

Understanding Buprenorphine Formulations

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Disclosures

There are no relevant financial relationships with ACCME-defined commercial interests for anyone who was in control of the content of this activity.



Overview

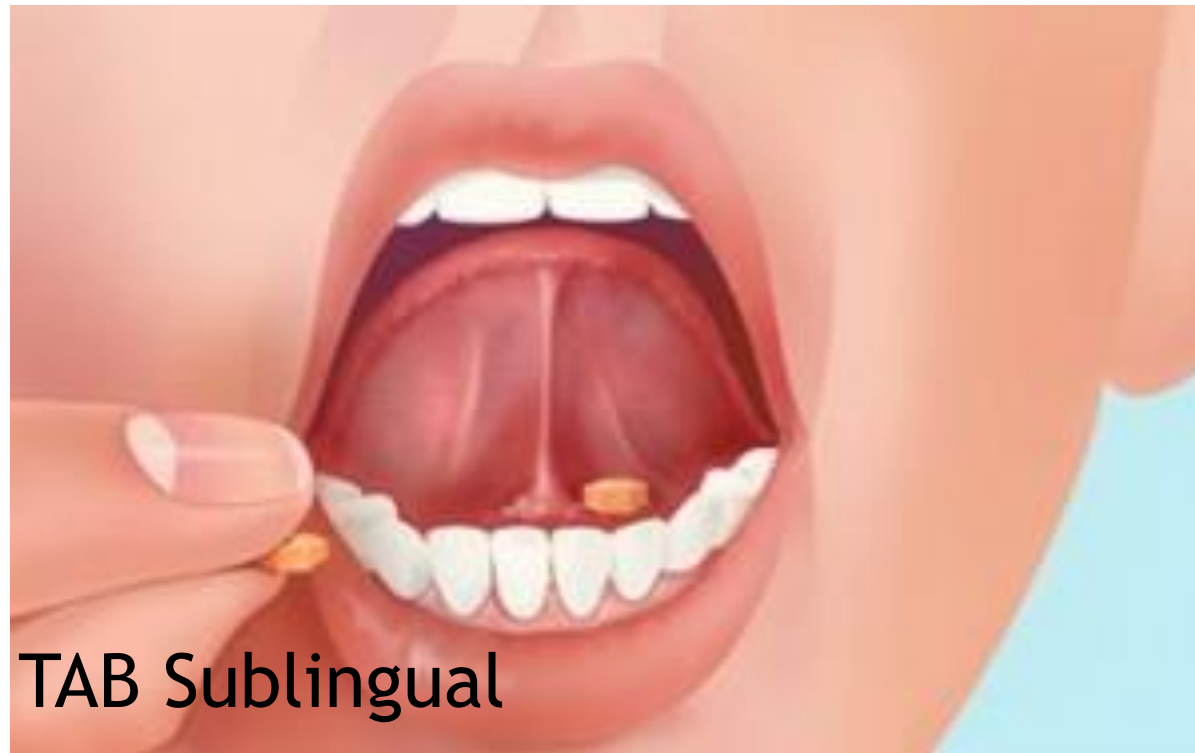
- ▶ Buprenorphine formulations
- ▶ Choosing the most appropriate formulation
- ▶ Questions and discussion



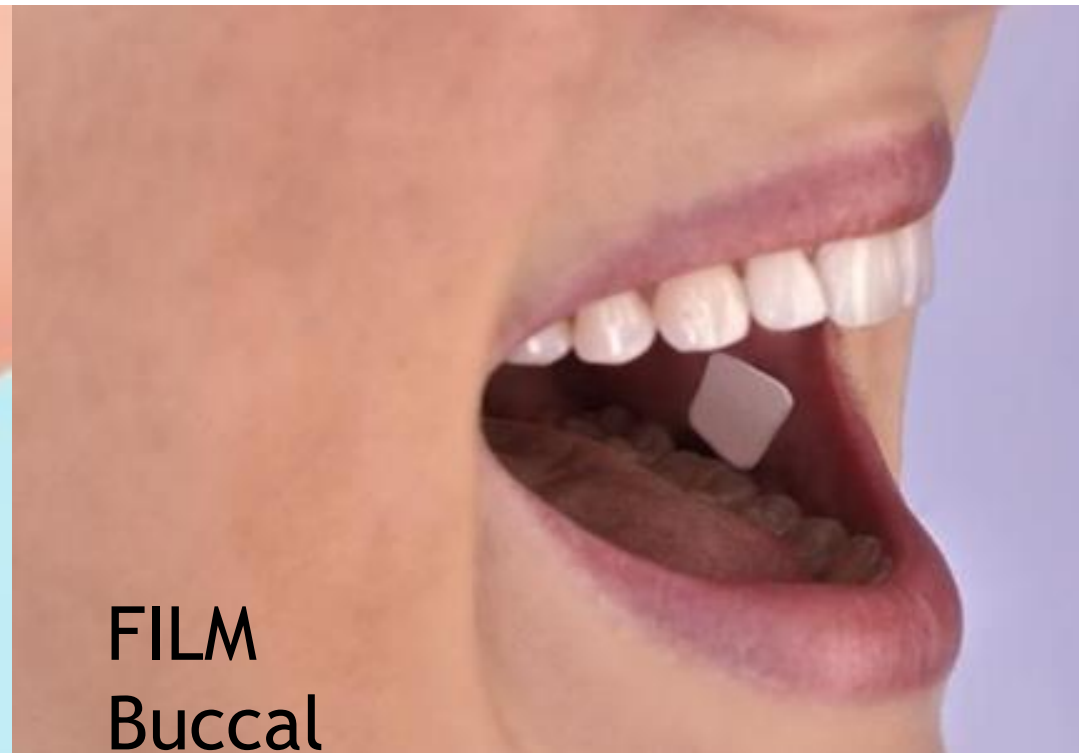
Buprenorphine



Transmucosal Buprenorphine Formulations



TAB Sublingual



FILM
Buccal



FILM Sublingual

ZUBSOLV™ (4:1 Bup/Nlx)	GENERIC (4:1 Bup/Nlx)
0.7 mg/ 0.18 mg	-
1.4 mg/ 0.36 mg	2 mg/ 0.5 mg
2.9 mg/ 0.71 mg	-
5.7 mg/ 1.4 mg	8 mg/ 2 mg
8.6 mg/ 2.1 mg	-
11.4 mg/ 2.9 mg	-

