SITOX
19° Congresso Nazionale
Società Italiana di Tossicologia
BOLOGNA
11-12 Febbraio 2020
Savoia Regency Hotel
Paracelso nel XXI secolo:
«Dosis sola facit, ut venenum non fit»

Trattamento della dipendenza da oppiacei: certezze e nuove prospettive

Dr. Lorenzo SOMAINI
Servizio Dipendenze, ASL Biella
lorenzo.somaini@aslbi.piemonte.it

S.I.Pa.D.
Società Italiana Patologie da Dipendenza
AZIENDA SANITARIA LOCALE DI BIELLA

Disclosure

Dr Somaini has been involved in previous work for companies on

opioid use disorder

- MOLTENI FARMACEUTICI
- INDIVIOR
- CAMURUS
- GILEAD
- MERCK

Overview: what is treatment and what is the expected benefit?

Components of effective integrated OUD care

1 Pharmacotherapy	2 Harm reduction	3 Psychosocial & behavioral therapies
• Buprenorphine, methadone, other	• Needle equipment programs	• Peer support, counselling, talking therapy

General healthcare: HCV, mental health. smoking, COPD, …

Access to **good quality treatment** saves lives, reduces illicit drug use, improves long term quality of life, reduces overdose risk, and reduces criminal behaviour

Source: NICE 2007 (UK), Public Health England 2014, DoH 2017 (UK, Clinical guidelines for Drug misuse and dependence)

Risks related to people with opioid use disorder (OUD)

Mortality

- Level of mortality is 15x higher in people who inject drugs[1]

Health

- 78% transmissions of HCV are attributable to injecting drugs[2]

Unemployment

- Problematic substance use increases likelihood of unemployment[3]

Crime

- 80% of people with OUD involved in crime[4]

Source: 1. UNODC 2015, 2. EMCDDA 2016, 3. Henkel 2011, 4. RKI 2016

What are the goals of intervention in opioid use disorder?

Evolution of treatment goals

- Limit crime and HIV, HCV transmission
- Needle equipment programs
- Methadone

- Access to integrated care, pharmacotherapy
- Harm reduction

- Towards normal living?
- Someone to love, somewhere to live, something to do

Source: Edwards 2014

OUD therapy is associated with lower all-cause mortality

Meta analysis of **all-cause** mortality in patients in OUD care. Data shown for patients on methadone (N=122,885, 1-14 y)

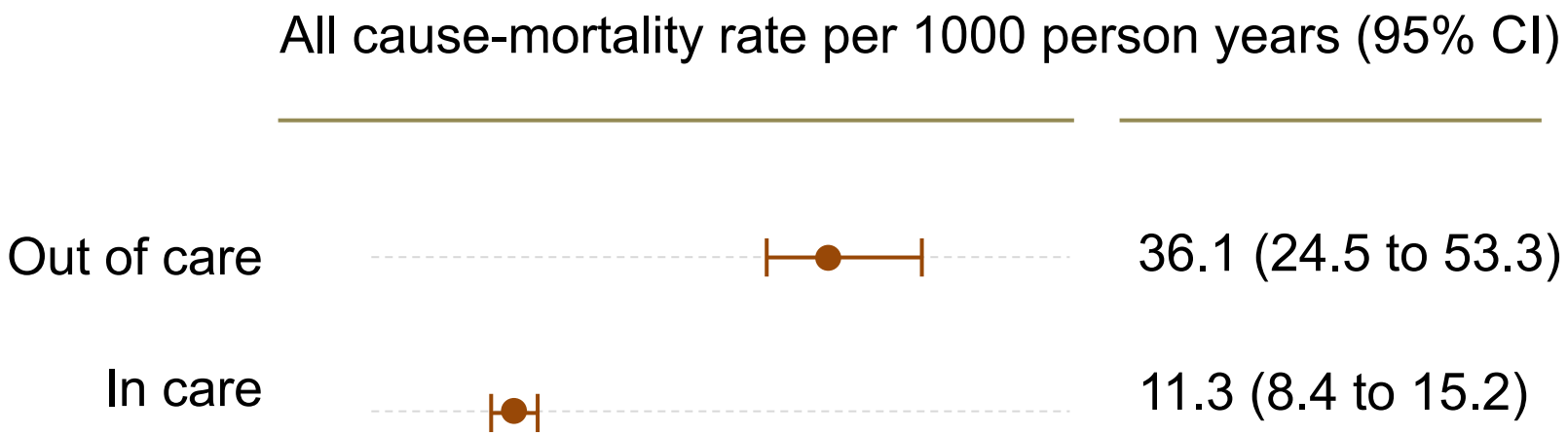


Figure adapted from Sordo 2017

OUD therapy is associated with lower overdose mortality rate

Meta analysis of **overdose** mortality in patients in OUD care. Data shown for patients on methadone (N=122,885, 1-14 y)

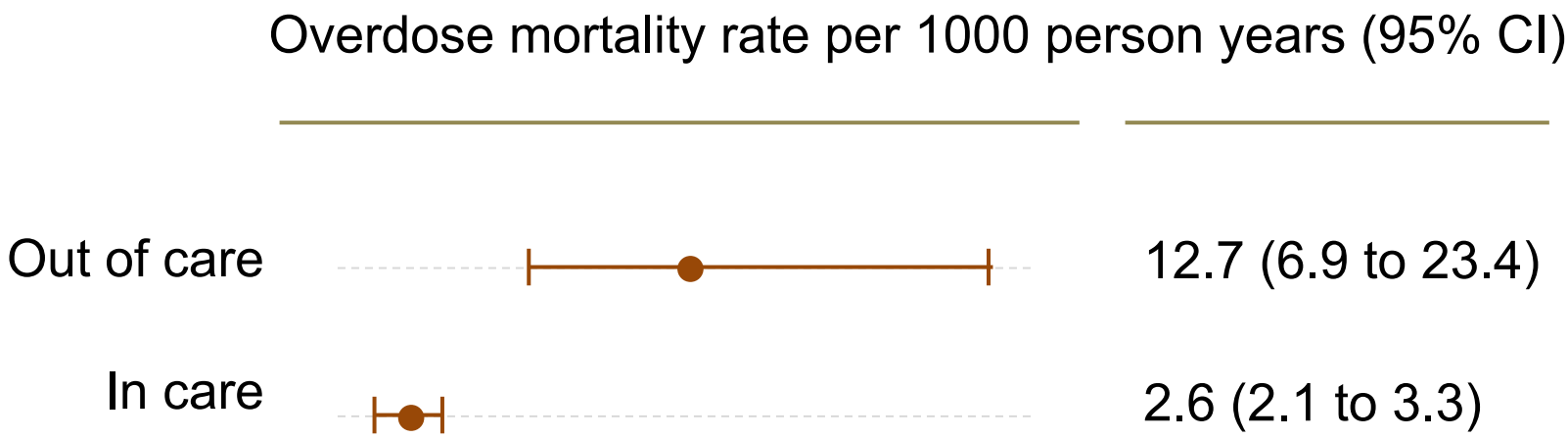


Figure adapted from Sordo 2017

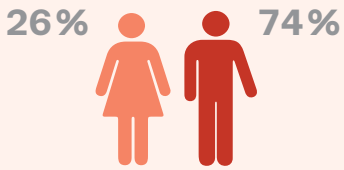
Danni correlati al consumo di droga e relative risposte

PAZIENTI IN TERAPIA SOSTITUTIVA PER LA DIPENDENZA DA OPPIACEI

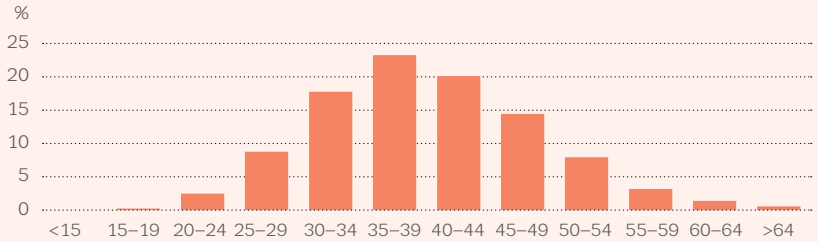
Popolazione

628 000 UE

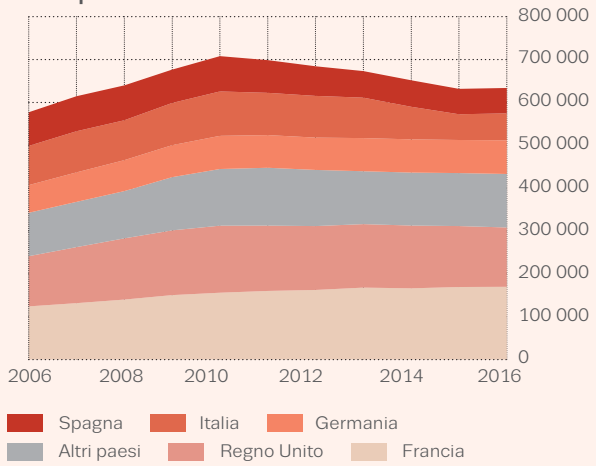
636 000 UE + Norvegia



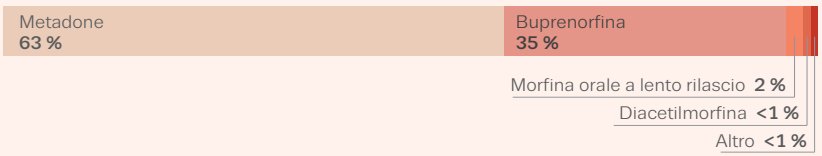
Distribuzione per età



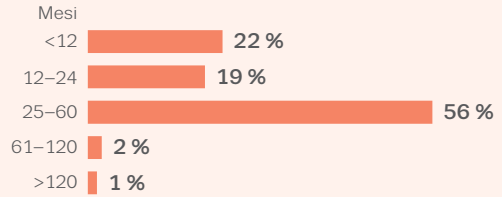
Tendenze nel numero di pazienti in terapia sostitutiva



Tipo di farmaco



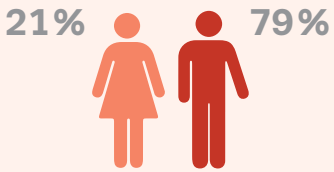
Durata del trattamento



Danni correlati al consumo di droga e relative risposte

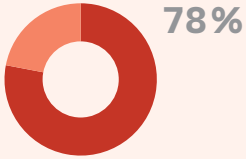
DECESSI CAUSATI DAL CONSUMO DI STUPEFACENTI

Caratteristiche

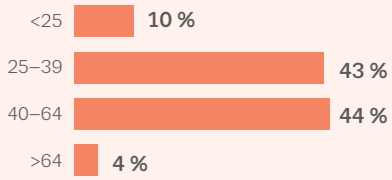


Età media al decesso: **39** anni

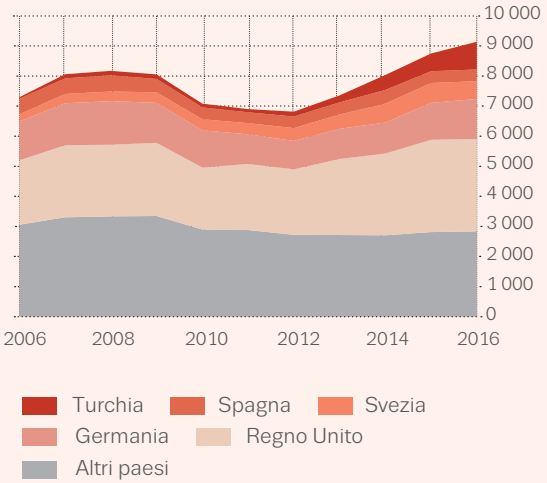
Decessi con presenza di oppiacei



Età al decesso



Tendenze nei decessi per overdose



Numero di decessi

NB: dati per Stati membri dell'UE, Turchia e Norvegia (UE + 2).

