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REVIEW

Recent Innovations to Detect and Intervene to Prevent Opioid Overdose Deaths

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Abstract

Opioid overdose deaths have become a rapidly growing global health crisis, with current estimates indicating over 125,000 deaths annually worldwide. This crisis has reached particularly high levels across North America, where the USA recorded over 100,000 opioid-related deaths in 2022, while the UK has seen mortality rates surpass those from road traffic accidents. Despite the scale and urgency of this public health emergency, opioid overdose remains an area of strangely 'undone science'. Five interconnected areas of research are examined, addressing critical gaps in our understanding and our response to opioid overdose events. We analyse epidemiological evidence establishing the scope and patterns of opioid-related mortality, explore laboratory-based overdose research, investigate technological solutions for overdose detection through wearable devices, examine emergency alert systems and community-based interventions, and address innovations in overdose prevention, encompassing both current developments in naloxone formulations and emerging technological advances that may shape future interventions. A comprehensive examination describes how recent innovations enable experimental investigation of heroin overdose in the clinical laboratory alongside the testing of wearable sensors to detect overdose, and the development of new formulations of naloxone, which are more tailored for use by a non-medical and non-clinical workforce. Through such approaches, we can examine previously overlooked areas of research and will, in future, be able to detect and intervene more effectively to prevent opioid overdose deaths.

Key words: opioid-related disorders; opiate overdose; naloxone; respiratory depression; wearable electronic devices; emergency treatment; preventive health services; harm reduction

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Introduction

Opioid overdose represents one of the most pressing global health challenges of the 21st century. Global deaths from opioid overdose have more than doubled since the early 2000s. Current estimates indicate that opioid use contributes to approximately 125,000 deaths annually worldwide (Ritchie et al, 2022; World Health Organization, 2023). This crisis has reached particularly alarming levels across North America, where the USA recorded over 100,000 opioid-related deaths in 2022, marking a five-fold increase from 2000 (NIDA, 2024). In Canada, opioid

overdose now accounts for more than 20 deaths per 100,000 population annually, representing one of the highest rates globally (Belzak and Halverson, 2018). The UK has also witnessed a concerning trend, with opioid-related deaths rising from 8.4 deaths per million population in 1993 to 39.1 deaths per million in 2022, surpassing mortality rates from road traffic accidents (Office for National Statistics (ONS), 2023).

This crisis has evolved in distinct waves across different regions. In North America, the epidemic began with prescription opioid misuse in the early 2000s, transitioned to heroin in the 2010s, and now faces the devastating impact of synthetic opioids, particularly fentanyl and its analogues (Ciccarone, 2019). In contrast, European countries like the UK have thus far largely avoided the fentanyl crisis, with heroin remaining the primary contributor to overdose deaths (Pierce et al, 2021). However, mortality rates continue to rise, with the UK recording 2551 opioid-related deaths in 2023 alone (Office for National Statistics (ONS), 2023). The economic burden is equally staggering, with estimates suggesting annual costs exceeding $500 billion in the USA alone, including healthcare expenses, lost productivity, and criminal justice system involvement (Florence et al, 2021).

In this paper, we explore the concept of 'undone science' in the context of opioid overdose research and intervention. The term 'undone science' refers to areas of research that have been overlooked, despite their clear social and scientific importance. Such oversight often originates from various factors, including the influence of discrimination and stigma, which have historically impeded scientific investigation of substance use disorders.

This review examines five interconnected areas of 'undone science' in opioid overdose research and interventions. First, we analyse the epidemiological case for scientific study by examining mortality trends and patterns to establish the scope and urgency of this research priority. Second, we explore the feasibility and ethical considerations of laboratory-based overdose research, including innovative methods for studying opioid-induced respiratory depression. Third, we investigate the potential for technological solutions in overdose detection, particularly through wearable sensors and alert systems. Fourth, we examine the development and implementation of emergency response systems, including community-based interventions and alert mechanisms. Finally, we address innovation and future directions in overdose prevention, encompassing both current developments in naloxone formulations and emerging technological and strategic advances that may shape tomorrow's interventions.

The 'Undone Science' of Opioid Overdose: Does the Problem Warrant Scientific Study?

How large is the problem? And are there reasons to believe that we could mobilise more intervention to prevent the overdose crisis and/or to intervene more frequently and more effectively?

From a UK perspective, opioid overdose deaths are one of the leading causes of premature death across the age spectrum, with an annual figure of 3246 deaths from opioid overdose during 2022 (2261 England & Wales, 867 Scotland, 118 Northern

Ireland)—this is now a higher annual mortality rate than with road traffic accidents (Office for National Statistics (ONS), 2022). Deaths involving opioid overdose across England and Wales have risen substantially over the last 30 years from a 1993 figure of 8.4 deaths per million population to 39.1 deaths per million in 2022 (age-standardised mortality rates per million, see Fig. 1, Office for National Statistics (ONS), 2023), with similarly high rates across the rest of the UK—these are amongst the highest rates reported across Europe for drug overdose deaths. As illustration, the pattern of increase in deaths over the last three decades for England and Wales can be seen to have steadily risen through the 1990s, then plateaued through the 2000s, but then returned to continuing rise since 2010 (Fig. 1). These deaths more often involve men (approx 2:1) and approximately half of these drug-related deaths involve heroin or other opioids. People die of opioid overdose across the age spectrum, including younger and middle-aged opioid users, but with even greater risk among older individuals taking opioids, especially if physical co-morbidities exist or if several different types of drugs have been used in addition to opioids. Overall, the impact on years of life lost is considerable and is rising markedly. It's important to note that death registration data may underestimate the true burden of opioid-related mortality due to varying factors such as delays in toxicology reporting, potential misclassification of cause of death, poly-drug use or underlying health conditions.

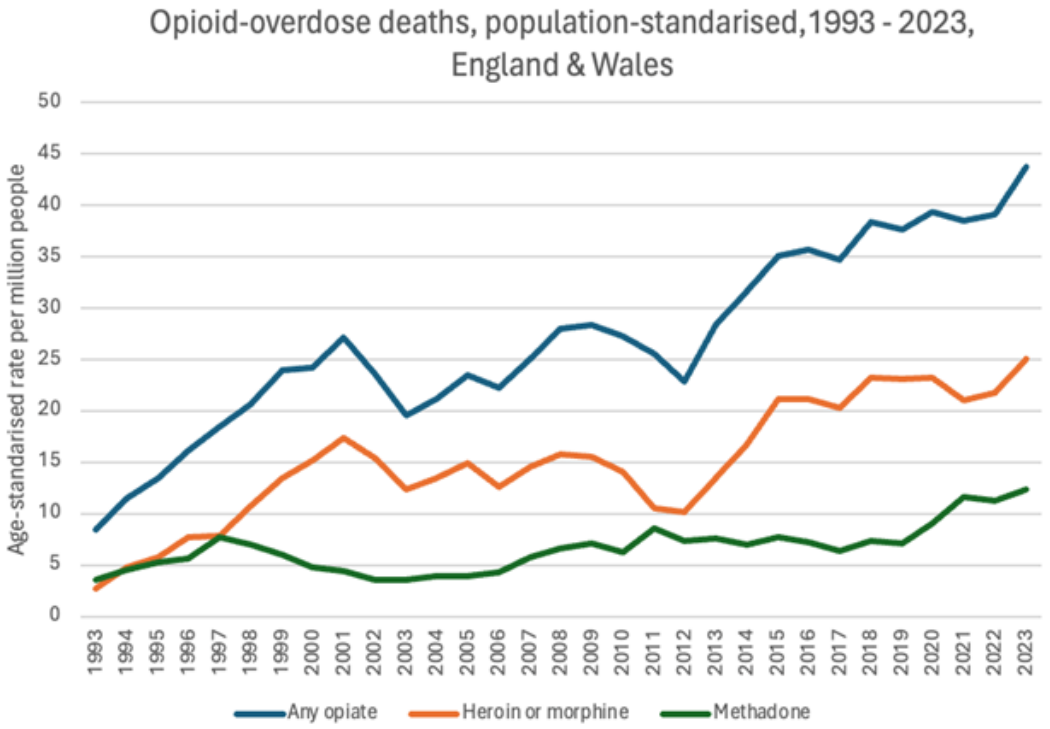

Fig. 1. Population-standardised rate of opioid-related deaths, 1993–2023, England & Wales. Redrawn using Microsoft Excel 365 (version 2502, Microsoft Corporation, Redmond, WA, USA) by the authors using data from the Office for National Statistics (ONS) (2022).

