تازه های درمان نگهدارنده بوپرنورفین

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Opioid Use Disorder

- FDA & WHO approved Medications
- Methadone
- Buprenorphine
- Naltrexone

Barriers & challenges for OST

- Limited access
- Availability in country
- Governmental regulation
- Strict guidelines & protocols
- Outpatient basis by licensed physician
- List of essential drugs by WHO

Global availability of opioid substitution therapy

Although heroin addiction is a global problem, much of the world remains without a form of substitution therapy.

Source: The Lancet

Infographic: Tom Howey

Barriers & challenges in MAW

- At least mild withdrawal
- Preferably moderate withdrawal
- Precipitated withdrawal
- Medically assisted withdrawal management
- High rate of relapse to opioid use
- Reduced physiological tolerance
- Risk of opioid overdose

Buprenorphine maintenance treatment

- buprenorphine compared to placebo
- compared to methadone
- low compared to high dose of buprenorphine
- low dose (2mg to 6mg/day)
- medium (7mg to 15mg/day)
- high dose (≥ 16 mg/day)

Buprenorphine versus Methadone

- Fixed-dose studies: neither medium dose buprenorphine to medium dose methadone, nor between high-dose buprenorphine and high-dose methadone
- Flexible-dose studies: better retention in treatment for methadone, similar opioid use outcomes

- Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Mattick RP, Breen C, Kimber J, Davoli M, Cochrane Database Syst Rev. 2014 Feb 6; (2):CD002207.

Buprenorphine versus Methadone

- methadone (mean dose: 93mg, range: 5mg to 397 mg) or buprenorphine (mean dose: 22mg, range: 2mg to 32mg):
- lower retention on buprenorphine (46%) compared to methadone (74%), similar urine-confirmed opioid abstinence between the two groups
- Higher retention in treatment and abstinence with higher dosage for methadone and buprenorphine

- Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W Addiction. 2014 Jan; 109(1):79-87

Buprenorphine versus Vivitrol

- Similar dropout rates between Vivitrol & sublingual buprenorphine
- rate of relapse by the end of 24 weeks: 57% on buprenorphine versus 65% on injection naltrexone

- Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J Lancet. 2018 Jan 27; 391(10118):309-318.

Importance of induction

- Early induction even at home
- Gentle induction in first doses
- Rapid titration in later doses
- Higher doses: better retention
- Avoiding precipitated withdrawal
- more severe than spontaneous withdrawal
- Fentanyl complicates buprenorphine initiation
- high lipophilicity of fentanyl
- high intrinsic activity of fentanyl at the receptors

Microdosing Protocol

- 3 patients on methadone 40-100 mg/day to buprenorphine 12-16 mg/day
- low-dose buprenorphine concurrently with each patient's full dose of methadone
- Bup dose gradually titrated up over 7 days
- On day 8, methadone discontinued

- Transitioning Hospitalized Patients with Opioid Use Disorder from Methadone to Buprenorphine without a Period of Opioid Abstinence Using a Microdosing Protocol Dale Terasaki,Christopher Smith,Susan L. Calcaterra First published: 26 July 2019