OUD treatment is available: pharmacological and psychosocial interventions

Pharmacological

- Methadone, buprenorphine, buprenorphine/ naloxone, naltrexone

Psychosocial

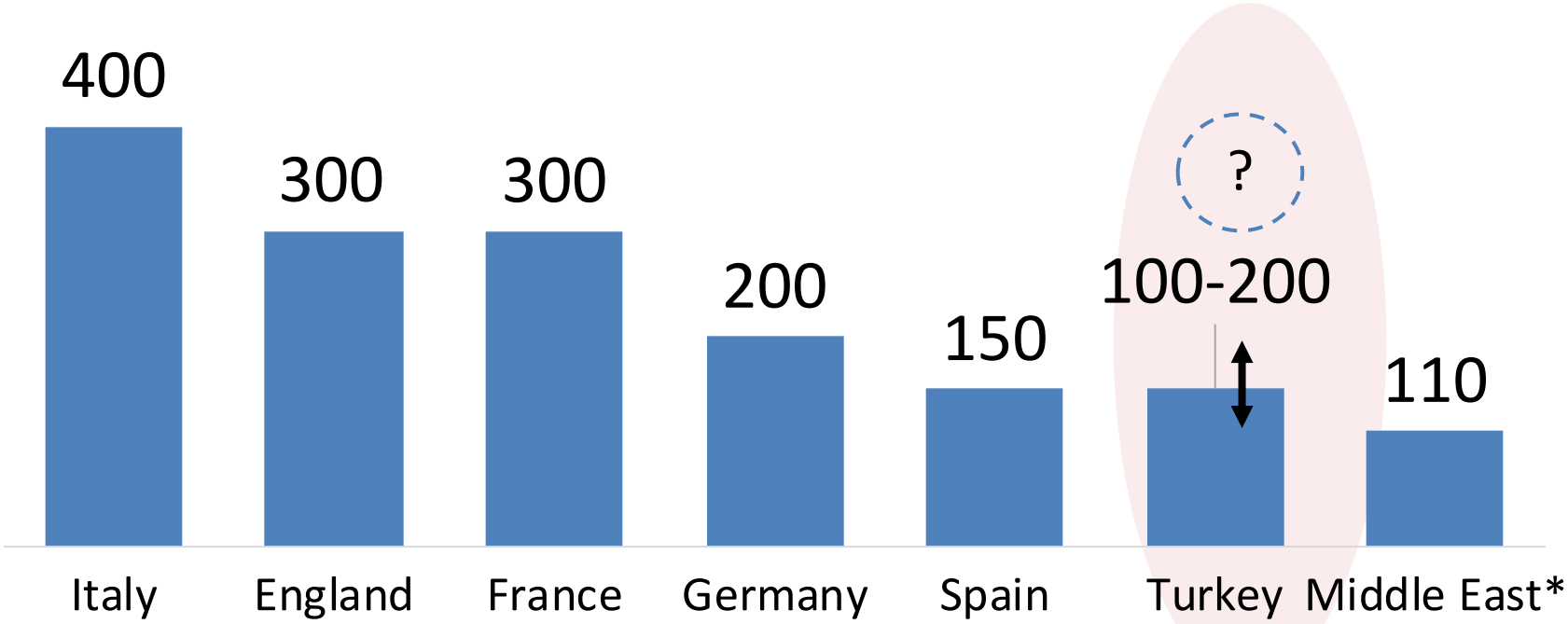
- Individual/ group therapy, cognitive behavioural therapy etc…

Integrated treatment programs involving pharmacological and psychosocial interventions are proven to be effective

Source: Dugosh 2016

In Europe and Middle East, an estimated 2M people may need OUD care

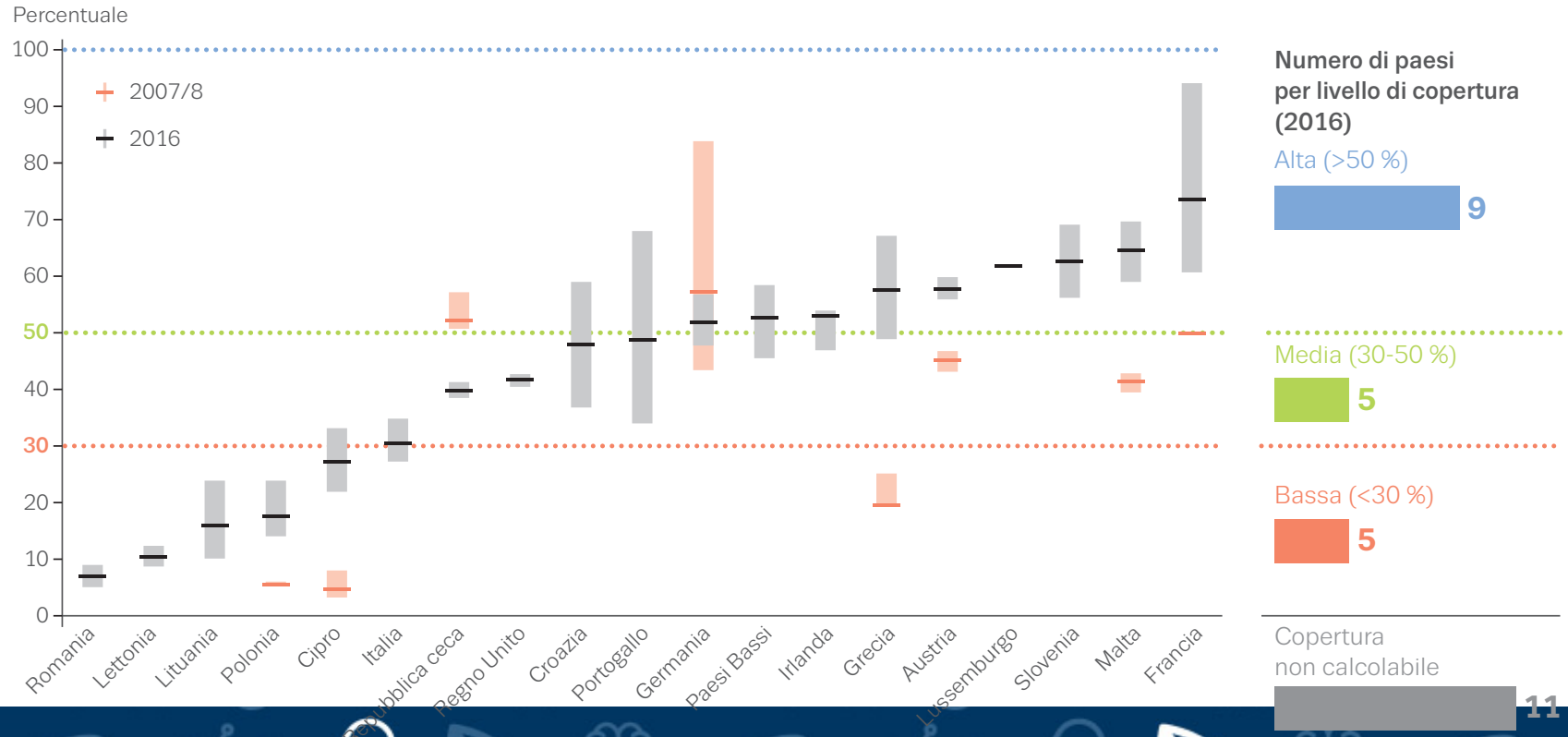
Estimated number of people with OUD (K)



*Focused countries include Bahrain, Egypt, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, UAE, Estimated based on publication and expert viewpoints. Source: Wright 2017, Wright ISAM/ CSAM-SMCA Montreal presentation 2016, Mumtaz 2014, UNODC 2012, Alam-mehrjerdi 2014

Danni correlati al consumo di droga e relative risposte

Copertura del trattamento sostitutivo per la dipendenza da oppiacei (percentuale della stima dei consumatori di oppiacei ad alto rischio che ricevono l'intervento) nel 2016 o nell'anno più recente e nel 2007-2008



Three status of treatment archetypes defined, based on level of access to therapy

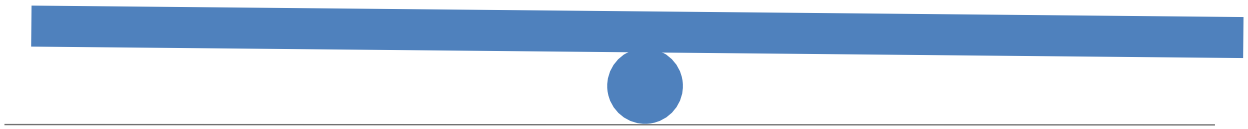
Type	Approach to OUD	In care (%)	Countries
Progressive	OAT widely available, some barriers	50	Italy, England, France, Germany, Spain
Evolving	OAT available, access limited	5-40	Turkey, Iran, Kuwait, Lebanon, UAE
Restricted	Other treatment, OAT not available	0	Bahrain, Egypt, Saudi Arabia, Oman

Source: Wright 2017, Wright ISAM/ CSAM-SMCA Montreal presentation 2016, Mumtaz 2014, UNODC 2012, Alam-mehrjerdi 2014

Overview: which factors determine access to treatment?

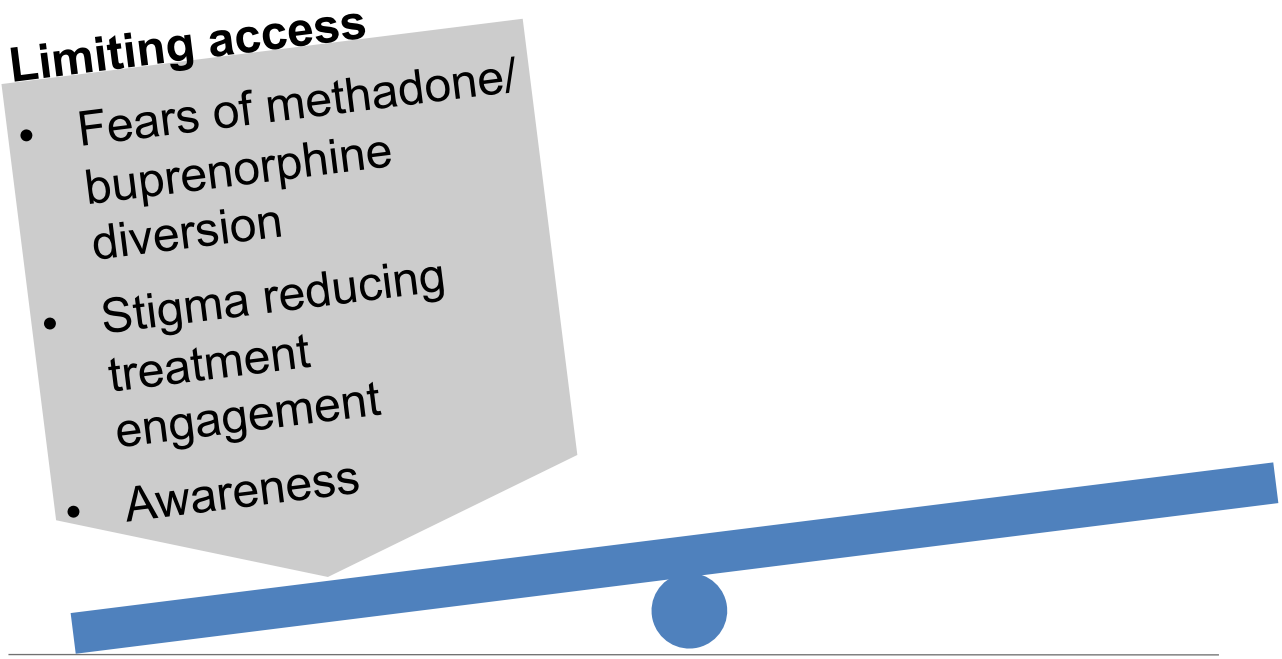
Which factors limit access to treatment?

Which factors promote access to treatment?



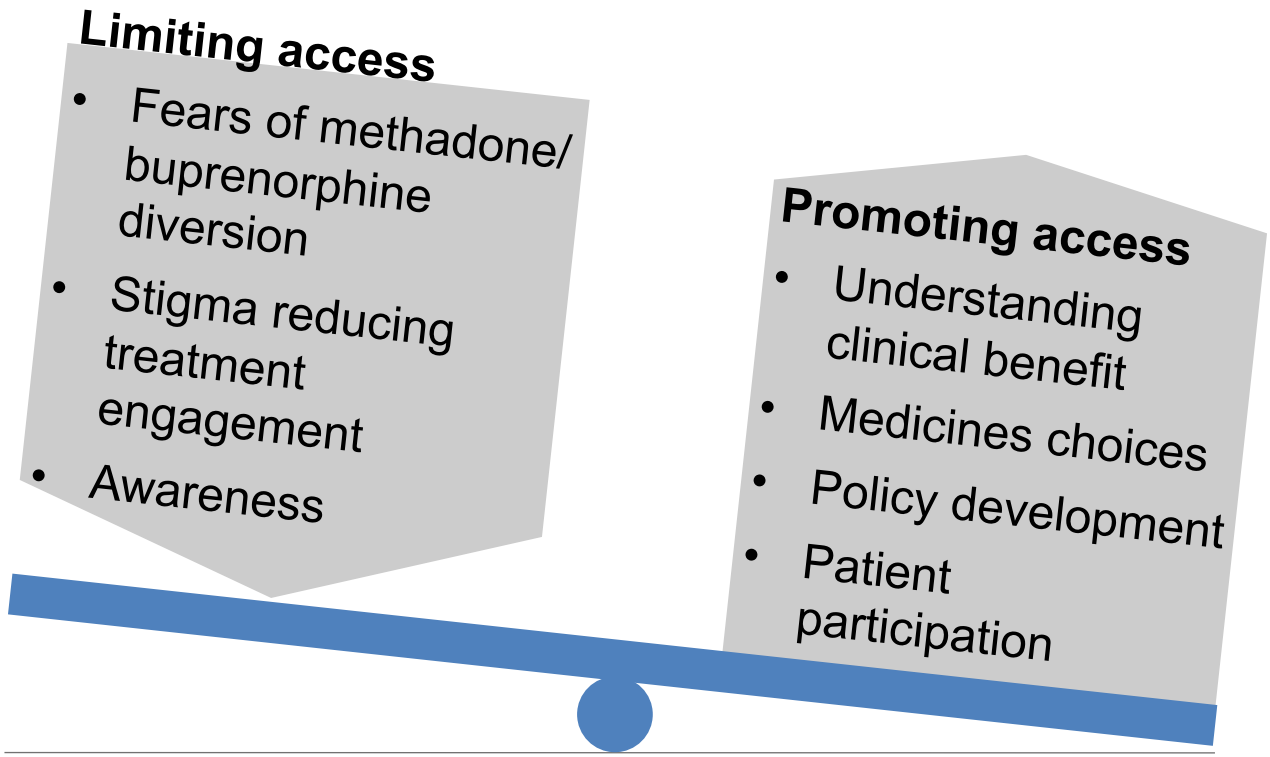
Source: NICE 2007 (UK), Public Health England 2014, DoH 2017 (UK, Clinical guidelines for Drug misuse and dependence)

Overview: treatment for OUD limited access due to stigma, fears of diversion, awareness?