North America has particularly suffered a large increase in opioid overdose deaths, affecting Canada as well as the USA. In Fig. 2, we can see the continuing rapid increase in annual mortality from opioid overdose across the USA, with the latest available annual mortality rate for deaths involving opioids at an unprecedented level of more than 100,000 opioid overdose annual deaths for 2023 (Spencer et al, 2022).

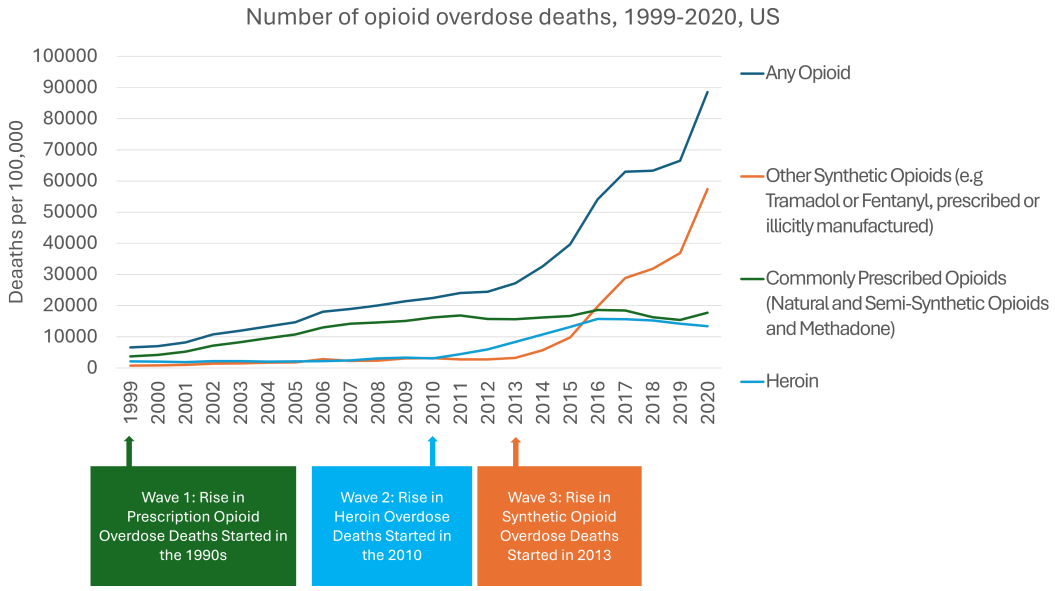

Fig. 2. Overlapping epidemics within opioid overdose deaths, 1999–2020, USA. Data source: CDC WONDER database, https://wonder.cdc.gov/ (the Centers for Disease Control and Prevention (CDC), National Center for Health Statistics). The figure illustrates mortality trends within the opioid crisis. Data visualisation created by authors using Microsoft Excel 365. CDC WONDER, Atlanta, GA: USA Department of Health and Human Services; 2023.

This problem can most meaningfully be considered as three overlapping epidemics over the first quarter of this century (Fig. 2). Firstly, through the first decade of the century, the number of overdose deaths in the USA associated with prescription opioids more than tripled from less than 5000 to 15,000, prompting increased regulatory control and change in clinical practice, with the number having plateaued thereafter (Ciccarone, 2019).

But, following the increased regulatory control, there was then a surge in the extent of use of illicitly obtained heroin (which had previously been relatively stable and at a lower level). This surge in heroin overdose deaths was from approximately 3000 in 2010 to more than 15,000 by 2016, and then also plateaued and thereafter declined.

However, this is not the end of the story. Fentanyl, an opioid which had previously been used extensively for medical purposes and was rarely used as a recreational drug, has subsequently become widely abused, including, increasingly, as illicitly-imported illicit-manufactured fentanyl and even more potent newer fentanyl analogues (Stanley, 2014). Fentanyl and several fentanyl analogues are now the leading illicit opioids used across the USA, with an exponential increase in an-

nual mortality rate, taking the annual mortality rate from opioid overdose in the USA well above 100,000 deaths per annum.

In the UK, in sharp contrast (as of the time of writing), deaths from fentanyl remain rare. Fentanyl deaths occur, of course, but recorded deaths from fentanyl and fentanyl analogues at less than 100 annually (as of 2023), thus at a rate which is orders of magnitude lower than in North America and still much lower than overdose deaths from heroin across the UK (Office for National Statistics (ONS), 2023).

Clinicians and policy makers also need to consider whether there are factors which might indicate when and where, and with whom, overdoses may occur. It transpires that there are periods of time and special situations, where the risk of opioid overdose death is particularly increased: these may tell us where preventative or active emergency interventions could be considered. To the clinician and policy maker, there are three situations which stand out.

(1) The early weeks of methadone treatment: even though there is greatly reduced risk of overdose once established on stable methadone treatment, there is a slightly increased risk of opioid overdose death during the first few weeks whilst the patient is being introduced to, and stabilised on, their personalised dose of methadone maintenance treatment. This can be seen in the national general practice (GP) study of opioid overdose deaths where a brief increased risk of overdose death was then followed by marked reduced risk throughout the methadone treatment but then followed by a brief period of increased risk in the weeks following cessation of treatment (Cornish et al, 2010). The objective during these first few weeks is to replace the patient's prior use of illicit heroin with the new prescribed opioid substitution treatment (OST; usually methadone or buprenorphine), and it is likely that these overdose deaths are partly a result of insufficient supervision and monitoring of the dose induction alongside the patient's failure to disengage properly from their prior use of heroin.

(2) Immediately following discharge from hospital or residential rehab, and after termination of opioid substitution treatment: this period, with no pharmacologic protection, is, for many individuals, a time of great vulnerability to relapse (Lewer et al, 2021; Merrall et al, 2013). It is also a time when the unexpected use of a dose previously tolerated may prove to be, for the individual who no longer has their previous drug tolerance, a fatal overdose. It is important for clinicians, commissioners and policy makers to remain attentive to the need for support and monitoring of patients beyond the period of prescribed medication or highly structured protective environments. Indeed, the clinician needs to be attentive to the vulnerability of a recently detoxified individual returning to the home environment where their previous heroin problem was active, as instances of relapse can be particularly dangerous in view of the loss of pharmacological tolerance. Just as with the termination of medications for many other disorders, the clinician must remain vigilant in the post-medication period, since there is an increased risk of re-emergence of the condition for which the treatment was originally prescribed.

