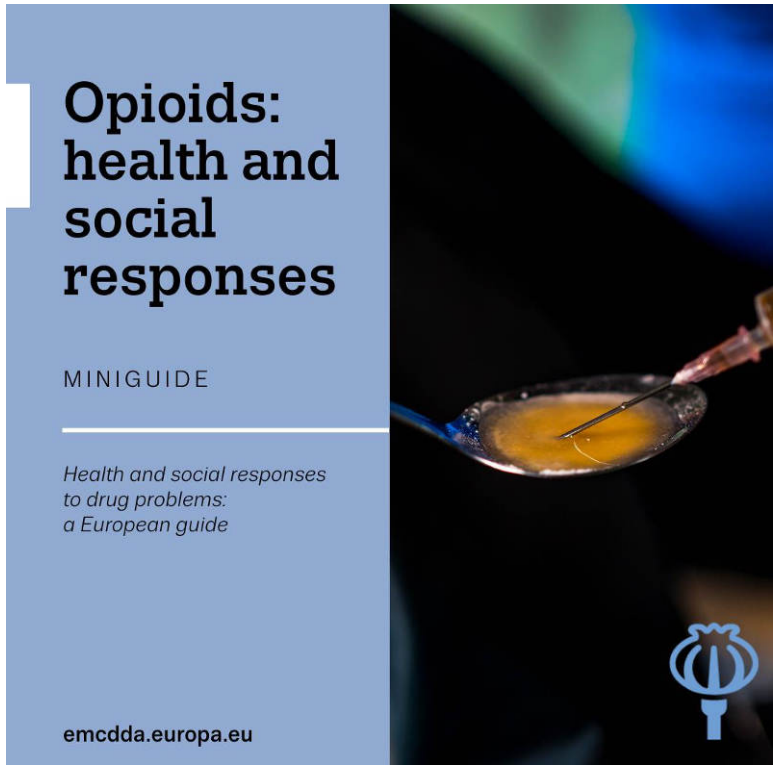
Nuove formulazioni di farmaci nel trattamento del disturbo da uso di oppioidi

Lorenzo Somaini
DIRETTORE SC Ser.D-ASL Biella

- Consulente per Indivior
- Consulente per Gilead
- Consultant per Molteni Farmaceutici
- Consulente per GL Pharma
- Consulente per AbbVie
- Consulente per Alkaloid

IMPLICATIONS FOR POLICY AND PRACTICE



- The core intervention is OAT (effective way to reduce illicit opioid use and mortality)
- Therapeutic choices should be based on individual needs, involve a dialogue with patients and be subject to regular review
- Optimise service delivery: the quality of treatment delivery is important; it is vital to ensure that adequate doses of OAT are prescribed, as well as maintaining continuity of care and links to other health and social support services
- Increasing access to OAT should remain a public health priority
- New formulations of medications are in development, including slow-release products, that may increase the treatment options available

European Monitoring Centre for Drugs and Drug Addiction (2021), Opioids: health and social responses, https://www.emcdda.europa.eu/publications/mini-guides/opioids-health-and-social-responses_en

NIDA'S MEDICATION DEVELOPMENT PRIORITIES IN RESPONSE TO THE OPIOID CRISIS: TEN MOST WANTED

NIDA's DTMC ten most wanted

Orexin-1 or 1/2 antagonists or NAMs [17–19]

Kappa opioid antagonists or NAMs [20, 21]

GABA-B agonists or PAMs [22, 23]

Muscarinic M5 antagonists or NAMs [24, 25]

AMPA antagonists, NAMs or PAMs [26–28]

NOP/ORL agonists, antagonists, NAMs or PAMs [29–31]

mGluR2/3 agonists or PAMs [32–34]

Ghrelin antagonists or NAMs [35, 36]

Dopamine D3 partial agonists, PAMs, antagonists or NAMs [37, 38]

Cannabinoid CB-1 antagonists or NAMs [39, 40]

PAM positive allosteric modulator, *NAM* negative allosteric modulator, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *NOP* nociceptin opioid peptide receptor, *ORL* opioid receptor like, *mGluR* metabotropic glutamate receptor, *5HT* 5-hydroxytryptamine, *MOP* mu opioid protein

Other mechanisms of interest:

5HT2C agonists or PAMs, with or without 5HT2A antagonist/NAM activity [41, 42]

Biased Mu Opioid agonists or PAMs [43, 44]

NOP/MOP bifunctional agonists or PAMs [45, 46]

Respiratory stimulants (including nicotinic agonists) [47, 48]

Rasmussen K, White DA, Acri JB. NIDA's medication development priorities in response to the Opioid Crisis: ten most wanted. Neuropsychopharmacology. 2019 Mar;44(4):657-659

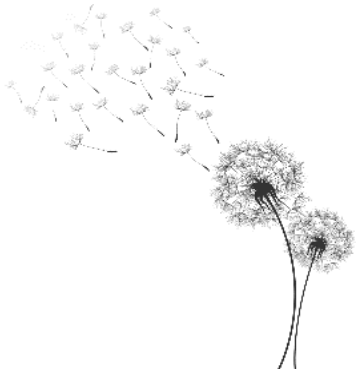
DOES PERFECT TREATMENT EXIST?

"Although recent advances in neurobiology of addictions may lead to the development of new pharmacotherapies, **a major challenge lies in delivering existing treatments more effectively**".

"None of the imminent pharmacotherapies are likely to provide a magic bullet to treat opioid addiction. Combining pharmacotherapies with psychosocial support strategies that are **tailored to meet the patients' needs** represents the best way to treat opioid addiction effectively"

Lobmaier P, Gossop M, Waal H, Bramness J. The pharmacological treatment of opioid addiction--a clinical perspective. Eur J Clin Pharmacol. 2010 Jun;66(6):537-45

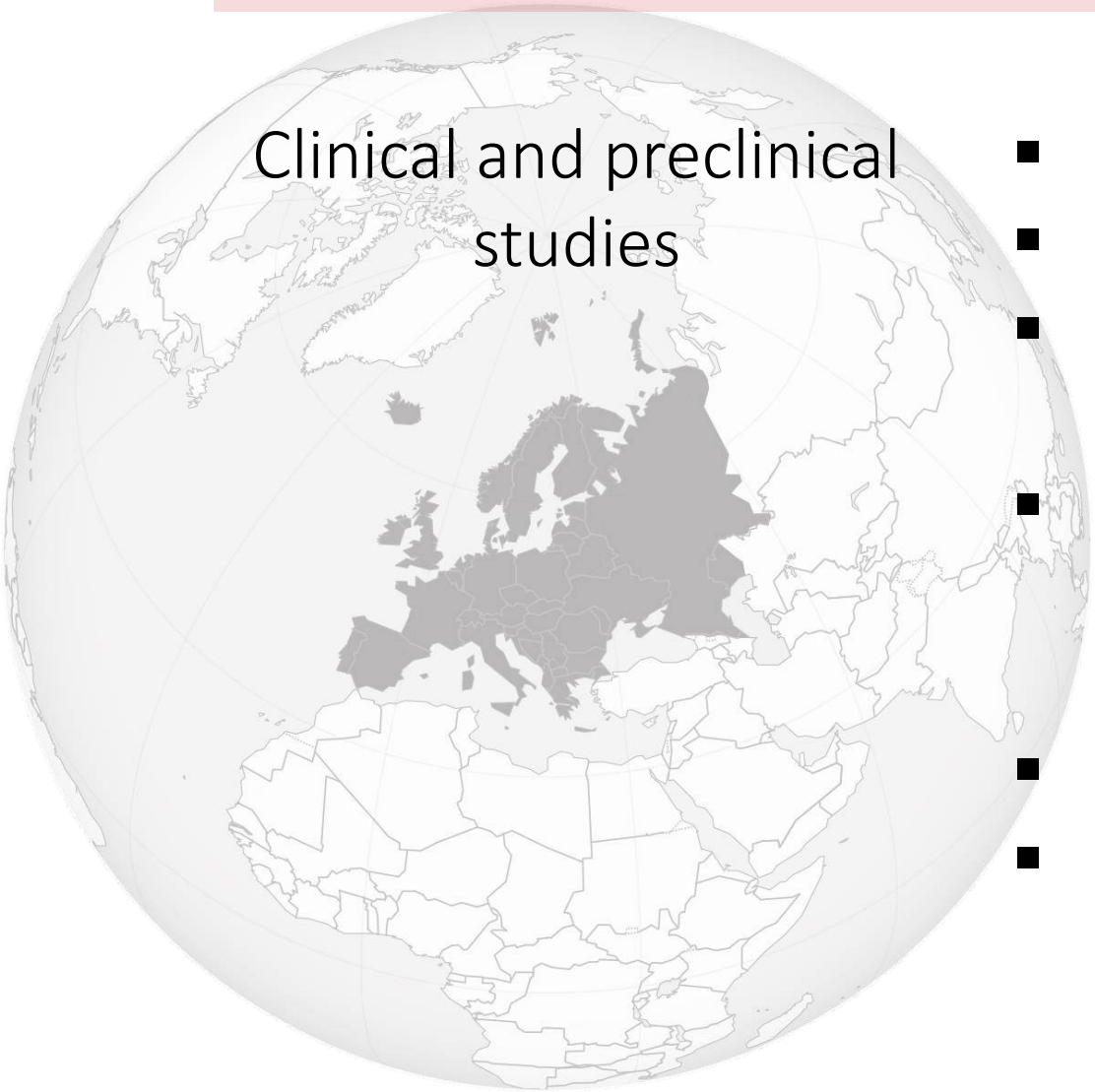
	METHADONE	LEVOMETHADONE	BUPRENORPHINE	BUPRENORPHINE + NALOXONE
Liquid formulation	Syrup	Syrup	-	-
Solid formulation	Tablets	Tablets	SL tablets	SL tablets Film