Source: NICE 2007 (UK), Public Health England 2014, DoH 2017 (UK, Clinical guidelines for Drug misuse and dependence)

Overview: treatment for OUD limited access due to stigma, fears of diversion, awareness?



Source: NICE 2007 (UK), Public Health England 2014, DoH 2017 (UK, Clinical guidelines for Drug misuse and dependence)

Key challenge: why is treatment engagement limited?

Reasons for not engaging in treatment:

Stigma

Therapy pathway/ daily treatment difficult

System rules/ obligations

Failed previous therapy experience

Lack of infrastructure, capabilities

Source: Stöver 2011, Finkelstein 2011, speaker analysis

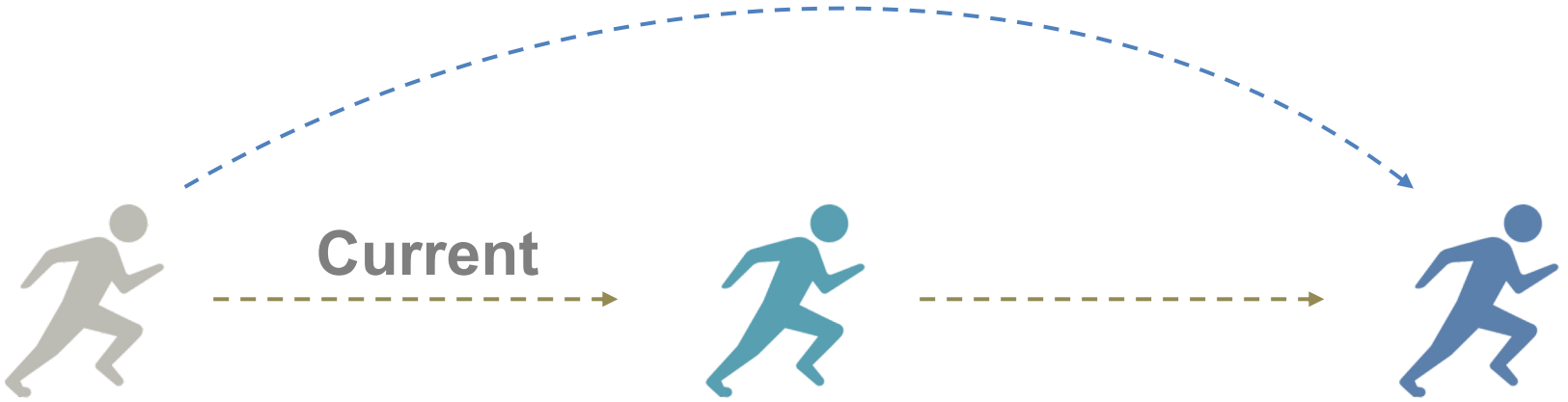
Future vision of OUD care: goals & innovation options

Goals	Future innovation
More choice Planning treatment on an individual basis	**Medication** New meds, reduce risk, burden of care?
Better data AI to really understand patient needs?	**Tools** Digital tools for psychological therapy

Source: DDN Feb 2018, speaker analysis

How can innovation advance OUD care in countries where treatment is more limited?

Jump to lead best practice with focus on innovation



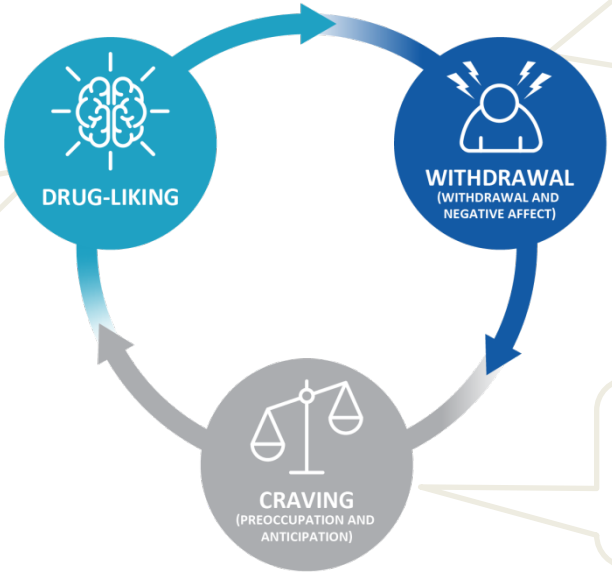
Detox/ no treatment

Current limited therapy (methadone problems, engagement)

Full potential therapy

There is potential to leap ahead and avoid key challenges associated with existing approaches for maintenance therapy

The three pillars in addiction treatment



Drug liking
- Positive response to a drug that causes pleasure or euphoria, increasing the probability of further drug taking

Withdrawal
- Drives use of opioids and related substances to alleviate or avoid the noradrenergic storm experienced by dependent patients

Craving
- Intense desire or compulsion to take opioids

Adapted from: US Department of Health and Human Services. Facing addiction in America: The Surgeon General's report on alcohol, drugs, and health. 2016.

- OUD, opioid use disorder.

1. US Department of Health and Human Services. Facing addiction in America: The Surgeon General's report on alcohol, drugs, and health. Washington, DC: HHS, 2016.
Available at: www.ncbi.nlm.nih.gov/books/NBK424857/pdf/Bookshelf_NBK424857.pdf (accessed January 2019).

How can innovation improve treatment outcomes?

	Innovation	Future, expected new options
Patient	Medication	• Depot forms of OUD medication[1]
Patient	Non-medication	• Technology-driven affordable and on-demand mental health support (e.g. Tess[2], Woebot[3])
System	Data	• Better data sharing to integrate substance misuse services between prison and community[4]

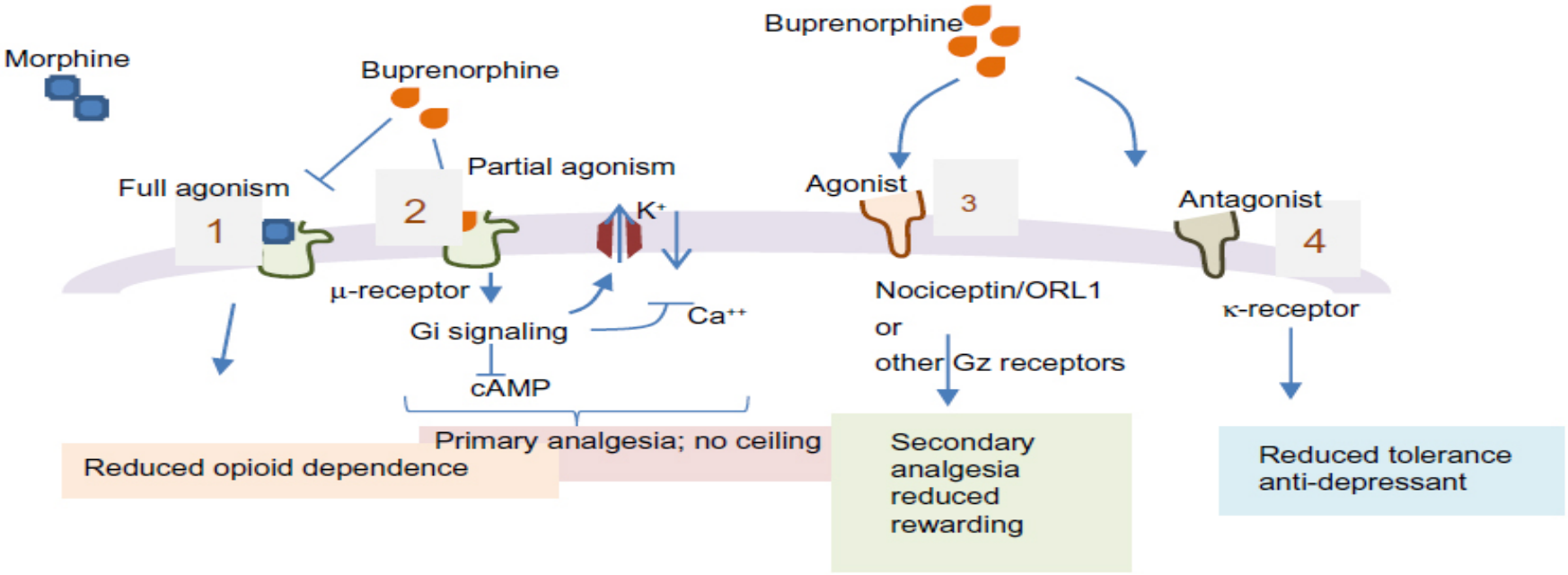
Source: 1 Itzoe 2017, 2. X2 AI, 3. Woebot, 4. NHS England 2018

New products in OUD care: depot forms of buprenorphine

Company	Product
TITAN PHARMACEUTICALS	Buprenorphine implant for subdermal administration[1]
INDIVIOR	Buprenorphine extended-release injection[2]
camurus	Long-acting buprenorphine[3]

Pharmacology of buprenorphine

Opioid receptor	Ki (nM)	Agonist/antagonist
μ	1.5	Partial agonist
δ	6.1	Antagonist
κ	2.5	Antagonist
Nociceptin or ORL1	77.4	Agonist



Development Objectives of Depot medication

- **Achieve opioid blockade**
  - from the first dose and across the entire dosing interval
  - at buprenorphine plasma concentrations that are well-tolerated
- **Achieve clinically significant control of craving and withdrawal symptoms**
- **Reduce illicit opioid use**
- **Limit possibility of abuse/misuse, diversion, and accidental overdose**