(3) Release from prison: this is an important area where its importance is frequently overlooked, perhaps partly because of confusion between, on the one hand, the law-and-order orientation of imprisonment and release, and, on the other hand,

the therapeutic and rehabilitative importance of the prison release period (Farrell and Marsden, 2008). The prison population has a remarkably high concentration of individuals with a previous history of substance use disorders as well as wider mental health problems, including, typically, between a quarter to a third of prisoners having histories of non-medical use of heroin or other opioids. Even though many of this population make plans to engage with treatment services post-release, or to engage with mutual-aid organisations such as Narcotics Anonymous, these plans frequently fail, often stalling within hours of leaving the prison gate. In a UK study of the excess mortality rate amongst individuals with history of prior involvement with heroin use who are then released from prison, the finding of an overall excess mortality rate across the whole of the first-year post-release was then eclipsed by the magnitude of risk of opioid overdose death in the first fortnight post-release (Singleton et al, 2003). This striking excess mortality in the immediate post-release period (the first week, especially) is illustrated in Fig. 3. Clearly, there are times of major risk of overdose death, but how do we approach the development of interventions? Can the problem be brought into the laboratory so that it can be studied?

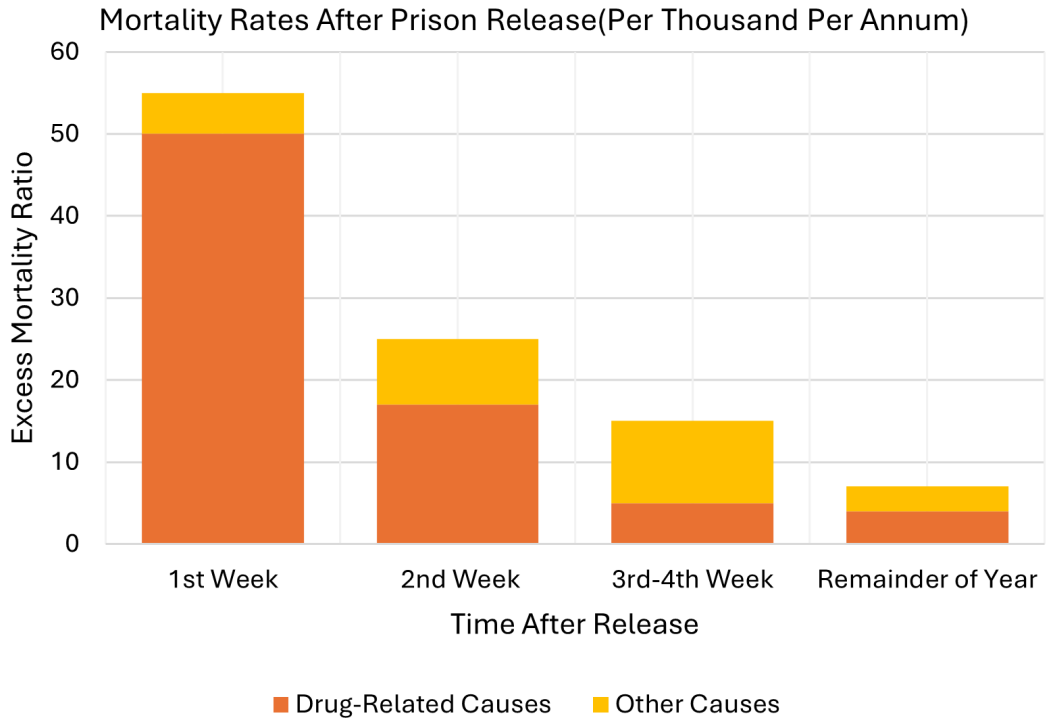

Fig. 3. Excess mortality in the weeks and months post-release from prison. Adapted from Singleton et al (2003), available under the Creative Commons License.

The 'Undone Science' of Opioid Overdose: Can It Be Studied in the Laboratory?

Epidemiologic, public health, and policy analyses can certainly be undertaken, as with the deaths analysis post-release, and this can valuably shed light on the frequency and nature and cluster rings of opioid overdose deaths. But might it also be possible to study the problem in the laboratory?

In this next section, we present innovative work from our group in which we describe recent ongoing studies which have involved, for example, bringing the opioid overdose problem into the laboratory (our Clinical Research Facility) and creating a human model of controlled and limited heroin overdose, so that we can study the physiological parameters and also test the potential to detect and intervene.

The experimental investigation of opioid effects in human subjects required careful ethical consideration. All studies were conducted under strict ethical oversight with approval from relevant research ethics committees, with results and findings placed in the public domain (Tas et al, 2025). Several key ethical principles guided this work: (1) participant selection was limited to individuals already prescribed pharmaceutical heroin, ensuring no introduction to opioid use; (2) dosing was carefully controlled and was anchored around participants' regular prescribed doses; (3) continuous medical monitoring was maintained throughout with immediate access to emergency medical care; and (4) informed consent processes emphasized the voluntary nature of participation and participants' right to withdraw at any time.

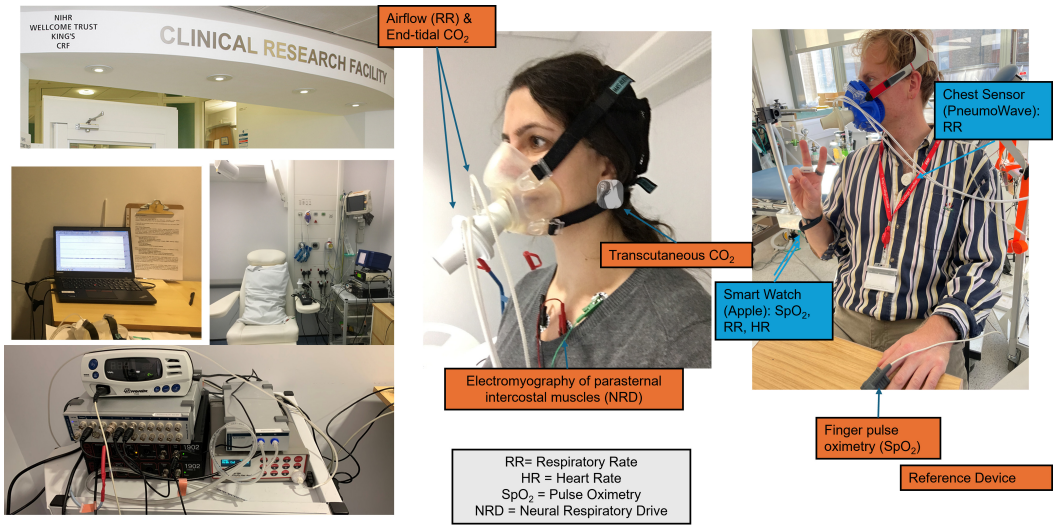

Fig. 4. Illustration of experimental setup at the Clinical Research Facility showcasing a range of bench-based equipment for monitoring physiological responses including a pneumotachograph and face mask (AD Instruments, Dunedin, New Zealand), oximeter (Nonin, Plymouth, MN, USA), end-tidal capnograph (iWorx, Dover, NH, USA), transcutaneous capnograph (Radiometer Medical, Brønshøj, Denmark) and parasternal intercostal muscle electromyogram using an analog-to-digital converter (AD Instruments) and amplifier (CED, Cambridge, UK), as well as new wearable devices including Pneumowave's chest sensor (PneumoWave Ltd, Glasgow, UK), an Apple watch (Apple Inc., Cupertino, CA, USA), Oura ring (Oura Health Oy, Oulu, Finland), and a SLEEPON Go2Sleep ring (SLEEPON, Shenzhen, China). The individuals shown in the photographs, taken by the authors themselves, are co-authors who have provided their consent for image use.