NEW AGONIST OPIOID FORMULATIONS

WHAT WE KNOW

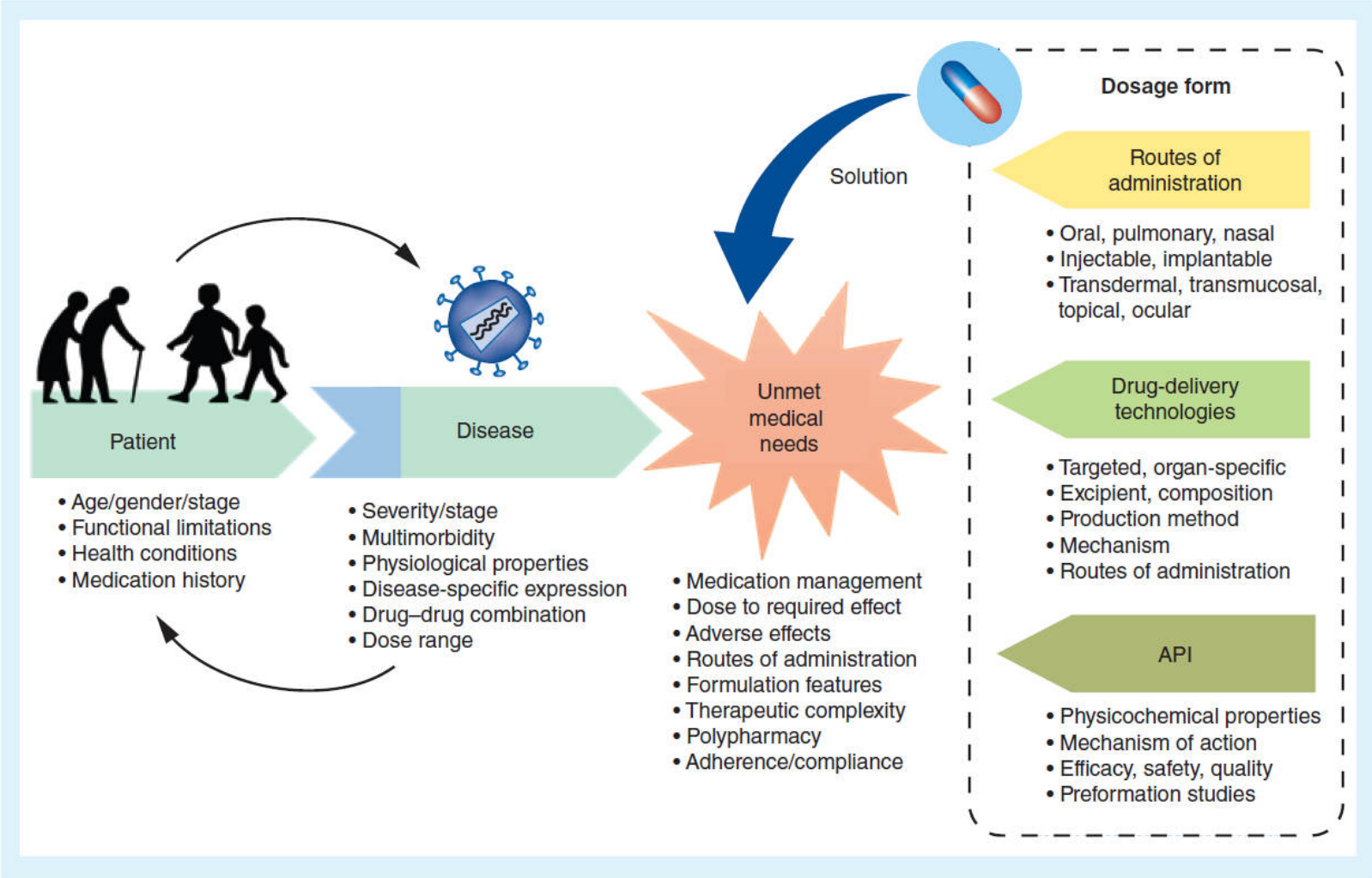
Clinical and preclinical studies

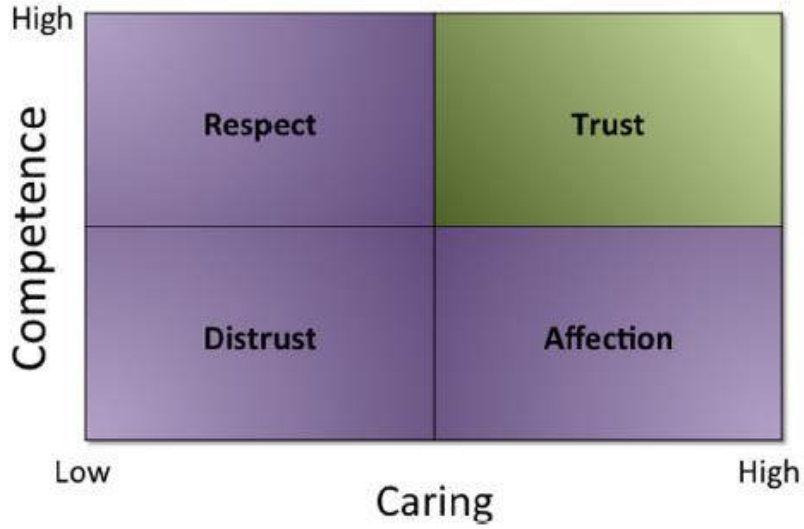


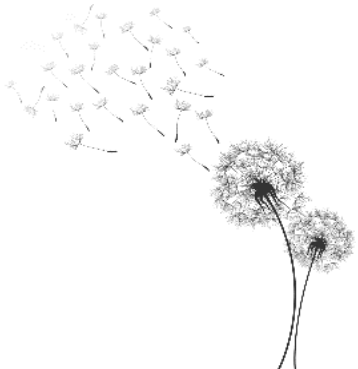
WHAT WE NEED TO LEARN

- How to use them
- When to use them
- How to switch from one formulation to another
- How to convince our health care systems that our patients' therapeutic adherence is worth
- How to explain them to patients
- How to integrate them into the care paradigm

MEDICATION ADHERENCE



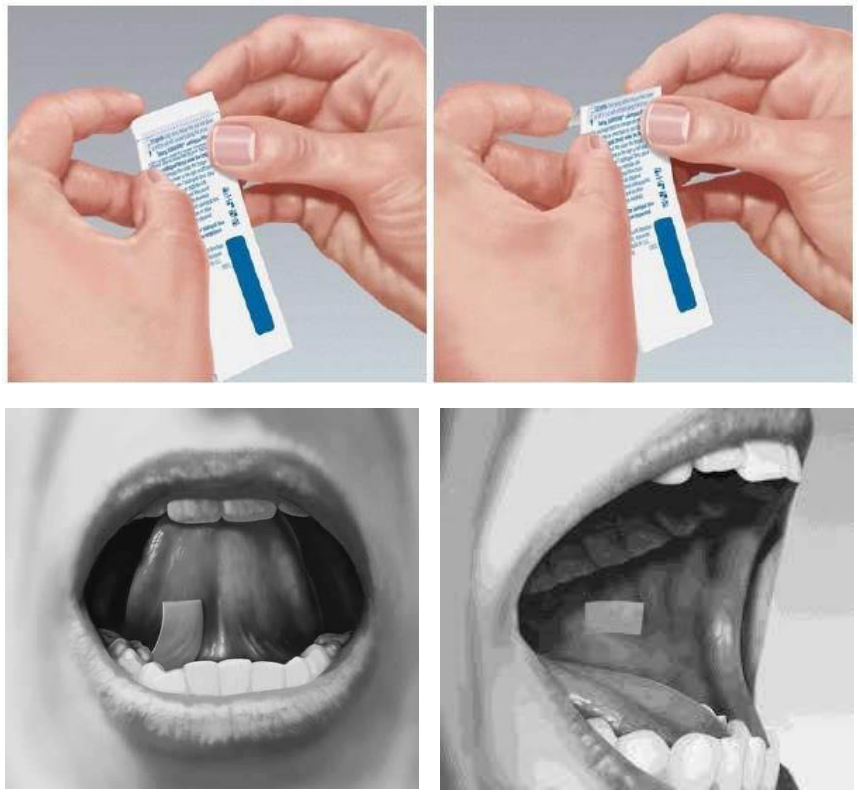




Park C, Meghani NM, Amin HH, Nguyen VH, Lee BJ. Patient-centered drug delivery and its potential applications for unmet medical needs. Ther Deliv. 2017 Aug;8(9):775-790

Brown MT, Bussell J, Dutta S, Davis K, Strong S, Mathew S. Medication Adherence: Truth and Consequences. Am J Med Sci. 2016 Apr;351(4):387-99

BUPRENORPHINE/NALOXONE FILM



DOSAGE FORMS AND STRENGTHS

- buprenorphine 2 mg/ naloxone 0.5 mg
- buprenorphine 4 mg/ naloxone 1 mg
- buprenorphine 8 mg/ naloxone 2 mg
- buprenorphine 12 mg/ naloxone 3 mg

Combination of water-soluble film forming polymers that sticks to the mucosal surface vigorously, ensuring optimal treatment effect and inhibiting the ease of removal for non-compliance, diversion or misuse.

EMA/302500/2020 Committee for Medicinal Products for Human Use (CHMP). Assessment report. Suboxone

BUPRENORPHINE/NALOXONE FILM

- Due to the potentially greater relative bioavailability of Suboxone® film compared to Suboxone ® SL tablets, patients switching from SL tablets to film should be monitored for over-dose.

- Combining different formulations or alternating between film and sublingual tablet formulations is not advised.

- Once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

- Strategies to counteract removability of applied doses: safeguarding that patients moisten their mouth prior to dosing and not applying more than two films at once.

EMA/302500/2020 Committee for Medicinal Products for Human Use (CHMP). Assessment report. Suboxone

BUPRENORPHINE/NALOXONE FILM
outpatient multi-site double-blind double-dummy parallel group trial

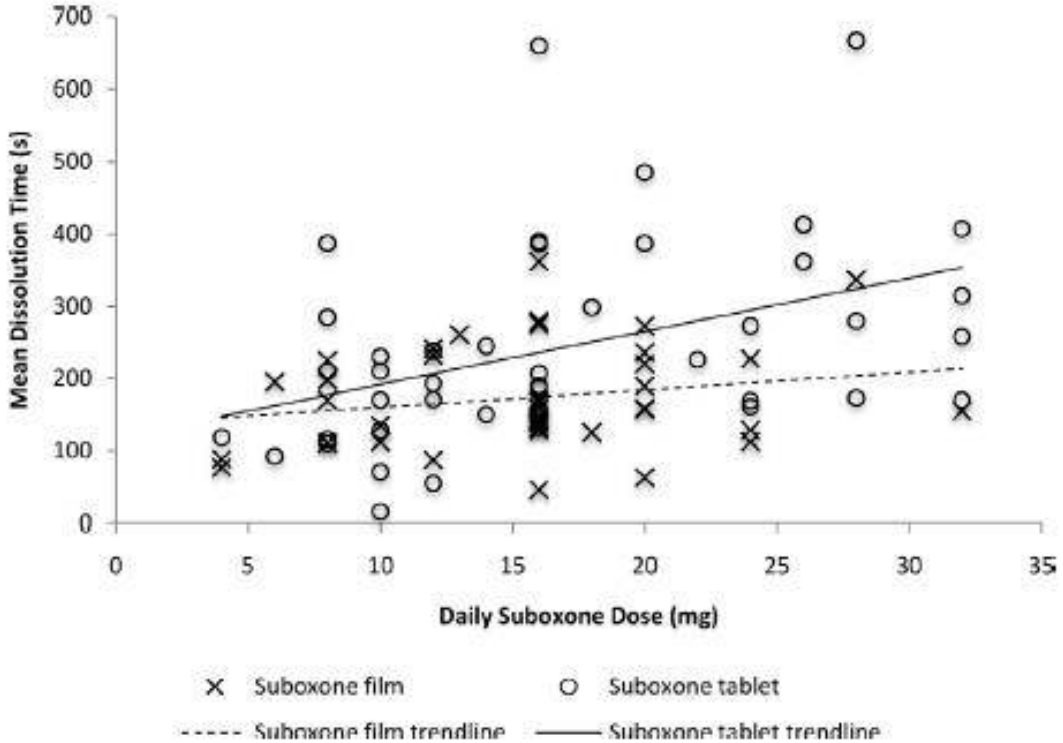


Fig. 3. The relationship between mean dissolution time and daily buprenorphine–naloxone dose (mg) for patients randomised to tablets and film.

Conclusions

The buprenorphine–naloxone film appears comparable to the existing tablet preparations across measures of dose effect, adverse events, plasma levels and global clinical outcomes. Most patients should be able to freely transfer between preparations with little need to adjust dosages. The real benefit of the film appears to be the reduced time required to effectively supervise dosing (generally within 30 s) compared to the tablets (several minutes), which should make supervised dosing less inconvenient and costly, and more effective in reducing the intentional removal of doses by patients and any subsequent injection or diversion to others, and is a an example of an abuse deterrent opioid formulation.

Lintzeris N, Leung SY, Dunlop AJ, Larance B, White N, Rivas GR, Holland RM, Degenhardt L, Muhleisen P, Hurley M, Ali R. A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. Drug Alcohol Depend. 2013 Jul 1;131(1-2):119-26

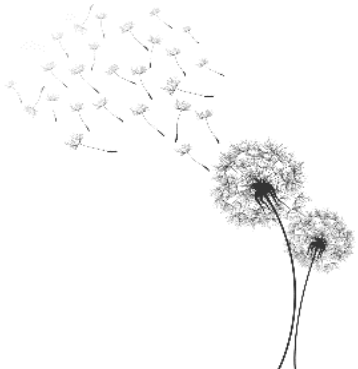
BUPRENORPHINE/NALOXONE FILM: ADVANTAGES

Objectives: To compare patient persistence and resource utilization between buprenorphine/naloxone film and tablets for the treatment of opioid dependence.

Methods: Longitudinal, retrospective cohort analysis to compare persistence and healthcare costs in a private US insurance claims database over the 6- and 12-month periods after treatment initiation.

Persistence: the proportion of patients continuing treatment for at least 6 months. Film and tablet groups included 2796 and 1510 patients.

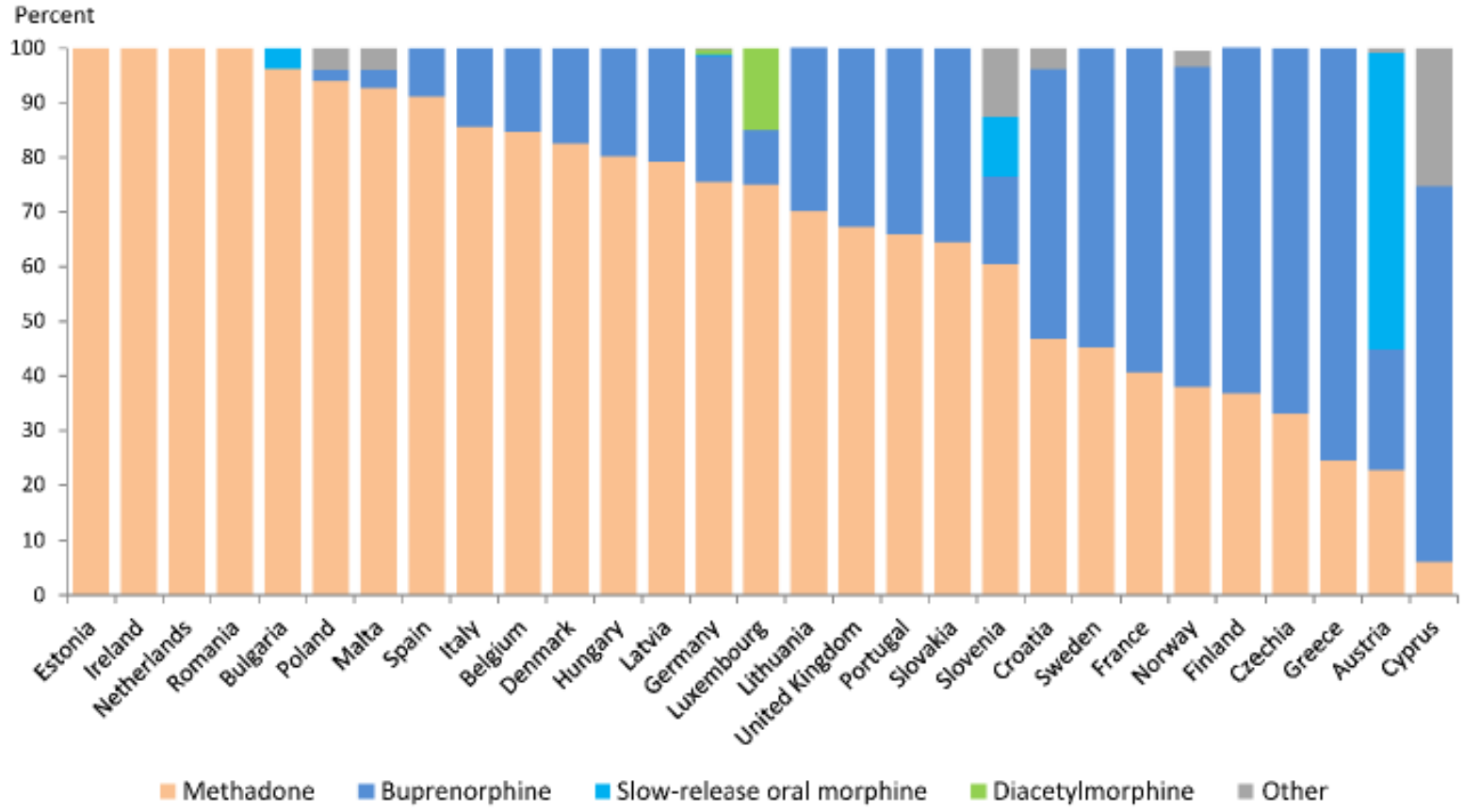
Results: Persistence rates were 63.78% with film vs 58.13% with tablet.
Patients treated with film had significantly more outpatient visits (+4%) and lower probability to be hospitalized (-17%), resulting in lower total healthcare costs over the 12-month period after initiation (-27%).



