatment.[44] Overdose victims are also at risk for suicide,[45] so a discharge plan that includes counselling on substance abuse programs should be designed. In an ideal world, follow-up would be provided. Another difficult challenge is predicting an appropriate naloxone dose for a given situation. Effective antagonism depends upon "the amount of opioid present and its potency, as well as its interactions with the opioid receptor."[28] The specific opioid, dose taken, route of administration, patient's ability to clear the drug and other substances present (and other medications that may be present) can all complicate the choice of correct dose of naloxone. As an all-too-common example, the greater potency of fentanoids may require higher doses of naloxone.

Pharmacological stimulation of respiratory function is an interesting approach, although the available options are limited with respect to efficacy or adverse effects. The medications which have been used to stimulate respiration include caffeine, 5-hydroxytryptamine type 1A agonists and ampakines.[46] Phrenic nerve stimulation has also been used.[42]

As an alternative to naloxone, nalmefene, currently off-market in the United States, has been suggested as a better option in IMF overdose cases, but more research is needed.[23] It has also been suggested that a combination of naltrexone and naloxone might give better results.[31]

Certain overdose settings require special consideration, for example:

- the use of naloxone for tramadol overdose is considered only partially effective by some authors, but effective by others,[47,48]
- buprenorphine has a high affinity for opioid receptors; therefore, higher doses of naloxone are required for buprenorphine ovedose,[49]
- some authors have expressed concern that the use of naloxone for tramadol overdose can elicit seizures, but seizures in tramadol toxicity occur even in the absence of naloxone (15%-35% incidence),[50]
- and there is a developing consensus that seizures are not elicited by naloxone in tramadol toxicity,[50]
- olanzapine overdose has been described as mimicking opioid overdose.[51]

Currently, there are only three approved naloxone formulations: IV, IM and nasal spray.[52] The nasal spray was developed through a partnership between the National Institute on Drug Abuse (NIDA) and industry, and was approved in 2015.[53] It provides similar blood levels of naloxone as does parenteral administration.[53] Certain states allow nasal naloxone available without a prescription throughout the United States.[52] Higher-concentration intranasal naloxone (2 mg/mL) seems to have efficacy similar to that of IM naloxone for reversal of opioid overdose, with little difference in adverse events.[54]

2.6 | Polysubstance abuse and overdose

Experience has shown that polysubstance abuse in overdose is very common, and it has been demonstrated in a number of studies.[55-61] In polysubstance overdose, it is difficult to determine which drug is "responsible" for the death, and research on polysubstance use is made difficult by changing patterns of use and inaccurate histories.[62]

Toxicology serum or urine levels are not helpful in the acute setting. Data collected by coroners and medical examiners are frequently "inadequate, incomplete, and inconsistent with regard to polydrug use … and patient characteristics."[63] The chief of the US CDC (Centers for Disease Control and Prevention) mortality branch at the NCHS (National Center for Health Statistics) has acknowledged that about one in three death certificates are inaccurate or "wrong."[64] Whenever multiple substances are identified in post-mortem toxicology screens, certifiers frequently record imprecise causes of death that have little epidemiological value, such as "mixed drug intoxication" or "polypharmacy."[65] Further, serum levels rarely correlate with overdose, and post-mortem blood draws can frequently be misinterpreted.[66] This led Marion 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."[67]

3 | WHAT IS NEW AND CONCLUSION

What seems clear is that a scripted approach to opioid overdose patients may present problems. Patients in the current environment of IMF may need higher doses or multiple doses of naloxone. Although protocols can be helpful, there is little literature supporting these approaches.[68] These patients need close monitoring and may well need to have therapies beyond a standard protocol. The notion of a "coma cocktail" in critical unconscious patients has been rightly criticized: "the modern approach to a patient with an altered level of consciousness should not be protocolized, empirical administration of fixed doses with an end point of analepsis, but rather the targets correction of immediate threats to life."[50] In the future, other therapies for opioid overdose may be available, perhaps even fentanyl vaccines.[69]

In the increasingly common setting of polysubstance overdose, the use of an ORA such as naloxone is increasingly less effective. This has to do with the mechanistic approach, not the particular ORA. An alternative approach, one that would be independent of the causative agonist or combination of substances, is needed. One possible approach, respiratory stimulation, would bypass/override receptor occupation and thus would be "agnostic" to the cause of the respiratory depression. Unfortunately, no current drugs have the requisite efficacy/safety profile. What the literature currently can best advice is close monitoring with a low level of clinical suspicion, and the giving of higher and more frequent doses of an ORA.