In Fig. 4, we illustrate the experimental clinical research setting where we incorporate a range of different measurements, including respiratory function. Respi-

ratory depression can be measured through various ways, and our aim was to find practical and reliable measures of respiratory depression for this specific population of people who have injected drugs long-term. This was initially borne out of the focus to safely examine various aspects of mild heroin overdose to assess respiratory function post-dose. This particular work was conducted under controlled conditions with a volunteer patient population already receiving pharmaceutical heroin as part of their prescribed treatment. The results of the post-dose respiratory depressant effect of heroin is explored in more detail later. Additionally, this model has also been used to test novel wearable devices that purport to measure respiratory depression and potentially have a role in detecting overdose. We have been testing these devices in comparison to standard laboratory bench-based methods as well as clinical pulse oximetry as demonstrated by Fig. 4 across a wide range of populations: e.g., among healthy volunteers, without injection of any drug, and among participants who are used to administering opioids. This work is discussed further later.

Whilst this model and approach is unusual, it adheres to established ethical and clinical research protocol. The approach also follows the same general principle as the method that might be adopted for studying influences on the perception of pain, for example, in which pain is inflicted, such as immersion of hand in ice-cold water, to a level determined by the participant, and then the pain-relieving effect of different analgesic strategies can be tested. In this way, we have been able to identify distinctive changes in breathing pattern directly associated with the injection of heroin by the study subjects, with marked disruption of breathing (and clinically significant falls in oxygen levels, etc.) observed in subjects injecting what they consider to be their 'normal' dose of heroin, even before we test the effect of the administration of a slightly increased dose.

Here, in Fig. 5, we can see one of our earlier traces from monitoring finger pulse oximeter readings on subjects whilst they self-administered their 'normal' dose of heroin, and the striking degree of drop in oxygen levels post-injection. We have subsequently extended our studies to examine these measures, alongside others, looking for the best possible sensors to detect, reliably and promptly, the potential imminent crisis.

Through subsequent study in our Clinical Research Facility, we find distinctive apnoeic episodes immediately following injection of diamorphine, as seen in the traces from one individual participant in Fig. 6 below. The traces show three key physiological measurements: airflow (measured through a facemask connected to a 200 L/min pneumotachograph, AD Instruments) in the top trace; blood oxygen saturation (percentage measured by peripheral fingertip pulse oximetry, Nonin 7500) in the middle trace; and end-tidal CO_2 (measured with a capnograph, GA-200, iworx) in the bottom trace (Tas et al, 2025). Whilst not observed pre-injection, these occur frequently post-injection, with duration of absolute apnoea frequently of more than 30 seconds and sometimes of up to a minute and without any observable evidence of distress or even awareness on the part of the participant.

In subsequent studies, we have found it possible to detect the disruption to breathing pattern more specifically and more quickly by measuring cessation of

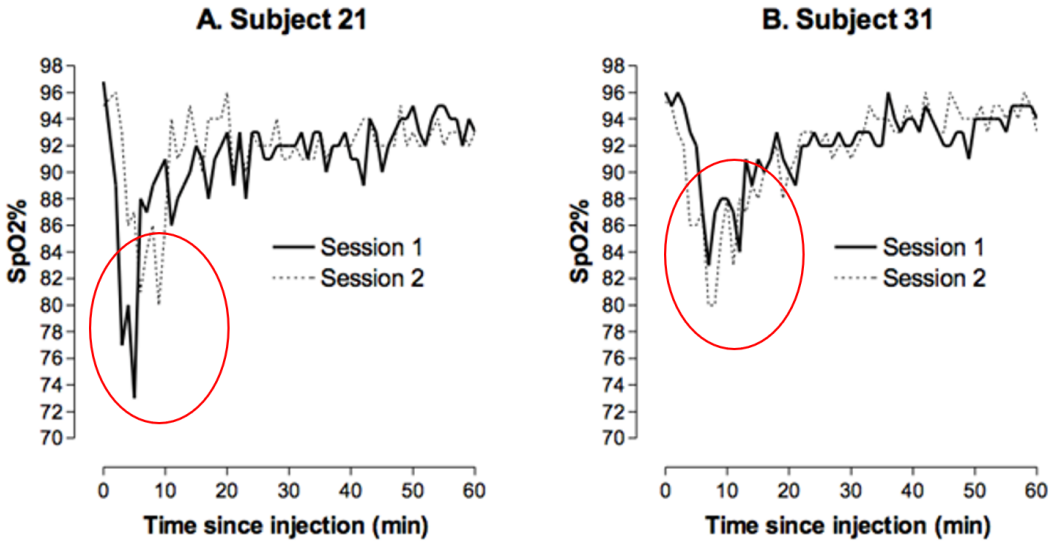

Fig. 5. Plunging peripheral venous oxygen saturation following intravenous (IV) and intramuscular (IM) injection of heroin (diamorphine). Subject 21 (41-year-old male) injected 180 mg of heroin intravenously on both occasions. Subject 31 (42-year-old female) injected 150 mg intramuscular heroin in session 1 and 160 mg heroin in session 2. Heroin was injected at time zero. The red circles highlight the close temporal relationship, especially with IV administration, between the moment of drug administration and the onset of respiratory depression.

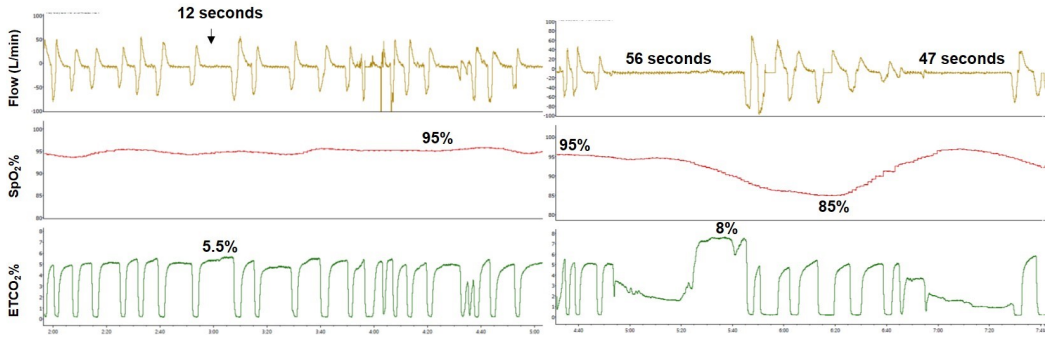

Fig. 6. Real-time monitoring of breathing patterns and apnoeic episodes before & after IV heroin administration. Recordings were taken of the participant as part of the ongoing study in a Clinical Research Facility. Left image: baseline, pre-diamorphine dose across 3 minutes; right image: 4 minutes post-diamorphine dose (30 mg, usual 100% dose session) across 3 minutes. Top yellow trace: respiratory flow (L/minute); middle red trace: oxygen saturation (%); bottom green trace: end-tidal CO_2 (%). $ETCO_2$, End-Tidal CO_2.

chest wall movement (which we take to indicate apnoea) and for this to be detectable more quickly than could be detected by tracking peripheral venous oxygen levels (Oteo et al, 2023). These striking findings clearly demonstrate the feasibility of studying opioid overdose in the laboratory.