Clay E, Khemiri A, Zah V, Aballéa S, Ruby J, Asche CV. Persistence and healthcare utilization associated with the use of buprenorphine/naloxone film and tablet formulation therapy in adults with opioid dependence. J Med Econ. 2014 Sep;17(9):626-36

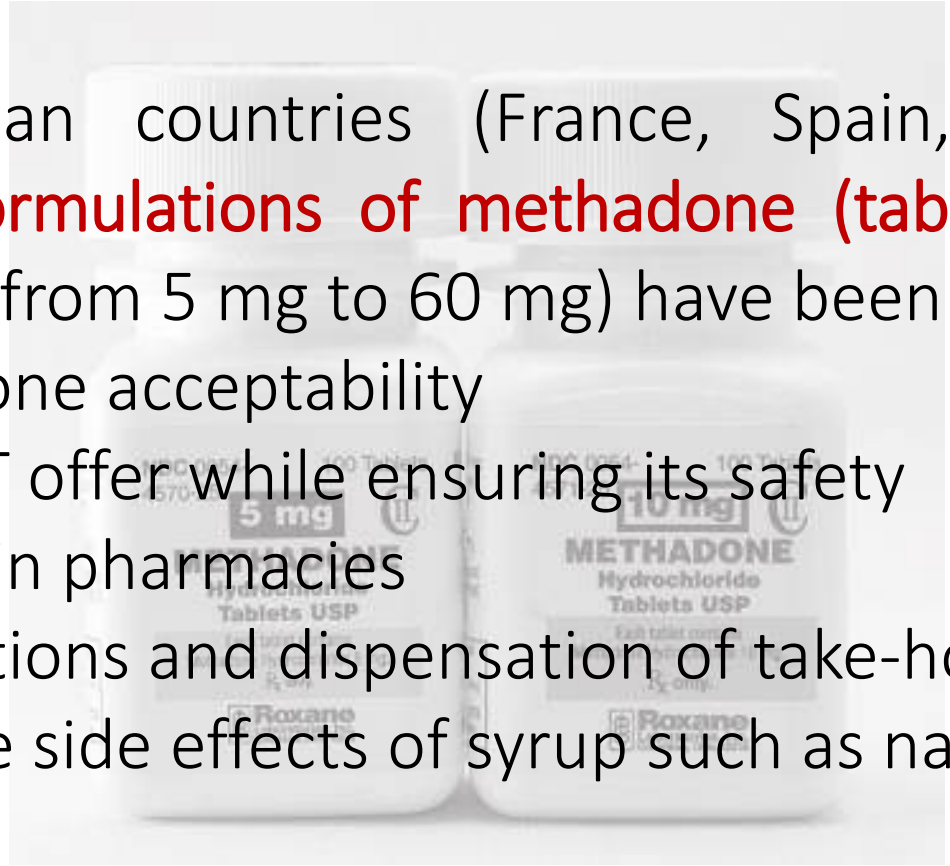
METHADONE PRESCRIPTION FOR OUD IN EUROPE

Figure 5. Proportion of clients receiving different types of prescribed opioid substitution medication in 2017



European Monitoring Centre for Drugs and Drug Addiction (2021), Balancing access to opioid substitution treatment with preventing the diversion of opioid substitution medications in Europe: challenges and implications, Technical report, Publications Office of the European Union, Luxembourg

METHADONE AND LEVOMETHADONE NEW FORMULATIONS



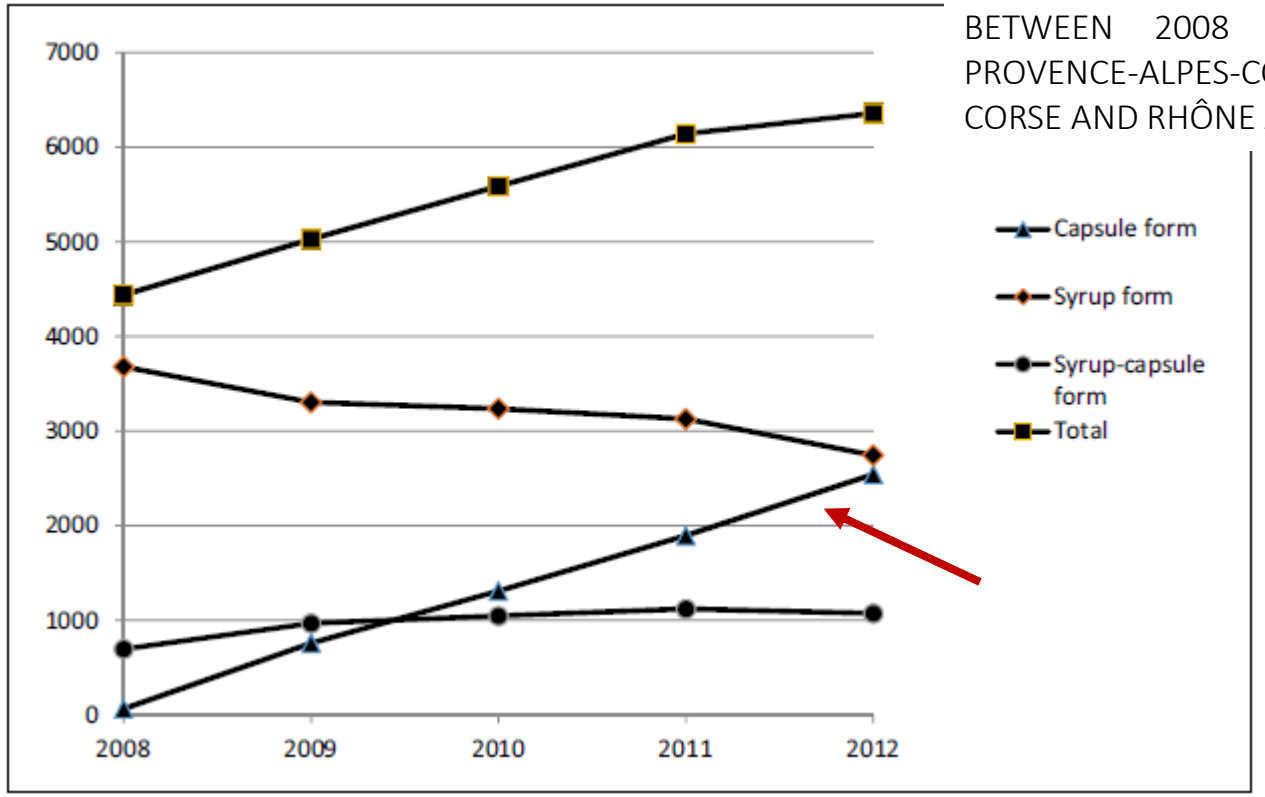
In several European countries (France, Spain, Netherlands and Germany) **solid formulations of methadone (tablets, capsules)** with different strengths (from 5 mg to 60 mg) have been introduced to:

- improve methadone acceptability
- diversify the OMT offer while ensuring its safety
- facilitate storage in pharmacies
- facilitate preparations and dispensation of take-home doses
- avoid some of the side effects of syrup such as nausea/vomiting.

Boucherie Q, Frauger E, Thirion X, Mallaret M, Micallef J. New methadone formulation in France: results from 5 years of utilization. Therapie. 2015 Mar-Apr;70(2):223-34

METHADONE CAPSULES: FRENCH EXPERIENCE

NUMBER OF METHADONE USERS BASED ON THE DOSAGE FORM USED BETWEEN 2008 AND 2012 IN PROVENCE-ALPES-CÔTE D'AZUR, CORSE AND RHÔNE ALPES REGIONS



Capsule users were older and had a higher dose per issue than syrup users.

The proportions of patients with at least one benzodiazepine (BZD) or antidepressant (ATD) issue were greater in the capsule group (+6.6% for BZD in 2012 and +7.8% for ATD in 2012).

Boucherie Q, Frauger E, Thirion X, Mallaret M, Micallef J. New methadone formulation in France: results from 5 years of utilization. Therapie. 2015 Mar-Apr;70(2):223-34

METHADONE CAPSULES: FRENCH EXPERIENCE

	Patients (N=41)
1. Concerning methadone syrup form	
Included in a maintenance protocol (N=40)	37 (92.5%)
Prescribed in center	37 (90.2%)
Median duration of therapy (N=40) [months] [$IQR_{25-75\%}$]	12 (12-36)
Median dose at the switch (N=36) [mg/d] [$IQR_{25-75\%}$]	75 (42-105)
Side effects	33 (80.5%)
• Disorders linked to sugar	17 (41.5%)
• Nasty taste	10 (24.4%)
• Gastric disorders	13 (31.7%)
• Sweating	10 (24.4%)
Reasons for switch	
• Patient choice	31 (75.6%)
• Physician suggestion	15 (36.6%)
• Other (poor tolerance)	5 (12.2%)
Switch-related to syrup side-effects	32 (78.0%)
Illicit consumption	26 (63.4%)
• Cannabis	• 13
• Amphetamine (MDMA)	• 1
• Cocaine	• 2
• Substances not specified	• 10
2. Concerning Methadone capsules form	
Dosage adjustment (increase)	4 (9.75%)
Median duration of therapy (months) [$IQR_{25-75\%}$]	12 (4-18)
Difference in time to onset of pharmacologic effect	13 (32.5%)
Withdrawal sensation	6 (14.6%)
Acceptability	40 (97.5%)

IQR: interquartile range; **MDMA**: 3,4-methylene-dioxy-N-methylamphetamine

To assess the patient acceptability after the switch methadone syrup/capsules and the diversion/misuse liability of the methadone capsule, a study through an anonymous questionnaire.

26.8% of patients reported that the medication was available at the “street market”.
Three patients have tried to solubilize and eight have tried to snooze it.

All patients recognize the contribution of this new formulation concerning the use, side-effects and transport. None of them returned to the syrup.

Eiden C, Léglise Y, Bertomeu L, Clavel V, Faillie JL, Petit P, Peyrière H. New formulation of methadone for opioid dependence in France: acceptability and diversion/misuse liability. Therapie. 2013 Mar-Apr;68(2):107-11

METHADONE CAPSULES: FRENCH EXPERIENCE

OPPIDUM study, a cross-sectional survey carried out annually since 1995.

Objective: to determine which psychotropic medications are illegally obtained and through which ways they are acquired by individuals.

In 2015, the OPPIDUM trial reported that

- 7% have illegally obtained the methadone capsule form,
- 9% have illegally obtained the syrup form.

In the capsule group more people had a job, stable housing, precariousness, comparable oral dosages, less intra-nasal and intravenous misuse.

Frauger E, Pochard L, Boucherie Q, Giocanti A, Chevallier C, Daveluy A, Gibaja V, Caous AS, Eiden C, Authier N, Le Boisselier R, Guerlais M, Jouanjus É, Lepelley M, Pizzoglio V, Pain S, Richard N, Micallef J; le Réseau français d'addictovigilance. Dispositif pharmacoépidémiologique de surveillance des substances psychoactives : intérêts du programme national OPPIDUM du Réseau français d'addictovigilance [Surveillance system on drug abuse: Interest of the French national OPPIDUM program of French addictovigilance network]. Therapie. 2017 Sep;72(4):491-501

METHADONE TABLETS: GERMAN EXPERIENCE

In a sample of 824 opioid users, lifetime, 30-day and 24-h prevalence of non-prescribed use of opioid replacement therapy:

	Lifetime Prevalence	30 day prevalence	24 hours prevalence
Methadone liquid	**58,5%**	**12,1%**	**3,9%**
Methadone tablets	**31,2%**	**10,2%**	**2,1%**
Bup/nal tablets	**10%**	**5,6%**	**0,5%**

Schulte B., Schmidt C. S., Strada L., Gotzke C., Hiller P., Fischer B., Reimer J. (2016): Non-Prescribed Use of Opioid Substitution Medication: Patterns and Trends in Sub-Populations of Opioid Users in Germany. Int J Drug Policy. 29: 57-65

Different formulations of methadone and levomethadone in the management of Opioid Use Disorder

Lorenzo Somaini[1], Sarah Vecchio [1], Salvatore De Fazio [2], Anita Ercolini [3], and Claudio Leonardi [4]

- Opioid Agonist Treatment (OAT) has been found to be effective in treating Opioid Use Disorder (OUD), and methadone is still the most used drug worldwide for this purpose.
- **However serious consideration should be given to the modality of methadone delivery, as it influences not only treatment outcomes, but also the attitudes of policy makers and the community.**
- Treatment systems, providing a correct management of different methadone and levomethadone formulations based on patients' characteristics, have an impact on phenomena such as misuse and diversion of OAT.
- Availability of methadone tablets in many European countries has increased therapeutic strategies for the management of OUD improving the treatment outcomes.
- **Identifying the correct treatment regimens along with choosing the most suitable drug formulations, adapted to the individual needs of the patient, is critical to avoid misuse and diversion during OAT.**

Heroin Addict Relat Clin Probl 2021; 23(6): 41-50

METHADONE TABLETS: ITALIAN PERSPECTIVE

SITOX Informa

SITOX INFORMA - Periodico della Società Italiana di Tossicologia - Fondata nel 1967 - Riconosciuta con DPR 16/05/1972, n. 378 - Codice fiscale: 96330980580
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 351 pag. 606 vol. II - Dir. Resp. Sarah Vecchio - Anno XXV n. 1 - Marzo 2022 - ISSN 2282-5738

Indice:

Editoriale

Sarah Vecchio

Il numero di SITOX Informa del dicembre 2021 si chiudeva con l'augurio che la rivista potesse trasformarsi, in un'ottica di modernizzazione e attualità, per andare a rivestire il giusto ruolo all'interno dei nuovi strumenti comunicativi, informativi e formativi di SITOX. L'auspicio, grazie all'aiuto di tutti i colleghi del Consiglio Direttivo e del Comitato Editoriale, è diventato realtà e dalla prossima uscita SITOX Informa, così come lo abbiamo sempre conosciuto, si trasformerà e prenderà il nome di "Giornale Italiano di Tossicologia" o G.I.T. – organo ufficiale della Società Italiana di Tossicologia. Sentivamo l'esigenza di avere uno spazio di comunicazione e scambio di informazioni con un target chiaramente identificato nei professionisti che operano nel vasto mondo della tossicologia in tutte le sue sfaccettature, lasciando a sito, social e blog aspetti più informativi e divulgativi e pur mantenendo a tutti i livelli l'elevata scientificità e onestà intellettuale che contraddistingue la Società.