BUNAVIL™ (6:1 Bup/Nlx)
-
2.1 mg/ 0.3 mg
4.2 mg/ 0.7 mg
6.3 mg/ 1 mg

SUBOXONE™ (4:1 Bup/Nlx)
-
2 mg/ 0.5 mg
4 mg/ 1 mg
8 mg/ 2 mg
12 mg/ 3 mg
-

GENERIC SUBUTEX (Bup only)
2 mg
8 mg

BELBUCCA (Bup only)
75-900 mcg
For Pain



Buprenorphine for Opioid Use Disorder

- ▶ FDA approved 2002, age 16+
- ▶ Mandatory certification from DEA (100 pt. limit)
- ▶ Mechanism: partial mu agonist
- ▶ Office-based, expands availability
- ▶ Analgesic properties
- ▶ Ceiling effect
- ▶ Lower abuse potential
- ▶ Safer in overdose



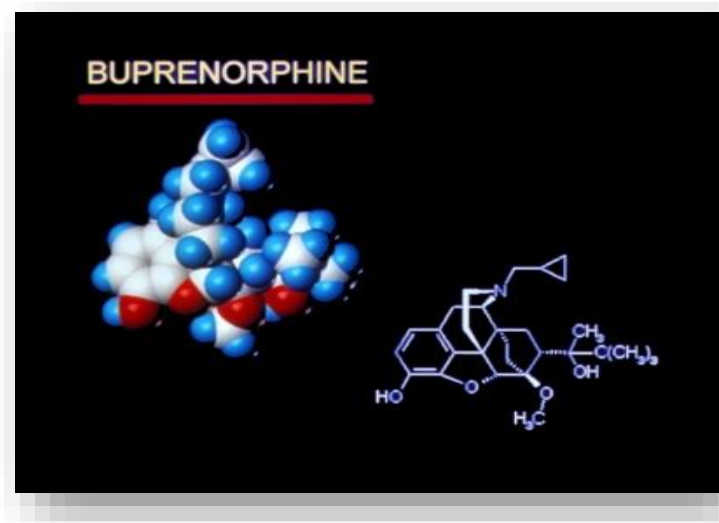
Suboxone Tablets 8mg. and 2mg

FDA-approved Buprenorphine Products Approved for Opioid Dependence

▶ TRANSMOCOSAL

- ▶ Subutex (buprenorphine) (2mg, 8mg)
 - ▶ Suboxone (4:1 bup:naloxone)
 - ▶ Zubsolv (4:1 bup:naloxone)
 - ▶ Bunavail (6:1 buccal film bup:naloxone)
- ▶ Propuphine (subdermal implant)
- ▶ Sublocade (subcutaneous injection)
- ▶ <https://www.fda.gov/drugs/information-drug-class/>

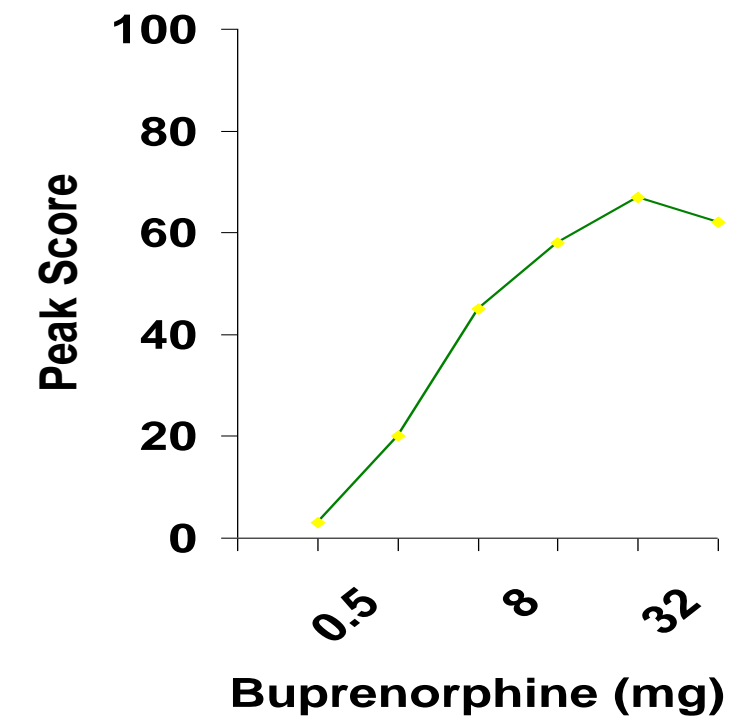
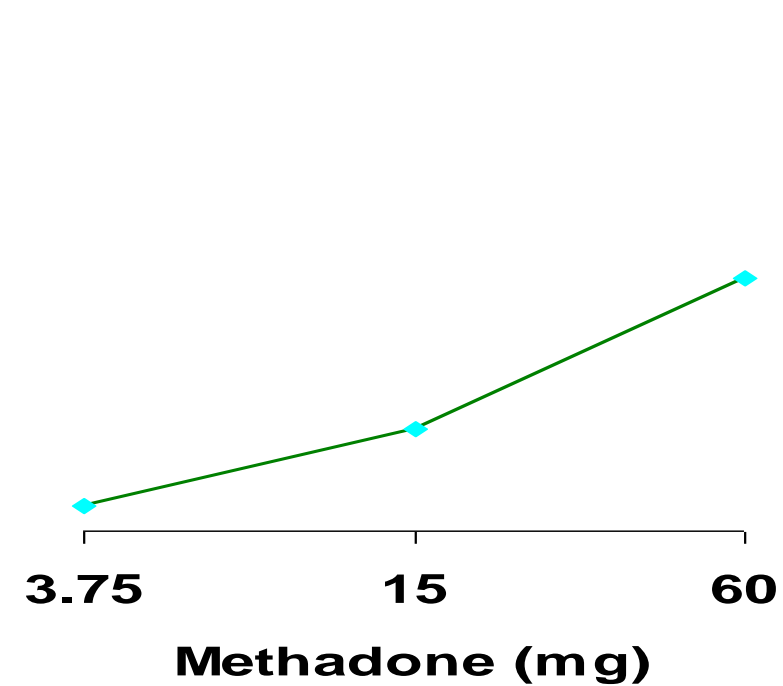