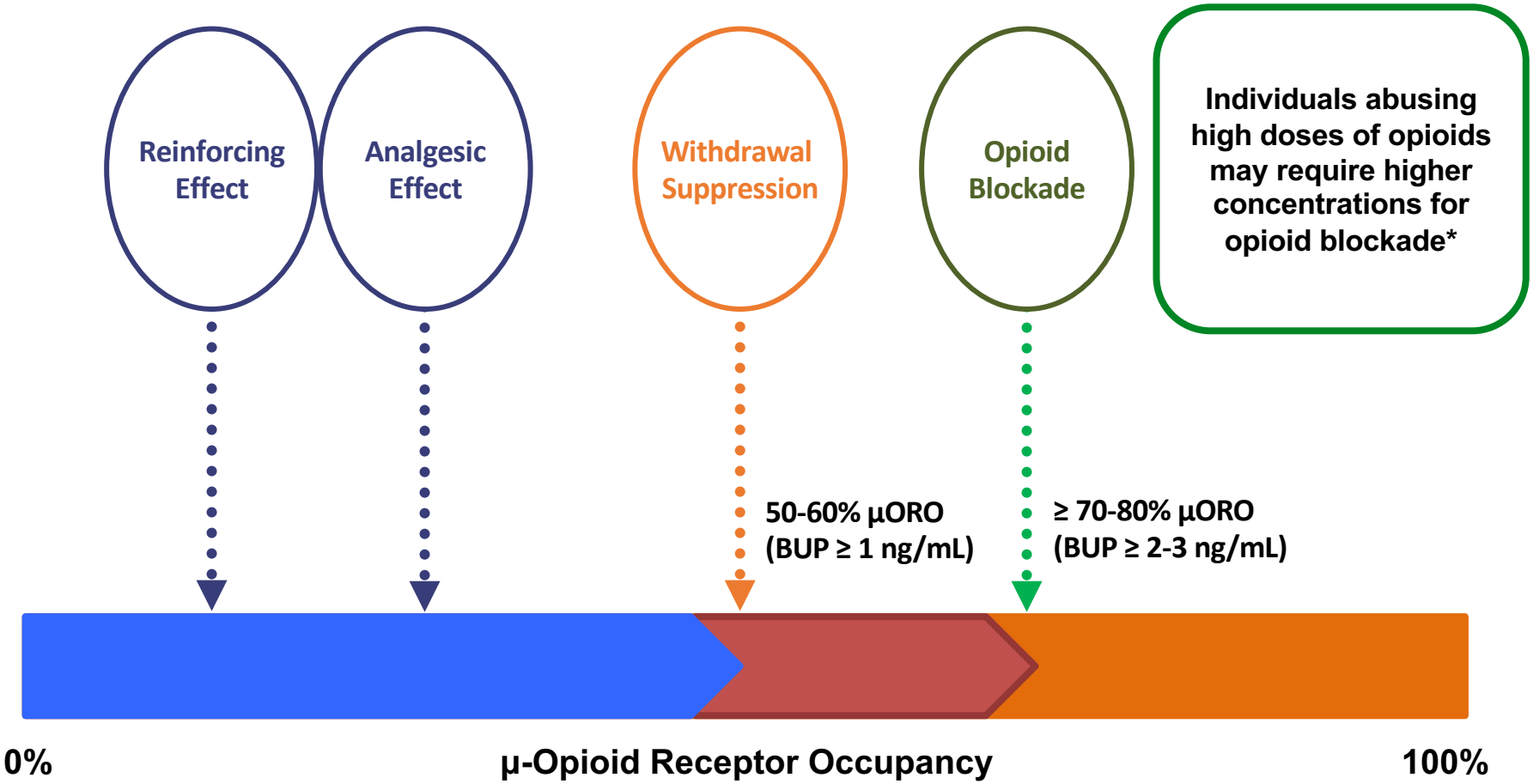
NARCOTIC BLOCKADE— A MEDICAL TECHNIQUE FOR STOPPING HEROIN USE BY ADDICTS*

By VINCENT P. DOLE, MARIE E. NYSWANDER AND MARY JEANE KREEK

NEW YORK, NEW YORK

(From Rockefeller University and Beth Israel Medical Center, New York, New York)

Effect of μu-Opioid Receptor Occupancy on Withdrawal Suppression and Blockade of Opioid Subjective Effects



1. Greenwald M et al. *Biol Psychiatry*. 2007;61(1):101-110. **2.** Greenwald M et al. *Drug Alcohol Depend*. 2014;144:1-11. **3.** Nasser AF et al. *Clin Pharmacokinet*. 2014;53:813–824

Depot product characteristics (1)

	Titan	Indivior	Camurus
Drug delivery technology	Implantable rods	Atrigel	Fluid crystal
Duration	6 months	≥ 1 month	1 week (q1w) & 1 month (q4w)
Buprenorphine dose	80 mg	100 mg & 300 mg	8, 16, 24, 32 mg (q1w) 64, 96, 128, 160 mg (q4w)

Source: FDA , Molteni 2020, Indivior 2017, Camurus 2018

Depot product characteristics (2)

	Titan	Indivior	Camurus
Administration	Subdermal implant in upper arm	Subcutaneous injection in abdomen	Subcutaneous injection in abdomen, upper arm, thigh or buttock
Injection volume	-	0.5 & 1.5 mL	0.16 – 0.64 mL
Delivery device	4 implantable rods	Prefilled syringe (19G)	Prefilled syringe (23G)
Storage	Room temperature	Refrigerated 2 - 8°C Room temperature for 7 days	Room temperature

Source: FDA, Molteni 2020, Indivior 2017, Camurus 2018

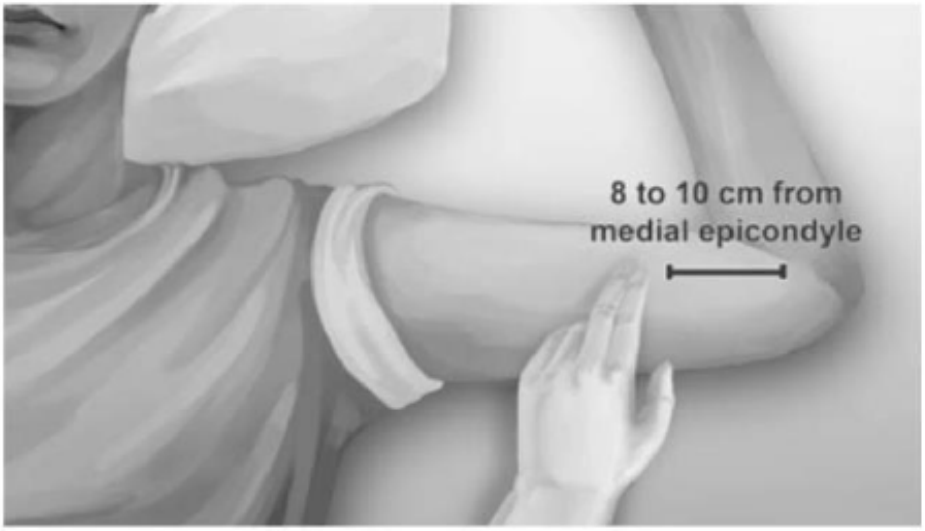
Pharmacodynamics

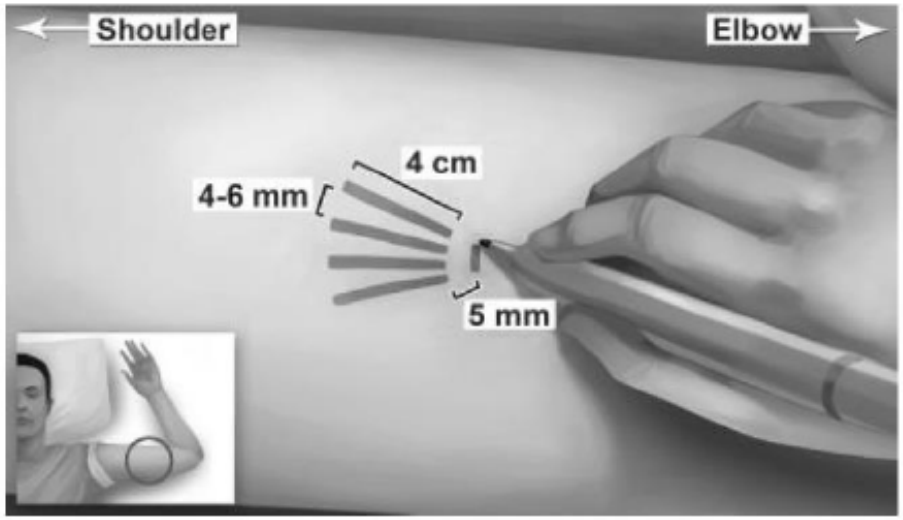
- Each Implant contains 80 mg of buprenorphine HCl uniformly distributed throughout the ethylene vinyl acetate co-polymer (EVA) matrix
- 4 Implants inserted subdermally in the upper arm
- Continuous delivery over 6 months

- Four implants deliver circulating drug blood levels comparable to the average plasma concentrations observed following daily doses of: 8 mg Subutex or Suboxone tablet equivalent.

Source: Molteni 2020

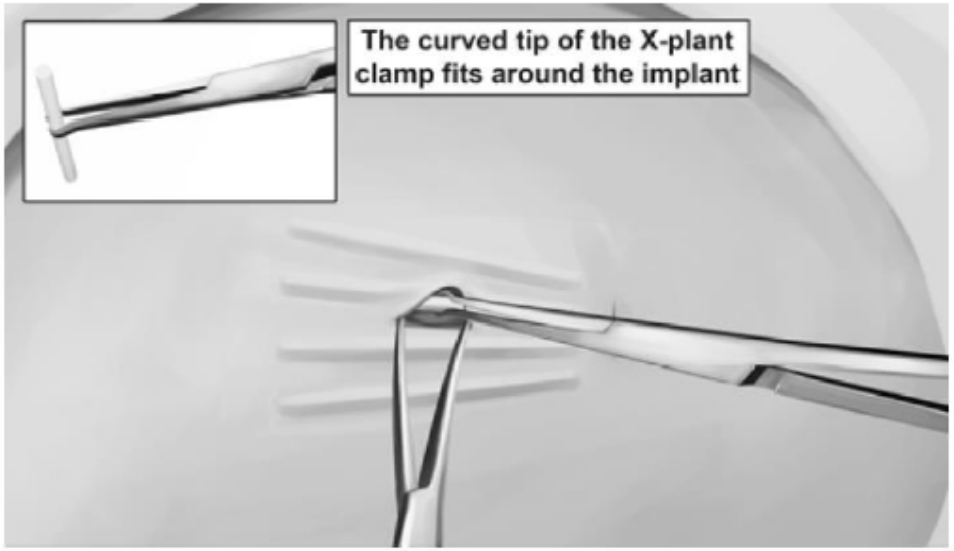
Details on implant insertion procedures





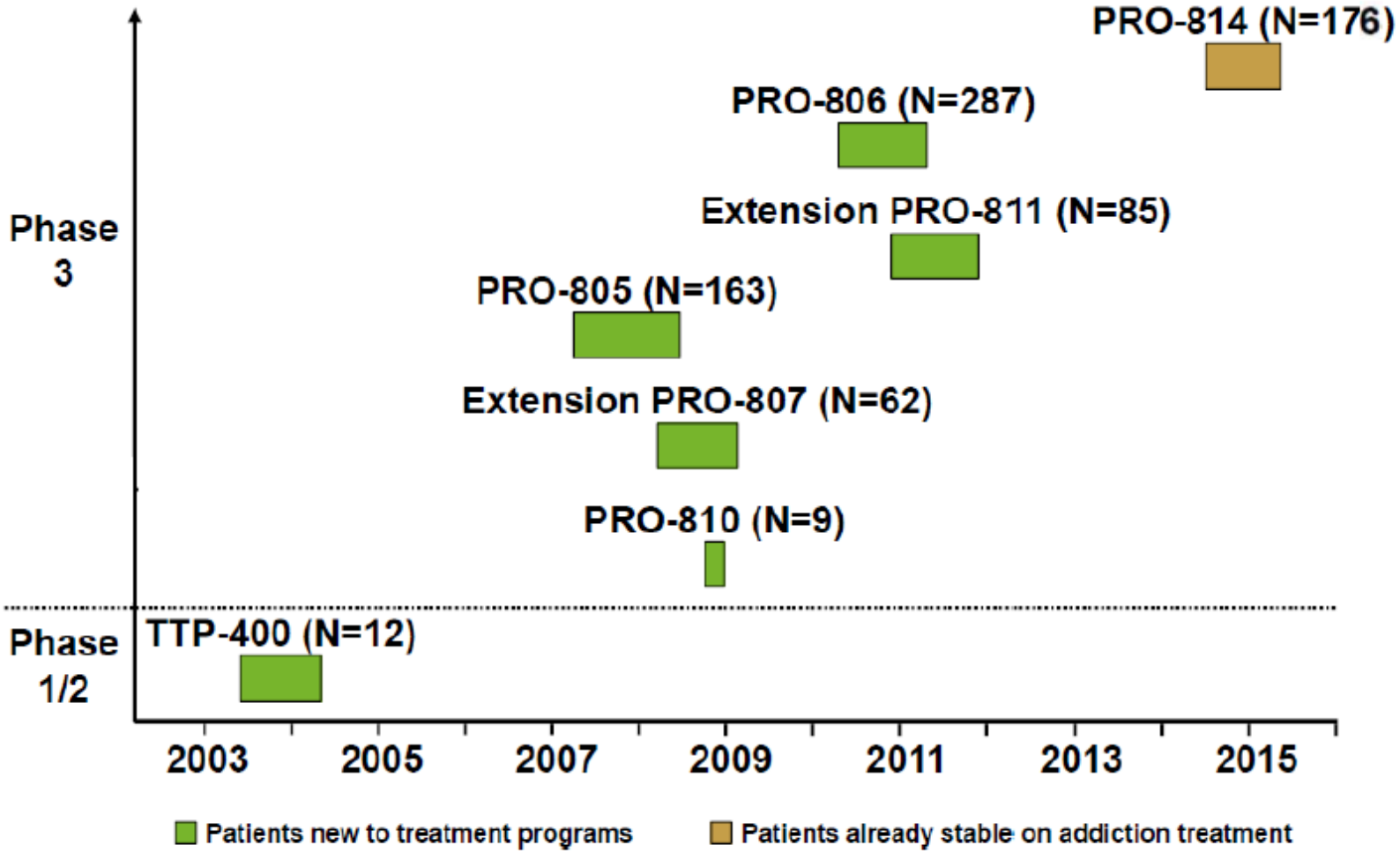
Source: Molteni 2020

Details on implant removal procedures



Source: Molteni 2020

Overview Probuphine clinical program



Source: Molteni 2020

Summary of phase 3 clinical program results

- Efficacy and safety was shown in 3 randomized, controlled Phase 3 studies (805, 806, 814); All studies met their pre-specified primary and secondary endpoints.
- Study PRO-805 demonstrated superiority over placebo.
- Study PRO-806 showed superiority over placebo, and non-inferiority to open-label, sublingual buprenorphine/naloxone (12-16 mg/day)
- Study PRO-814 demonstrated non-inferiority of Probuphine to sublingual buprenorphine/naloxone (≤8 mg/day).

