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NALOXONE TRAINING FOR PROVIDERS

TRAINING MATERIALS

- Demonstration naloxone kit

Intranasal Kit Contents	Intramuscular Kit Contents
Zip type bag 6 x 10"	Fit Pack Black 10 x 1 ml sharps container
Overdose prevention and survival brochure	S.C.A.R.E.M.E. rescue label
2 x Intranasal Mucosal Atomization Device	2 x 3 mL Luer Lock Tip with 22G x 1 ½ " syringe

TRAINING OUTLINE

- A. Risk factors and prevention
- B. Opioid overdose
 - I. Causes
 - II. Signs and symptoms
- C. Naloxone
- D. Opioid overdose response
- E. California civil code § 1714.22

RISK FACTORS & PREVENTION^[1, 2]

RISK FACTORS	
Mixing Drugs <ul style="list-style-type: none"> • Alcohol (Alcohol is involved in many overdose deaths) • Antidepressants <ul style="list-style-type: none"> ○ Serotonin Selective Reuptake Inhibitors (SSRIs) ○ Tricyclic Antidepressants (TCAs) • Sedative/hypnotics <ul style="list-style-type: none"> ○ Barbituates – Phenobarbital ○ Benzodiazepines- Xanax, Valium, Klonopin, Ativan ○ Non-benzodiazepine hypnotics- Ambien, Sonata, Lunesta • Stimulants- cocaine, amphetamines <ul style="list-style-type: none"> ○ About one-half of prescription painkiller deaths involve at least one other drug, including benzodiazepines, cocaine, and heroin 	Strength/Dose <ul style="list-style-type: none"> • High dose opioid prescription (≥ 100 mg/day morphine equivalence) • Methadone prescription (accounts for 1 in 3 opioid related overdose deaths) • Buprenorphine prescription • Opioid medication being changed to different type or dose • Acetaminophen-containing opioids <ul style="list-style-type: none"> ○ Potential for liver damage taking more than maximum daily allowance
Tolerance <ul style="list-style-type: none"> • Taking pain medication following a period of abstinence <ul style="list-style-type: none"> ○ Recent release from incarceration/prison/jail ○ Hospitalization ○ Recent discharge from opioid detoxification or abstinence-based program 	Physical Health <ul style="list-style-type: none"> • Respiratory illness: smoking, COPD, emphysema, asthma, sleep apnea, or respiratory infections • Immunocompromised: HIV/AIDS • Renal or hepatic disease
Ingesting Opioids Without Others Present <ul style="list-style-type: none"> • Cannot be found if overdose occurs 	Substance Use History <ul style="list-style-type: none"> • Suspected or confirmed history of substance use disorder • Recent medical care for opioid poisoning/intoxication/overdose <ul style="list-style-type: none"> ○ Previous overdose is the primary risk factor for another overdose

Other risk factors:

- Difficulty accessing emergency medical services (distance, remoteness)
- Male gender
- Age 45-54 years old
- Caucasians and American Indian or Alaska Natives
- Low-income individuals
- Comorbid mental illness (e.g. depression)

PREVENTION	
Don't mix pain medications with other drugs or alcohol	Make sure there is a friend/family member around if taking opioids for the first time, trying a new opioid, haven't used an opioid in awhile
Only take medications prescribed to you and never share or sell your medications	Teach family and friends how to respond to an overdose
Know how much active ingredient is in the medication	Eat, stay hydrated with plenty of water, sleep, see your doctor, carry inhaler if you have asthma, treat infections
Know the difference between "immediate release" and extended release" formulations	Store prescription painkillers in a secure place and dispose of them properly <ul style="list-style-type: none"> ○ More than three out of four people who misuse prescription painkillers use drugs prescribed to someone else
Don't take more than instructed by your prescriber	Only see one doctor for prescription painkillers
Never take larger or more frequent doses of your prescription painkillers to try to get faster or more powerful effects	

Other important prevention tips:

Remind patients to store their medications in a secure place at all times and properly dispose of any unused/expired/unneeded medications

- Take advantage of community drug take-back programs that allow patients to bring unused medications to a central location for proper disposal (many local pharmacies participate in these initiatives)
- Over 70% of individuals aged 12 and older who used pain relievers non-medically in 2009-2010 got them from friends or family
 - 55% got them from a friend or relative for free; 11.4% bought them from a relative or friend; 4.8% took them from a friend or relative without asking

OPIOID OVERDOSE^[3, 4]