Buprenorphine: Pharmacological Characteristics

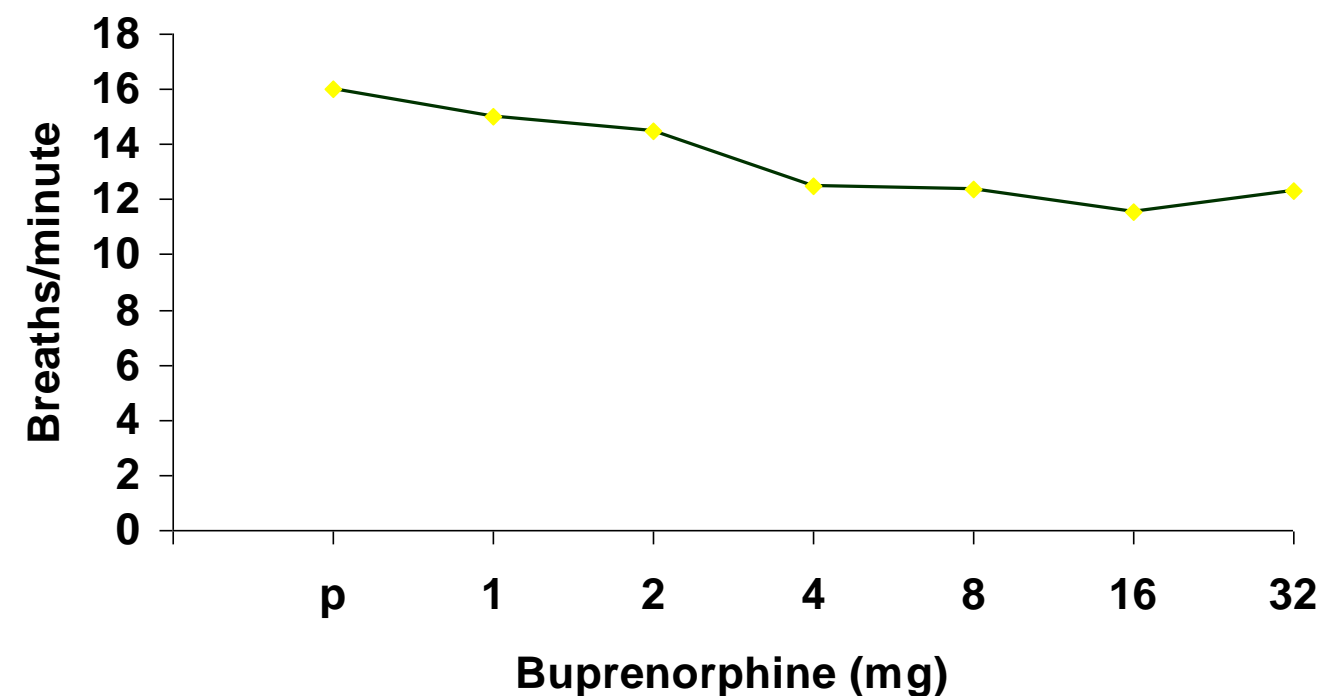
Partial Agonist (ceiling effect)