Source: Molteni 2020

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine

A Randomized Clinical Trial

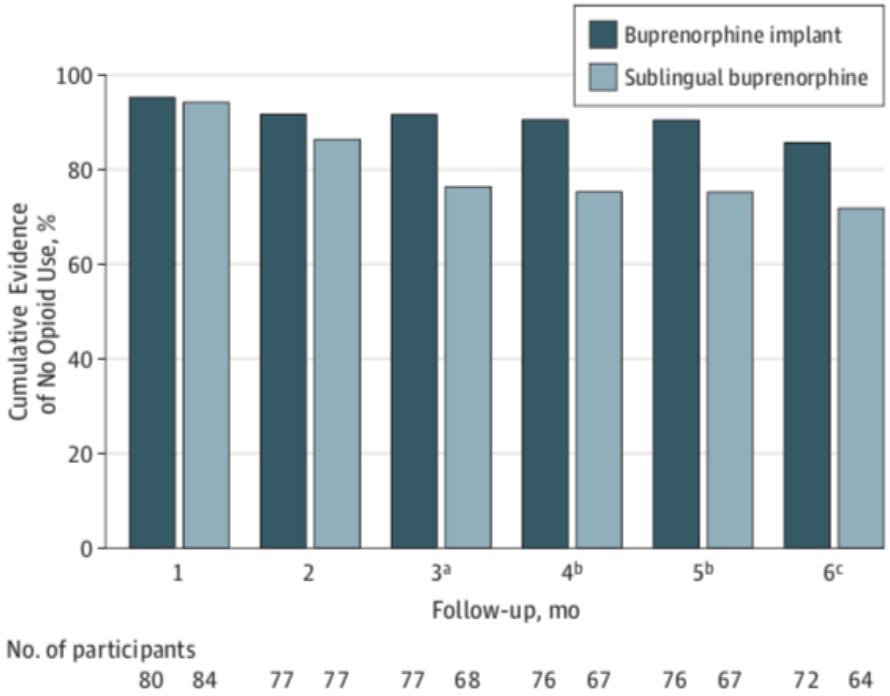
- Randomized double-blind, double-dummy study in adults who met DSM-IV-TR criteria for opioid dependence as their primary diagnosis and clinically stable on 8mg or less of sublingual buprenorphine
- 176 subjects randomized 1:1 to either:
  - Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
  - Four 80 mg Probuphine implants + daily SL placebo tablets
- Patients were seen monthly for 6 months and were also required to provide 6 scheduled, 4 randomly-scheduled urine samples for toxicology.
- Efficacy was evaluated through urine toxicology screening and patient self-report to detect opioid use, over the 6-month treatment period.

Rosenthal et al. JAMA 2016

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine

A Randomized Clinical Trial

Proportion with no evidence of illicit opioid use over 6-mo follow-up (Bup implant, N=87, Bup sublingual, N=89)



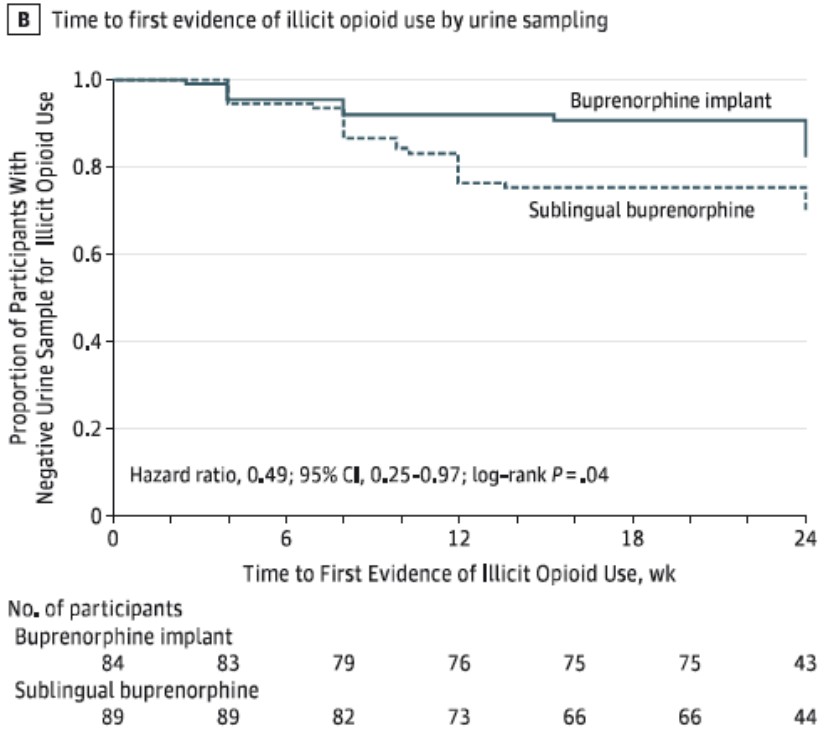
Relative to sublingual buprenorphine, a larger proportion of participants receiving buprenorphine implants demonstrated no evidence of illicit opioid use throughout 6 months of treatment

Rosenthal et al. JAMA 2016

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine

A Randomized Clinical Trial

Time to first evidence of illicit opioid use by urine sampling



Time to first evidence of illicit opioid use was significantly longer for buprenorphine implants relative to sublingual buprenorphine (hazard ratio, 0.49; 95% CI, 0.25-.97; *P* = .04)

Rosenthal et al. JAMA 2016

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine

A Randomized Clinical Trial

Adverse events (1) occurring in ≥2% of participants receiving buprenorphine implants and all adverse events related to implant site. One instance of accidental pediatric exposure occurred in the sublingual buprenorphine group.

	No. (%) of Participants	
	Buprenorphine Implants (n = 87)	Sublingual Buprenorphine (n = 89)
Non-implant site related		
Participants with ≥1 adverse event	42 (48.3)	47 (52.8)
Gastrointestinal	7 (8.0)	1 (1.1)
Constipation	4 (4.6)	0
Diarrhea	2 (2.3)	1 (1.1)
Vomiting	2 (2.3)	1 (1.1)
General pain, pain at administration site	2 (2.3)	1 (1.1)
Infections and infestations	20 (23.0)	17 (19.1)
Bronchitis	2 (2.3)	3 (3.4)
Viral gastroenteritis	4 (4.6)	3 (3.4)
Influenza	2 (2.3)	3 (3.4)
Localized infection	2 (2.3)	0
Nasopharyngitis	7 (8.0)	4 (4.5)
Sinusitis	2 (2.3)	2 (2.2)
Urinary tract infection	4 (4.6)	3 (3.4)
Nervous system disorders	8 (9.2)	3 (3.4)
Headache	6 (6.9)	3 (3.4)
Somnolence	2 (2.3)	0
Psychiatric disorders	8 (9.2)	5 (5.6)
Anxiety	3 (3.4)	4 (4.5)
Depression	6 (6.9)	2 (2.2)
Hypertension	2 (2.3)	2 (2.2)

Rosenthal et al. JAMA 2016

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine

A Randomized Clinical Trial

Adverse events (2) occurring in ≥2% of participants receiving buprenorphine implants and all adverse events related to implant site. One instance of accidental pediatric exposure occurred in the sublingual buprenorphine group.

Participants with ≥1 adverse event	20 (23.0)	12 (13.5)
Administration site conditions	12 (13.8)	7 (7.9)
Implant site pain	4 (4.6)	4 (4.5)
Implant site pruritus	4 (4.6)	1 (1.1)
Implant site bruising	1 (1.1)	1 (1.1)
Implant site erythema	1 (1.1)	1 (1.1)
Implant site hemorrhage	1 (1.1)	0
Peripheral edema	1 (1.1)	0
Device expulsion	0	1 (1.1)
Implant site discoloration	0	1 (1.1)
Infections and infestations	3 (3.4)	3 (3.4)
Cellulitis	1 (1.1)	1 (1.1)
Incision site infection	0	1 (1.1)
Purulent discharge	1 (1.1)	0
Wound infection	1 (1.1)	1 (1.1)
Skin and subcutaneous tissue disorders	2 (2.3)	3 (3.4)
Contact dermatitis	1 (1.1)	2 (2.2)
Rash	1 (1.1)	0
Skin irritation	0	1 (1.1)
Injury, poisoning, and procedural complications	2 (2.3)	1 (1.1)
Contusion	0	1 (1.1)
Incision site complication	1 (1.1)	0
Postoperative wound complication	1 (1.1)	0

Rosenthal et al. JAMA 2016

Depot BPN as SUBLOCADE™ (RBP-6000)

Monthly dose options

- 100 mg and 300 mg

- Ready-for-use in **prefilled syringe**
  - 0.5 ml or 1.5 ml
- Four-week **SC injection** by HCP (not to be dispensed to patient)
- **Cold-storage requirements** (4°C), can be stored at room temperature for 7 days
- Approved in **the US** and **Canada**; Australia and some EU countries submitted
- **Single** injection site (abdomen)

Food and Drugs Administration. FDA advisory committee briefing document: RBP-6000 (extended-release buprenorphine). https://www.fda.gov/media/108382/download [Accessed May 2019]
Indivior UK Ltd. Product monograph: SUBLOCADE. https://pdf.hres.ca/dpd_pm/00048406.PDF[Accessed May 2019]

Overview of RBP-6000 Clinical Development Program

- **Based on relationship between buprenorphine levels, mu-opioid receptor occupancy, and clinical effects on patients with OUD**

First-in-human (FIH) study
(20 mg)

Single ascending dose (SAD) Study
(50, 100, 200 mg)

Multiple ascending dose (MAD) study
(50, 100, 200, 300 mg)

Molecular weight (MW) study
(300 mg)

Opioid blockade (OB) study
(300 mg)

Phase 3, double-blind (DB), placebo-controlled study
(300/100, 300/300 mg)

Phase 3, long-term, open-label (OL) safety study
(300 mg → Flex dosing)

Treatment extension study
(Flex dosing)

OUD=opioid use disorder.
Indivior PLC. Data on file.

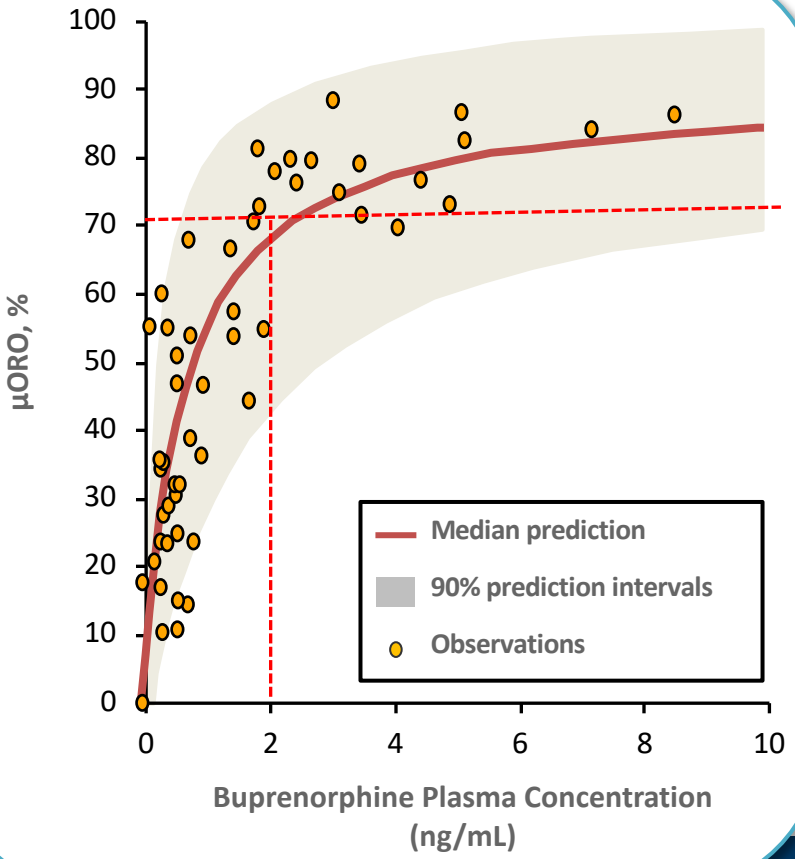
The Relationship Between Buprenorphine Concentration, Brain Mu-opioid Receptor Occupancy, and Pharmacodynamics Was Modeled in the Study

Pharmacodynamic Results

At least 70% receptor occupancy needed to achieve both:

- Suppression of subjective effects of a mu-opioid receptor full agonist (hydromorphone)
- Suppression of withdrawal symptoms

Mu-opioid Receptor Occupancy vs PK



PK=pharmacokinetic.