Common Opioids Associated with Overdose

Natural	Semi-Synthetic	Synthetic
Morphine Codeine	Hydromorphone Hydrocodone Oxycodone Buprenorphine Heroin	Fentanyl Meperidine Tramadol Propoxyphene (removed from U.S. market) Methadone

BACKGROUND

- Therapeutic and toxic effects are mediated by opioid receptors
- Chronic opioid users develop tolerance to analgesia and euphoric effects, but less so to the respiratory depression effects

Receptor	Functions
μ1	Supraspinal and peripheral analgesia; sedation and euphoria
μ2	Spinal analgesia; respiratory depression ; physical dependence; gastrointestinal dysmotility; bradycardia and pruritis
κ1	Spinal analgesia and miosis
κ2	Dysphoria and psychotomimesis
κ3	Supraspinal analgesia
δ	Supraspinal and spinal analgesia

CAUSES – PATHOPHYSIOLOGY

- **Overview**
 - When large opioid doses saturate hepatic elimination mechanisms, it transitions from first-order to zero-order elimination kinetics
 - In zero order kinetics, the following occurs:
 - Small increases in the drug dose can lead to disproportionate increases in plasma concentrations and hence intoxication
 - Constant amount (as opposed to a constant proportion) of drug is eliminated per unit of time

Summary of Opioid Overdose Pathophysiology

Clinical Findings	Mechanism of Action	Notes
Respiratory Depression* (≤ 12 breaths/min) <i>*Primary Finding Apnea, pulmonary edema, hypercarbia, hypoxia, and cyanosis</i>	<ul style="list-style-type: none"> • Depression of the ventilatory response to increased CO₂ • Depress ventilator response to hypoxia through effect upon carotid and aortic body chemosensors • Increase chest wall rigidity and diminishing upper airway patency 	<u>Factors that exacerbate opioid-induced respiratory depression:</u> Co-ingestion of respiratory depressants (alcohol, sedative-hypnotics, tranquilizers); comorbid conditions; chronic cardiopulmonary, renal, and liver disease; COPD and sleep apnea; age (elderly); sleep; pain relief
Miosis	<ul style="list-style-type: none"> • Due to μ receptor agonism 	Pupillary dilation can be seen in polysubstance ingestions, meperidine, tramadol, propoxyphene
Seizures	<ul style="list-style-type: none"> • Primarily mediated by non-opioid receptors, due to inhibition of inhibitory interneurons and direct stimulatory effects on G-protein 	Rare but may be result of hypoxia or due to ingestion of meperidine (<i>normeperidine</i> metabolite), tramadol, or propoxyphene
Hypotension / Bradycardia Skin Flushing Sweating Pruritis	<ul style="list-style-type: none"> • Peripheral dilation due to mast cell histamine release • Reflex vasoconstriction caused by increased PCO₂ • Peripheral dilation due to mast cell histamine release 	Skin of face, neck, and upper thorax become flushed
Hypothermia Nausea and Emetic Effects	<ul style="list-style-type: none"> • Alteration of equilibrium point of hypothalamic heat-regulatory mechanisms • Stimulation of chemoreceptor trigger zone in the postrema of medulla 	Suppression of the cough reflex by direct effect on cough center in medulla. Aspiration pneumonia – common complication due to loss of choking reflex.
Absent or Hypoactive Bowel Sounds	<ul style="list-style-type: none"> • Reduced resting tone in the musculature of the gastric reservoir • μ₂ agonism of intestinal wall increases tonic contracture of the antral musculature in duodenum • μ/δ agonism on submucosal plexus secretomotor neurons - reduced intestinal secretions 	Decrease GI motility

SIGNS & SYMPTOMS ^[5]

- Respiratory depression or failure (*primary finding*)
- Stupor
- Miosis
- Cyanosis (typically lips and fingertips)
- Hypotonia
- Cold clammy skin
- Bradycardia
- Nausea and vomiting
- Hypothermia
- Coma
- Choking sounds or gurgling

* Triad of stupor, miosis, and respiratory depression strongly suggests opioid poisoning

INTOXICATION VS. OVERDOSE

INTOXICATION	OVERDOSE
Muscles become relaxed	Deep snoring or gurgling
Speech is slowed or slurred	Blue tinge skin – usually lips and fingertips (lack of oxygen)
Sleepy looking	Pale clammy skin
Will respond to verbal or physical stimulation	Heavy nod, not responsive to stimulation
Nodding out	Breathing is very slow, irregular, or has stopped/faint pulse

NALOXONE

CLINICAL PHARMACOLOGY ^[6]

- Synthetic N-allyl derivative of oxymorphone
- Pure opioid antagonist - Competitive opioid antagonist at the μ , κ , and δ receptors, and has a greater affinity for the μ receptor than for the κ or δ receptors
 - Only clinically used opioid receptor antagonist with higher affinity for the μ than for the other receptors
 - No pharmacologic activity in the absence of opioids or other agonists
 - Antagonizes many opioid effects, including the respiratory depression, analgesia, and miosis.