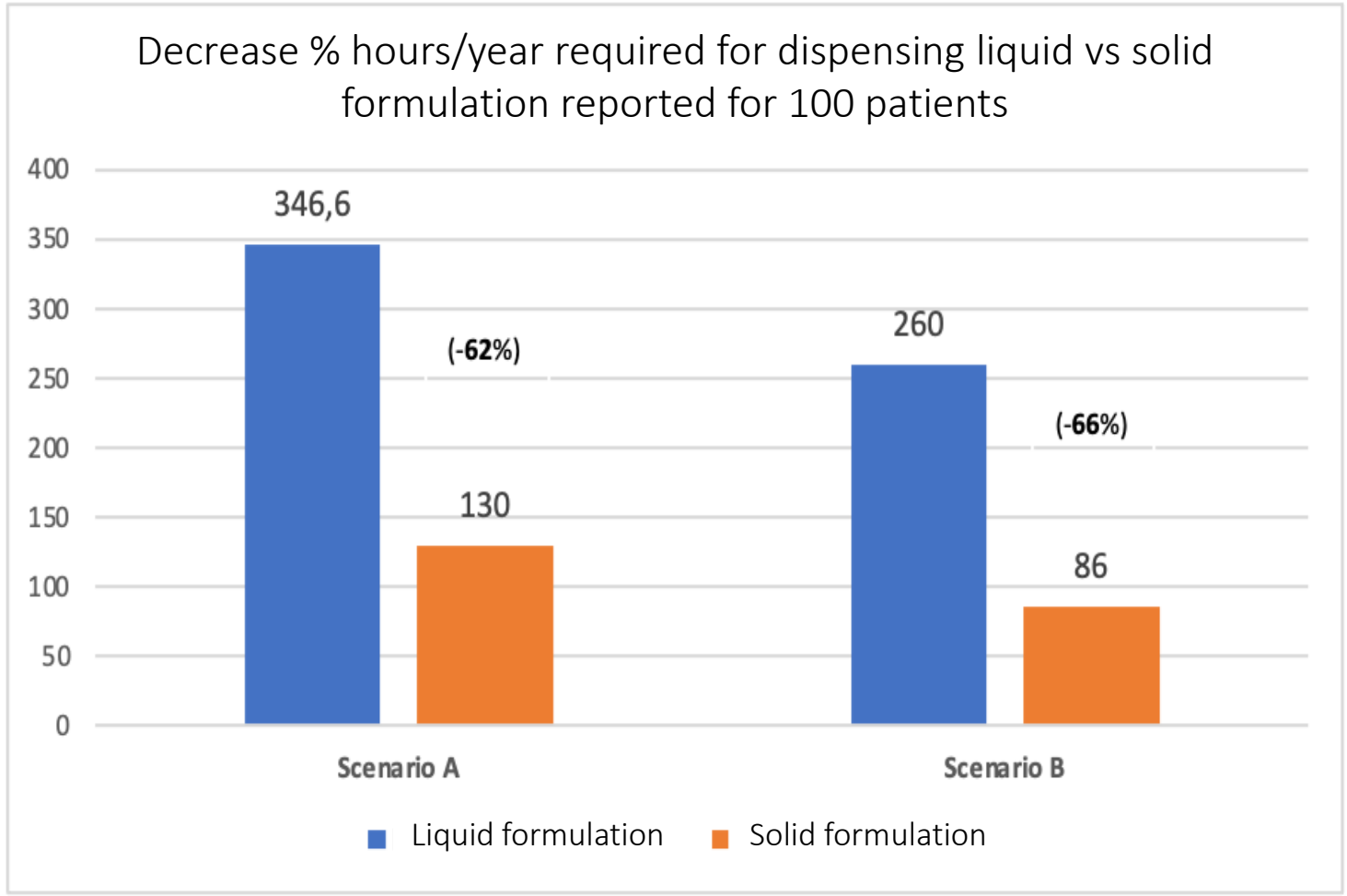
Per questo "ultimo" numero della rivista abbiamo dato spazio a contributi che rispecchiano alcuni degli obiettivi che sono all'ordine del giorno della Società e che troveranno ampio spazio di discussione anche nel G.I.T. Ospitiamo infatti la lettera congiunta SIF (Società Italiana di Farmacologia) – SITOX – SINS (Società Italiana di Neuroscienze) relativa alla proroga al 1° luglio 2025 dell'applicazione del divieto che impedisce ai ricercatori italiani di impiegare animali nella sperimentazione che riguarda lo studio delle proprietà d'abuso

Comparison of **SO**lide and **LI**quid formulations of opioid agonist drugs in the treatment of Opioid Use **D**is**o**rder (SO.LI.D.O Study)

Lorenzo Somaini[1], Claudio Leonardi[2], Salvatore De Fazio[3], Sarah Vecchio[1].

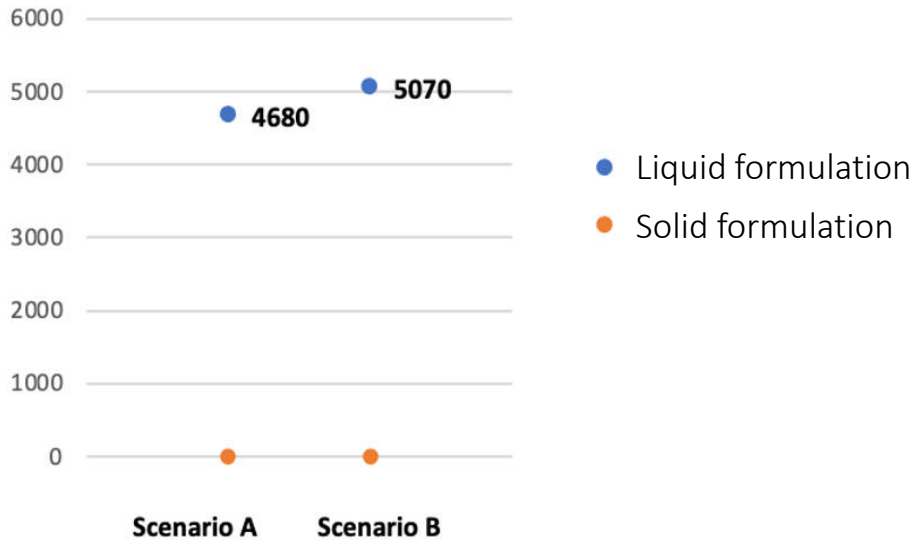
[1] Lorenzo Somaini, SERD ASL Biella, Biella
[2] Claudio Leonardi, SERD ASL Roma2, Rome
[3] Salvatore De Fazio, SERD ASL Brindisi, Brindisi

METHADONE TABLETS: ITALIAN PERSPECTIVE
SO.LI.D.O Study



METHADONE TABLETS: ITALIAN PERSPECTIVE
SO.LI.D.O Study

Drug	Formulation	Scenario	Cost of vial and its cap (euro)	Number of vials/year
Methadone 60 mg /die	Syrup	A	0,15	31200
Methadone 60 mg /die	Syrup	B	0,15	33800



Total annual cost (euro) of take-home dose preparation materials referred to 100 patients divided by scenario A and B

	METHADONE	LEVOMETHADONE	BUPRENORPHINE	BUPRENORPHINE + NALOXONE
Liquid formulation	Syrup	Syrup	-	-
Solid formulation	Tablets	Tablets	SL tablets	SL tablets Film
Extended-release formulations			Injectable extended-release formulations (1 week, 1 month) Subdermal implant (6 months)	

DEVELOPMENT OBJECTIVES OF EXTENDED-RELEASE FORMULATIONS

- Achieve opioid blockade
- Achieve clinically significant control of craving and withdrawal symptoms
- Reduce illicit opioid use
- Limit possibility of abuse/misuse, diversion and accidental overdose
- Improve adherence (fewer missed doses) and therefore outcomes
- Reduce discrimination and stigma
- Improve quality of life
- Reduce costs

EXTENDED-RELEASE BUPRENORPHINE FORMULATIONS

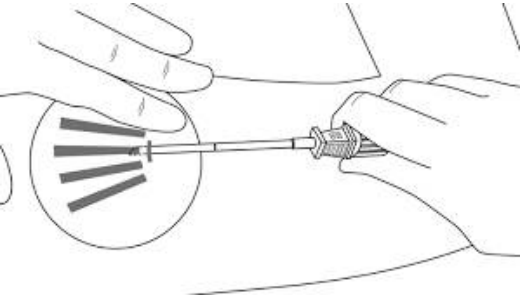
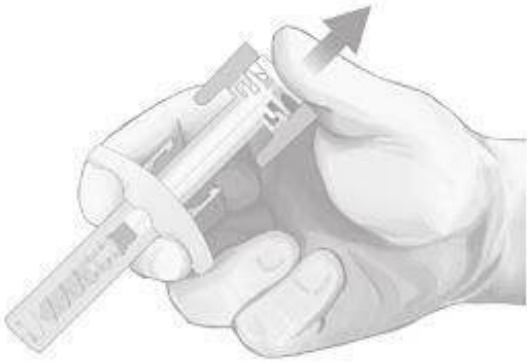
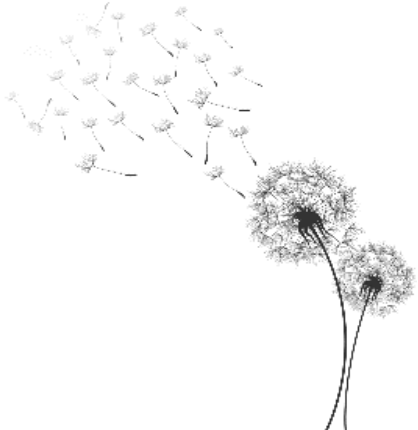


Table 2 Main features of the different prolonged-release formulations of buprenorphine approved or planned to be approved in the European Union.

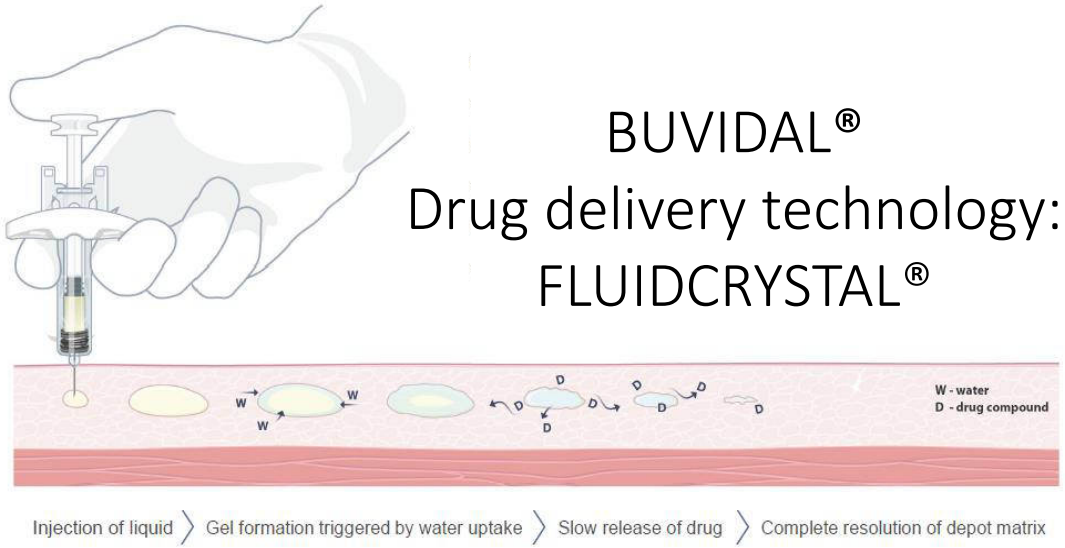
	Sixmo® Titan Pharmaceuticals®	Sublocade® (unknown European trade name) Indivior®	Buvidal® Camurus®
Type	Implant	Subcutaneous depot	Subcutaneous depot
Duration of action	6 months	One month	One week or one month
Dosage(s)	74.2 mg	300 mg (first two doses) then 100 mg or 300 mg	8, 16, 24 or 32 mg (weekly) 64, 96 or 128 mg (monthly)
Storage	Room temperature	Refrigerator (7 days at room temperature)	Room temperature
Demonstrated non-inferiority vs. sublingual form	Yes	No (2020)	Yes
Indication	No opioid use for ≥30 days Relay from sublingual form	No opioid use for ≥7 days Relay from sublingual form	Relay from sublingual form or initiation
Duration of treatment	No more than 12 months	Unlimited	Unlimited
Frequency of ADRs related to injection	27.2%	16.5%	10 to 20%
Advantages (authors' viewpoint)	Duration of action	Easy administration	Easy administration Two-duration forms Wide range of dosages Possible initiation
Disadvantages (authors' viewpoint)	Administration constraints Indication limitations (not applicable if sublingual buprenorphine dosing exceeds 8 mg per day) Limited to 12 months May require adjunctive sublingual treatment	No compared efficacy vs. sublingual form (early 2020) Pharmacy: required being kept cold Limited range of doses	Possible confusion between sublingual dosage (daily) and injectable (weekly)