Nasser AF et al. *Clin Pharmacokinetics.* 2014;53(9):813-824.

Summary of Clinical Pharmacology

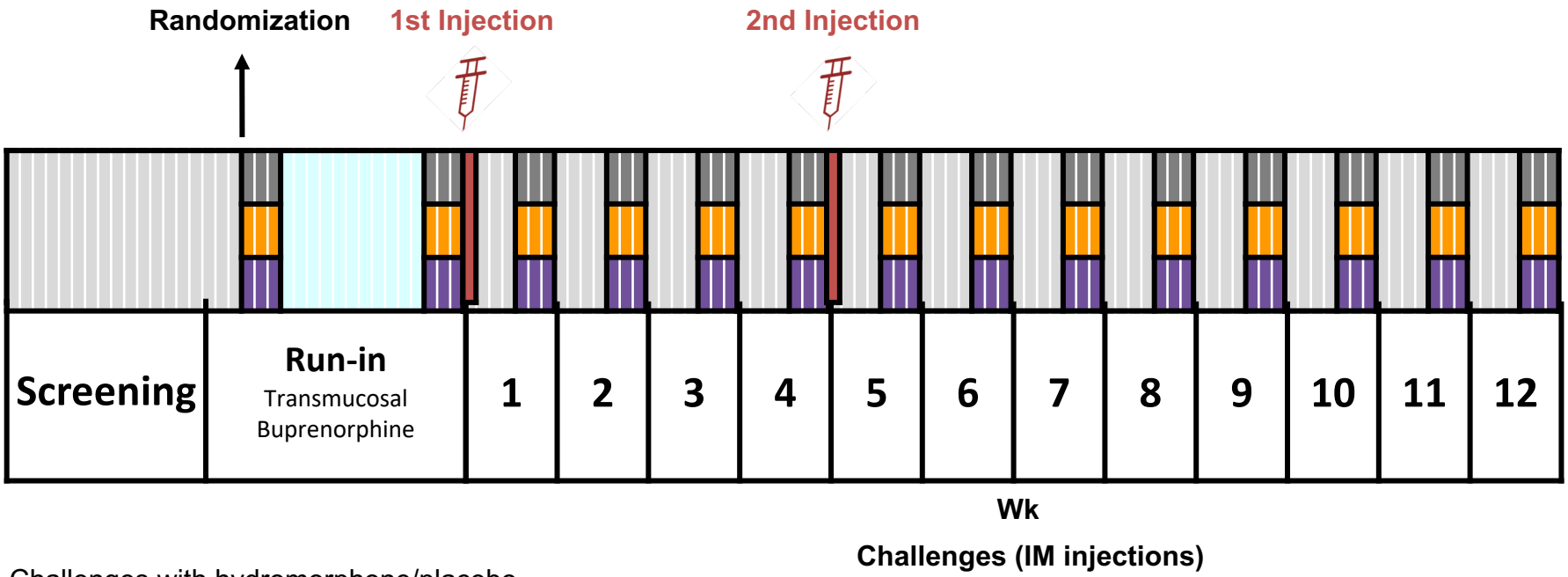
- RBP-6000 is designed based on totality of data to help maximize the benefits of buprenorphine for patients with OUD
- Clinical pharmacology program led to dosing regimens for phase 3

Doses	300/100 mg	300/300 mg
2 Initial Doses	300 mg provides opioid blockade from first dose[a]	
Subsequent Maintenance Doses[b]	100 mg would maintain average target concentrations (2 to 3 ng/mL)	300 mg would provide average levels of 5 to 6 ng/mL at steady-state

[a]Wide variability was seen across patients.
[b]Based on simulations.

1. Indivior PLC. Data on file. **2.** SUBLOCADE [prescribing information]. North Chesterfield, VA: Indivior Inc; 2018.

Opioid Blockade Study Designed to Assess Ability of RBP-6000 to Block Subjective Effects (VAS) of Mu-opioid Full Agonist[1,2]



Challenges with hydromorphone/placebo were administered in a randomized fashion on 3 consecutive days.

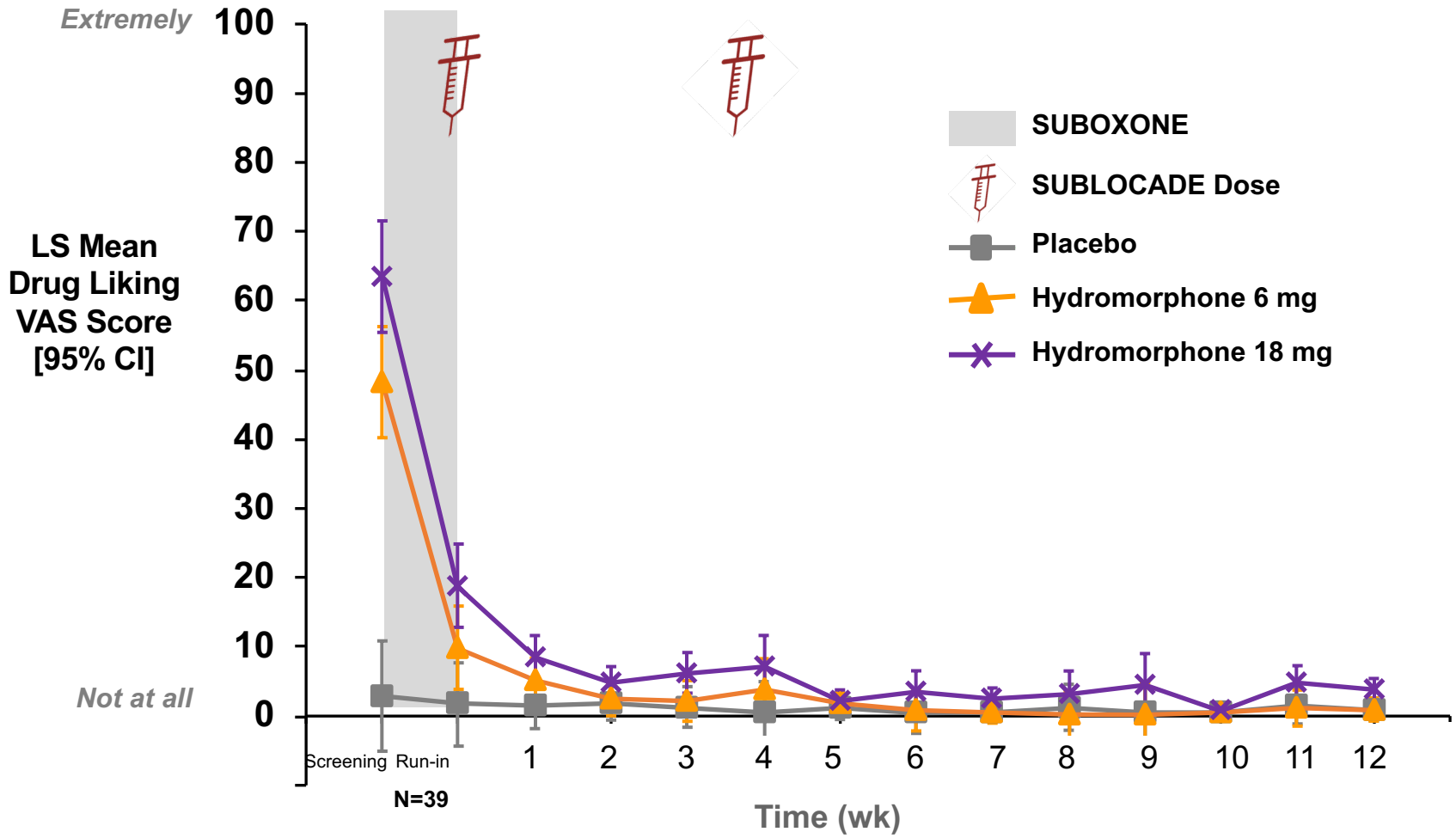
N=39 nontreatment-seeking, opioid-dependent patients. N decreased over the course of the study.

- Transmucosal Buprenorphine
- RBP-6000 300 mg
- Placebo
- Hydromorphone 6 mg
- Hydromorphone 18 mg

IM=intramuscular; VAS=visual analogue scale.

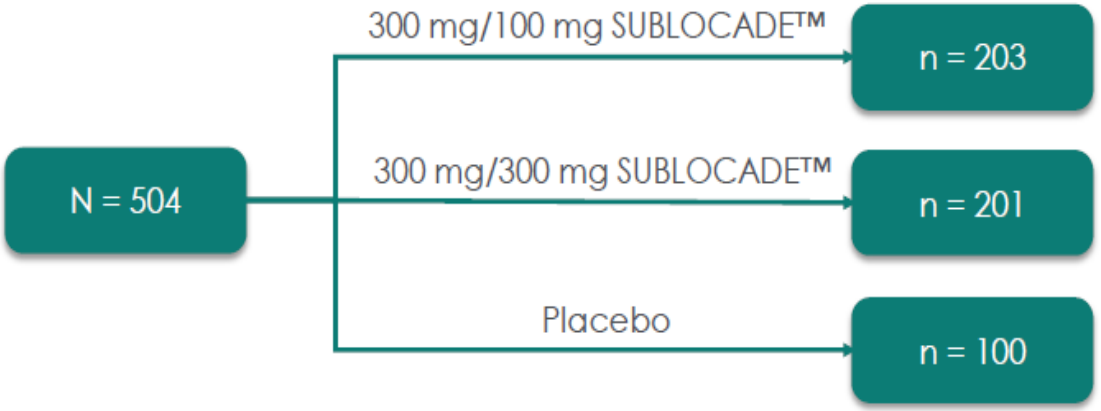
1. SUBLOCADE [prescribing information]. North Chesterfield, VA: Indivior Inc; 2018. **2.** Indivior PLC. Data on file.

RBP-6000 300 mg Blocked Opioid Subjective Effects



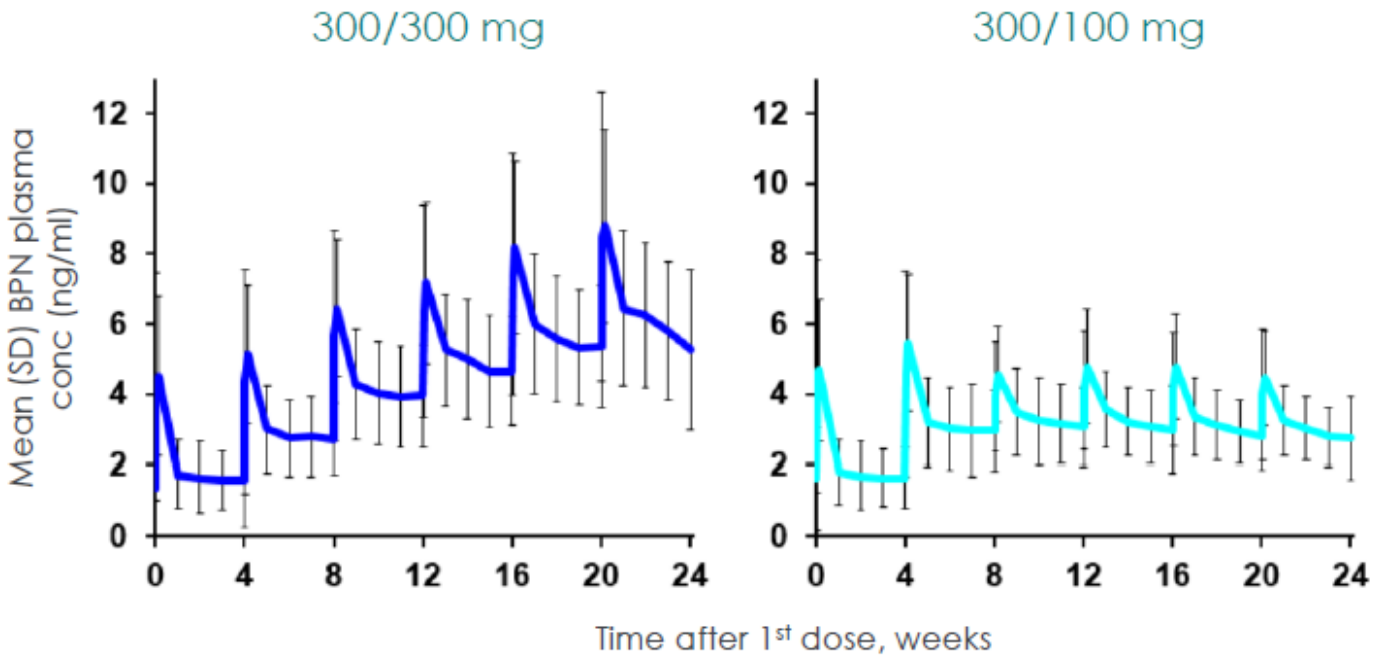
SUBLOCADE™: RCT evidence

- Double-blind, 6-month, placebo-controlled
- Treatment-seeking adults aged 18–65 years who had moderate or severe opioid use disorder