CONFLICT OF INTEREST

Consultant Relmada Therapeutics, New York. Consultant Medical Monitor Relmada Therapeutics, New York.

ORCID

Robert B. Raffa https://orcid.org/0000-0002-1456-4451

REFERENCES

1. Kamp J, Campo-Flores A.The Opioid Crisis, Already Serious, Has Intensified During Coronavirus Pandemic. Wall Street Journal. Accessed October 28, 2020.
2. Niles JK, Gudin J, Radcliff J, Kaufman HW. The Opioid Epidemic Within the COVID-19 Pandemic: Drug Testing in 2020. *Popul Health Manag*. 2021;24(S1):S-43.
3. Azzam AAH, McDonald J, Lambert DG. Hot topics in opioid pharmacology: mixed and biased opioids. *Br J Anaesth*. 2019;122(6):e136-e145.
4. Boyer EW. Management of opioid analgesic overdose. *N Engl J Med*. 2012;367(2):146-155.
5. Valentino RJ, Volkow ND. Untangling the complexity of opioid receptor function. *Neuropsychopharmacology*. 2018;43(13):2514-2520.
6. Shenoy S, Lui F. Biochemistry, Endogenous Opioids. In: StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; 2020 Jan-. 2018 [Updated 2020 Jul 26];2018.
7. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and exogenous opioids in pain. *Annu Rev Neurosci*. 2018;07(41):453-473.
8. Toubia T, Khalife T. The Endogenous Opioid System: Role and Dysfunction Caused by Opioid Therapy. *Clin Obstet Gynecol*. 2019;62(1):3-10.

