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Naloxone auto-injector (Evzio) for opioid substance use disorder

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LAY SUMMARY

Opioids are a type of drug that are used to treat pain but they may also be misused as they are highly addictive and lead to temporary feelings of intense pleasure. Addiction to opioids can develop very quickly, even when taken in small amounts. Treatment for opioid addiction can involve addicts being given carefully prescribed alternative drugs to reduce withdrawal symptoms and cravings. People who take opioids are at risk of overdose, which can lead to death. Symptoms of opioid overdose include drowsiness, muscle spasms and slow, shallow breathing.

Evzio is being developed as an injectable device that contains naloxone, a drug used to reverse the effects of opioid drug overdose. It is designed to be easily administered by non-health professionals in a non-clinical setting. If licensed it has the potential to improve emergency responses to opioid overdoses as it can be used in the home environment, enabling caregivers to respond quickly and confidently due to the voice and visual guidance provided with the device.

TARGET GROUP

Opioid substance use disorder – emergency use by non-clinicians

TECHNOLOGY

DESCRIPTION

Naloxone is a benzylisoquinoline derivative which acts as narcotic antagonist. . Naloxone works by binding to mu-opioid receptors with a high affinity, and a lesser degree to kappa- and gamma-opioid receptors in the central nervous system in a competitive manner, thereby reversing or inhibiting characteristic opioid effects (including analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence).[1]

Naloxone is currently in phase III development in an auto-injector to be used by non-clinicians in the treatment of opioid substance use disorder.[2] It is administered by intramuscular or subcutaneous injection at a dose of 2 mg/0.4 mL in a pre-filled auto-injector and is intended to be used in an emergency setting followed by initiation of emergency medical assistance.[3,4]

Naloxone is currently licensed in the UK for the treatment of postoperative respiratory depression, opioid overdose in children (1 month – 17 years) and adults, and opioid overdose in adults in a non-medical setting. Common adverse events (occurring in >1/100 people) listed are cardiac arrest, dyspnoea, hyperventilation and pulmonary oedema in children, and dizziness, headache, hypertension, hypotension and vomiting.[5]

INNOVATION and/or ADVANTAGES

Naloxone is yet to be used in an auto-injector system and Evzio provides the first and only auto-injector system to be used in the home environment. It utilises voice and visual guidance to enable caregivers to respond rapidly and take confident action in administering naloxone in an opioid emergency.[3]

If licensed, the naloxone auto-injector, has the potential to improve emergency responses to opioid overdoses, through its unique drug delivery system.

DEVELOPER

Kaleo Pharmaceuticals

AVAILABILITY, LAUNCH or MARKETING

Naloxone auto-injector is currently marketed in the USA, however, the company could not be contacted and did not provide any marketing/licensing plans for EU.

PATIENT GROUP

BACKGROUND

An opioid is either a natural derivative of opium or a synthetic substance with agonist, partial agonist, or mixed agonist and antagonist activity at opioid receptors.[6] There are a large number of opiate/opioid medicines, including codeine, morphine, dihydrocodeine, methadone, buprenorphine, and diamorphine (also known as heroin).[7] Opioids are used medically for pain relief have analgesic and central nervous system depressant effects, but also have the potential to cause euphoria.[8] All opioids have dependence potential to varying degrees; diamorphine is considered to have the greatest potential for dependency, especially when injected.[9]

Opioid dependence develops after a period of regular use of opioids, with the time required varying according to the quantity, frequency and route of administration, as well as factors of individual vulnerability and the context in which drug use occurs.[10] Characteristic features of opioid dependence include drug craving and maladaptive behaviour focused on obtaining opioids at any cost, which can cause physical, psychological and social harm to the user and others around them.[11] Opioid dependence can occur as a result of misuse of prescribed opioid medications, use of diverted opioid medications, and use of illicitly obtained opioids (e.g. heroin).[8]