In parallel to our overdose laboratory, we have also explored the potential to detect injecting behaviours, and thereby detect and respond to a potential overdose situation, by measuring distinctive arm movements whilst injecting. We call these 'motion signatures'. Similar work, and in fact real-life devices, are already used to monitor abnormal movements in activities of daily life, e.g., to respond to falls

or other hazardous incidents in the elderly or the development of abnormal health rhythm patterns (Ataiants et al, 2021; Marcu et al, 2020; Schwartz et al, 2020). Injecting movement 'signatures' are distinct and can be broken down into several component parts, such as extreme supination of the extended arm at the same time as unusual twisting of the other wrist, which holds the syringe. We have also observed a distinctive absence of movement in the upper limbs whilst injecting and holding the syringe in position (whilst not disturbing the needle in the vein). Using accelerometers (3 tri-axial, recorded at 100 Hz, placed bilaterally on the upper limb), we constructed an injection simulation task to look at whether upper limb accelerometers distinguish simulated injecting movements from non-injection upper limb tasks such as lifting a cup or opposite limb scratching. Raw accelerometer data in this simulation task showed a goodness of fit for the upper arm and therefore distinguished injecting tasks from other non-injection tasks. We plan to operationalise this task in future among healthy volunteers and among those who inject drugs to determine whether a unique personalised 'injecting' or 'motion' signature is detectable objectively. For an animation to illustrate 'motion signatures', see first the figure below (Fig. 7), on which the left arm and fingers of the subject are shown by the orange lines and the right arm and fingers by the yellow lines.

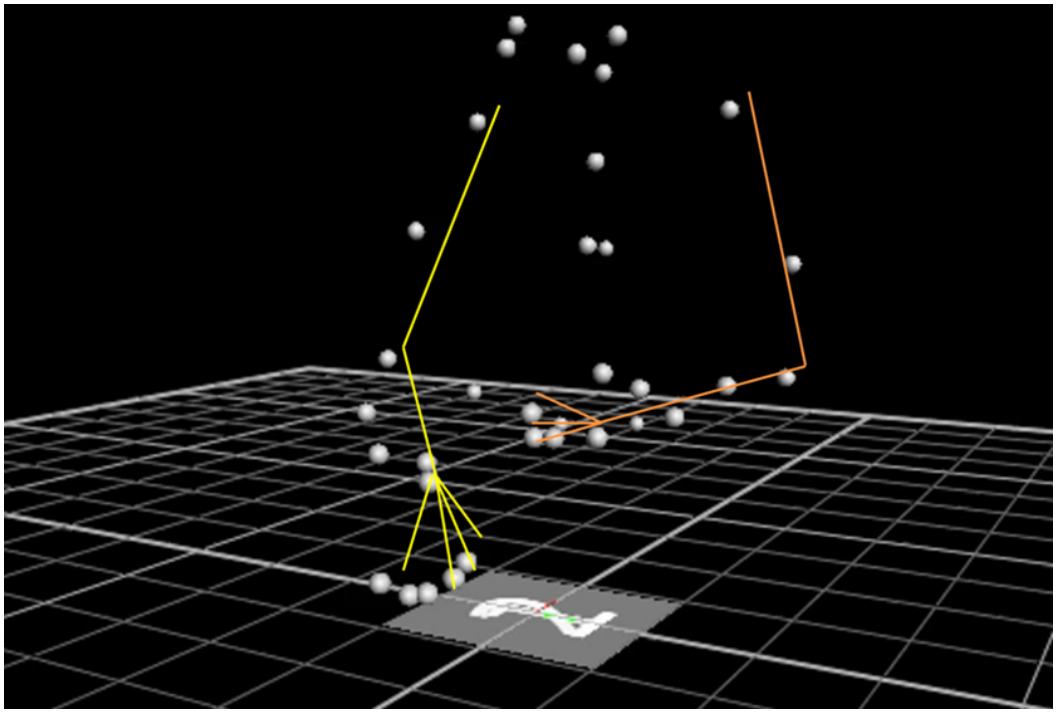

Fig. 7. Screenshot of 'motion signature' capture to indicate left and right arms. Produced by Irene Di Giulio, Basak Tas and John Strang at King's College London. The left arm and fingers of the subject are shown by the orange lines and the right arm and fingers by the yellow lines.

The objective is to be able to capture distinctive movements which, together, reliably indicate preparation by this left-handed participant, in this example, for an imminent intravenous injection into a vein in the antecubital fossa of the right arm. The distinctive 'motion signature' can then be seen in **Supplementary material**.

The 'Undone Science' of Opioid Overdose

Could Overdose Crises Be Detected in the Real World?

Apps are already being developed to offer monitoring and alert functions which the drug user can activate prior to an instance of drug use (Ataiants et al, 2021; Marcu et al, 2020; Schwartz et al, 2020). The objective here is to enable to drug user to connect remotely to a peer of family member and to alert them if problems develop. The comprehensive process of overdose detection and alert is illustrated in Fig. 8, showing the pathway from physiological monitoring through to emergency response.

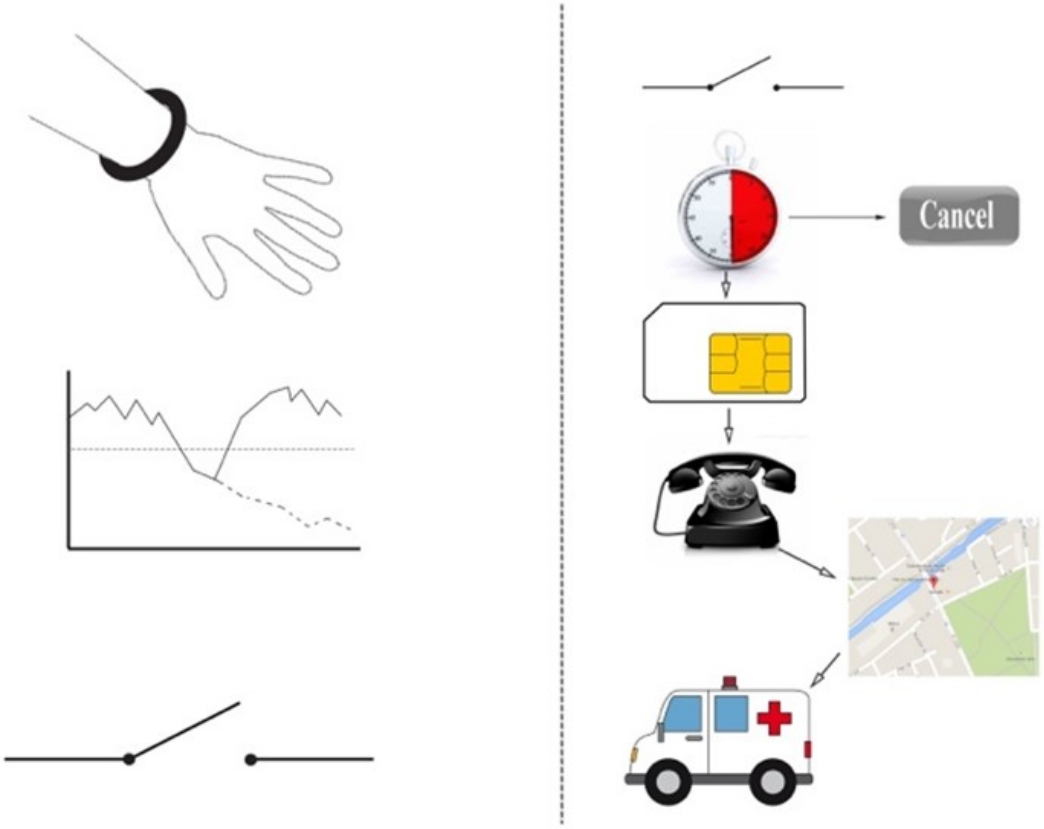

Fig. 8. Comprehensive schematic of overdose detection and alert system. The process begins with physiological monitoring via a wearable sensor that detects respiratory patterns. When potentially dangerous patterns are identified (such as prolonged apnoeic episodes), the system activates a multi-tiered alert protocol. Alerts can be configured to notify designated emergency contacts (such as family members, friends, or support workers) and, if no detected intervention in a defined period of time, an alert and geo-location to emergency medical services. Schematic produced by lead author (JS).