9. Kenichi N, Yamamoto S, Yamaga T, Horigome N, Hanaoka M. Peripherally acting μ-opioid antagonist for the treatment of opioid-induced constipation: Systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2019;30(5):818-829.
10. Labroo R, Paine M, Thummel K, Kharasch E. Fentanyl metabolism by human hepatic and intestinal cytochrome P 450 3A4: Implications for interindividual variability in diposition, efficacy and drug interactions. *Drug Metab Dispos*. 1997;25(9):1072-1080.
11. Wilde M, Pichini S, Pacifici R, et al. Metabolic Pathways and Potencies of New Fentanyl Analogs. *Front Pharmacol*. 2019;10:238.
12. Leen JLS, Juurlink DN. Carfentanil: a narrative review of its pharmacology and public health concerns. *Can J Anaesth*. 2019;66(4):414-421.
13. Gill H, Kelly E, Henderson G. How the complex pharmacology of the fentanyls contributes to their lethality. *Addiction*. 2019;114(9):1524-1525.
14. Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. *Neurosci Biobehav Rev*. 2019;11(106):49-57.
15. Counterfeit Prescription Pills Containing Fentanyls: A Global Threat. DEA-DCT-DIB-021-16.
16. Burns G, DeRienz RT, Baker DD, Casavant M, Spiller HA. Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse? *Clin Toxicol (Phila)*. 2016;54(5):420-423.
17. Trujillo C, Rudd D, Ogutcu H, Dong F, Wong D, Neeki M. Objective Characterization of Opiate-Induced Chest Wall Rigidity. *Cureus*. 2020;12(6):e8459.
18. SB L. Opioid Antagonists in pain management. Practical Pain Management; 2009.
19. Weijlard John, Erickson AE. N-Allylnormorphine. *J Am Chem Soc*. 1942;64(4):869-870.
20. La W. The pharmacology of nalorphine (N-allylnormorphine. *Pharmacol Rev*. 1956;175-198.
21. H B. Narcotic antagonist activity of naloxone. In: HB D, editor. Federation Proceedings; 1965. p. 676.
22. Dixon R, Howes J, Gentile J, et al. Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther*. 1986;39(1):49-53.
23. Skolnick P. On the front lines of the opioid epidemic: Rescue by naloxone. *Eur J Pharmacol*. 2018;835:147-153.
24. Shader RI. Antagonists, inverse agonists, and protagonists. *J Clin Psychopharmacol*. 2003;23(4):321-322.
25. YS C. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid related constipation. In: JA B, editor.: J Pain Symptom Manage 2002; 2002.
26. Fellows SE, Coppola AJ, Gandhi MA. Comparing methods of naloxone administration: a narrative review. *J Opioid Manag*. 2017;13(4):253-260.
27. Weber JM, Tataris KL, Hoffman JD, Aks SE, Mycyk MB. Can nebulized naloxone be used safely and effectively by emergency medical services for suspected opioid overdose? *Prehosp Emerg Care*. 2012;16(2):289-292.
28. Rzasa Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Ther Adv Drug Saf*. 2018;9(1):63-88.
29. Smith K, Hopp M, Mundin G, et al. Low absolute bioavailability of oral naloxone in healthy subjects. *Int J Clin Pharmacol Ther*. 2012;50(5):360-367.
30. Strickland D, Burson J. Sublingual absorption of naloxone in a large clinical population. *J Drug Metab Toxicol*. 2018;9(2):1-4.
31. Krieter P, Chiang CN, Gyaw S, Skolnick P, Snyder R. Pharmacokinetic Interaction between Naloxone and Naltrexone Following Intranasal Administration to Healthy Subjects. *Drug Metab Dispos*. 2019;47(7):690-698.
32. Lee MC, Wagner HN, Tanada S, Frost JJ, Bice AN, Dannals RF. Duration of occupancy of opiate receptors by naltrexone. *J Nucl Med*. 1988;29(7):1207-1211.
33. Moss RB, Pryor MM, Baillie R, et al. Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxone-fentanyl competition at the opioid mu receptor level. *PLoS One*. 2020;15(6):e0234683.
34. Somerville NJ, O'Donnell J, Gladden RM, et al. Characteristics of Fentanyl Overdose - Massachusetts, 2014–2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(14):382-386.
35. Faul M, Lurie P, Kinsman JM, Dailey MW, Crabaugh C, Sasser SM. Multiple Naloxone Administrations Among Emergency Medical Service Providers is Increasing. *Prehosp Emerg Care*. 2017;21(4):411-419.
36. Belz D, Lieb J, Rea T, Eisenberg MS. Naloxone use in a tiered-response emergency medical services system. *Prehosp Emerg Care*. 2006;10(4):468-471.
37. Buajordet I, Naess AC, Jacobsen D, Brørs O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur J Emerg Med*. 2004;11(1):19-23.
38. Administration FD. EVZIO® (naloxone hydrochloride injection) Auto-Injector for intramuscular or subcutaneous use: HIGHLIGHTS OF PRESCRIBING INFORMATION. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209862lbl.pdf. Accessed November 2, 2020.
39. Dadpour B, Vahabzadeh M, Mostafazadeh B. Comparison of the efficacy of an infusion pump or standard IV push injection to deliver naloxone in treatment of opioid toxicity. *Acute Crit Care*. 2020;35(1):38-43.
40. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Jansook P, Dale O. Pharmacokinetics of a new, nasal formulation of naloxone. *Eur J Clin Pharmacol*. 2017;73(5):555-562.
41. Levy B, Spelke B, Paulozzi LJ, et al. Recognition and response to opioid overdose deaths-New Mexico, 2012. *Drug Alcohol Depend*. 2016;167:29-35.
42. Algera MH, Kamp J, van der Schrier R, et al. Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal. *Br J Anaesth*. 2019;122(6):e168-e179.
43. Peckham AM, Niculete ME, Steinberg H, Boggs DL. A Survey of Prescribers' Attitudes, Knowledge, Comfort, and Fear of Consequences Related to an Opioid Overdose Education and Naloxone Distribution Program. *J Public Health Manag Pract*. 2018;24(4):310-317.
44. Rudolph SS, Jehu G, Nielsen SL, Nielsen K, Siersma V, Rasmussen LS. Prehospital treatment of opioid overdose in Copenhagen–is it safe to discharge on-scene? *Resuscitation*. 2011;82(11):1414-1418.
45. Olfson M, Crystal S, Wall M, Wang S, Liu SM, Blanco C. Causes of death after nonfatal opioid overdose. *JAMA Psychiatry*. 2018;75(8):820-827.
46. Dahan A, van der Schrier R, Smith T, Aarts L, van Velzen M, Niesters M. Averting opioid-induced respiratory depression without affecting analgesia. *Anesthesiology*. 2018;128(5):1027-1037.
47. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther*. 1992;260(1):275-285.
48. Marquardt KA, Alsop JA, Albertson TE. Tramadol exposures reported to statewide poison control system. *Ann Pharmacother*. 2005;39(6):1039-1044.
49. Foster B, Twycross R, Mihalyo M, Wilcock A. Buprenorphine. *J Pain Symptom Manage*. 2013;45(5):939-949.
50. Eizadi-Mood N, Ghandehari M, Mansourian M, Sabzghabaee AM, Samasamshariat S, Sadeghi E. Risk of seizure after naloxone therapy in acute tramadol poisoning: a systematic review with meta-analysis. *Int J Prev Med*. 2019;10:183.
51. O'Malley GF, Seifert S, Heard K, Daly F, Dart RC. Olanzapine overdose mimicking opioid intoxication. *Ann Emerg Med*. 1999;34(2):279-281.