Patients with opioid dependence may have a range of health and social care problems, which may or may not be directly associated with drug misuse. Although drug misuse exists in most areas in the UK, it is more prevalent in areas characterised by social deprivation, which in turn is associated with poorer health. Drug misusers, especially injecting drug users, are vulnerable to contracting and spreading blood-borne viruses and other infections. In England, Wales and Northern Ireland an estimated 1% of people injecting drugs were infected by HIV, 0.5% were infected by active hepatitis B and 90% were infected by hepatitis C.[9] Additional complications of opioid misuse include venous and arterial thrombosis, dental disease, sepsis, infective endocarditis, poor nutrition and overdose, which ultimately can lead to death.[6,11]

Opioid overdose is a potentially lethal condition that not only results from illicit drug misuse but also poor prescribing practices, inadequate patient understanding on the risk of medication misuse, and errors in drug administration.[12] The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines drug-related death as a death 'directly due to use of illegal substances, although these often occur in combination with other substances, such as alcohol or psychoactive medicines'. These deaths occur generally shortly after the consumption of the substance and are therefore considered 'directly caused by drugs.[13]

Opioids depress the respiratory drive and overdose is characterised by apnoea, myosis and stupor. A severely reduced respiration rate results in hypoxaemia, leading to cerebral hypoxia and impaired consciousness. Prolonged cerebral hypoxia is the mechanism for brain injury and death in opioid overdose, resulting from apnoea or cardiac dysrhythmias and cardiac arrest. Patients who inject opioids and have HIV infection have an increased risk of overdose, but it is unclear if the mechanism is direct or relates to a combination of biological, risk-behavioural and structural factors.[14] Combining opioids with alcohol and sedative medication increases the risk of respiratory depression and death, and combinations of opioids, alcohol and sedatives are often present in fatal drug overdoses.[15] Most opioid overdoses occur in private homes, and most of these are witnessed by close friends, a partner or family members.[14]

CLINICAL NEED and BURDEN OF DISEASE

In 2015-16, there were 149,807 adults using Drug and Alcohol Treatment Services for opiate misuse in England. The average age of this population were 39 years old.[16] In 2015 54% of all deaths related to drug poisoning involved an opioid drug (excluding opioids which are contained in paracetamol compounds such as co-codamol).[17] Approximately 63% of patients receive substitution therapy with either methadone (83%) or buprenorphine (17%).[18] Treatment was successful for 30% of those having treatment for opiate use.[15]

In 2014-15, there were 14,279 hospital admissions in England with a primary diagnosis of poisoning by illicit drugs. In 2014, there were a total of 2,248 deaths in England and Wales related to drug misuse.[19] In 2016-17, there were 239 hospital admissions for acute intoxication of opioids (ICD 10: F11.0) of which, 212 were emergency cases, resulting in 262 finished consultant episodes and 1204 bed days.[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Methadone and buprenorphine for the management of opioid dependence (TA114). January 2007.
- NICE technology appraisal. Naltrexone for the management of opioid dependence (TA115). January 2007.
- NICE clinical guidelines. Self-harm: longer-term management (CG133). November 2011.
- NICE clinical guidelines. Common mental health problems: identification and pathways to care (CG123). May 2011.
- NICE clinical guidelines. Psychosis with coexisting substance misuse: Assessment and management in adults and young people (CG120). March 2011.
- NICE clinical guidelines. Drug misuse – psychosocial interventions (CG51). July 2007.
- NICE clinical guidelines. Drug misuse – opioid detoxification (CG52). July 2007.
- NICE guidelines. Drug misuse prevention: targeted interventions (NG64). February 2017.
- NICE guidelines. Coexisting severe mental illness and substance misuse: community health and social care services (NG58). November 2016.
- NICE quality standard in development. Drug misuse prevention. Expected April 2018.
- NICE quality standard. Drug use disorders (QS23). November 2012.
- NICE public health guidance. Interventions to reduce substance misuse among vulnerable young people (PH4). March 2007.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for High Secure Mental Health Services (Adults). C02/S/a.
- NHS England. 2013/14 NHS Standard Contract for Medium and Low Secure Mental Health Services (Adults). C03/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Pain. D08/S/a.

