Commentary on McDonald et al. (2018): Intranasal naloxone—from the laboratory to the real world

It is timely that research and technology combine to develop products addressing barriers to naloxone administration in community and prison settings. Addressing potential implementation barriers and understanding outcomes with real-world use will maximize the opportunities to prevent opioid overdose deaths.

The work by McDonald and colleagues [1] is a welcome addition to what is known about naloxone bioavailability and pharmacokinetics, combined with the promise of a fit-for-purpose naloxone product for lay-person administration. Intranasal and other non-injectable naloxone formulations have clear benefits for community supply to carers and family members. Prison settings may also benefit given the potential barriers posed by injectable products.

This healthy volunteers study demonstrates an intranasal product with comparable onset with the widely used 0.4 mg naloxone intramuscular dose. Data from healthy volunteers represent much of the data informing our knowledge about naloxone pharmacokinetics and bioavailability. A gap in our collective knowledge is how these data translate to clinical populations, including those who are opioid-dependent, those with poor physical health and those who may have consumed multiple substances. There is a need to extend knowledge of use of intranasal naloxone in real-world settings to understand how different route options may translate to clinical outcomes in overdose reversal. This is particularly relevant where small differences in onset-time can impact upon the damage due to anoxic brain injury.

There are other aspects of naloxone delivery that are also critical to understand more clearly. To date, only limited research has examined doses of naloxone required to reverse overdoses with higher potency opioids, such as fentanyl and fentanyl analogues. Naloxone is likely to be key in responding to increasing mortality with these higher potency opioids [2,3], yet little information exists to guide a public health response. Higher doses of naloxone will probably be required. Where products are packaged as a single-dose product, this may mean that programmes supplying naloxone need to consider supplying multiple units. Alternatively, multiple-dose products may represent a more rational way to supply naloxone, but may introduce infection risk if administered to multiple people. Cost implications of both options may impact upon the feasibility of naloxone supply.

The availability of intranasal naloxone does not address all barriers to naloxone use. Macdonald et al. [1] highlight concerns with ‘over-antagonism’, which may pertain to higher doses. A dose-dependent reversal of fentanyl-induced respiratory depression was demonstrated in a small study of anaesthetized patients [4], suggesting that dose is important. Concerns with withdrawal symptoms have been noted with higher doses, and in contrast, the emergence of withdrawal symptoms or aggression were rarely reported in a study using intramuscular doses of 0.4 mg [5]. Clarke et al. [6] recommend using a dose just sufficient to reverse opioid toxicity to reduce the precipitation of acute withdrawal symptoms, supporting a dose titration approach; however, they also note that there is insufficient research to understand the relationship between dose and acute withdrawal symptoms [6]. The dose required will depend upon the amount and type of opioid consumed so a universal dose is unlikely to exist, and multiple doses will probably remain the standard of care. Further basic and applied pharmacological research may inform this area more clearly.

Knowledge is not the only barrier to naloxone expansion. Regulatory barriers need to be addressed in many countries to allow supply of naloxone to laypeople by non-health professionals such as peer workers. Many organizations that work with people who use drugs are not resourced to employ health-care professionals. This means that addressing these regulatory barriers is an important step towards making naloxone as widely available as possible. Further, concerns with reliable drug supply exist. The observed patterns of increasing shortages of drugs such as naloxone [7] are concerning in times of increasing opioid overdose mortality.

Finally, with the increased range of naloxone products, a new challenge is emerging in providing consistent messaging for effective use regardless of which naloxone product is being administered. There is the risk with differing products that dose and administration messages could become confusing. Along with consistent messaging around drug administration, consistent messaging regarding other steps in the overdose response, such as when to call an ambulance relative to naloxone administration is also lacking. Leadership from those with expertise, and informed specifically by those with lived experience, is needed. Easy-to-administer products at effective doses with minimal barriers to supply are critical. The continuing rise in opioid-related deaths puts this issue into sharp focus.

Declaration of interests

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