Naloxone

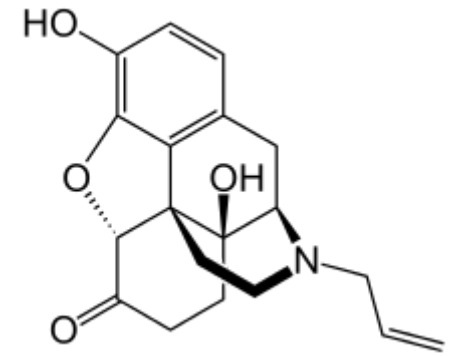
Naloxone, sold under the brand name **Narcan** among others, is a medication used to block the effects of opioids.[1] It is commonly used for decreased breathing in opioid overdose.[1] Naloxone may also be combined with an opioid (in the same pill) to decrease the risk of opioid misuse.[1] When given intravenously, naloxone works within two minutes, and when injected into a muscle, it works within five minutes;[1] it may also be sprayed into the nose.[3] The effects of naloxone last about half an hour to an hour.[4] Multiple doses may be required, as the duration of action of most opioids is greater than that of naloxone.[1]

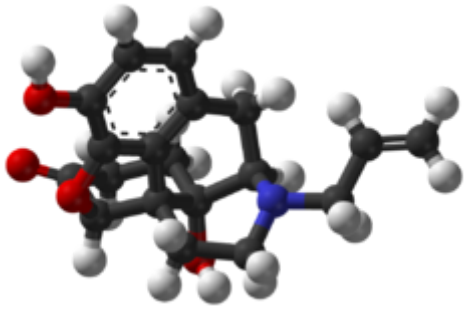
Administration to opioid-dependent individuals may cause symptoms of opioid withdrawal, including restlessness, agitation, nausea, vomiting, a fast heart rate, and sweating.[1] To prevent this, small doses every few minutes can be given until the desired effect is reached.[1] In those with previous heart disease or taking medications that negatively affect the heart, further heart problems have occurred.[1] It appears to be safe in pregnancy, after having been given to a limited number of women.[5] Naloxone is a non-selective and competitive opioid receptor antagonist.[6][7] It works by reversing the depression of the central nervous system and respiratory system caused by opioids.[1]

Naloxone was patented in 1961 and approved for opioid overdose in the United States in 1971.[8][9] It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.[10] Naloxone is available as a generic medication.[1] Its wholesale price in developing countries is between $0.50 and $5.30 per dose.[11] Vials of naloxone are not very expensive (less than $25) in the United States.[12] As of 2020, the price for a package of two auto-injectors in the US is $178.[13][14][15] The 2018 price for the NHS in the United Kingdom is about £5 per dose.[16] In Australia, a single dose without prescription costs AU$20 while with a prescription five doses is AU$40.[17]

Contents

Naloxone





Clinical data	
Trade names	Narcan, Evzio, others
Other names	EN-1530; *N*-Allylnoroxymorphone; 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/naloxone-hydrochloride.html)
License data	EU EMA: by INN (http://www.ema.europa.eu/ema/index.jsp?curl=%2Fpages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Au

Medical uses

Opioid overdose

Naloxone is useful in treating both acute opioid overdose and respiratory or mental depression due to opioids.[1] Whether it is useful in those in cardiac arrest due to an opioid overdose is unclear.[18]

It is included as a part of emergency overdose response kits distributed to heroin and other opioid drug users and emergency responders. This has been shown to reduce rates of deaths due to overdose.[19] A prescription for naloxone is recommended if a person is on a high dose of opioid (>100 mg of morphine equivalence/day), is prescribed any dose of opioid accompanied by a benzodiazepine, or is suspected or known to use opioids nonmedically.[20] Prescribing naloxone should be accompanied by standard education that includes preventing, identifying, and responding to an overdose; rescue breathing; and calling emergency services.[21]

If minimal or no response is observed within 2–3 minutes, dosing may be repeated every 2 minutes until the maximum dose of 10 mg has been reached. If no response occurs at this time, alternative diagnosis and treatment should be pursued.