- ▶ -less euphoria
- ▶ -safer in overdose

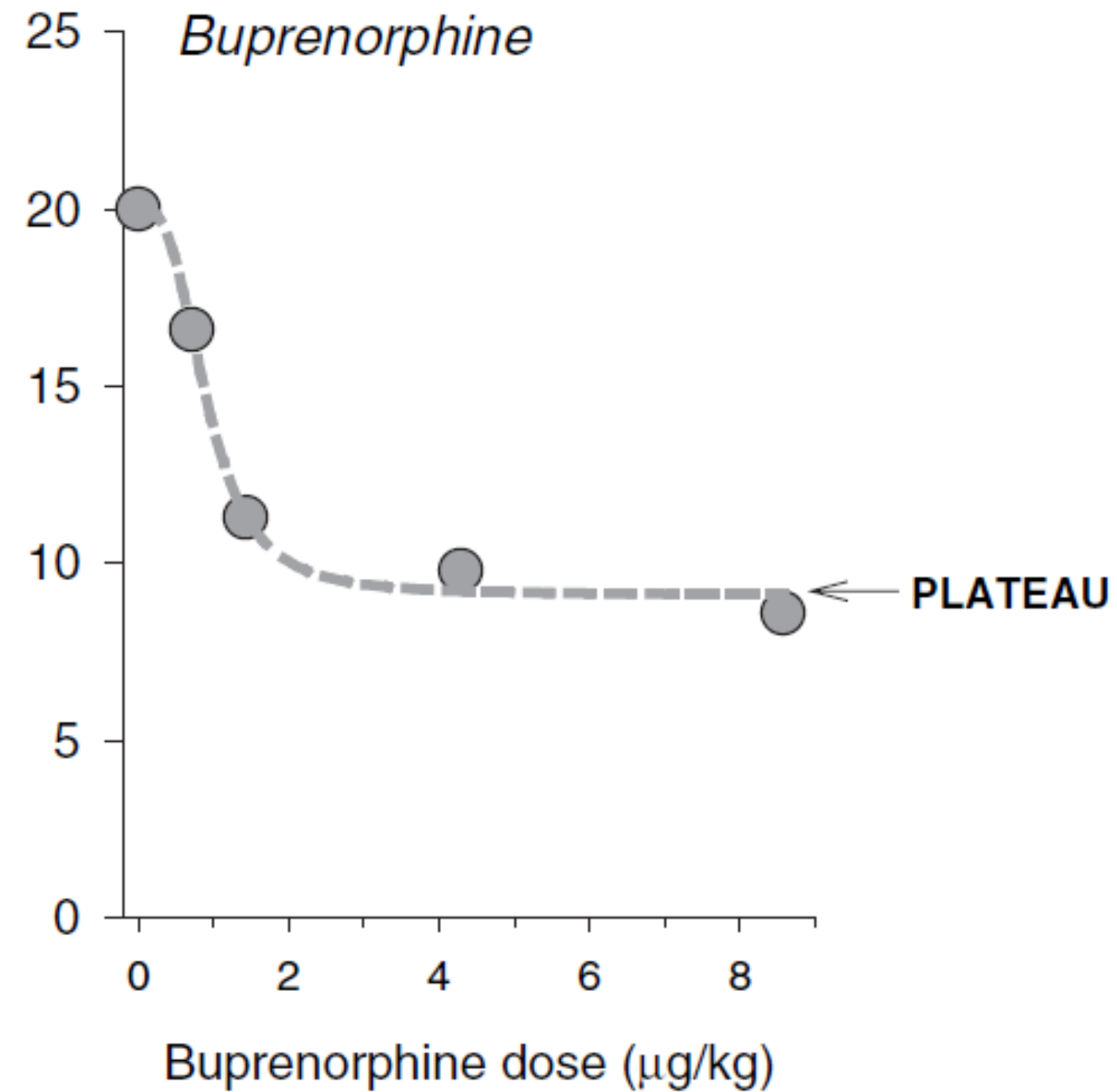
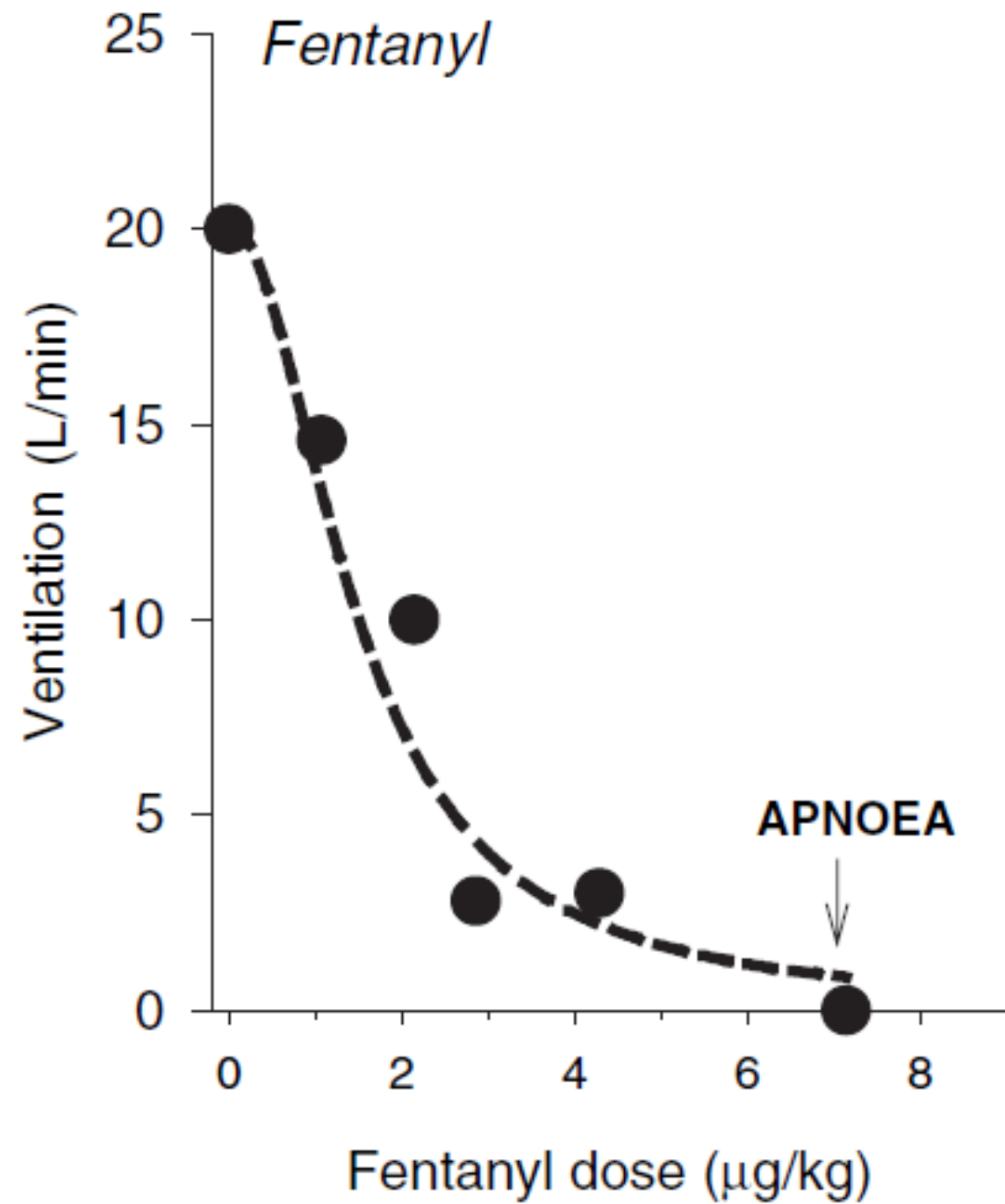