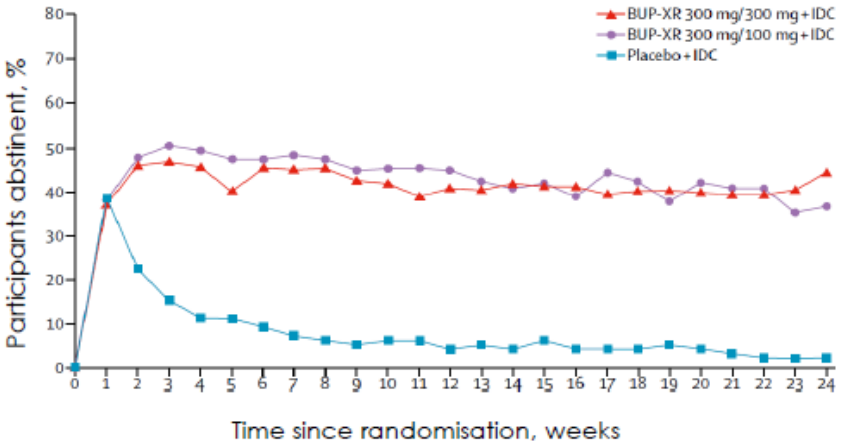
Haight BR et al. *Lancet*. 2019; 393: 778–90

SUBLOCADE™ PK profile

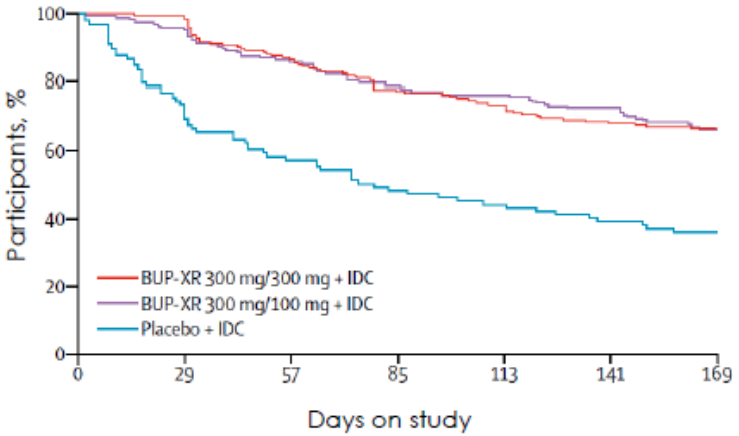


SUBLOCADE™: RCT evidence

Patient retention



Urine analysis



- Abstinence was **significantly higher** with both doses of SUBLOCADE™
- **No difference** between SUBLOCADE™ doses

SUBLOCADE™: clinical considerations

- **Initiation and dosing**
  - Must be on SL BPN ≥ 7 days before starting SUBLOCADE™
  - Commence 300 mg monthly for first two doses (2 x 4 weeks)
  - Thereafter, choose between 100 mg or 300 mg injections
  - Recommend no fewer than 26 days between doses, and up to 14 days 'late' without concerns (i.e. 4–6 week doses)
- **Pharmacology**
  - Peak effects seen within 24 hours post dose
  - 4–8 weeks, depends on dose and duration; $t_{1/2}$ = 43–60 days
  - Steady state equilibrium after 3–5 doses
- **Supplemental BPN doses**
  - Add low dose SL BPN (no 'top up' depot doses) if required
- **Adverse events**
  - Local site reactions (redness, pain) generally mild and transient in about 10–20% patients
  - Small 'lump' common

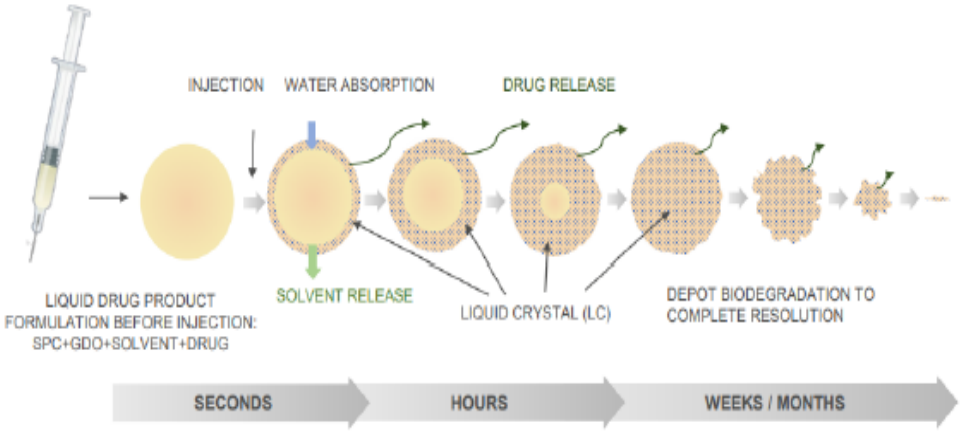
Food and Drugs Administration. FDA advisory committee briefing document: RBP-6000 (extended-release buprenorphine). https://www.fda.gov/media/108382/download [Accessed May 2019]

Safety results

- No new or unexpected safety findings; generally well-tolerated
- No serious injection site reactions
- 1 subject discontinued treatment due to injection site reaction

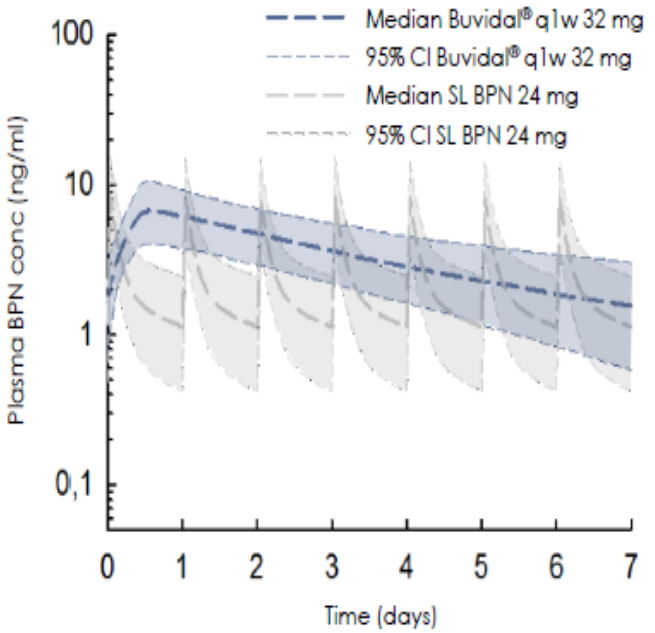
Occurrence (%)	RBP-6000 300/300 mg + IDC (N=201)	RBP-6000 300/100 mg + IDC (N=203)	Placebo + IDC (N=100)
Any TEAE	66.7	76.4	56.0
Serious TEAE	3.5	2.0	5.0
TEAE leading to discontinuation	5.0	3.4	2.0
Any injection site TEAE	18.9	13.8	9.0
Serious injection site TEAE	0	0	0
Injection site TEAE leading to discontinuation	0.5	0	0

Buvidal® PK profile



- Population pharmacokinetic (PK) analysis and modelling based on data from four clinical studies (N = 236)
- Diagnostic testing demonstrated predictive BPN concentrations and good agreement between observed and predicted data percentiles

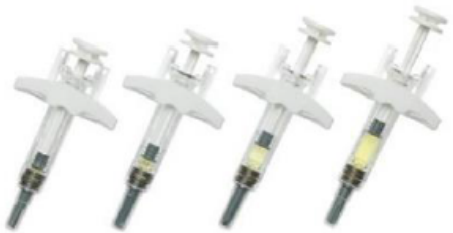
Weekly Buvidal® versus daily SL BPN



Depot BPN as Buvidal® (CAM2038)

Weekly and **monthly** dose options

- Weekly: 8 mg, 16 mg, 24 mg and 32 mg
- Monthly: 64 mg, 96 mg and 128 mg



- Ready-for-use in **prefilled syringe** (0.16–0.67 ml)
- **SC injection** by healthcare professional (HCP) (not to be dispensed to patient)
- Approved in **Europe** and **Australia**
- Stored at **room temperature**
- **Injections rotated between multiple sites** (buttock, abdomen, arm, thigh)

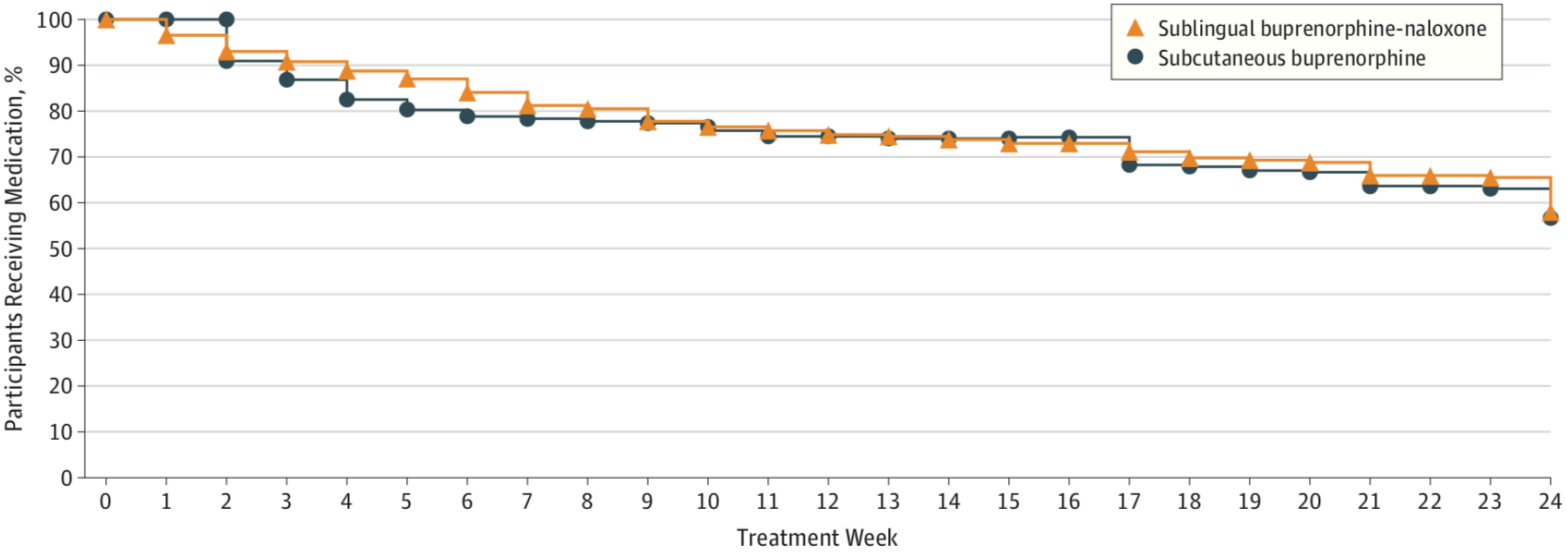
Camurus AB. Summary of product characteristics: Buvidal 64/96/128 mg prolonged-release solution for injection. https://www.medicines.org.uk/emc/product/9706/smpc [Accessed May 2019]
Camurus AB. Summary of product characteristics: Buvidal 8/16/24/32 mg prolonged-release solution for injection. https://www.medicines.org.uk/emc/product/9705/smpc [Accessed May 2019]
Camurus Pty Ltd. Australian product information: Buvidal weekly. http://www.medicines.org.au/files/capbuviw.pdf [Accessed May 2019]
Camurus Pty Ltd. Australian product information: Buvidal monthly. http://www.medicines.org.au/files/capbuvim.pdf [Accessed May 2019]
Tiberg F. Presented at SSA Annual Meeting 2018, Newcastle, UK, 8–9 November

Dose conversion table

Daily SL BPN	Buvidal® Weekly	Buvidal® Monthly
≤6 mg	8 mg	No equivalent
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-32 mg	32 mg	128 mg