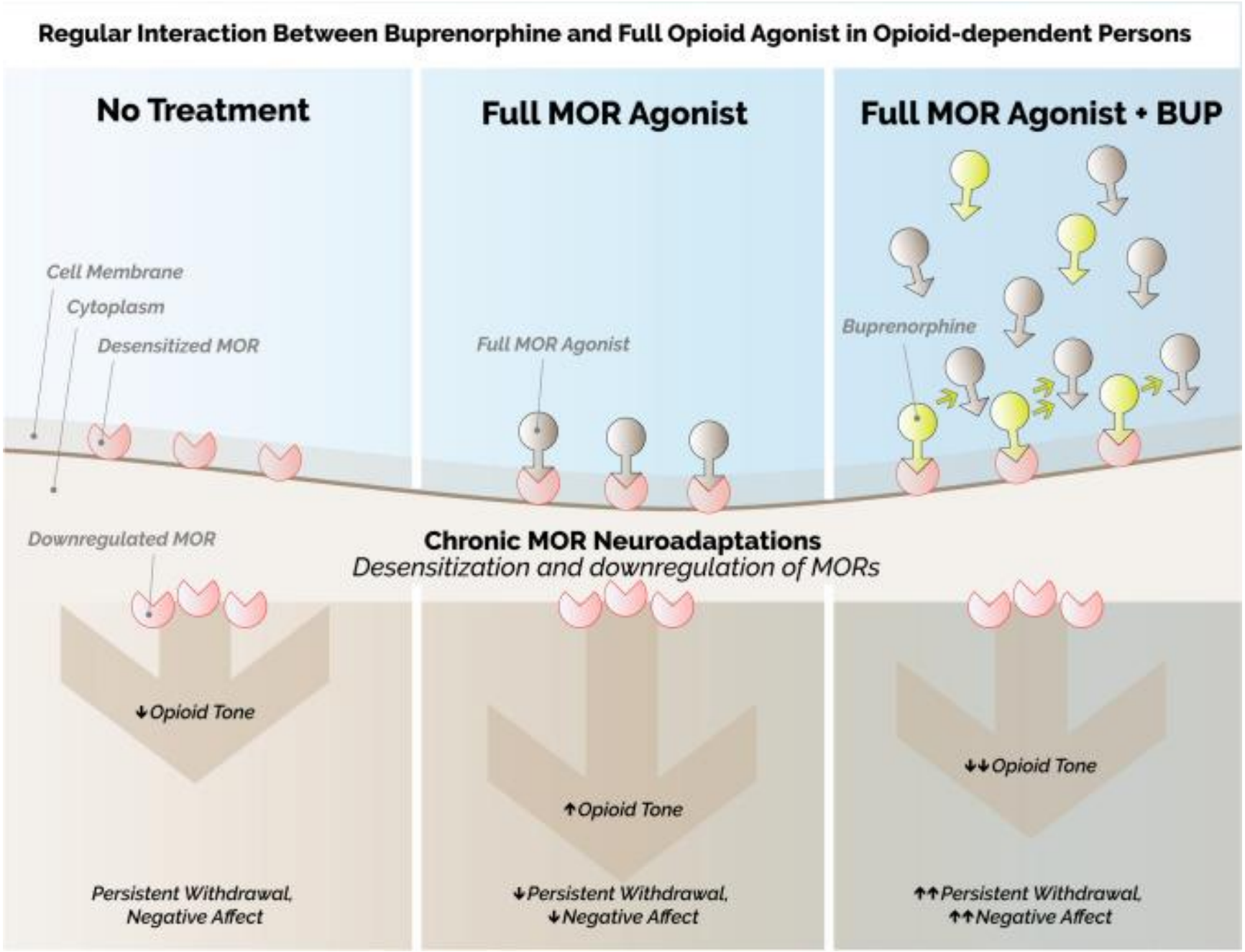
Buprenorphine Microinduction

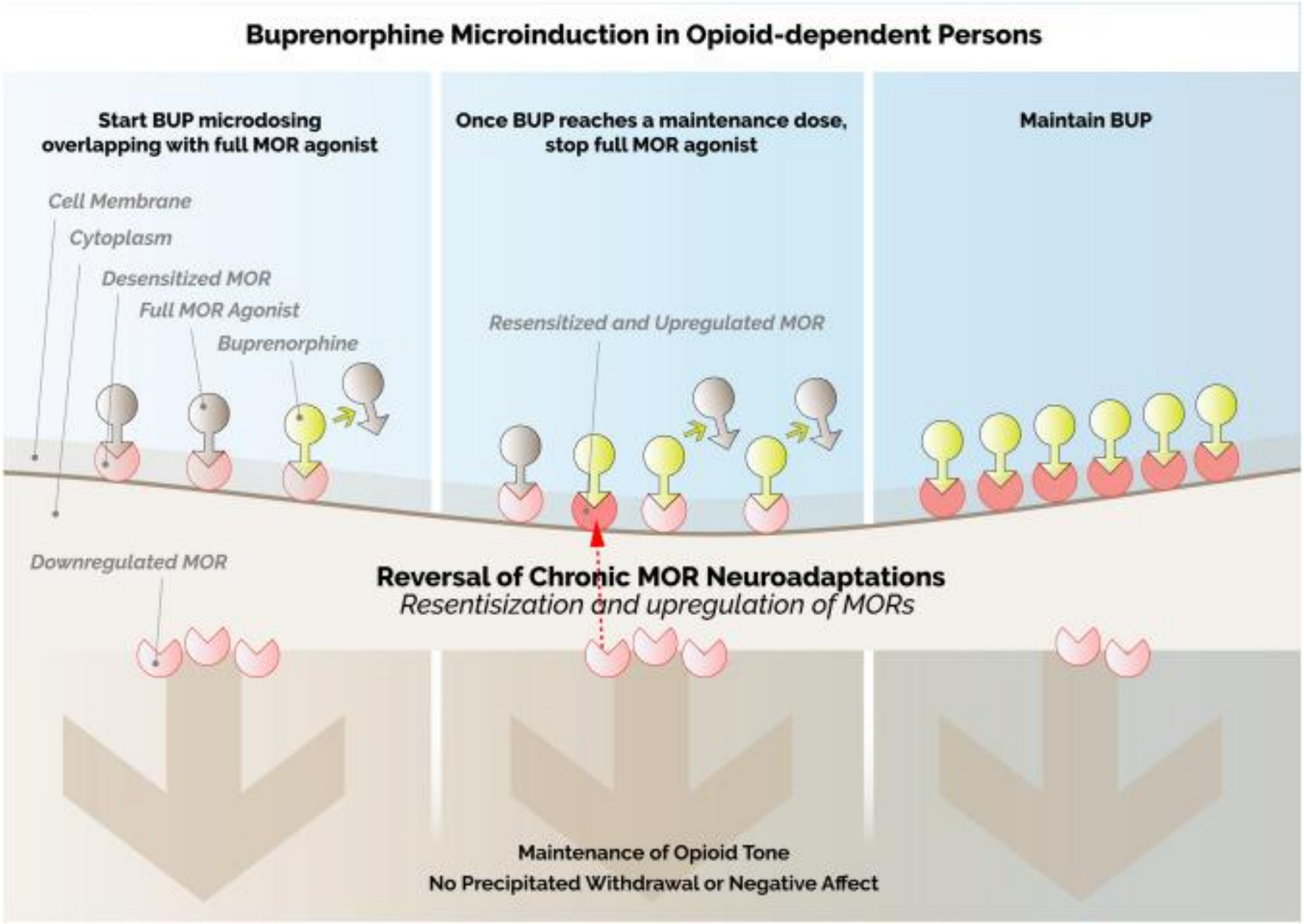
- affinity of BUP for MOR is 5.4 and 6.2 times greater than that of morphine and fentanyl,
- small doses of BUP as 0.25–2 mg/day of sublingual or 5–20 μg/h of transdermal BUP
- gradual increases of both the dose and frequency of administration
- 3 to 10 days period

Buprenorphine Microinduction

- 2, 16, and 32 mg/day SL BUP for OUD reduced whole-brain MOR binding availability by 41%, 80%, and 84%,
- receptor desensitization
- downregulation of surface MOR,

- The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder, Joao P. De Aquino,corresponding author1,2 Suprit Parida,1,2 and Mehmet Sofuoglu1,2, Clin Drug Investig. 2021; 41(5): 425–436. Published online 2021 Apr 5. doi: 10.1007/s40261-021-01032-7