	thorised&status=Withdrawn&status=Suspended&status=Refused&keywordSearch=Submit&searchType=inn&taxonomyPath=&treeNumber=&searchGenericType=generics&keyword=Naloxone)
Pregnancy category	AU: B1 US: C (Risk not ruled out) [1]
Routes of administration	Endotracheal, intranasal, IV, IM, IO
ATC code	A06AH04 (WHO (https://www.whocc.no/atc_ddd_index/?code=A06AH04)) V03AB15 (WHO (https://www.whocc.no/atc_ddd_index/?code=V03AB15))
Legal status	
Legal status	AU: S3 (Pharmacist only) [2] DE: § 48 AMG/§ 1 MPAV (Prescription only) UK: POM (Prescription only) US: ℞-only
Pharmacokinetic data	
Bioavailability	2% (by mouth, 90% absorption but high first-pass metabolism) 50% (intranasally)
Metabolism	Liver
Onset of action	2 min (IV), 5 min (IM)[1]
Elimination half-life	1–1.5 h

Depending on the severity of overdose, a high dose exceeding 10 mg may be needed.[22] The effects of naloxone may wear off before those of the opioids, and they may require repeat dosing at a later time. Patients experiencing effects should be monitored for respiratory rate, heart rate, blood pressure, temperature, ABGs and level of consciousness. Those with a greater risk for respiratory depression should be identified prior to administration and watched closely.[23]

Clonidine overdose

Naloxone can also be used as an antidote in overdose of clonidine, a medication that lowers blood pressure.[24] Clonidine overdoses are of special relevance for children, in whom even small doses can cause significant harm.[25] However, there is controversy regarding naloxone's efficacy in treating the symptoms of clonidine overdose, namely slow heart rate, low blood pressure, and confusion/somnolence.[25] Case reports that used doses of 0.1 mg/kg (maximum of 2 mg/dose) repeated every 1–2 minutes (10 mg total dose) have shown inconsistent benefit.[25] As the doses used throughout the literature vary, it is difficult to form a conclusion regarding the benefit of naloxone in this setting.[26] The mechanism for naloxone's proposed benefit in clonidine overdose is unclear, but it has been suggested that endogenous opioid receptors mediate the sympathetic nervous system in the brain and elsewhere in the body.[26] Some poison control centers recommend naloxone in the setting of clonidine overdose, including intravenous bolus doses of up to 10 mg naloxone.[27][28]

Preventing opioid abuse

Naloxone is poorly absorbed when taken by mouth, so it is commonly combined with a number of oral opioid preparations, including buprenorphine and pentazocine, so that when taken by mouth, only the opioid has an effect.[1][29] However, if the opioid and naloxone combination is injected, the naloxone blocks the effect of the opioid.[1][29] This combination is used in an effort to prevent abuse.[29]

Other uses

In people with shock, including septic, cardiogenic, hemorrhagic, or spinal shock, those who received naloxone had improved blood flow. The importance of this is unclear.[30]

Naloxone is also experimentally used in the treatment for congenital insensitivity to pain with anhidrosis,[31] an extremely rare disorder that renders one unable to feel pain or differentiate

Duration of action	30–60 min[1]
Excretion	Urine, bile
Identifiers	
IUPAC name	(4*R*,4a*S*,7a*R*,12b*S*)-4a,9-dihydroxy-3-(prop-2-en-1-yl)-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one
CAS Number	465-65-6 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=465-65-6) ✓
PubChem CID	5284596 (https://pubchem.ncbi.nlm.nih.gov/compound/5284596)
IUPHAR/BPS	1638 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=1638)
DrugBank	DB01183 (https://www.drugbank.ca/drugs/DB01183) ✓
ChemSpider	4447644 (http://www.chemspider.com/Chemical-Structure.4447644.html) ✓
UNII	36B82AMQ7N (https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=36B82AMQ7N)
KEGG	D08249 (http://www.kegg.jp/entry/D08249) ✓
ChEBI	CHEBI:7459 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:7459) ✗
ChEMBL	ChEMBL80 (https://www.ebi.ac.uk/chembldb/index.php/compou

temperatures.[32]

Naloxone can also be used to treat itchiness brought on by opioid use,[33] as well as opioid-induced constipation.[34]

Special populations

Pregnancy and breastfeeding

Naloxone is pregnancy category B or C in the United States.[1] Studies in rodents given a daily maximum dose of 10 mg naloxone showed no harmful effects to the fetus, although human studies are lacking and the drug does cross the placenta, which may lead to the precipitation of withdrawal in the fetus. In this setting, further research is needed before safety can be assured, so naloxone should be used during pregnancy only if it is a medical necessity.[35]