OTHER GUIDANCE

- Royal College of Anaesthetists. Core standards for pain management services in the UK. 2015.
- World Health Organization. Community management of opioid overdose. 2014.
- The British Pain Society. Guidelines for pain management programmes for adults. 2013.
- British Medical Association. Drugs of dependence: the role of medical professionals. 2013.
- Centre for Addiction and Mental Health. Clinical practice guideline: buprenorphine/naloxone for opioid dependence. 2011.
- Royal College of General Practitioners. Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care. 2011.
- The British Pain Society. Opioids for persistent pain: good practice. 2010.

CURRENT TREATMENT OPTIONS

Treatments for opioid use disorder can be acute (treatment for opioid overdose) or substitution therapy (to aid withdrawal from opioid use). Individuals who overdose on opioids typically receive treatment when ambulance or emergency medical care arrives, at which point the opioid antagonist naloxone is most commonly given. It rapidly reverses opioid overdose and has been used in clinical and hospital overdose management since the 1970s.[13] Access to naloxone is generally limited to health professionals and is normally given by the intravenous, intramuscular or subcutaneous routes.[13,15]

Methadone and buprenorphine are used as substitution therapies in opioid dependence[21] and are both approved by NICE for the treatment and prevention of withdrawals from opioids and for maintenance programmes.[9,18] The aims of maintenance therapy are to reduce or prevent withdrawal symptoms, provide an opportunity to stabilise drug intake and lifestyle while breaking with illicit drug use and associated risky behaviours.[9] Substituting illicitly obtained opioids with legally obtained prescribed opioid agonist helps to protect against the risk of overdose and blood-borne infections.[9,22] There is a risk of overdose during induction on methadone, highest during the first two weeks. This risk is increased if there is a low opioid tolerance, the patient is on other central nervous system depressants (including alcohol and benzodiazepines), the initial dose is too high, the increase in dose are too rapid, or if there is slow methadone clearance. The risk of overdose in the induction phase is less with buprenorphine because at low doses it works as a potent opioid agonist but at increasing doses, it has mixed agonist-antagonist properties.[23]

Naloxone is also available as a sublingual formulation with buprenorphine which is used as a substitution therapy in opioid dependence. Naloxone is included in the formulation in order to alleviate concerns that the sublingual tablet of buprenorphine would be dissolved and injected by opioid misusers. Naloxone is poorly absorbed sublingually and orally but is well-absorbed intravenously. As a result, an opioid-dependent patient injecting buprenorphine/naloxone will suffer a withdrawal syndrome secondary to naloxone's occupation of opioid receptors.[22]

EFFICACY and SAFETY

Trial	NCT02669901; naloxone auto-injector; phase III
Sponsor	Kaleo Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[2]
Location	USA
Design	Open-label, uncontrolled, single group assignment trial.
Participants	n=400 (planned); aged ≥18 years; opioid substance use disorder
Schedule	Not reported
Follow-up	Not reported
Primary Outcomes	Number of fatal over dose deaths by use of naloxone auto-injector co-prescribing from the University of New Mexico Addiction and Substance Abuse Program (UNM ASAP) over two years Number of near fatal overdoses prevented by use of naloxone auto-injector co-prescribing from the UNM ASAP over two years
Secondary Outcomes	Not reported
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as Apr 2018.

ESTIMATED COST and IMPACT

COST

Naloxone is already marketed in the UK for suspected acute opioid overdose and for reversal of opioid-induced respiratory and other central nervous system depression. For solution for injection in ampoules, the price of naloxone for 20 microgram/ ml (10 x 2 ml) costs £55.00 and for 400 microgram/ ml (10 x 1 ml) costs £41.00.[24]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: *easy to use with guided voice and visual instructions for the non-clinician*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: the cost for the auto-injector

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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