Strong Receptor Binding

- ▶ -long duration of action
- ▶ -1st dose given during withdrawal



Fentanyl vs. Buprenorphine



Dahan et al., 2006

Buprenorphine Injection: Sublocade

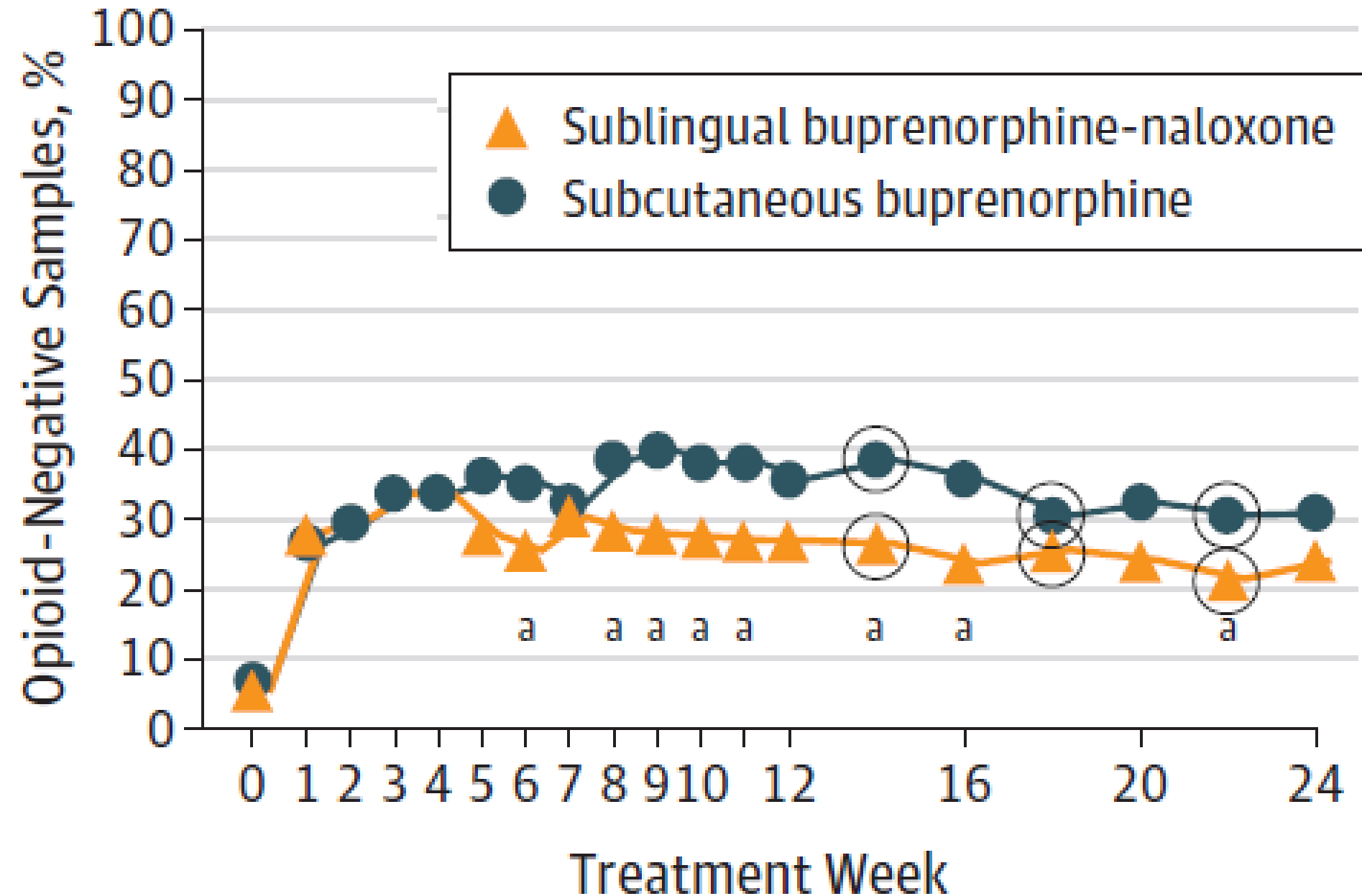


Buprenorphine Injection: Sublocade

- ▶ Sublocade is a monthly injectable formulation of buprenorphine approved in 2017 for the treatment of moderate to severe OUD in individuals who have initiated a transmucosal buprenorphine product and have been stabilized on treatment for at least seven days.
- ▶ The approved dosing regimen is 300 mg administered subcutaneously for the first two months, followed by maintenance doses of 100 mg/month.
- ▶ It must be prescribed as part of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the product is not distributed directly to patients.