Opioid Receptor Affinity for Selected Drugs ^[7, 8]				
		Opioid Receptor		
Drug	Activity	μ	δ	κ
Heroin	agonist	(rapidly hydrolyzed to morphine)		
Morphine	agonist	+++ (14)		+ (538)
Hydromorphone	agonist	+++		+
Codeine	agonist	+++ (79)		
Fentanyl	agonist	+++ (0.39)		
Methadone	agonist	+++ (0.72)		
Buprenorphine	partial agonist	+/- (0.12)		--
Naloxone	antagonist	--- (0.93)	- (17)	-- (2.3)
Receptor binding affinity Ki value (nM) – antagonist; + agonist; +/- partial agonist				

PHARMACOKINETICS ^[9-15]

- Onset of Action from Administration to Clinical Response

Reference	IN Naloxone	IM Naloxone	IV Naloxone	P Value
Kelly, et al.	8 min (n=84)	6 min (n=71)		0.006
Robertson, et al.	12.9 min (n=50)		8.1 min (n=104)	0.02

- Duration
 - Approximately 30 – 90 minutes (*much shorter than most opioids*)
 - Since naloxone's action is shorter than that of many opioids, repeated doses are sometimes needed
- Absorption

Route of Administration	Bioavailability
Oral	Less than 1%
Intramuscular	36%
Intranasal	4%

- Distribution
 - Distribution half-life: 4.7 minutes
 - Volume of distribution: 200 liters
 - Following parenteral administration, naloxone rapidly distributes in the body and readily crosses the placenta
 - Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin
- Metabolism – Hepatic
 - Rapidly metabolized primarily by conjugation with glucuronic acid
 - Undergoes extensive first pass metabolism
 - Three *inactive* metabolites detected in urine
 - Naloxone-3-glucuronide
 - N-allyl-7, 8-dihydro-14-hydroxynor-morphine (reduced naloxone)
 - 7, 8-dihydro-14-hydroxynormorphinone (dealkylated naloxone)
- Elimination half life
 - In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 +/- 112 minutes)
- Excretion - Renal
 - After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours

INDICATIONS & USAGE

- Complete or partial reversal of acute opioid intoxication, including respiratory depression induced by natural and synthetic opioids, including heroin, morphine, propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, and butorphanol
 - When administered in usual doses to patients who have not recently received opiates, naloxone exerts little or no pharmacologic effect.
 - *Note:* intranasal naloxone for opioid overdose reversal is an “off label” use
 - Standard practice in many large cities in the U.S.
 - Nasal spray version *can* be prescribed
 - As effective as parenteral route with no risk of needle stick exposure

ADVERSE EFFECTS ^[11]

- Opioid withdrawal in opioid-dependent patients
 - Abrupt reversal of opioid agonists may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness
- In postoperative patients:
 - Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest
 - Death, coma, and encephalopathy have been reported as sequelae of these events

DRUG ABUSE & DEPENDENCE

- Naloxone is an *opioid antagonist*
 - Physical dependence has *not* been reported
 - Tolerance is *not* known to occur
 - Safe and effective with no potential for abuse
 - Not a controlled substance but does require a prescription

WARNINGS/PRECAUTIONS

Cardiovascular Effects ^[16]

- When used to reverse opioids post-operatively cases of adverse cardiac events have been reported.
- Adverse events included hypertension, atrial tachycardia, ventricular tachycardia and fibrillation, left ventricular failure, pulmonary edema, severe hypertension with premature atrial contractions, sudden death, and hypertension with rebleeding of ruptured cerebral aneurysm
- Except for 2 cases all patients were medically compromised
- In the context of multiple drug administration during anesthesia a causal relationship is difficult to discern

Conclusion of cardiovascular risk: Naloxone has been used for decades with only a limited number of adverse cardiac events which occurred primarily in the post-operative setting

Seizures ^[17]

- Convulsions, including grand mal convulsions, have been associated with the use of naloxone hydrochloride injection in postoperative patients (1 case report)
- Use caution in patients with history of seizures
- Opioid overdose ^[11]
 - Recurrence of respiratory depression is possible if the opioid involved is long-acting
 - Observe patients until there is no reasonable risk of recurrent respiratory depression
- Geriatric considerations– no specific information for use in elderly
 - Clinical studies of naloxone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects

- Other reported clinical experience has not identified differences in responses between the elderly and younger patients
- In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
- Pregnancy- Category C ^[11, 18]
 - High dose opioid use during pregnancy is associated with fetal adverse effects which include physical dependence and withdrawal, retardation of growth, and neonatal respiratory depression
 - Teratology studies conducted in mice and rats at doses 4- and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m²), demonstrated no embryotoxic or teratogenic effects due to naloxone
 - No adequate and well controlled studies in pregnant women
 - Effects on the developing fetus are unknown
 - However, naloxone crosses the placenta and may precipitate fetal and maternal withdrawal
 - Because animal reproduction studies are not always predictive of human response, **naloxone should be used during pregnancy only if the maternal condition justifies the potential risk to the fetus**

DOSAGE

- **INTRANASAL NALOXONE** ^[11]
 - Available as 1 mg/mL concentration, and comes as 2 mL single dose disposable prefilled needleless syringe (2mg/2mL)
 - **Administer one-half of syringe into each nostril** upon signs of opioid overdose. **May repeat x 1**
 - **Note:** Onset of action is slightly delayed compared to parenteral routes (**see pharmacokinetics**)
- **INTRAMUSCULAR NALOXONE** ^[11]
 - Available as 0.4 mg/mL concentration - 1 mL single dose vial
 - Inject 0.4 mg (1 mL) intramuscularly upon signs of opioid overdose. **May repeat x 1**
- Post-Naloxone Administration
 - If no response (respiratory depression persists), may repeat in 3 minutes
 - Naloxone has less direct effect on consciousness, so the patient may remain drowsy for many hours
 - Not harmful provided that respiration is well maintained
 - **The duration of action of some opioids may exceed that of naloxone (see table below)**
 - The patient should be kept under continued surveillance
 - Repeated doses of naloxone should be administered, as necessary

CONTRAINDICATIONS - Hypersensitivity to naloxone or any component of the formulation

DISPENSING INSTRUCTIONS

- Store at room temperature (68-77°F) and protect from light
- Trained responders need to be aware of the expiration date on the box and to obtain refill of naloxone before that date.

Duration of Action of Opioid Agonists & Antagonists ^[19]		
Long Acting		
Drug	Route	Durations (hrs)
Methadone (Dolophine)	Oral	2-10 (↑ with repeated dosing)
Buprenorphine (Suboxone)	Oral	6.75 – 24
Morphine CR (MS Contin)	Oral	8-12
Oxymorphone ER (Opana ER)	Oral	12
Oxycodone CR (Oxycontin)	Oral	12
Morphine SR (Kadian)	Oral	12-24
Morphine ER (Avinza)	Oral	12-24
Fentanyl (Duragesic)	Transdermal	48-72
Short Acting		
Drug	Route	Duration (hrs)
Naloxone	IM	1-1.5
Hydromorphone (Dilaudid)	Oral	3.6
Diacetylmorphine (Heroin)	IM	3-4
Meperidine (Demerol)	Oral	3-5
Morphine (Kadian, MS Contin)	Oral	4
Propoxyphene	Oral	4-6
Codeine	Oral	4-6
Oxymorphone (Opana)	Oral	4-6
Oxycodone (Roxicodone)	Oral	4-6
Hydrocodone (Vicodin)	Oral	4-6
Tramadol (Ultram)	Oral	4-6

OPIOID OVERDOSE RESPONSE ^[3]

STIMULATION

- Check for responsiveness by giving a light pinch or shake
- Call their name or say "I'm going to Narcan you!"

CALL 911 FOR HELP

- Clearly give address or nearest intersection
- Keep loud noise in background to a minimum – if it sounds chaotic, they will dispatch police to secure the scene and protect the paramedics
- Avoid using words like drugs or overdose – stick to what you see: "not breathing, turning blue, unconscious, nonresponsive."
 - All they have to say is "my friend (or family member) is unconscious and I can't wake them up" or "my friend (or family member) isn't breathing"

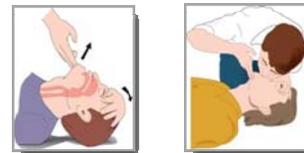
RECOVERY POSITION

- If you must leave the person alone to call 911 or at anytime before the paramedics arrives, place them in the **recovery position** (see image)
 - *Helps to prevent the person from choking if they vomit*