Chappuy M, et al. Prolonged-release buprenorphine formulations: Perspectives for clinical practice. Therapies (2020), https://doi.org/10.1016/j.therap.2020.05.007

INJECTABLE EXTENDED- RELEASE BUPRENORPHINE FORMULATIONS



BUVIDAL®
Drug delivery technology: FLUIDCRYSTAL®

Buvidal® Weekly and Monthly

Buvidal® Weekly and Monthly contain BPN in FluidCrystal® injection depot technology

Subcutaneous (SC) injections in prefilled syringes with 23 gauge needle. Administration via upper arm, thigh, abdomen or buttocks

Buvidal® Weekly: 8mg/0.16mL, 16mg/0.32mL, 24mg/0.48mL; 32mg/0.64mL

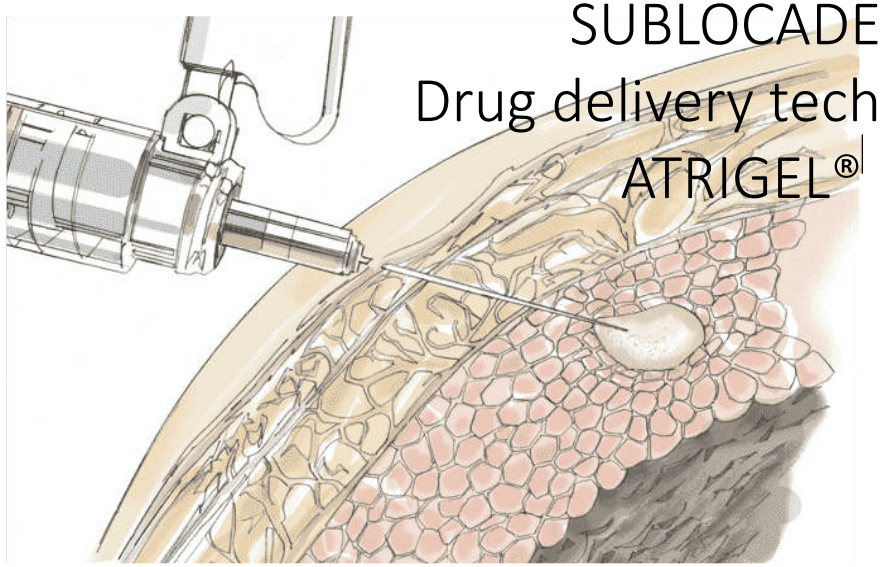
Buvidal® Monthly: 64mg/0.18 mL, 96mg/0.27 mL; 128/0.36 mL

Sublocade®

Sublocade® contains BPN in the ATRIGEL® Delivery System

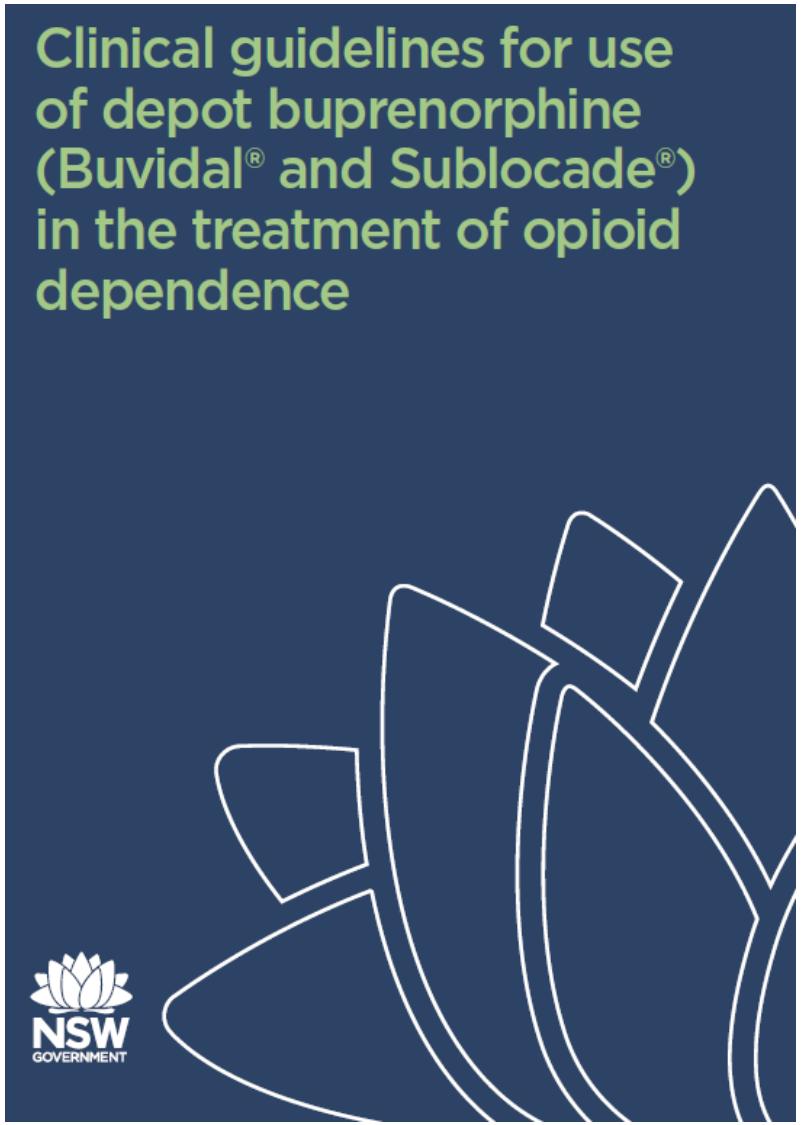
SC injections in prefilled syringes with 19 gauge needle administered in abdomen

Monthly doses: 100mg/0.5mL or 300mg/1.5mL



SUBLOCADE®
Drug delivery technology: ATRIGEL®

INJECTABLE EXTENDED- RELEASE BUPRENORPHINE FORMULATIONS

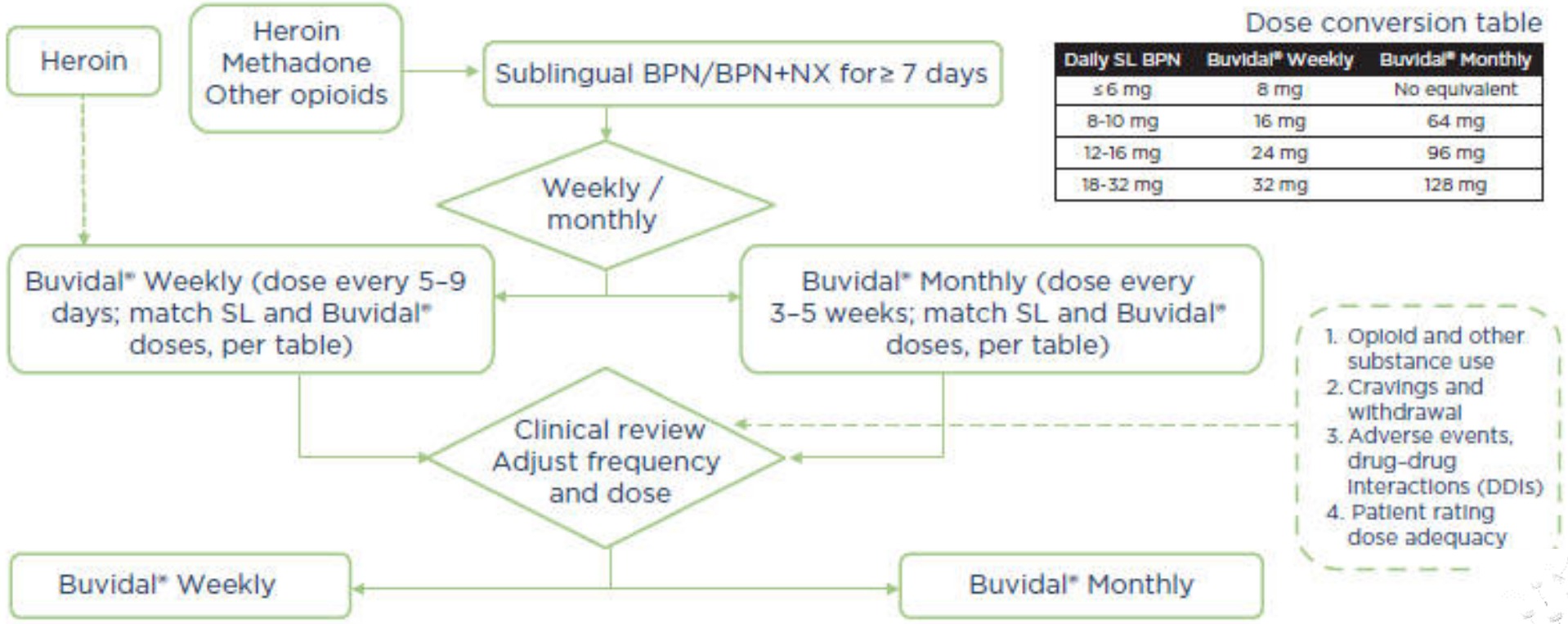


- Clinical pharmacology
- Pharmacokinetic properties (absorption and onset of effects, elimination and duration of effects…)
- Side effects and safety issues
- Warnings (risk of serious harm or death with intravenous administration, precipitation of opioid withdrawal in patients dependent on full agonist opioids…)
- Providing treatment with depot BPN (Selecting treatment options, assessment and treatment planning, client and clinician factors in choosing depot BPN compared with other OAT options…)
- Discontinuing depot BPN treatment
- Managing Travel
- …

Lintzeris N, Dunlop A, Masters D (2019) Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia

INJECTABLE ER BUPRENORPHINE FORMULATIONS: BUVIDAL®

Figure 4 Overview dosing with Buvidal®



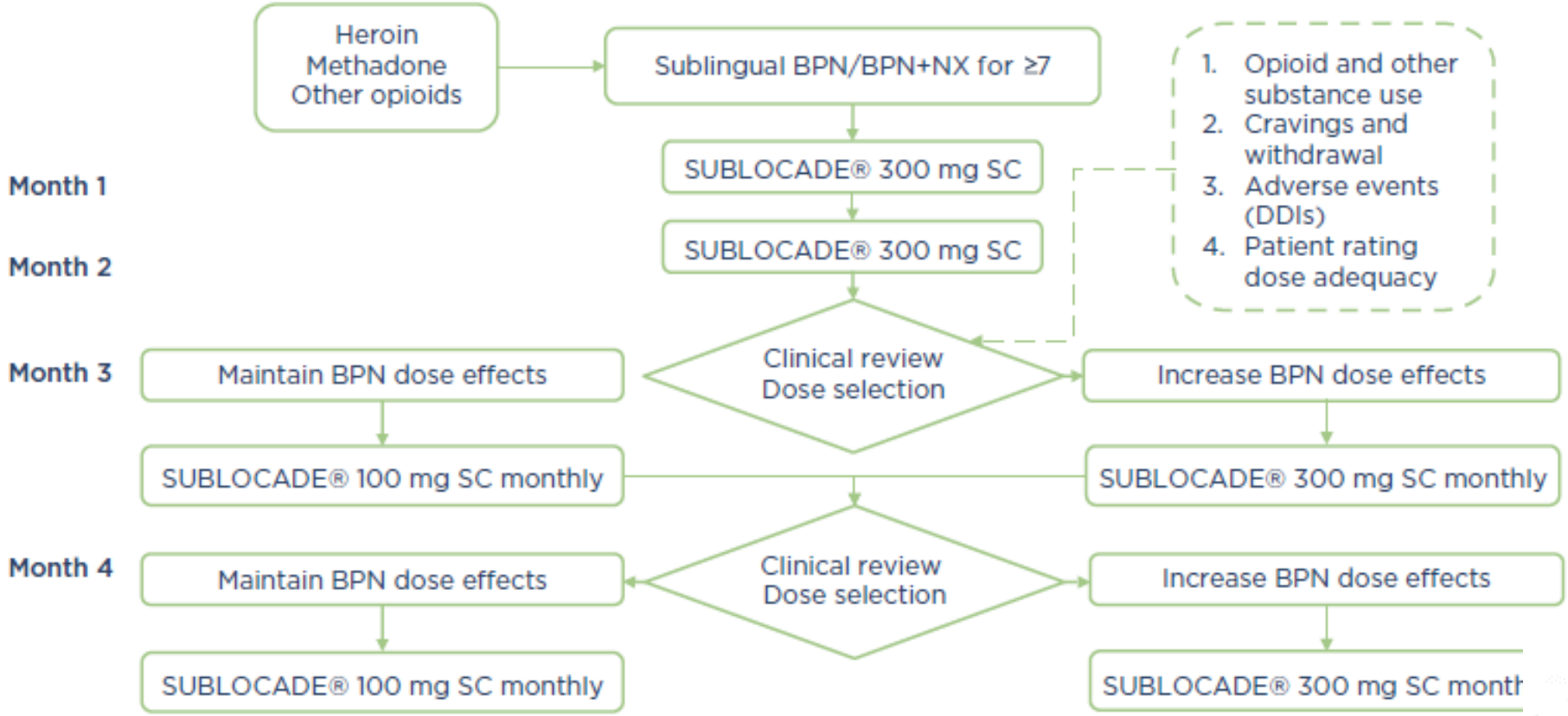
Dose conversion table

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

Lintzeris N, Dunlop A, Masters D (2019) Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia

INJECTABLE ER BUPRENORPHINE FORMULATIONS: SUBLOCADE®

Figure 5: Overview dosing with Sublocade*



Lintzeris N, Dunlop A, Masters D (2019) Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia

INJECTABLE ER BUPRENORPHINE FORMULATIONS
Paradigm shift in treatment

- Treatment with depot BPN formulations potentially challenges the way in which the components of OAT services are co-ordinated and structured.
- Conventional OAT with methadone and SL BPN treatment usually involves frequent attendance for (supervised) dosing, providing the opportunity to schedule regular clinical reviews, medical appointments and psychosocial interventions (e.g. counselling).
- The less frequent dosing with depot BPN formulations may require a different approach to structuring clinical reviews, psychosocial interventions and treatment care planning.
- It should be emphasised that safe and effective OAT is more than the provision of medication, and that regular reviews, treatment planning, and psychosocial interventions are important elements of OAT.