SL-BUP compared to XR-BUP

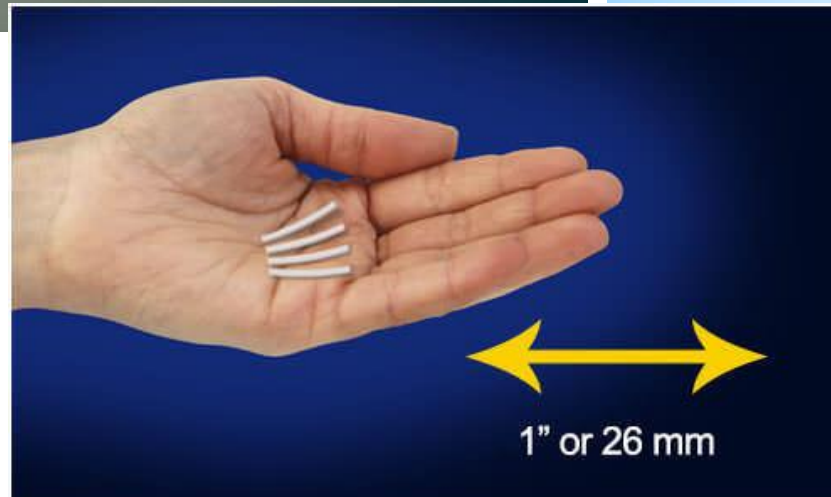
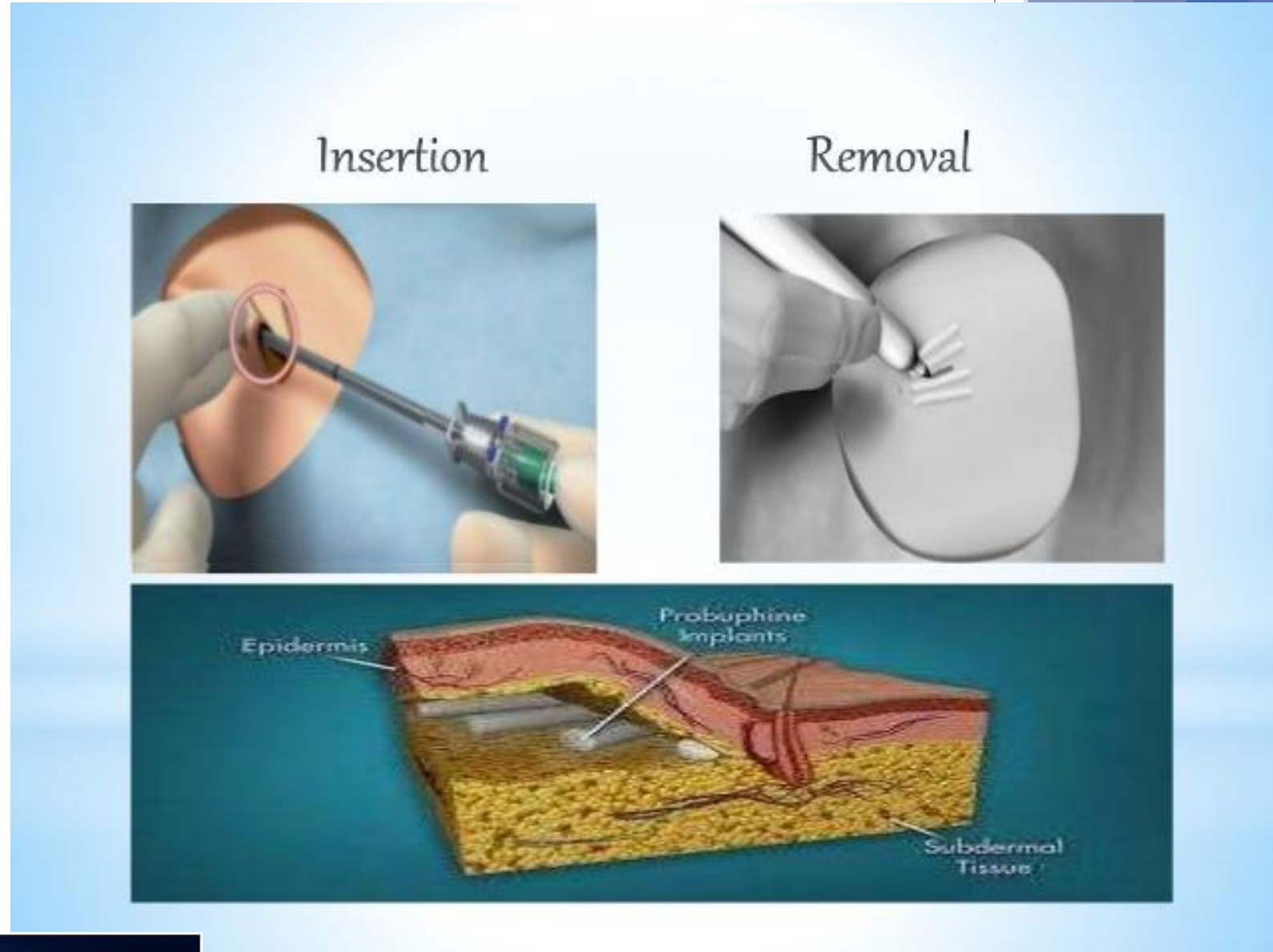
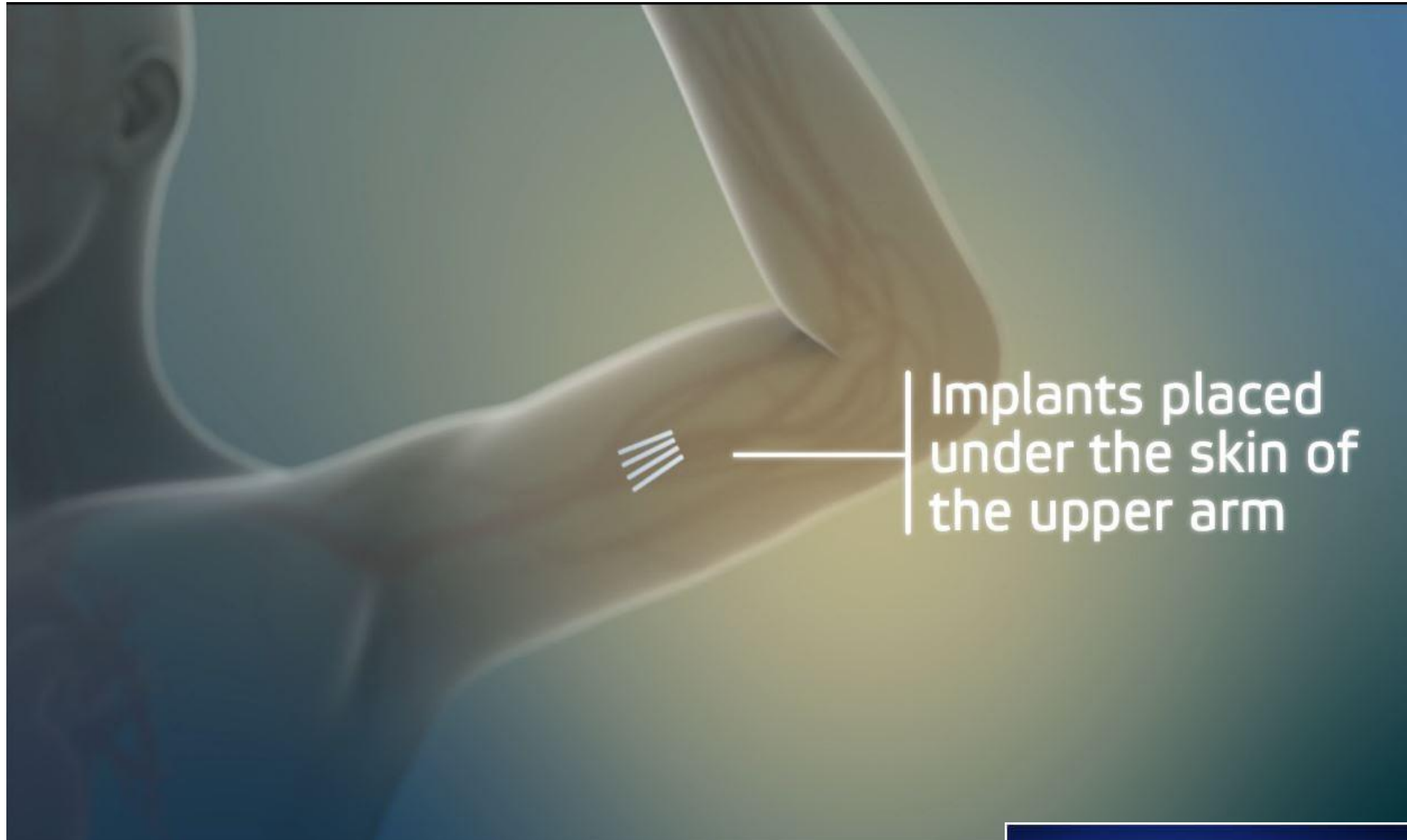