If the identification of prolonged apnoeic episodes is found to be reliably associated with emerging overdose, then might it be possible to develop a wearable sensor which might send an alert to a partner, family or emergency services? Might it be possible to develop such sensors for detection of risk, as has recently been proposed (Huang et al, 2024), in much the same way as tracking cardiac rhythm through live data transmission from a pacemaker, or 'fall detection' on recent wearable devices?

Working with the recently created company, Pneumowave, and with supplementary funding from the Chief Scientist's Office in Scotland and the UK government Office for Life Sciences 'Addictions Mission', we have begun testing a wearable chest sensor which detects chest wall movement, from which analysis of altered signals can be analysed and generate an alert to onset of prolonged apnoeic episodes, as shown in Fig. 9, where the 3D accelerometry signals are analysed to identify episodes of breath-taking. We have recently completed a study with colleagues in Australia to test this technology in a Supervised Injecting Facility (SIF), and now have data from 1145 episodes during which attendees at the SIF injected a range of illicit drugs, predominantly heroin, so that we can test the ability of the sensor to detect altered breathing patterns of concern. From initial scanning of the data, alongside clinical reports from staff at the SIF, there were 82 instances of potential concern warranting checking from the SIF staff, including 10 clear overdose emergency situations (Tas et al, 2024a). We will report more on this at a future date.

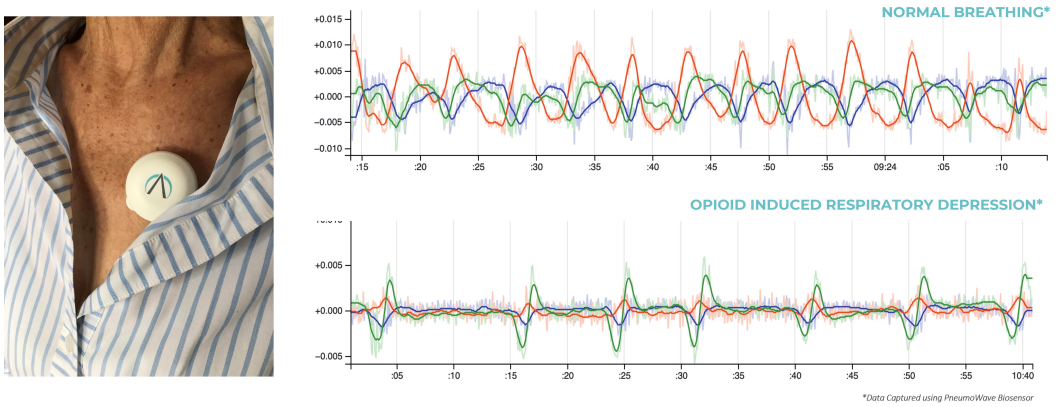

Fig. 9. Graphic of 3D accelerometry tracing via Pneumowave chest sensor. Upper trace shows normal regular breathing pattern, while lower trace demonstrates disrupted breathing pattern with periods of respiratory depression following opioid administration. These traces were collected from participants in a study conducted at the Sydney Medically Supervised Injecting Centre (MSIC). The traces show chest wall movement patterns captured by the Pneumowave sensor, with X (lateral), Y (vertical), and Z (anteroposterior) axes represented in different colors, clearly illustrating the contrast between normal respiratory function and opioid-induced respiratory depression. Left panel: demonstration of correct chest sensor placement. Image collected with participant's informed consent.

With sensors which can reliably detect changes identifying the onset of an opioid overdose emergency, then a whole new body of inquiry and exploration is required to gauge the acceptability and feasibility of such monitoring on the part of the target population of opioid users, as well as the acceptability and feasibility to the friends, family, hostel workers or emergency service practitioners to whom the alert might be sent. We have begun to explore this area (Tas et al, 2024b; World Health Organization, 2014), and have examined the extent would public monitoring be acceptable to the target population (i.e., drug users themselves, including occasional users as well as regular users) for what is often regarded as an essentially

private behaviour? What level of sensitivity and specificity would be necessary for this to be acceptable to ambulance services, or to hostel staff, for example? False-positive alerts would irritate all parties concerned, and false negatives would reduce the value and damage the reputation of the preventive approach. Consideration of these future real-world implementations is finally now occurring after years of being overlooked. Hopefully, with sensitive exploration and negotiation, acceptable wearable products and alert algorithms can be developed.

As an illustration of this exploration, we have reviewed acceptability and have conducted interviews and focus groups among individuals with current or historical heroin/opioid use who have been presented with a variety of devices. There was broad enthusiasm towards the concept of wearable devices, although with differing beliefs about what would be a facilitator or barrier to the acceptability of using wearable devices. Accuracy of overdose detection and inconspicuousness were identified as important facilitators, whereas poverty (digital as well as monetary) and suspicion about technology and services were identified as barriers to acceptability.

In the future, we anticipate that such devices will be used to identify 'at-risk' users and potentially allow for targeted early detection of opioid overdose. This might also include giving the active drug user personalised feedback of the number of apnoeic episodes that have been observed over a measured period of time, and this might then be harnessed as a trigger for behaviour change. It is also feasible that this type of monitoring could be conducted in users before treatment and, in the future, even be used as a means of engaging with drug users before they are willing to enter treatment, perhaps through outreach partnerships, so that the threshold for future entry into treatment may become a smaller step. However, use of these methods for such purposes would require examination of acceptability among the target population and validation in larger-scale, prospective studies.

Could Detection Trigger an Alert? Could Emergency Intervention Be Enabled?

An alert could be life-saving, but only when the alert enables a life-saving action. At one level, a loud audible alarm or haptic vibration might be a sufficient stimulus, or an alert to a partner or family member might be more appropriate since it would enable summoning of emergency medical services, if required. An alternative, from a technological point of view, would be to use the location service function of the wearable device, or a linked phone, to send an emergency call directly to the ambulance service. However, with overdose crises often detected at a point which is very close to actual death, then consideration is also needed of what emergency interim action might be implemented whilst awaiting the arrival of the emergency medical services. Just as with other sudden-onset emergencies such as ventricular fibrillation, status epilepticus, or an obstructed airway, there may be great benefit from considering the public citizens (including peers, family, or passing bystanders) as a potential intervention workforce. If this were to be the case, consideration needs to be given to what training they should have previously been given and also what resources would need to be at hand. In this next section, we give this consideration, especially in light of the increasingly widespread provision

of training in the management of opioid overdose and the increasing availability and pre-placement of emergency supply of the opioid antagonist naloxone (now available in nasal spray form as well as the long-established injectable form).

Since its first serious articulation in the British Medical Journal (BMJ) more than quarter of a century ago, the provision of basic training on how to manage an opioid overdose whilst awaiting an ambulance including the option of administration of an interim emergency dose of naloxone has now become the norm, and the strength of the evidence base recognised (McDonald et al, 2018; Strang et al, 1996). This includes the development of guidelines from World Health Organization (2014) and from United Nations in such policy and practice alongside steady spread of the workforce who are trained to develop such competence (including not only staff in homeless hostels, for example, but also police officers in many police forces across the UK and globally) (World Health Organization, 2014). Scotland was the first country in the world to introduce the provision of take-home naloxone as part of expected routine clinical practice, including provision to individuals with a previous drug use history at the point of release from prison, with Wales soon thereafter. The United Nations 90-90-90 initiative is commendable, with its objective that 90% of all those who may be there at a future overdose crisis should have already received training, of whom 90% should also have been pre-provided with an emergency take-home supply of naloxone, of whom 90% will be carrying it on them or have it close at hand at time of future need.