Whether naloxone is excreted in breast milk is unknown, however, it is not orally bioavailable and therefore is unlikely to affect a breastfeeding infant.[36]

Children

Naloxone can be used on infants who were exposed to intrauterine opiates administered to mothers during delivery. However, there is insufficient evidence for the use of naloxone to lower cardiorespiratory and neurological depression in these infants.[37] Infants exposed to high concentrations of opiates during pregnancy may have CNS damage in the setting of perinatal asphyxia. Naloxone has been studied to improve outcomes in this population, however the evidence is currently weak.[38][39]

Intravenous, intramuscular, or subcutaneous administration of naloxone can be given to children and neonates to reverse opiate effects. The American Academy of Pediatrics recommends only intravenous administration as the other two forms can cause unpredictable absorption. After a dose is given, the child should be monitored for at least 24 hours. For children with low blood pressure due to septic shock, naloxone safety and effectiveness is not established.[40]

Geriatric use

For patients 65 years and older, unclear if there is a difference in response. However, older people often have decreased liver and kidney function that may lead to an increased level of naloxone in their body.[41]

Side effects

	nd/inspect/ChEMBL80) ✓
CompTox Dashboard (EPA)	DTXSID8023349 (https://comptox.epa.gov/dashboard/DTXSID8023349)
ECHA InfoCard	100.006.697 (https://echa.europa.eu/substance-information/-/substanceinfo/100.006.697)
Chemical and physical data	
Formula	$C_{19}H_{21}NO_4$
Molar mass	327.380 g·mol^{-1}
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=O%3DC1%5BC%40%40H%5D2OC3%3DC%28O%29C%3DCC4%3DC3%5BC%40%40%5D2%28%5BC%40%5D5%28CC1%29O%29CCN%28CC%3DC%29%5BC%40%40H%5D5C4)
SMILES	O=C1[C@@H]2OC3=C(O)C=CC4=C3[C@@]2([C@]5(CC1)O)CCN(CC=C)[C@@H]5C4
InChI	InChI=1S/C19H21NO4/c1-2-8-20-9-7-18-15-11-3-4-12(21)16(15)24-17(18)13(22)5-6-19(18,23)14(20)10-11/h2-4,14,17,21,23H,1,5-10H2/t14-,17+,18+,19-/m1/s1 ✓ Key:UZHSEJADLWPNLE-GRGSLBFTSA-N ✓
✗✓ (what is this?) (verify)	

Naloxone has little to no effect if opioids are not present. In people with opioids in their system, it may cause increased sweating, nausea, restlessness, trembling, vomiting, flushing, and headache, and has in rare cases been associated with heart rhythm changes, seizures, and pulmonary edema.[42][43]

A naloxone kit as distributed in British Columbia, Canada

Besides the side effects listed above, naloxone also has other adverse events, such as other cardiovascular effects (hypertension, hypotension, tachycardia, ventricular fibrillation, ventricular tachycardia) and central nervous system effects, such as agitation, body pain, brain disease, and coma. In addition to these adverse effects, naloxone is also contraindicated in people with hypersensitivity to naloxone or any of its formulation components.[44]

Naloxone has been shown to block the action of pain-lowering endorphins the body produces naturally. These endorphins likely operate on the same opioid receptors that naloxone blocks. It is capable of blocking a placebo pain-lowering response, if the placebo is administered together with a hidden or blind injection of naloxone.[45] Other studies have found that placebo alone can activate the body's μ-opioid endorphin system, delivering pain relief by the same receptor mechanism as morphine.[46][47]

Naloxone should be used with caution in people with cardiovascular disease as well as those that are currently taking medications that could have adverse effects on the cardiovascular system such as causing low blood pressure, fluid accumulation in the lungs (pulmonary edema), and abnormal heart rhythms. There have been reports of abrupt reversals with opioid antagonists leading to pulmonary edema and ventricular fibrillation.[48]

Hypersensitivities

Naloxone preparations may contain methylparaben and propylparaben and is inappropriate for use by people with a paraben hypersensitivity. If a person is sensitive to nalmefene or naltrexone, naloxone should be used with caution as these three medications are structurally similar. Cross-sensitivity among these drugs is unknown.[49] Preservative-free preparations are available for those with paraben hypersensitivities.