Lintzeris N, Dunlop A, Masters D (2019) Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia

INJECTABLE ER BUPRENORPHINE FORMULATIONS
Paradigm shift in treatment

Table 4 Situations and publics for which prolonged-release buprenorphine could be particularly fitted (expert opinion [33]).

Situations	Examples
People concerned with avoiding daily OAT intake (practical aspects and stigma)	Living in the parental home, in a reintegration home, in incarceration Frequent travelers, especially abroad Reinserted subject wishing to limit their contacts with the drug consumer environment and the healthcare environment (pharmacy and doctor), and no longer take daily medication
People having difficulty ensuring daily buprenorphine taking and motivated to do it. Take care relay with risk of interruption	Precarious social situation, entourage consumer of recreational opioids Out of prison, from reintegration home, from psychiatric hospitalization A move out
People with diversion their OAT or selling a part of them and wishing to stop	

Chappuy M, et al. Prolonged-release buprenorphine formulations: Perspectives for clinical practice. Therapies (2020), https://doi.org/10.1016/j.therap.2020.05.007

Limitations of OAT standard-of-care…

- *Many service users do not stay for as long as they – or we – would hope*

  (English cohort study: 41,928 people admitted in England (2018-19), 16,477 (39.3%) left by 12 weeks **1**)

- *Early non-response predicts continued non-response*

  (US RCT: 95 [26.4%] of 360 service users were using non-medical opioids after 2 weeks of maintenance **2**)

- *Response is often sub-optimal during maintenance*

  (In an England study of 21,075 people, 37% abstinent after 6 months; 33% if using cocaine at admission **3**)

- *Even among the long-term retained, non-response is common*

  (English cohort study: 7,719 people retained for 5 years, 15% started well but then relapsed after 6 months, and a further 22% did well but then relapsed after 2.5 years **4**)

1 English National Drug Treatment Monitoring System; **2** McDermott et al. J Clin Psychiatry 2006; 76:189–94;
3 Marsden et al Lancet 2009; 374:1269–1270; **4** Adapted from Eastwood B, et al. *J. Drug Alcohol Depend* 2018;188:200–8.

EXPO study: an open-label randomised controlled trial

Interventions [1]

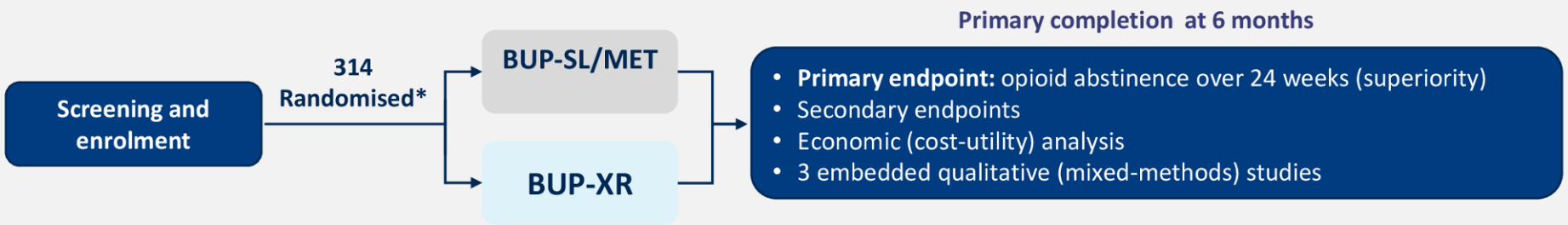
Standard of care (BUP-SL/MET)

- All forms of transmucosal buprenorphine
- Methadone
- Dose titrated to clinical effect

BUP-XR *(Sublocade®)*

- Loading dose: two 300 mg doses 1 month apart (≥ 21 days)
- Maintenance: 100 mg or 300 mg monthly
- Rescue sublingual buprenorphine at any time after first dose of BUP-XR

Study schema[2]



Schematic produced from EXPO Clinical Trial Protocol

*90% powered target sample was 304 participants

1 Marsden J et al. *Trials* 2022;23:697; 2. EXPO Clinical Trial Protocol, EudraCT number: 2018-004460-63.

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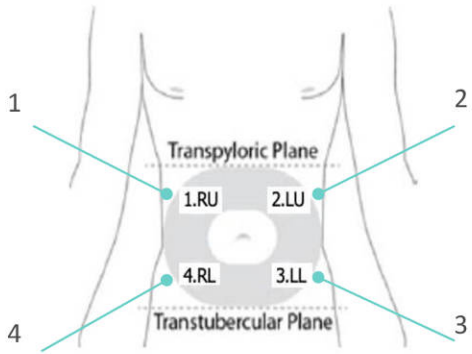
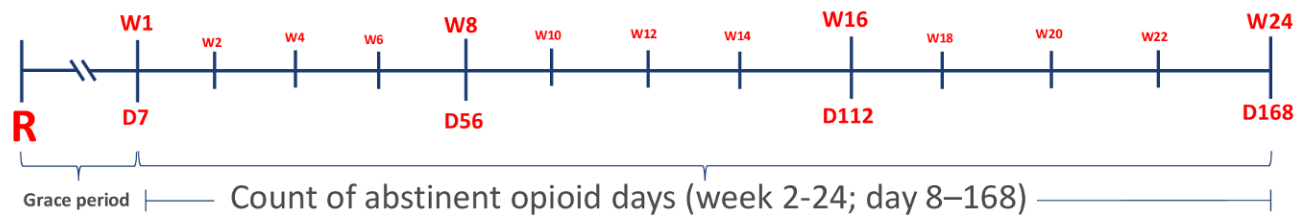
EXPO: BUP-XR dosing schedule

INJECTION	DAY	WEEK	WINDOW (days)	Dose (mg)
1	1	Baseline	-	300
2	28	4	21-42	300
3	56	8	54-70	100 or 300
4	84	12	82-98	100 or 300
5	112	16	110-126	100 or 300
6	140	20	138-168	100 or 300



Dose 3–6 could be adjusted according to symptom control, preference, and safety

Primary outcome



R Randomisation
W study week
D study day

Outcome measured by:

- Timeline Follow-back interview at visit every study week (recall period 14 days, but could be up to the maximum valid recall period for this interview method [i.e. 90 days]) [1]
- Point-of-care Urine Drug Screen (UDS) at visits from week 2 (12 tests)
- If UDS positive for opioids day of test and previous 2 days marked as using days
- UDS always trumped self-report
- Primary outcome ranged from 0–161 days

[1] Participants received local agreed payments for visits to complete research measures to offset travel costs and time

Secondary clinical outcomes, include:

Retention

- Days enrolled in OAT from weeks 2-24 (i.e. day 8–168; range 0–161 days; as primary outcome)
- Days from randomisation to first OAT discontinuation (if this occurred)

DSM-5 OUD and cocaine use disorder [CUD] remission

- By SCID-2-RV interview at week 12 and week 24 visit

Craving for opioids and craving for cocaine measured

- By frequency version of Craving Experiences Questionnaire (CEQ-F) at week 4,8,12,16,20,24

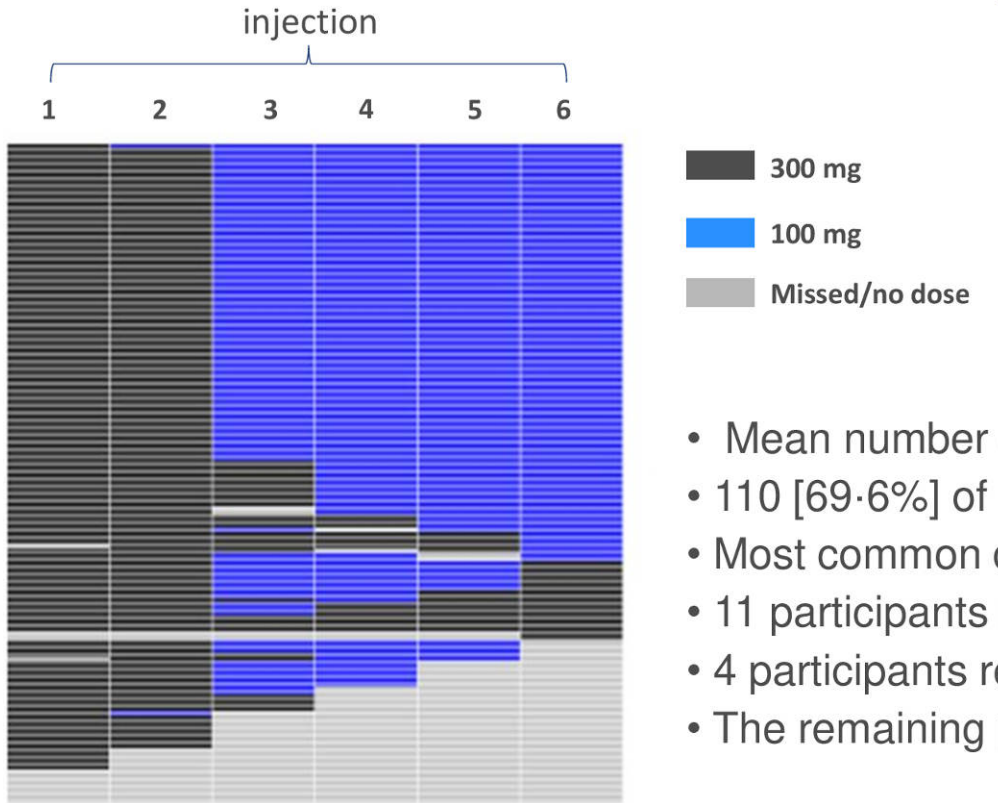
Abstinence from cocaine and benzodiazepines

- By TLFB and UDS as for the primary outcome (i.e. day 8-168; range 0–161 days)

Patient Reported Outcome (PRO) and Clinician Reported Outcome (ClinRO) for improvement

- PRO-I and Service Service User Recovery Evaluation (SURE) at week 24
- ClinRO Global Severity Index (GSI-I) at week 24

Results – Receipt of BUP-XR (n=158)



- Mean number of injections received was 4·98 (SD 1·84)
- 110 [69·6%] of 158 participants received all 6 injections.
- Most common dosing profile 2 x 300mg and 4 x 100mg (75%)
- 11 participants received 3 x 300mg then 3 x 100mg.
- 4 participants received 6 x 300mg.
- The remaining participants had a mixed pattern

Results – Primary outcome

Primary outcome – mean days abstinent

- BUP-SL/MET 104.9 days
- BUP-XR 123.4 days

Adjusted IRR 1.18; 95% 1.05–1.33; p-value 0.004

Model is mixed-effects regression with stratification factors (fixed) and treatment centre (random intercept) and multiple imputation for management of missing data.

IRR, interval rate ratio.