^a $P \leq .05$ per time point (using analysis of variance) between groups;

Lofwall et al., 2018



Buprenorphine Implant: Probuphine



Buprenorphine Implant: Probuphine

- ▶ Probuphine™ is an implantable formulation of buprenorphine HCL (80 mg) approved for the treatment of opioid use disorder in patients stabilized on 8 mg/day or less sublingual buprenorphine
- ▶ Probuphine is inserted subdermally into the inner side of the upper arm in a brief in-office procedure under local anesthetic, and provides sustained release of buprenorphine for 6 months
 - ▶ At the end of each 6-month period, Probuphine is removed in a brief, in-office procedure



Subdermal and extended release buprenorphine formulations in Pregnancy

- **Probuphine (buprenorphine) implant for subdermal administration**
 - The use of Probuphine in pregnancy has not been studied and is not indicated for use in pregnancy
 - John Evangelista, MD, MPH Medical Science Liaison for Titan Pharmaceuticals
- **Sublocade (buprenorphine extended-release) injection for subcutaneous use**
 - **Animal reproduction studies:** Potential risk to fetus due to excipient, NMP (N methyl 2 pyrrolidone)
 - **At doses equiv in sublocade:** preimplantation losses, delayed ossification, reduced fetal weight, developmental delays and reduced cognitive function
 - **At 2x dose:** Decreased pup survival
 - **At 3x dose:** malformation and post-implantation losses



Overdose Risk Factors

- History of prior overdose
 - Release after emergency care for overdose
- Opioid use disorder
- Prescribed more than 50 mg of oral morphine equivalents daily
- Recent release from incarcerated or residential setting
- Combining opioids with other central nervous system depressants (e.g. alcohol, benzos)
- Medical conditions (e.g. pulmonary diseases)





Naloxone

Short-acting opioid antagonist

- ▶ High affinity for mu opioid receptor
- ▶ Displaces opioids from receptor
- ▶ Rapidly reverses effects of opioid overdose (minutes)
- ▶ Effects last 20-90 mins
- ▶ FDA approved for IV, SC, IM, intranasal use
- ▶ Opioid overdose-related deaths can be prevented when naloxone is administered in a timely manner.
- ▶ [PrescribeToPrevent.org](https://www.PrescribeToPrevent.org)





Naloxone

Short-acting opioid antagonist

▶ HOW TO OBTAIN NALOXONE

▶ ANYONE can get Naloxone in CA

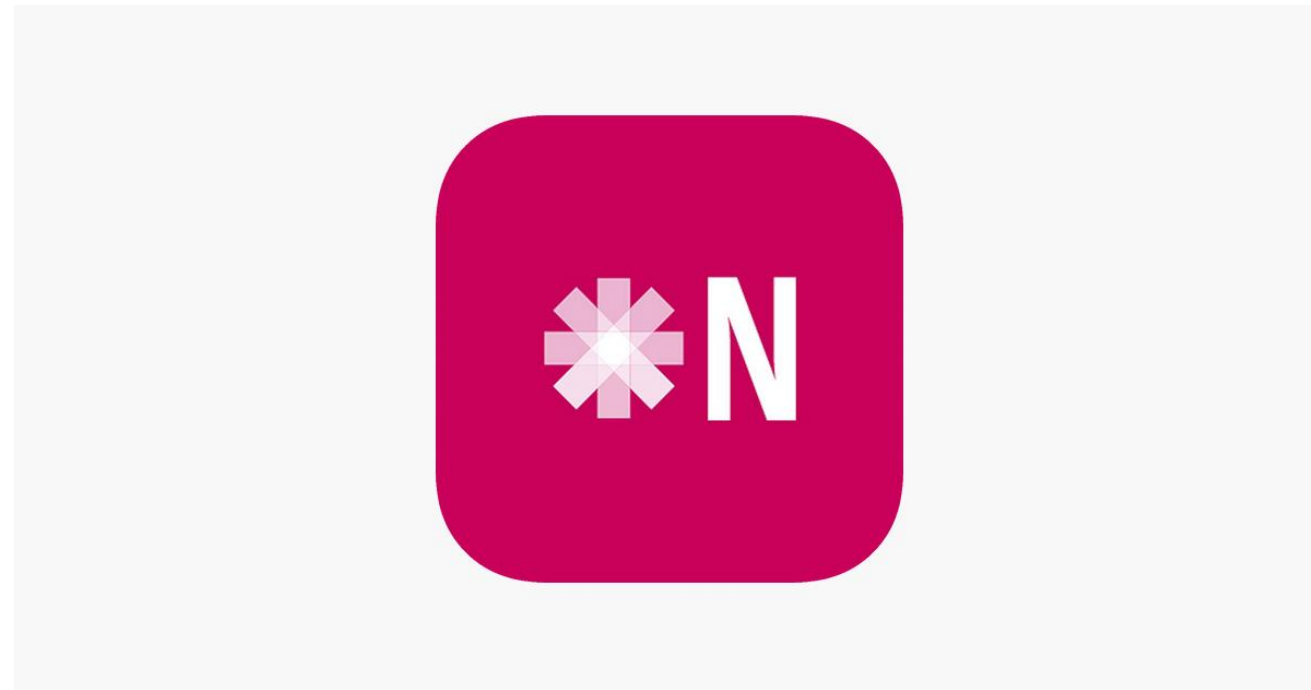
- 1) Obtain a prescription from your **health care provider**
- 2) Visit your **local pharmacist** -- a pharmacist can provide Naloxone without a prescription (authorized by CA Business and Professions Code Section 4052.01)
- 3) **Community organizations** who offer naloxone at low or no cost under the State-Wide Naloxone Grant Program and the Statewide Naloxone Prescription Order