Earlier uncertainty as to how frequently the overdose crisis might be observed has proved to be only partially founded. Whilst some opioid overdoses do indeed occur while the individual is alone, the majority of overdoses occur in the company of others, and occur in home situations (even if not the home of the individual themselves). Furthermore, there is now evidence of widespread willingness to intervene on the part of peers (both generally and also with peer drug users) and of family members, as well as workers in the health and social sector and in police and criminal justice settings.

Innovation and Future Directions in Overdose Prevention

The Development of More Publicly Comfortable Formulations of Naloxone

Naloxone has been available as an injectable drug across much of the world for many decades, but only became available as a nasal spray in Europe in 2018 (one year earlier in the USA). The possibility of take-home naloxone schemes therefore raised issues about how the general public and politicians, and commissioners would regard the idea of provision of an injectable antidote, naloxone, to individuals whose problem is often related to injectable drug use. Furthermore, it was originally only available in the form of ampules or as a kit, which required some degree of familiarity for prompt injectable administration. Hence, an important early step was the appearance of a five-dose prefilled syringe, which was then adapted with the inclusion of needles in the packaging case (marketed in the UK and across Europe as ‘Prenoxad’) for layperson administration.

In some countries and some settings, the injection-only format was accepted, but in other countries and settings, it was enough to result in blocking or obstruction

of proposals for take-home naloxone schemes. With this in mind, the concept of a concentrated naloxone nasal spray was investigated so that, currently, perhaps half a dozen different commercial nasal sprays now have regulatory approval in different parts of the world. For these new naloxone nasal sprays, they have approximately 50% bioavailability, thus, a 2 mg nasal spray might deliver an absorbed dose of 1 mg naloxone by the injectable route. In the UK, the currently available nasal formulations include the 'Nyxoid' nasal spray, which was brought to market in 2018 as a twin pack of nasal sprays, each containing 1.8 mg of naloxone base, equivalent to 2 mg of naloxone hydrochloride; and since 2023, the Accord generic nasal spray, based around the Norwegian 'Ventizolve' nasal spray, as a twin pack of 1.26 mg of naloxone base (equivalent to 1.4 mg of naloxone hydrochloride).

Of interest from study of the pharmacokinetics (Fig. 10) is the higher and longer-lasting plasma levels of naloxone, which persist with the nasal sprays. This possibly derives from some degree of surface or tissue storage of the nasal route and might be considered an advantage since it could be expected to result in a longer duration of action of the reversal of the respiratory depressant effect of the opioid that caused the overdose. Strangely, this has not attracted the clinical considerations that it warrants.

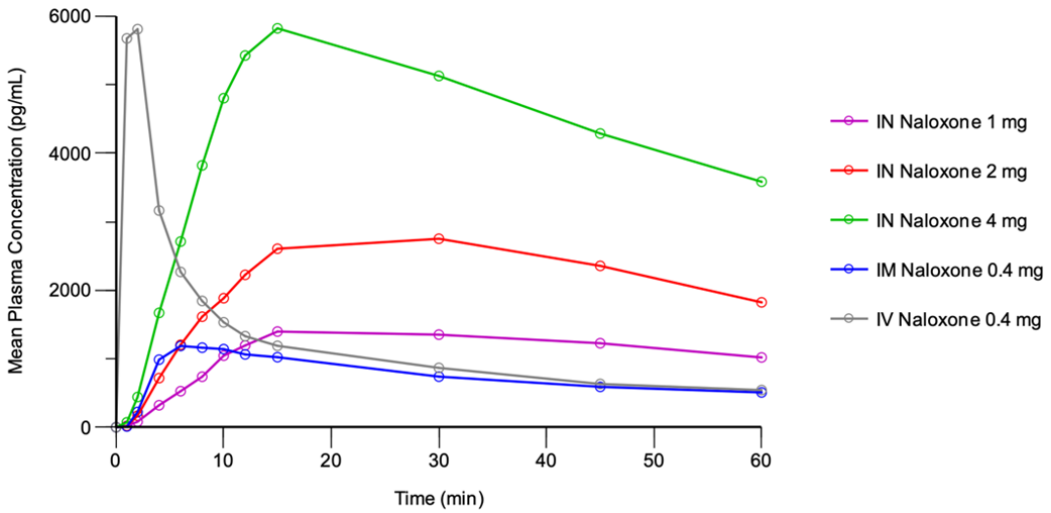

Fig. 10. Plasma levels of naloxone following IV or IM administration versus three different intranasal naloxone doses. Adapted from McDonald et al (2018), Addiction, available under the CC BY-NC 4.0 (https://creativecommons.org/licenses/by-nc/4.0/).

This introduction of a non-injectable form of naloxone has made it possible to introduce schemes for naloxone provision across many more countries and settings and to many more potential intervention workforces (e.g., police), and the widening of provision still continues (in the UK and globally).

There continues to be uncertainty and differences of opinion about the most appropriate dose to provide to non-medical persons for interim emergency care (Carpenter et al, 2020; Rock et al, 2024; Wong et al, 2019). On the one hand, the dose needs to be sufficient to rapidly achieve reversal of the life-threatening opioid-induced respiratory depression, and maintain this reversal for the duration

of the overdose. On the other hand, it is important to avoid unnecessary precipitation of a full-blown withdrawal syndrome, not only on the grounds of avoiding unnecessary distress and an iatrogenic different clinical crisis but also because such 'over-antagonism' has been found to be the trigger for self-discharge and further drug-seeking, thereby creating a potentially dangerous compound opioid overdose as the life-saving effect of the naloxone diminishes (Neale and Strang, 2015). This would be of particular concern if the overdose was caused by an opioid with a longer duration of action.

The need for more portable naloxone: with these developments, it might be thought that there is successful, wide availability of emergency naloxone when future needs might arise. However, as with the EpiPen and with the defibrillator, it depends crucially on whether the emergency intervention is immediately at hand, since time is not on the side of someone experiencing an overdose. A disturbing finding in recent years has been that, despite strong endorsement and acceptability, carriage rates at times of subsequent survey indicate that only 10–20% of people who had been given naloxone were carrying it on their person—a long way short of the 90% target identified by United Nations (Burton et al, 2021). Part of the problem is the size of the naloxone kits (what we informally refer to as the 'Levi's jeans test'). 'If it doesn't fit in my jeans, it won't be on me at the unexpected future time of need'. This is a major problem and indicates a need for a new solution.

Current exploration of ultra-portable buccal naloxone wafers in credit-card format: current work within our group includes conceptualisation and production of a prototype ultra-portable multi-dose strip of naloxone doses in the form of a rapid-dispersal buccal wafer. The objective is to have naloxone in a format which could be placed in a wallet or purse (or perhaps on the back of a mobile phone?) so as to ensure it will be readily available when the unanticipated future emergency arises, using the same logic as the organ donor card or medicines alert.

Using 'Zydis' technology, a prototype buccal naloxone wafer has been successfully manufactured and is now moving to the next stage of Phase 1 healthy volunteer testing. Acceptability to the target populations will be essential, and findings from the Patient and Public Involvement (PPI) survey and focus groups are very positive thus far with, for example, the proposed buccal wafer format receiving the strongest declared willingness to administer naloxone (compared to either nasal or intramuscular administration). Of particular importance, the willingness of those who use opioids to carry naloxone on their person when away from home is reassuringly stronger with the proposed buccal wafer format. In a survey of responses from a mixed audience of 239 respondents from a range of different groups including frontline clinical workers, management staff, volunteers and also family members, the proposed buccal naloxone wafer was the most frequently selected preferred form of naloxone to administer (81% reporting feeling comfortable administering the novel buccal naloxone, versus 72% for nasal naloxone, versus 53% for intramuscular naloxone; valid sample size 214); and, in responses to enquiry about confidence that they would carry the naloxone with them, the novel naloxone wafer was again the most preferred (85% reporting feeling comfortable admin-

istering the novel buccal naloxone, versus 53% for nasal naloxone, versus 25% for intramuscular naloxone; valid sample size 213).