Secondary outcomes – Retention in OAT

Days enrolled in OAT from day 8–168

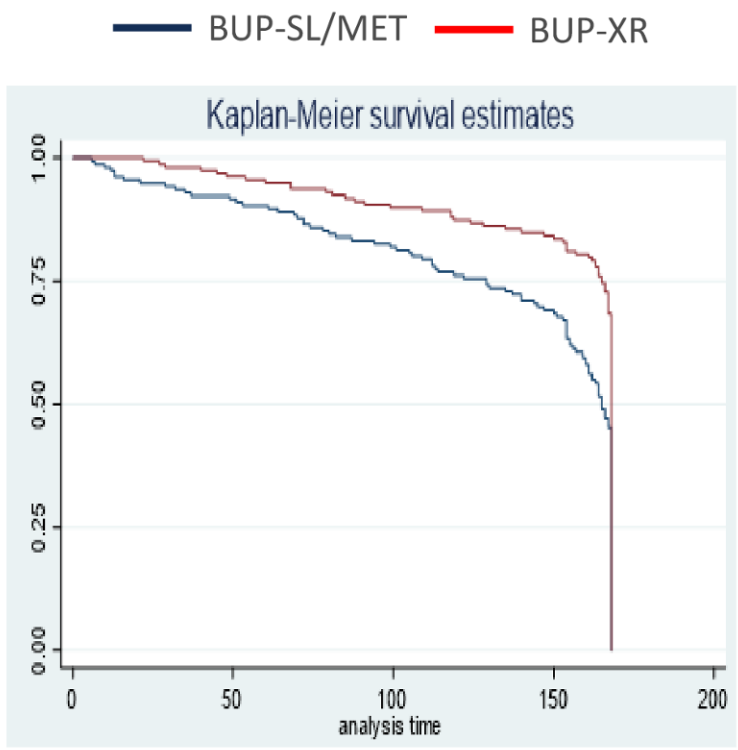
- 128·5 days (SE 4.82) in the BUP-SL/MET group
- 144·6 days (SE 2.54) in the BUP-XR group
- Adjusted IRR 1·12; 95% CI 1·01–1.25; p-value 0·029 *

BUP-XR group retained in more days of study treatment

Days from randomisation to first OAT discontinuation

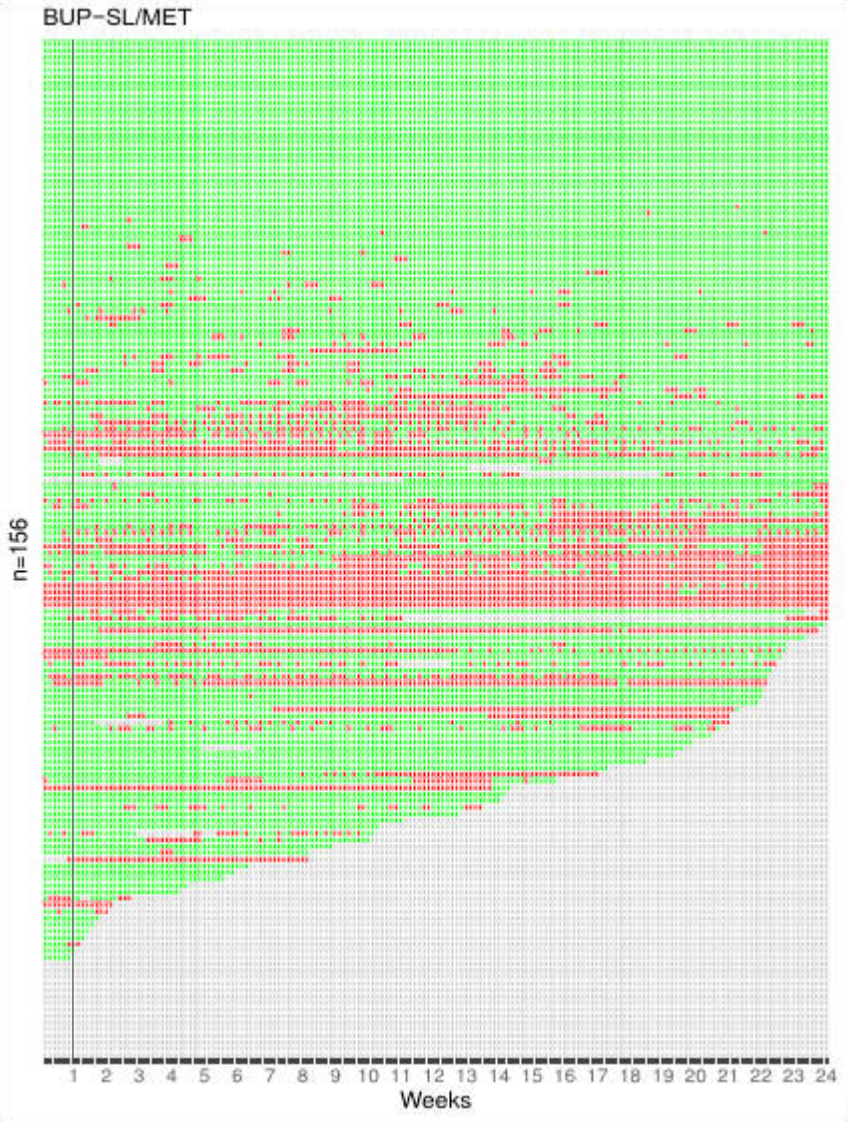
- 138·2 days (SD 47.7) in the BUP-SL/MET group
- 154·0 days (SD 33.6), in the BUP-XR group
- Adjusted HR 0·46; 95% CI 0·33–0.66; p-value 0·001

BUP-SL/MET group likely to discontinue earlier



IRR, interval rate ratio; HR, hazard ratio;
* Model is mixed-effects regression with stratification factors (fixed) and treatment centre (random intercept)

EXPO: Longitudinal course of opioid use for BUP-SL/MET

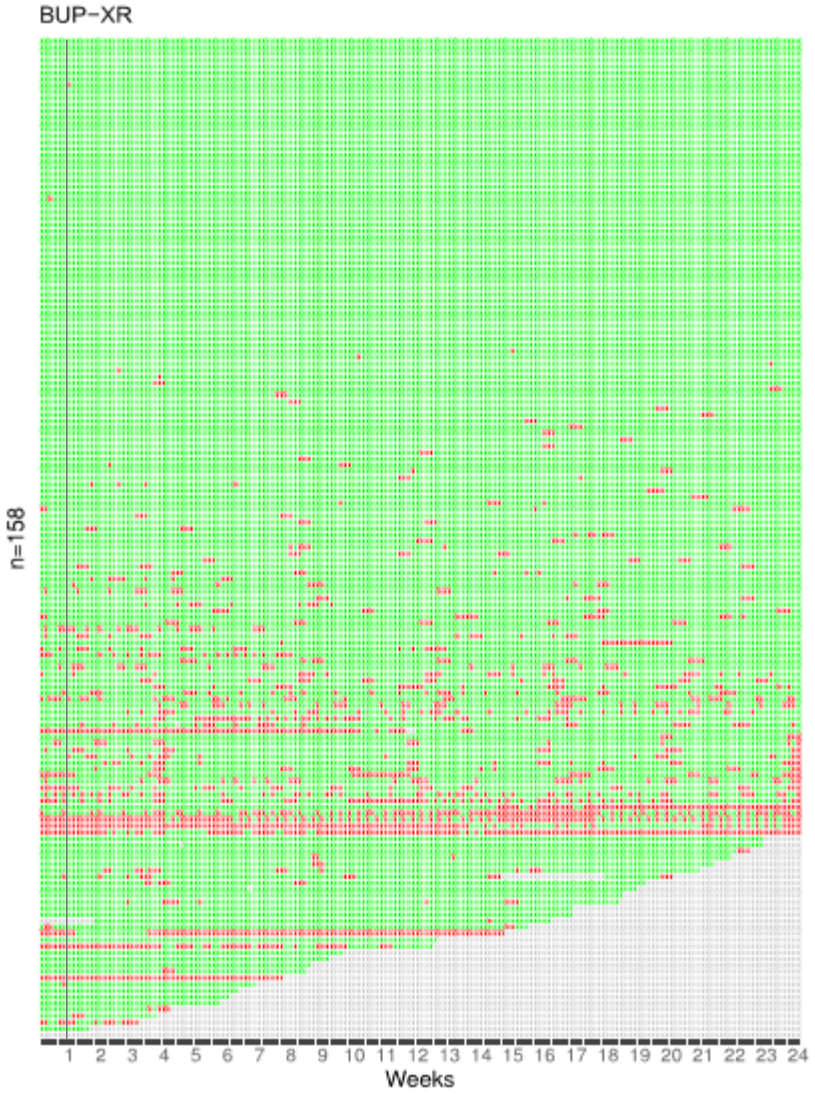


- Each row is data for for one participant from day 1–168.
- The participant rows are ordered by the number of days collected (decreasing), the number of days abstinent, and also whether day 168 was collected
- The vertical black line indicates the 1-week grace period after which primary effectiveness was assessed (days 8–168).
- **GREEN** is a day of opioid abstinence (negative report and available UDS negative).
- **RED** is a day of opioid use (positive report and available UDS positive).
- GREY denotes no data for that day (usually due to discontinuation).

Heat map shows:

- Sub-group retained and abstinent
- Larger sub-group retained but with sporadic/repeating opioid use
- Smaller sub-group retained but stably non-responding
- Mixed response among participants who discontinued

EXPO: Longitudinal course of opioid use for BUP-XR

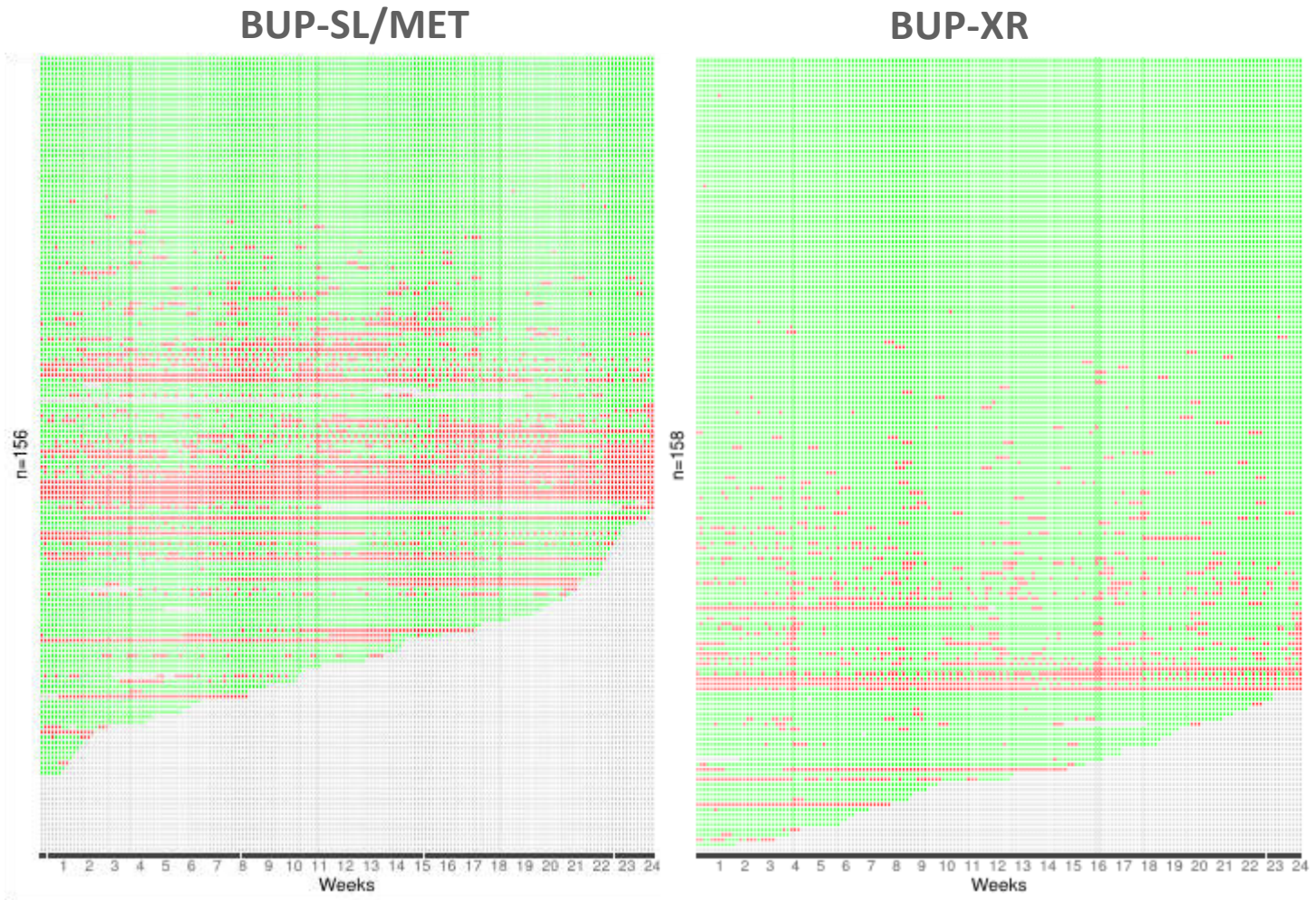


- Each row is data for for one participant from day 1–168.
- The participant rows are ordered by the number of days collected (decreasing), the number of days abstinent, and also whether day 168 was collected
- The vertical black line indicates the 1-week grace period after which primary effectiveness was assessed (days 8–168).
- **GREEN** is a day of opioid abstinence (negative report and available UDS negative).
- **RED** is a day of opioid use (positive report and available UDS positive).
- **GREY** denotes no data for that day (usually due to discontinuation).