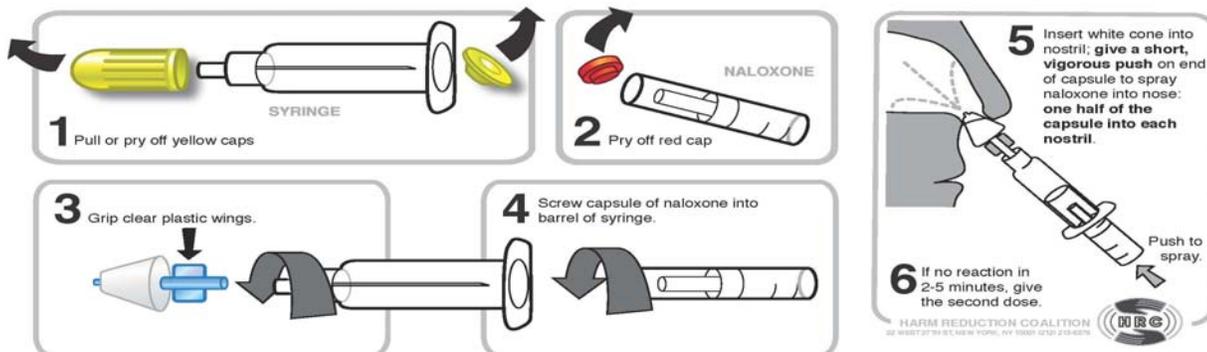
CHECK FOR BREATHING

- Airway – ensure nothing is in the mouth (i.e. undissolved pills, cheeked fentanyl patch, syringe cap)
- Rescue breathing - Breathe for them!
 - Place the person on their back
 - Perform head tilt-chin lift
 - With one hand, tilt head back
 - With two fingers of your other hand, lift chin up
 - Pinch nose closed
 - Make a tight seal over mouth and give 2 rescue breaths
 - Chest should rise, not stomach
 - If the chest does not rise, tilt the head back more and ensure that you are plugging their nose closed
 - If still not breathing, give **1 rescue breath about every 5 seconds**
 - **Continue rescue breathing until paramedics arrive**

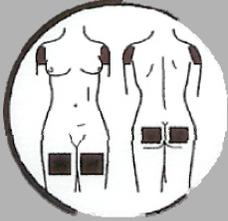


ADMINISTER NALOXONE

HOW TO GIVE INTRANASAL NALOXONE



HOW TO GIVE INTRAMUSCULAR NALOXONE

 <p>1. Remove cap from naloxone vial and uncover the needle</p>	 <p>2. Insert needle through rubber plug with vial upside down Pull back on plunger and take up 1 mL</p>	 <p>3. Inject 1 mL of naloxone at a 90 degree angle into a large muscle (upper arm/thigh, outer buttocks)</p>
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EVALUATE AND SUPPORT

- If breathing has resumed
 - Inform them what happened
 - **Help them not use more opioids right away**
 - Stay with them until paramedics arrive or the naloxone wears off to ensure the overdose doesn't return
 - Be prepared to administer an additional dose of naloxone since it can wear off in 30-90 minutes post administration (**remember that the opioid overdose can return**)
 - Comfort them - opioid withdrawal is uncomfortable, but *not life threatening*
 - Excessive yawning; lacrimation or rhinorrhea; piloerection, mydriasis, or sweating; muscle aches; dysphoric mood; nausea or vomiting; diarrhea; fever; insomnia
- If they are still *not* breathing
 - Continue rescue breathing at a rate of 1 breaths every 5 seconds
 - Administer another dose of intranasal naloxone in 3 minutes if no or minimal breathing or responsiveness

CALIFORNIA CIVIL CODE

California Civil Code §1714.22(c) and (a)(2)

Persons who administer naloxone in an emergency or who possess an opioid antagonist are protected from criminal prosecution or violation of any professional licensing statute, as long as the person meets the following criteria:

- Believes in good faith that the other person is experiencing a drug overdose; and
- Received specified training information
 - The causes of an opiate overdose
 - Mouth to mouth resuscitation
 - How to contact appropriate emergency medical services
 - How to administer an opioid antagonist

California Civil Code §11376.5

Protects those seeking medical assistance for someone or themselves overdosing

- **Not a crime to be under the influence /possess for personal use a controlled substance or drug paraphernalia**
- **Person can not obstruct medical or law enforcement personnel**
- **Does not protect against:**
 - **Selling, providing, giving, or exchanging drugs**
 - **Forcible administration of drugs against a person's will**
 - **Offenses that involve activities made dangerous by consumption of controlled substances (e.g. DUI)**

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