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder

Retention in medication regimen was similar between groups

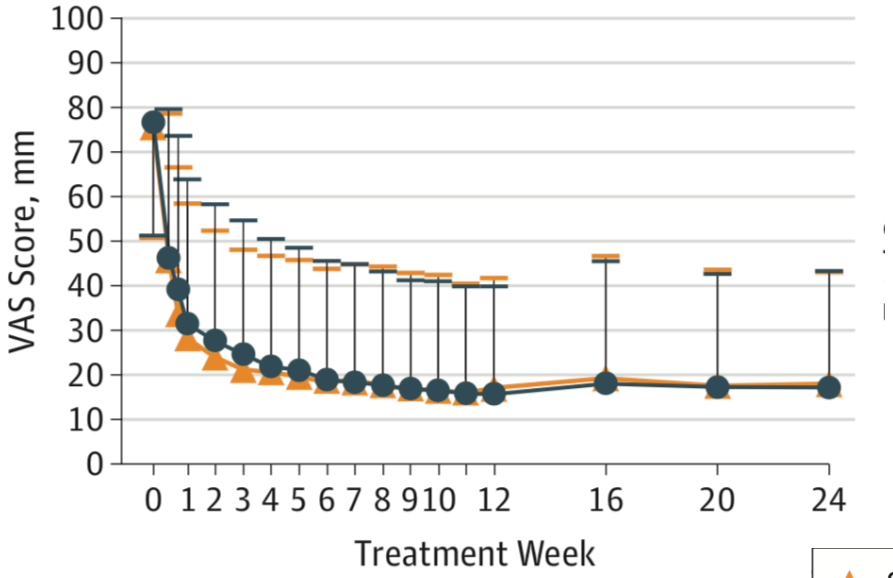


No. retained																									
SC-BPN group	213	213	194	185	176	171	168	167	166	165	163	159	159	158	158	158	158	146	145	143	142	136	136	135	121
SL-BPN/NX group	215	208	200	195	191	187	181	175	173	167	164	163	161	160	158	157	157	153	150	149	148	142	142	141	125

Source: Lofwall et al. 2018

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder

Mean (SD) VAS score of worst or strongest need to use opioids since the last visit (0=no need to use; 100=maximum need to use) over time

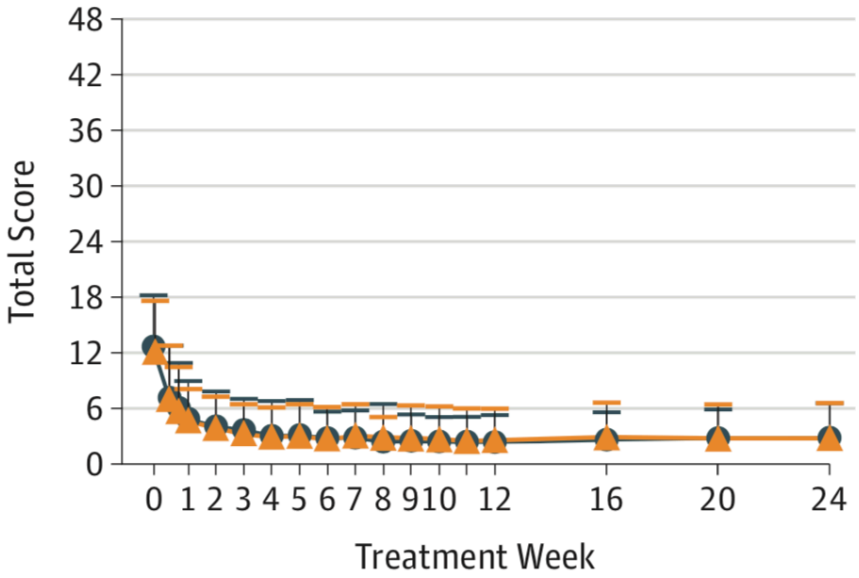


Opioid craving was suppressed immediately in both groups from day 1 throughout the study, without significant group differences.

Source: Lofwall et al. 2018

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder

Mean (SD) Clinical Opiate Withdrawal Scale total score over time, with the first 2 values plotted after week 0 representing days 2 and 4. Scores of 5 to 12 indicate mild withdrawal



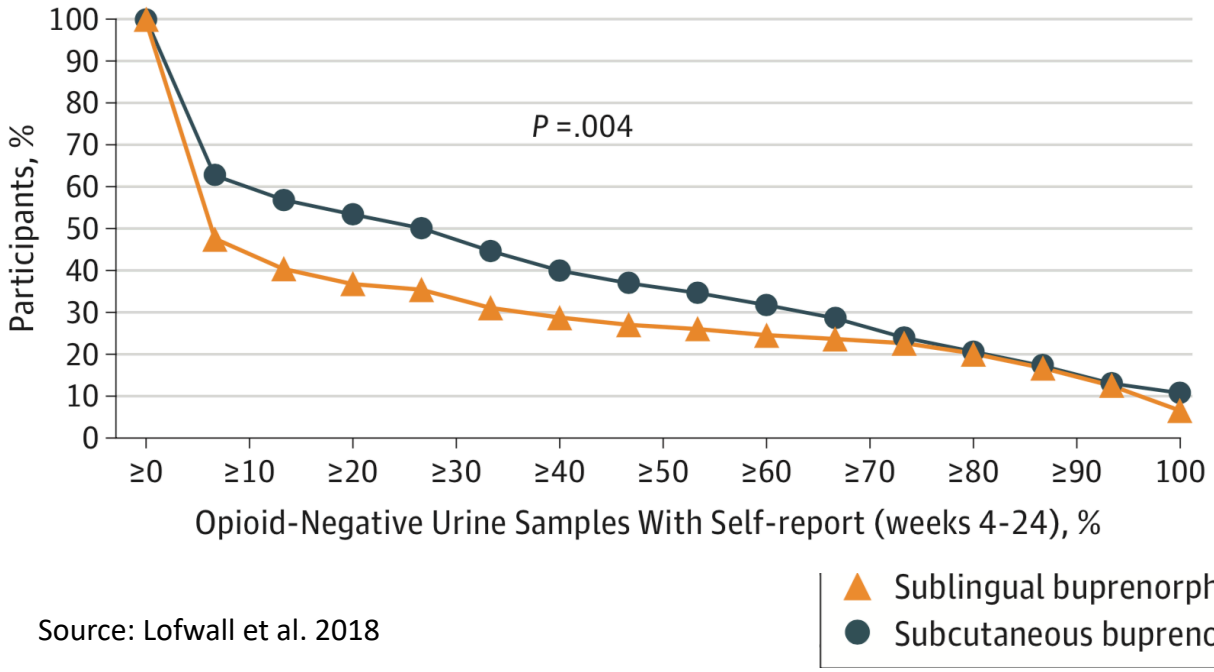
Withdrawal was suppressed immediately in both groups from day 1 throughout the study, without significant group differences.

▲ Sublingual buprenorphine-naloxone
● Subcutaneous buprenorphine

Source: Lofwall et al. 2018

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder

Cumulative distribution function of percentage of opioid-negative urine samples affirmed with no illicit opioid use by self-report from weeks 4 to 24



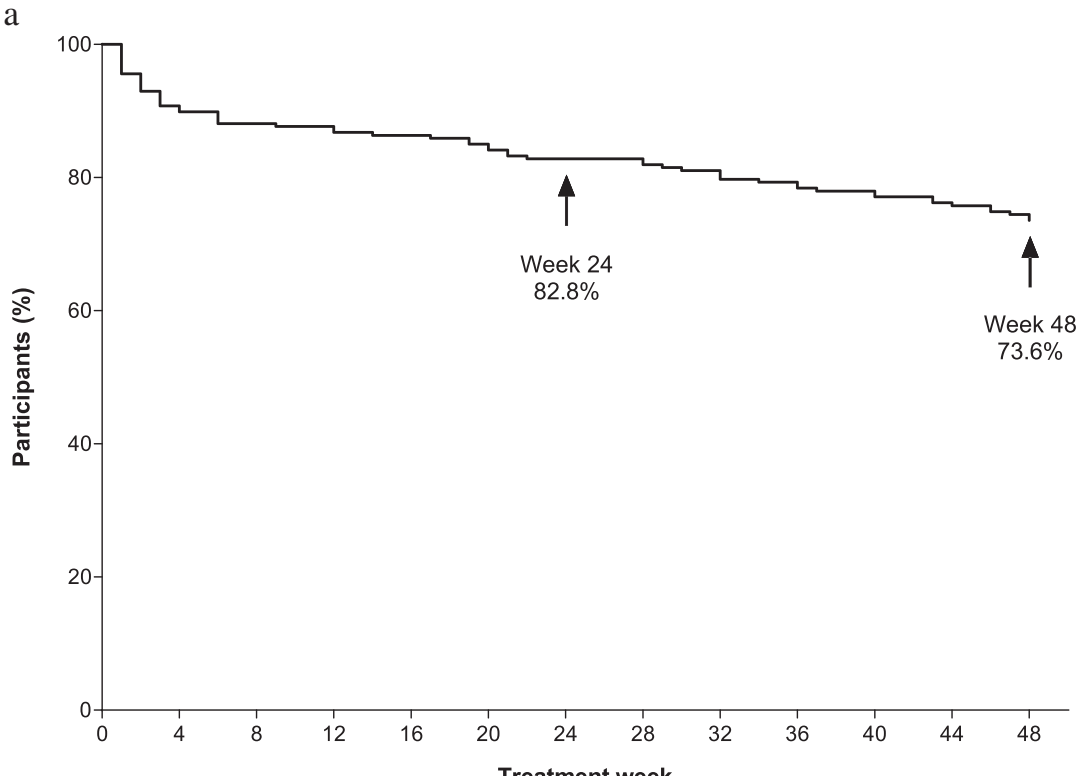
Superiority of SC buprenorphine depot to SL buprenorphine-naloxone demonstrated on the CDF of urine samples negative for illicit opioids

Source: Lofwall et al. 2018

Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder

Michael Frost[1], Genie L. Bailey[2,3], Nicholas Lintzeris[4,5], John Strang[6], Adrian Dunlop[7,8], Edward V. Nunes[9], Jakob Billeskov Jansen[10], Lars Chemnitz Frey[11], Bernd Weber[12], Paul Haber[13,14], Sonia Oosman[15], Sonnie Kim[15] & Fredrik Tiberg[16]

a



Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder

Michael Frost[1], Genie L. Bailey[2,3], Nicholas Lintzeris[4,5], John Strang[6], Adrian Dunlop[7,8], Edward V. Nunes[9], Jakob Billeskov Jansen[10], Lars Chemnitz Frey[11], Bernd Weber[12], Paul Haber[13,14], Sonia Oosman[15], Sonnie Kim[15] & Fredrik Tiberg[16]

Table 4 Summary of treatment-emergent adverse events (overall safety population).

Category	*Converted from SL BPN n = 190*	*New to BPN treatment n = 37*	*Overall N = 227*
≥ 1 TEAE	131 (68.9)	12 (32.4)	143 (63.0)
≥ 1 drug-related TEAE	58 (30.5)	2 (5.4)	60 (26.4)
Injection-site TEAE	43 (22.6)	2 (5.4)	45 (19.8)
Non-injection-site TEAE	23 (12.1)	1 (2.7)	24 (10.6)
≥ 1 severe TEAE	13 (6.8)	2 (5.4)	15 (6.6)
Deaths	0	0	0
≥ 1 SAE	10 (5.3)	2 (5.4)	12 (5.3)
≥ 1 drug-related SAE	0	0	0
Hospitalizations	9 (4.7)	1 (2.7)	10 (4.4)
TEAEs leading to discontinuations	4 (2.1)	1 (2.7)	5 (2.2)
TEAEs in ≥ 5% of participants			
Injection-site pain	33 (17.4)	2 (5.4)	35 (15.4)
Injection-site swelling	25 (13.2)	2 (5.4)	27 (11.9)
Injection-site erythema	20 (10.5)	1 (2.7)	21 (9.3)
Headache	18 (9.5)	0	18 (7.9)
Nasopharyngitis	17 (8.9)	1 (2.7)	18 (7.9)
Nausea	16 (8.4)	0	16 (7.0)
Urinary tract infection	9 (4.7)	3 (8.1)	12 (5.3)
Vomiting	12 (6.3)	0	12 (5.3)

Data presented as *n* (%). BPN = buprenorphine; SL BPN = sublingual buprenorphine; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

Conclusioni

- Esistono a tutt'oggi diverse barriere per l'accesso ai trattamenti;
- Ad oggi circa il 50% dei pazienti sono ancora al di fuori dei trattamenti;
- Le formulazioni depot di buprenorfina sono in grado di ridurre il misuo e
- la diversione;
- Le formulazioni depot si sono dimostrare efficaci e sicure nell'utilizzo clinico;
- Sarà necessario una formazione adeguata dei professionisti, dei pazienti e la stesure di linee giuda per il loro corretto utilizzo.