Pharmacology

Pharmacodynamics

Naloxone at opioid receptors

Compound	Affinities (K_i)			Ratio	Ref
	MOR	DOR	KOR	MOR:DOR:KOR	
Naloxone	1.1 nM	16 nM	12 nM	1:15:11	[50]
(−)-Naloxone	0.559 nM 0.93 nM	36.5 nM 17 nM	4.91 nM 2.3 nM	1:65:9 1:18:2	[51] [52]
(+)-Naloxone	3,550 nM 1,000 nM	122,000 nM 1,000 nM	8,950 nM 1,000 nM	1:34:3 ND	[51] [52]

Naloxone is a lipophilic compound that acts as a non-selective and competitive opioid receptor antagonist.[6][7] The pharmacologically active isomer of naloxone is (−)-naloxone.[51][53] Naloxone's binding affinity is highest for the μ-opioid receptor, then the δ-opioid receptor, and lowest for the κ-opioid receptor;[6] naloxone has negligible affinity for the nociceptin receptor.[54]

If naloxone is administered in the absence of concomitant opioid use, no functional pharmacological activity occurs, except the inability for the body to combat pain naturally. In contrast to direct opiate agonists, which elicit opiate withdrawal symptoms when discontinued in opiate-tolerant people, no evidence indicates the development of tolerance or dependence on naloxone. The mechanism of action is not completely understood, but studies suggest it functions to produce withdrawal symptoms by competing for opiate receptor sites within the CNS (a competitive antagonist, not a direct agonist), thereby preventing the action of both endogenous and xenobiotic opiates on these receptors without directly producing any effects itself.[55]

Pharmacokinetics

When administered parenterally (nonorally or nonrectally, e.g. intravenously or by injection), as is most common, naloxone has a rapid distribution throughout the body. The mean serum half life has been shown to range from 30 to 81 minutes, shorter than the average half life of some opiates, necessitating repeat dosing if opioid receptors must be stopped from triggering for an extended period. Naloxone is primarily metabolized by the liver. Its major metabolite is naloxone-3-glucuronide, which is excreted in the urine.[55] For people with liver diseases such as alcoholic liver disease or hepatitis, naloxone usage has not been shown to increase serum liver enzyme levels.[56]

Naloxone has low systemic bioavailability when taken by mouth due to hepatic first pass metabolism, but it does block opioid receptors that are located in the intestine.[34]

Chemistry

Naloxone, also known as N-allylnoroxymorphone or as 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one, is a synthetic morphinan derivative and was derived from oxymorphone (14-hydroxydihydromorphinone), an opioid analgesic.[57][58][59] Oxymorphone, in turn, was derived from morphine, an opioid analgesic and naturally occurring constituent of the opium poppy.[60] Naloxone is a racemic mixture of two enantiomers, (–)-naloxone (levonaloxone) and (+)-naloxone (dextronaloxone), only the former of which is active at opioid receptors.[61][62] The drug is a highly lipophilic, allowing it to rapidly penetrate the brain and to achieve a far greater brain to serum ratio than that of morphine.[57] Opioid antagonists related to naloxone include cyprodime, nalmefene, nalodeine, naloxol, and naltrexone.[63]

The chemical half-life of naloxone is such that injection and nasal forms have been marketed with 24-month and 18-month shelf-lives, respectively.[64] A 2018 study noted that the nasal and injection forms presented as chemically stable to 36- and 28-months, respectively, which prompted an as yet incomplete five year stability study to be initiated.[64] This suggests that expired caches of material in community and healthcare settings may still be efficacious substantially beyond their labeled expiration dates.[64]

History

Naloxone was patented in 1961 by Mozes J. Lewenstein, Jack Fishman, and the company Sankyo.[8] It was approved for opioid abuse treatment in 1971 by the FDA with opioid abuse kits being distributed by many states to medically untrained people beginning in 1996. From the period of 1996 to 2014, the CDC estimates over 26,000 cases of opioid overdose have been reversed using the kits.[65]

Society and culture

Names

Naloxone is the generic name of the medication and its INN, BAN, DCF, DCIT, and JAN, while *naloxone hydrochloride* is its USAN and BANM.[66][67][68][69]

The patent has expired and it is available as a generic medication. Brand names of naloxone include Narcan, Nalone, Evzio, Prenoxad Injection, Narcanti, Narcotan, among others.