52. Abuse NIoD. Opioid Overdose Reversal with Naloxone (Narcan, Evzio). https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-reversal-naloxone-narcan-evzio. Accessed October 28, 2020.
53. Volkow ND, Collins FS. The role of science in addressing the opioid crisis. *N Engl J Med*. 2017;377(4):391-394.
54. Chou R, Korthuis PT, McCarty D, et al. Management of suspected opioid overdose with naloxone in out-of-hospital settings: a systematic review. *Ann Intern Med*. 2017;167(12):867-875.
55. Lyons RM, Yule AM, Schiff D, Bagley SM, Wilens TE. Risk Factors for Drug Overdose in Young People: A Systematic Review of the Literature. *J Child Adolesc Psychopharmacol*. 2019;29(7):487-497.
56. Golladay M, Donner K, Nechuta S. Using statewide death certificate data to understand trends and characteristics of polydrug overdose deaths in Tennessee, 2013–2017. *Ann Epidemiol*. 2020;41:43-48.e1.
57. Cook S, Moeschler O, Michaud K, Yersin B. Acute opiate overdose: characteristics of 190 consecutive cases. *Addiction*. 1998;93(10):1559-1565.
58. Hygiene NYCDoHaM. Illicit drug use in New York City. NYC Vital Signs. 2010;1-4.
59. Andrews JY, Kinner SA. Understanding drug-related mortality in released prisoners: a review of national coronial records. *BMC Public Health*. 2012;12:270.
60. Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths: a DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases. *J Anal Toxicol*. 2003;27(2):57-67; discussion 67.
61. Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths. II. Evidence for toxic multiple drug-drug interactions. *J Anal Toxicol*. 2004;28(4):217-225.
62. Martins SS, Sampson L, Cerdá M, Galea S. Worldwide Prevalence and Trends in Unintentional Drug Overdose: A Systematic Review of the Literature. *Am J Public Health*. 2015;105(11):e29-e49.
63. Webster LR, Dasgupta N. Obtaining adequate data to determine causes of opioid-related overdose deaths. *Pain Med*. 2011;12(Suppl 2):S86-S92.
64. Priest J.One in 3 death certificates were wrong before coronavirus. It's about to get even worse USA Today. Corrected Copy by USA Today ed2020.
65. Davis GG. National Association of Medical E, American College of Medical Toxicology Expert Panel on E, Reporting Opioid D. Complete republication: National Association of Medical Examiners position paper: Recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *J Med Toxicol*. 2014;10(1):100-106.
66. Sastre C, Bartoli C, Baillif-Couniou V, Leonetti G, Pelissier-Alicot AL. Post Mortem Redistribution of Drugs: Current State of Knowledge. *Curr Pharm Des*. 2017;23(36):5530-5541.
67. Miron J. Are, "fatal" opioid concentrations really fatal? Cato Institute. https://www.cato.org/blog/are-fatal-opioid-concentrations-really-fatal. Accessed October 25, 2020.
68. Millichamp T, Johnston ANB. Interventions to support safe medication administration by emergency department nurses: An integrative review. *Int Emerg Nurs*. 2020;49:100811.
69. Raleigh MD, Baruffaldi F, Peterson SJ, et al. A Fentanyl Vaccine Alters Fentanyl Distribution and Protects against Fentanyl-Induced Effects in Mice and Rats. *J Pharmacol Exp Ther*. 2019;368(2):282-291.

How to cite this article: Peppin JF, Pergolizzi JV Jr., Dahan A, Raffa RB. Are opioid receptor antagonists adequate for "Opioid" overdose in a changing reality?. *J Clin Pharm Ther*. 2020;00:1–6. https://doi.org/10.1111/jcpt.13320