Future Advances—What Can We Envisage?

The development of interventions that can be administered by the general public, alongside other technological advances, opens up new avenues for developing the interventions of the future. We identify three categories.

Strategic advances for the future will draw on the recognition that there is a wider workforce that comes into contact with individuals with substance use problems. This includes staff working in homeless hostels and in drug-free rehabs who are already in contact with such individuals and are well-placed to administer early interventions to detect the onset of risk, including to those who may choose not to enter formal treatment. The wider workforce also includes groups such as prison officers (since a history of addiction problems is present for more than a third of prisoners) and also police officers (with naloxone kits now carried by police in approximately half of all police forces in the UK).

Therapeutic advances can now be developed which enable targeting of specific behaviours through new technologies. The immediacy of communication between user/patient and clinician makes it possible for interventions to be developed which might involve provision of feedback on risk behaviours, which, perhaps with a therapist to support, might then be modifiable. Other options from the live transmission of data might be the sending of cognitive 'circuit-breaker' messages to interrupt semi-automatic sequence of drug-taking behaviour (as might be used with alcohol problems, for example) or alternatively to monitor vital functions and offer two-way communication between an emergency clinician and an individual in crisis (Bolt et al, 2022).

Technological advances are becoming possible through developments such as miniaturisation of devices and through innovations in power sources. This will mean that today's rather chunky wearable devices may be no more than a stick-on plaster or may even be implantable, so that monitoring could be 24/7 and automated. Indeed, animal work on a prototype implantable device with the ability to detect overdose and automated administration of a naloxone dose has recently been described (Huang et al, 2024). For a generation familiar with smartphones and smartwatches, the opportunities for wider therapeutic application are immense, although barriers of stigma and shame will still need to be addressed and obstacles negotiated.

Bringing it all together: new research is exploring and developing novel solutions that address key limitations of traditional overdose prevention approaches. The development of credit card-sized naloxone wafers tackles the poor carriage rates of existing formulations, whilst also offering dose flexibility and better preparedness for the challenge that overdoses with fentanyl and other synthetic opioids could pose. Alongside this, the operationalisation and real-world testing, now underway, of wearable sensor technology enables real-time monitoring of respiratory activity and hence opens up the potential for sounding an alarm. However, important limitations remain. The wearable technology needs further validation in

diverse real-world settings, with questions not only about sensitivity and specificity but also about user acceptance and long-term adherence still to be addressed. Similarly, the ultra-portable naloxone formulation requires testing for speed of onset and duration of action, as well as long-term stability of the product if carried in a wallet or purse. Future research will also need to explore user acceptability with participants in different settings and will need to address institutional aspects such as the potential integration of these innovations into known risk settings such as police custody, prison cells and hostels for the homeless, as well as within existing healthcare systems and emergency response services.

Recommendations for Policy and Practice

As the extent of deaths from opioid overdose becomes more evident, clinicians and policy-makers need to review this evidence and introduce changes to clinical practice and policy. The following are identified.

• Healthcare practitioners who identify current or past opioid use should initiate conversations about overdose risk and ensure provision of 'take-home naloxone' kits, not only to the individuals at risk but also to their family members and peers who might witness such a future overdose. Instruction should also be given on fuller emergency actions (call ambulance, check breathing, and, when necessary, administer naloxone).

• Clinicians need to identify substance use behaviour in patients, even when it is not the presenting complaint. Whether associated with the presenting disorder or not, advice should be given on the risks of the behaviour, plus information on the pathway to treatment services. In addition, information should be given on how to manage a witnessed opioid overdose, including the emergency interim administration of nasal or injectable naloxone while awaiting an ambulance.

• Consideration should be given to extending this intervention to patients to whom opioids are being prescribed for pain relief, as evidence emerges of overdose deaths in this patient population also.

• Policymakers should ensure supportive frameworks for new technology adoption and expanding naloxone accessibility. As new forms of interim emergency intervention are developed and approved by regulators (e.g., the new naloxone nasal sprays), these should be incorporated as available options for clinicians to provide.

• Policymakers and regulators should further extend the ability for take-home naloxone kits to be accessible without specific clinical referral (e.g., direct from community pharmacy or from local substance use services), and for associated training to be easily accessible such as through overdose training events at local drug treatment services or their online equivalents.

• Community partnerships should ensure the comprehensive provision of overdose training for the general public to be competent first responders. This can include support for peer-led responses amongst drug-user networks.

• As new technologies, such as overdose sensors, reach the level of regulatory approval, emergency services should update their response protocols to integrate with new alert systems.

Conclusion

The global opioid overdose crisis is increasingly recognised as a major health challenge, and yet our understanding of the mechanisms of opioid overdose is still rudimentary, so that public planning and individual emergency responses remain best-guess. We are finally addressing the 'undone science' by developing controlled laboratory models of human opioid overdose and developing and testing new technologies. The results of these studies can harness new possibilities, such as wearables, to develop novel capabilities to detect overdose events when they occur and to send alert messages to peers, family or directly to emergency services. Together with the development of ultra-portable naloxone formulations to improve carriage rates of a life-saving intervention, a wider intervention workforce will have the knowledge and the tools to be able to respond with life-saving interventions at the time of future unexpected need.

Key Points

- Opioid overdose is a rapidly growing global problem and is an area of strangely 'undone science'.
- Family and opioid users themselves are now trained in overdose management and are provided with take-home naloxone to implement interim emergency resuscitation while awaiting emergency medical care.
- Through experimental investigation of heroin overdose in the clinical laboratory, we can now test the ability of wearable sensors to detect overdose and send alerts.
- Prolonged apnoeic episodes appear distinctive markers of opioid-induced respiratory depression and are a detectable measure to trigger emergency response.
- Current work on the detection of imminent or actual drug use may be capable of being used in future as a trigger for cognitive or behavioural interventions.
- New formulations of naloxone are now being developed which are more tailored for use by a non-medical intervention workforce.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

JS: Conceptualization, Methodology, Writing – Original draft; EAK: Conceptualization, Methodology, Writing – Original draft; EC: Conceptualization, Methodology, Writing – Original draft; MGU: Conceptualization, Methodology, Writing – Original draft; AH: Conceptualization, Methodology, Writing – Original draft;

WL: Conceptualization, Methodology, Writing – Original draft; BT: Conceptualization, Methodology, Writing – Original draft. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Informed consent was obtained by all participants in each individual studies described in this paper. The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interest

JS is a clinician and academic who has worked with local, national and international government and non-government agencies to develop and test new approaches to tackling addiction and related problems, including studies of maintenance and of withdrawal. Through his employer (King's College London), he and his colleagues have received research and project grant support from a range of government and research funders and charitable organisations and have also worked with pharma and tech companies, as described at https://www.kcl.ac.uk/people/john-strang (including, relevant to the work reported in this paper, Martindale and dne and Pneumowave, and the pharmaceutical manufacturer Catalent) in order to develop or study potentially improved formulations and devices. Current funding support for work described in this paper include from Scottish Chief Scientist's Office, the government Office for Life Sciences, the SME company Pneumowave, the Maudsley Charity, as well as from the Maudsley NIHR Biomedical Research Centre. The university has previously registered intellectual property on an innovative buccal naloxone with which JS is involved, and he has previously been named in a patent registration by a Pharma company as inventor of concentrated naloxone nasal spray. JS and his colleagues' research is supported by the National Insti-

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Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0941.

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