Identification

The CAS number of naloxone is 465-65-6; the anhydrous hydrochloride salt has CAS 357-08-4 and the hydrochloride salt with 2 molecules of water, hydrochloride dihydrate, has CAS 51481-60-8

Routes of administration

Intravenous

Naloxone is commonly injected intravenously, with an onset of 1–2 minutes and a duration of up to 45 minutes.[70] While the onset is achieved fastest through IV than through other routes of administration, it may be difficult to obtain venous access in patients who use IV drugs chronically. This may be an issue under emergency conditions.[71]

Intramuscular or subcutaneous

Naloxone can also be administered via intramuscular or subcutaneous injection. The onset of naloxone provided through this route is 2 to 5 minutes with a duration of around 30-120min.[72] Naloxone administered intramuscularly are provided through pre-filled syringes, vials, and auto-injector. Evzio is the only auto-injector on the market and can be used both intramuscularly and subcutaneously. It is pocket-sized and can be used in non-medical settings such as in the home.[18] It is designed for use by laypersons, including family members and caregivers of opioid users at-risk for an opioid emergency, such as an overdose.[73] According to the FDA's National Drug Code Directory, a generic version of the auto-injector began to be marketed at the end of 2019.[14]

Intranasal

Administration of naloxone intranasally is recommended for people who are unconscious or unresponsive.[72] While the onset of action is slightly delayed in this method of administration, the ease of use and portability are what make naloxone nasal sprays useful.[70][72] Narcan Nasal Spray was approved in 2015 and was the first FDA-approved nasal spray for emergency treatment or suspected overdose.[74] Narcan Nasal Spray is prepackaged, requires no assembly, and delivered a consistent dose.[75] It was developed in a partnership between LightLake Therapeutics and the National Institute on Drug Abuse.[76] The approval process was fast-tracked.[77] A generic version of the nasal spray was approved in the United States in 2019.[78]

However, a wedge device (nasal atomizer) can also be attached to a syringe that may also be used to create a mist to deliver the drug to the nasal mucosa.[79] This is useful near facilities where many overdoses occur that already stock injectors.[80]

Storage

Naloxone should be stored at room temperature and protected from light. For the auto-injector, naloxone should be stored in the outer case provided.[81] If the product is cloudy, discolored, or contains particulate matter, use is not recommended.[49]

Legal status

In the United States, naloxone is available without a prescription in every state with the exception of Hawaii.[82][83] However, not all pharmacies stock or dispense naloxone.[84][85] Depending on the pharmacy, a pharmacist may have to write a prescription or not be able to give naloxone to comply with accounting rules regarding prescription medications, as naloxone is still considered a prescription only medication under FDA rules.

While paramedics have carried naloxone for decades, law enforcement officers in many states throughout the country carry naloxone to reverse the effects of heroin overdoses when reaching the location prior to paramedics. As of July 12, 2015, law enforcement departments in 28 states are allowed to or required to carry naloxone to quickly respond to opioid overdoses.[86]

In Australia, as of February 1, 2016, naloxone is now available "over the counter" in pharmacies without a prescription.[87] It comes in single-use filled syringe similar to law enforcement kits.

In Canada, naloxone single-use syringe kits are distributed and available at various clinics and emergency rooms. Alberta Health Services is increasing the distribution points for naloxone kits at all emergency rooms, and various pharmacies and clinics province-wide. Also in Alberta, take-home naloxone kits are available and commonly distributed in most drug treatment or rehabilitation centres, as well as in pharmacies where pharmacists can distribute single-use take-home naloxone kits or prescribe the drug to addicts. All Edmonton Police Service and Calgary Police Service patrol cars carry an emergency single-use naloxone syringe kit. Some Royal Canadian Mounted Police patrol vehicles also carry the drug, occasionally in excess to help distribute naloxone among users and concerned family/friends. Nurses, paramedics, medical technicians, and emergency medical responders can also prescribe and distribute the drug.