Regular Interaction Between Buprenorphine and Full Opioid Agonist in Opioid-dependent Persons
No Treatment
Full MOR Agonist
Full MOR Agonist + BUP
Cell Membrane
Cytoplasm
Desensitized MOR
Full MOR Agonist
Buprenorphine
Downregulated MOR
Chronic MOR Neuroadaptations
Desensitization and downregulation of MORs
↓Opioid Tone
↑Opioid Tone
↓↓Opioid Tone
Persistent Withdrawal,
Negative Affect
↓Persistent Withdrawal,
↓Negative Affect
↑↑Persistent Withdrawal,
↑↑Negative Affect


Buprenorphine Microinduction in Opioid-dependent Persons
Start BUP microdosing overlapping with full MOR agonist
Once BUP reaches a maintenance dose, stop full MOR agonist
Maintain BUP
Cell Membrane
Cytoplasm
Desensitized MOR
Full MOR Agonist
Buprenorphine
Resensitized and Upregulated MOR
Downregulated MOR
Reversal of Chronic MOR Neuroadaptations
Resentisization and upregulation of MORs
Maintenance of Opioid Tone
No Precipitated Withdrawal or Negative Affect

Retention & Adherence

- variable motivation
- ongoing withdrawal symptoms or craving
- overconfidence
- Stigma
- contingency management
- involving significant others
- strongest predictor : maintenance medication

Risks and Side Effects

- constipation and sedation
- Respiratory depression
- Overdose with alcohol & benzodiazepines
- accidental overdose in young children
- serotonin syndrome
- adrenal insufficiency
- Hepatitis or elevated liver enzymes
- Alcoholic hepatitis or viral hepatitis

Metabolism and Drug Interaction

- alcohol, benzodiazepines, muscle relaxants
- inhibitor of CYP-2D6 and CYP-3A4
- serotonergic drugs
- monoamine oxidase inhibitors
- serotonin syndrome

Buprenorphine in Pregnancy

- Greater risk of dropout during pregnancy
- Less risk of neonatal abstinence syndrome
- Milder Neonatal Withdrawal Syndrome
- Shorter hospital stay of infant
- Lesser dose of morphine sulfat
- buprenorphine without naloxone

Antagonism effect on Kappa

- endogenous kappa system
- Opioids withdrawal dysphoria
- antidepressant effects
- Buprenorphine/samidorphan treatment of MDD
- Olanzapine/samidorphan treatment of schizophrenia

Buprenorphine formulations

- 2002: Buprenorphine/naloxone sublingual tablets (Suboxone);
- 2002: Buprenorphine sublingual tablets (Subutex).
- 2010: Buprenorphine/naloxone sublingual films.
- 2013: Buprenorphine/naloxone sublingual tablets (Zubsolv).
- 2014: Buprenorphine/naloxone buccal films (Bunavail).
- 2016: Buprenorphine implants (Probuphine).
- 2017: Buprenorphine extended-release injection (Sublocade).

Buprenorphine formulations

Indicated for Pain					
Intravenous/Intramuscular (Buprenex, buprenorphine hyrdocholoride, 1985)	0.3-0.6mg q6h/PRN	0.3 mg	<1	1.2–7.2	for acute or post-operative pain
Transdermal System (Butrans, buprenorphine transdermal system, 2010)	5 mcg/hr (if < 30mg oral morphine equivalents per day) or 10-20 mcg/hr (if 30-80mg oral morphine equivalents per day)	5, 7.5, 10, 15, 20 mcg/hr	72	26 (after patch removal)	7-day Transdermal patch
Buccal Film (Belbuca, buprenorphine buccal film, 2015)	75mcg daily or q12h (for first 4 days) - 900mcg q12h	75, 150, 300, 450, 600, 750, 900 mcg	2.5–3	16.4–38.8	dosed daily or q12h, has an adhesive and blocking layer to help fully absorb, peppermint flavored