○ <https://www.narcan.com/patients/how-to-get-narcan/>

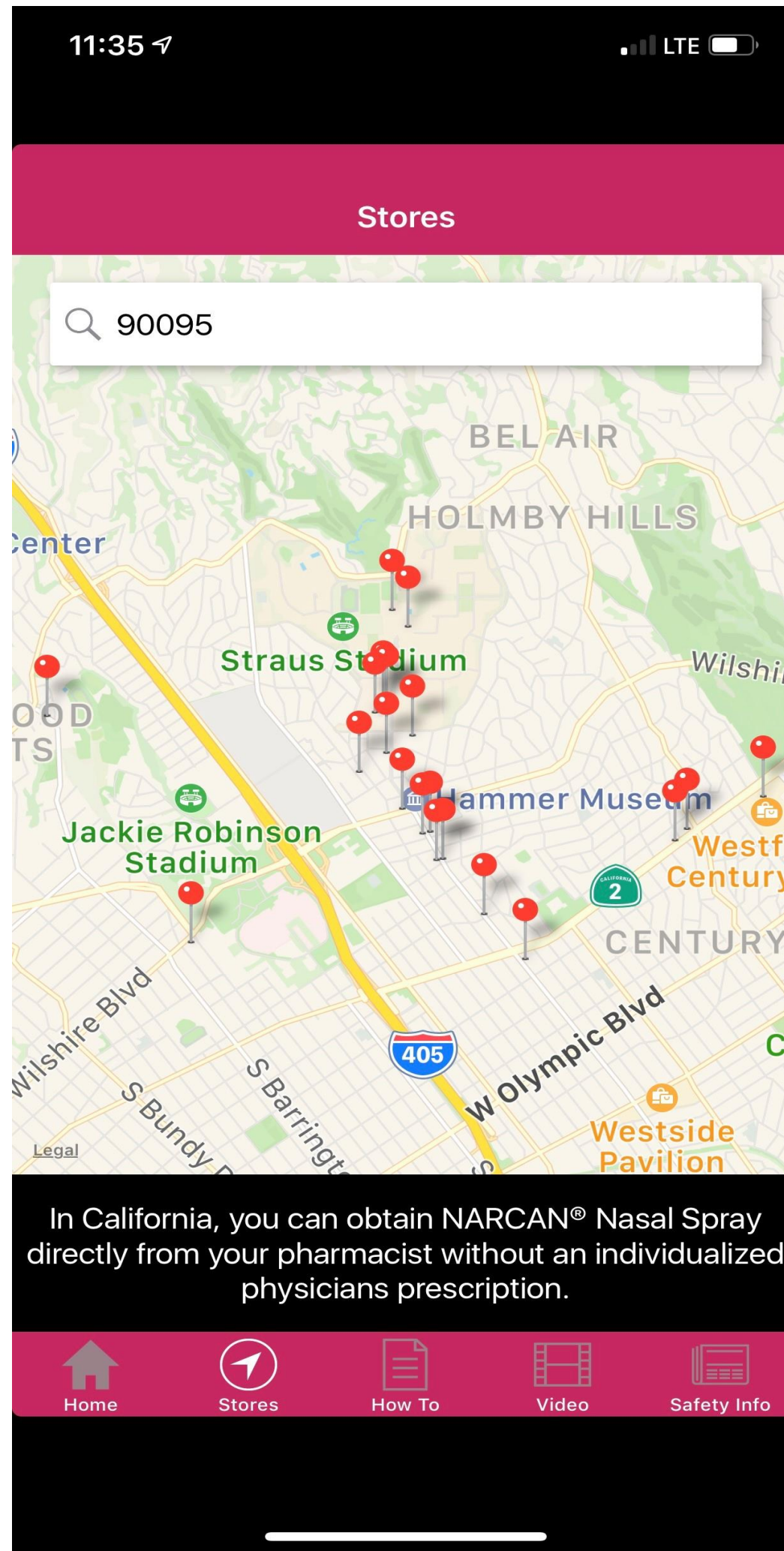
<https://www.cdph.ca.gov/Programs/CCDPHP/DCDIC/SACB/Pages/NaloxoneGrantProgram.aspx>



Narcan Now App







SAMHSA Decisions in Recovery Tool

Decisions in Recovery: Treatment for Opioid Use Disorder

Should I start?

Which do I start?

How do I start?

Recovery tools



I want to decide whether I should use medication for treatment

<https://mat-decisions-in-recovery.samhsa.gov/>



University of California Los Angeles
Integrated Substance Abuse Programs

Factors to Consider in Shared Decisions on Choosing Formulations - Sublingual/Buccal

- ▶ The most common dosage form in use
 - ▶ All patients must be stabilized on sublingual or buccal preparations prior to switch to injectable or implant
 - ▶ Can be administered at home or in the office (e.g., during office-based induction)
- ▶ For patients with limited or no insurance, the least expensive option
 - ▶ For patients with insurance it may be the only option
- ▶ Advantages are cost and flexibility
 - ▶ A wide range of doses can be prescribed for a few days or for 30 days with refills
- ▶ Disadvantages are the risk of diversion, the potential for drug holidays
 - ▶ Wrapper counts at each visit; Urine buprenorphine screening



Factors to Consider in Shared Decisions on Choosing Formulations - Injection

- ▶ Less commonly used because it is more recent (approved in 2017) and more logistically challenging
 - ▶ Only available from registered pharmacies, must be refrigerated, and can only be administered in the clinic setting
- ▶ In California, available at no charge to patients with Medi-Cal
- ▶ Covers a wide range of buprenorphine doses (8 to 24 mg daily)
- ▶ Advantages over films
 - ▶ No need for take medication daily (no lost prescriptions or missed doses); No diversion risk; Lasts for one month
- ▶ Disadvantages
 - ▶ Injection can be painful and leaves a lump that slowly dissolves over time



Factors to Consider in Shared Decisions on Choosing Formulations - Implant

- ▶ Less commonly used
 - ▶ Requires additional training (above X-waiver training) to prescribe and insert
 - ▶ Insertion is a surgical procedure done under sterile procedures and may be done in a separate location
- ▶ Advantages
 - ▶ The longest-acting dosage form - 6 months
- ▶ Disadvantages
 - ▶ Only approved for patients stabilized on buprenorphine doses of 8 mg or less
 - ▶ After one insertion in each arm, transition to oral is recommended
 - ▶ Procedure to implant is straightforward, but there are risks