Following Alberta Health Services, Health Canada reviewed the prescription-only status of naloxone, resulting in plans to remove it in 2016, allowing naloxone to be more accessible.[88][89] Due to the rising number of drug deaths across the country, Health Canada proposed a change to make naloxone more widely available to Canadians in support of efforts to address the growing number of opioid overdoses.[90] In March 2016, Health Canada did change the prescription status of naloxone, as "pharmacies are now able to proactively give out naloxone to those who might experience or witness an opioid overdose."[91]

Prehospital access

Laws in many jurisdictions have been changed in recent years to allow wider distribution of naloxone.[92][93] Several states have also moved to permit pharmacies to dispense the medication without the person first seeing a physician or other non-pharmacist professional.[94] Over 200 naloxone distribution programs utilize licensed prescribers to distribute the drug, often through the use of standing medication orders [95][96] whereby the medication is distributed under the medical authority of a physician or other prescriber (such as a pharmacist under California's AB1535). Additionally, 36 states have passed laws that provide naloxone prescribers with immunity against both civil and criminal liabilities.[97] Third-party prescriptions are also available for people, such as family and friends of people at risk for an overdose, who

may find themselves in a situation that requires them to administer naloxone. Local schools, government agencies, and nonprofit organizations hold training programs to educate laypeople on proper use of naloxone. It is estimated that programs like these have helped to reverse more than 26,000 overdoses.[97]

Following the use of the nasal spray device by police officers on Staten Island in New York, an additional 20,000 police officers will begin carrying naloxone in mid-2014. The state's Office of the Attorney General will provide US$1.2 million to supply nearly 20,000 kits. Police Commissioner William Bratton said: "Naloxone gives individuals a second chance to get help".[98] Emergency Medical Service Providers (EMS) routinely administer naloxone, except where basic Emergency Medical Technicians are prohibited by policy or by state law.[99] In efforts to encourage citizens to seek help for possible opioid overdoses, many states have adopted Good Samaritan laws that provide immunity against certain criminal liabilities for anybody who, in good faith, seeks emergency medical care for either themselves or someone around them who may be experiencing an opioid overdose.[100]

A survey of US naloxone prescription programs in 2010 revealed that 21 out of 48 programs reported challenges in obtaining naloxone in the months leading up to the survey, due mainly to either cost increases that outstripped allocated funding or the suppliers' inability to fill orders.[101] The approximate cost of a 1 ml ampoule of naloxone in the US is estimated to be significantly higher than in most Western countries.[95]

Projects of this type are under way in many North American cities.[101][102] CDC estimates that the US programs for drug users and their caregivers prescribing take-home doses of naloxone and training on its use have prevented 10,000 opioid overdose deaths.[101] States including Vermont and Virginia have developed programs that mandate the prescription of naloxone when a prescription has exceeded a certain level of morphine milliequivalents per day as preventative measures against overdose.[103] Healthcare institution-based naloxone prescription programs have also helped reduce rates of opioid overdose in North Carolina, and have been replicated in the US military.[95][104] Programs training police and fire personnel in opioid overdose response using naloxone have also shown promise in the US, and effort is increasing to integrate opioid fatality prevention in the overall response to the overdose crisis.[105][106][107][108]

Pilot projects were also started in Scotland in 2006. Also in the UK, in December 2008, the Welsh Assembly government announced its intention to establish demonstration sites for take-home naloxone.[109]

As of February 2016, Pharmacies across Alberta and some other Canadian jurisdictions are allowed to distribute take-home naloxone kits. Additionally, the Minister of Health issued an order to change basic life support provider's medical scope, within EMS, to administer naloxone in the event of a suspected narcotic overdose. These are part of the government's plan to tackle a growing fentanyl drug crisis.[110]

In 2018, a maker of naloxone announced it would provide a free kit including two doses of the nasal spray, as well as educational materials, to each of the 16,568 public libraries and 2,700 YMCAs in the U.S.[111]

Media

The 2013 documentary film *Reach for Me: Fighting to End the American Drug Overdose Epidemic* interviews people involved in naloxone programs aiming to make naloxone available to opioid users and people with chronic pain.[112]

See also

- Oxycodone/naloxone
- Buprenorphine/naloxone

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External links

- Chicago Recovery Alliance's naloxone distribution project (http://www.anypositivechange.org/NALOXONE/)
- Report on Naloxone and other opiate antidotes (http://www.inchem.org/documents/antidote/antidote/ant01.htm), by the International Programme on Chemical Safety
- What Is Naloxone? via Substance Abuse and Mental Health Services Administration| SAMHSA (https://www.samhsa.gov/medication-assisted-treatment/treatment/naloxone)
- Naloxone Overdose Prevention Laws | PDAPS.org (http://www.pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139)