Buprenorphine formulations

Indicated for Opioid Use Disorder					
Sublingual Tablet (Subutex [now only generic], buprenorphine, 2002)	2-8mg daily (first day) - 24mg daily	2mg, 8 mg	1.6-4.0	31-35	may be safer for use in pregnancy because does not contain naloxone
Sublingual Film (Suboxone [also generic], buprenorphine and naloxone, 2002)	2-8/.05-2 mg daily (first day) - 24/6mg daily	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg (buprenorphine/naloxone)	0.5–2.5	24–42 (buprenorphine) 2–12 (naloxone)	sublingual film absorbs faster than the tablet
Sublingual Tablet (Zubsolv, buprenorphine and naloxone, 2013)	1.4-2.8/0.36-0.72mg (1st dose, up to 5.7/1.4mg 1st day) - 17.1/4.2mg daily	0.7 mg/0.18 mg 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg (buprenorphine/naloxone)	0.5–2.5	24–42 (buprenorphine 2–12 (naloxone)	higher bioavailability vs. Subutex or Suboxone - 2.9mg of buprenorphine in Zubsolv equivalent to 4mg in Suboxone
Buccal Film (Bunavail, buprenorphine and naloxone,2014)	2.1/0.3mg - 12.6mg/2.1mg daily	2.1 mg/0.3, mg 4.2 mg/0.7 mg, 6.3 mg/1 mg (buprenorphine/naloxone)	0.5–2.5	16.4–27.5 (buprenorphine) 1.9–2.4 (naloxone)	has an adhesive and blocking layer to help fully absorb, citrus flavored

Buprenorphine formulations

Implant (Probuphine, buprenorphine implant, 2016)	74.2mg (1 dose only), 4 implants at a time	74.2 mg of buprenorphine per implant released over 6 months	12	24-48	cannot be dosed more than 8mg sublingual equivalents daily; implants must be removed after completion of 6 month dosing interval
Long acting injectable (Sublocade, buprenorphine extended-release, 2017)	300mg first 2 months, 100mg monthly after	100mg/0.5mL, 300mg/1.3mL prefilled syringe	24	terminal plasma half life: 43-60 days	subcutaneous injection in abdomen; forms a hard nodule in subcutaneous space, requires refrigeration before administration
Long acting injectable (Buvidal [EU], Brixadi [us] CAM-2038 q1w, approval in EU and tentative FDA approval 2018)	8-32mg weekly	8mg, 16mg, 24mg, 32mg prefilled syringe	20	5 days	subcutaneous injection in upper arm, abdomen, or buttocks; forms soft gel in subcutaneous space
Long acting injectable (Buvidal [EU], Brixadi [US] CAM-2038 q4w, approval in EU and tentative FDA approval 2018)	64-128mg monthly	64mg, 96mg, 128mg, 160mg prefilled syringe	4-10	19-25 days	

Sublingual Buprenorphine and Buprenorphine-Naloxone Tablets and Film

- Suboxone for maintenance treatment
- Subutex for medically supervised withdrawal
- sublingual buprenorphine-naloxone film:
- faster absorption,
- easier to cut and
- divide into multiple daily doses

Buprenorphine Implant

- Probuphine: implantable formulation
- 6-month duration of action
- long-term maintenance treatment
- 8mg/day or less of sublingual buprenorphine
- four plastic rods,
- each containing 80mg of buprenorphine
- inserted under the skin of the upper arm
- 0.5ng/ml to 1.0ng/ml range

Extended-Release Injectable Buprenorphine

- Sublocade: SC injectable formulation
- one-month duration of action
- after at least 7 days of transmucousal Bup
- prefilled syringes, refrigerated until use
- 300mg (2 months) and 100mg (4 months)
- injected under the skin of the abdomen
- 2.19 ng/ml : 12mg/day (1.71) and 24mg/day (2.91)

سپاس از توجه شما