Relative to BUP-SL/MET, heat map shows:

- Large sub-group retained and abstinent
- larger sub-group retained but with sporadic opioid use
- Very small sub-group retained but stably non-responding
- Generally abstinent pattern of response among those discontinued

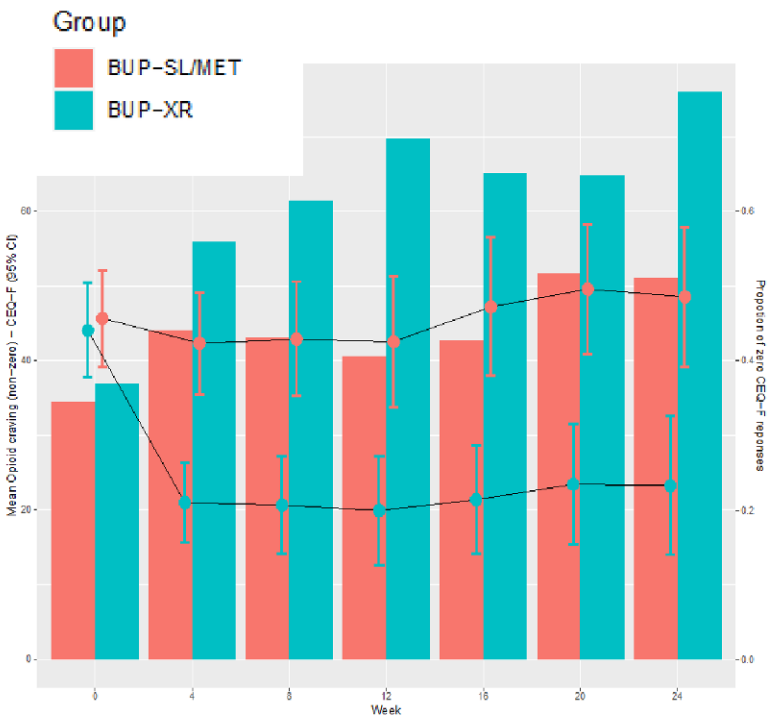
EXPO: Longitudinal course of opioid use by group



Relatively, BUP-XR associated with:

- More retention
- More continuous abstinence
- More retention and occasional opioid use
- Les retention and stable non-response

Secondary outcome – Craving for opioids



- Histogram is % with zero craving response in each group
- Lines are means (95% CI) for participants with non-zero response

BUP-XR

- Histogram shows progressive increase in zero craving *
- Line shows strong initial fall then stable craving frequency **

BUP-SL/MET

- Histogram shows slight increase in zero craving
- Line shows no change in craving frequency

* Adjusted endpoint analysis BUP-XR v BUP-SL/MET: OR 3.22; 95% CI 1.65–6.36; p-value 0.001
** Adjusted endpoint analysis BUP-XR v BUP-SL/MET: IRR 0.52; 95% CI 0.345–0.81; p-value 0.004

Craving measured by Craving Experiences Questionnaire (CEQ-F), score range 0-110

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EXPO STUDY

Results – Secondary endpoints

Early remission from OUD

- 97 [62.2%] of 156 in BUP-SL/MET
- 119 [75.3%] of 158 in BUP-XR

  Adjusted OR 1.9; 95% CI 1.02–3.52; p-value 0.042

PRO and ClinRO outcomes – BUP-XR effect

- PRO-I Odds Ratio 5.5; 95% CI 2.6–11.5; p-value 0.001
- SURE mean diff. 6.3; 95% CI 3.6–9.0; p-value 0.001
- GSI-I Odds ratio 6.9; 95% CI 3.2–4.9; p-value 0.001

Secondary outcome – mean days abstinent

Cocaine

- BUP-SL/MET 102.9 days
- BUP-XR 112.2 days
- Adjusted IRR 1.09; 95% 0.95–1.25; p-value 0.230

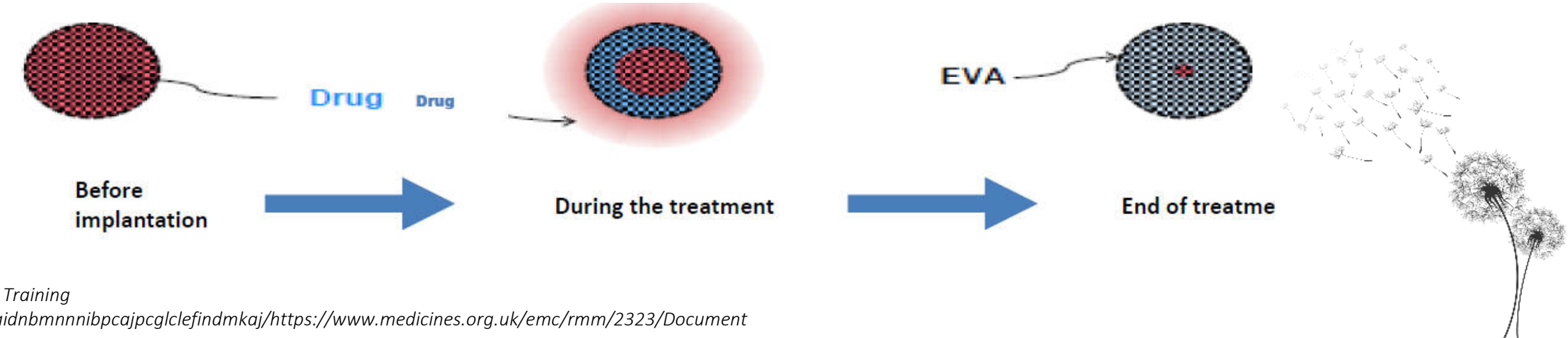
Benzodiazepines

- BUP-SL/MET 115.1 days
- BUP-XR 121.2 days
- Adjusted IRR 1.05; 95% 0.95–1.16; p-value 0.312

SIXMO® 74.2 mg IMPLANT BUPRENORPHINE

Sixmo delivers a continued steady state delivery of buprenorphine for 6 months through the ProNeura™ technology.

The ProNeura™ technology consists of a small solid rod made up of a mixture of ethylene vinylacetate (EVA) and active ingredient. The resulting product is a solid matrix that is implanted subcutaneously, in the inner arm with a simple surgical procedure, and is similarly removed at the end of the treatment period.



Sixmo 74.2 mg implant Training
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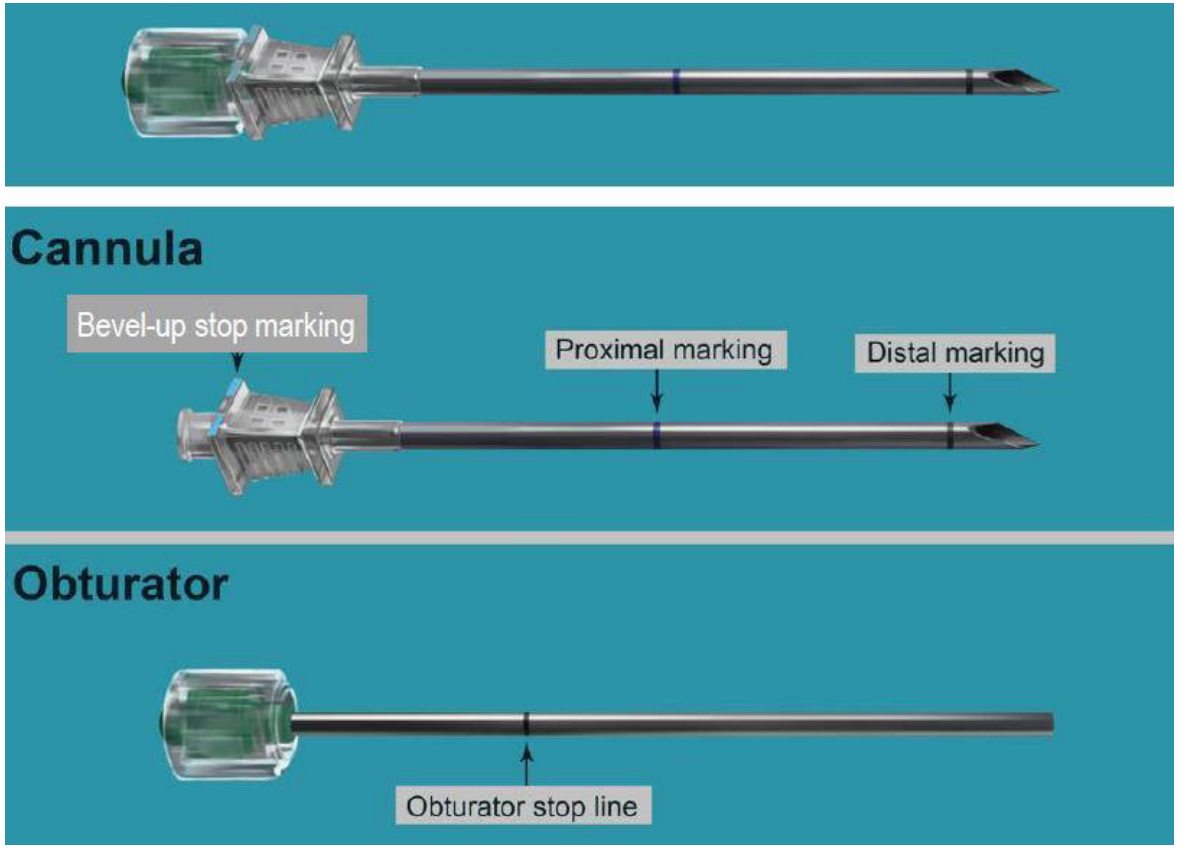
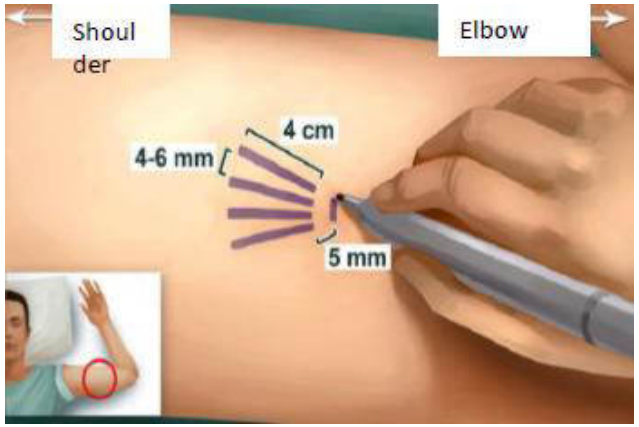
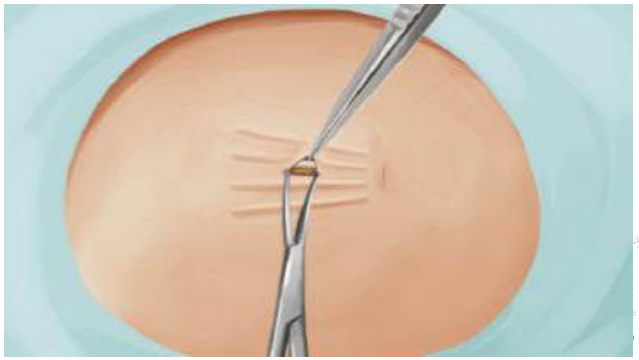
SIXMO® 74.2 mg IMPLANT BUPRENORPHINE







Sixmo 74.2 mg implant Training
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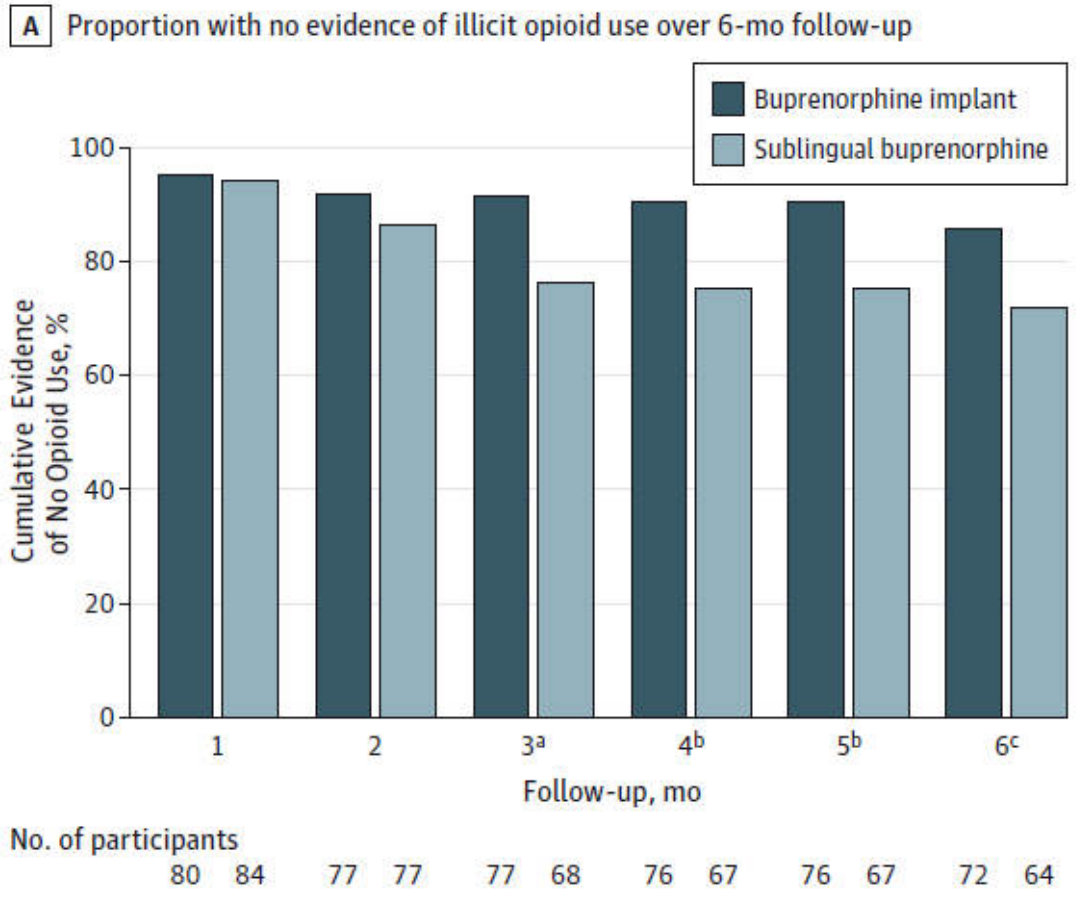
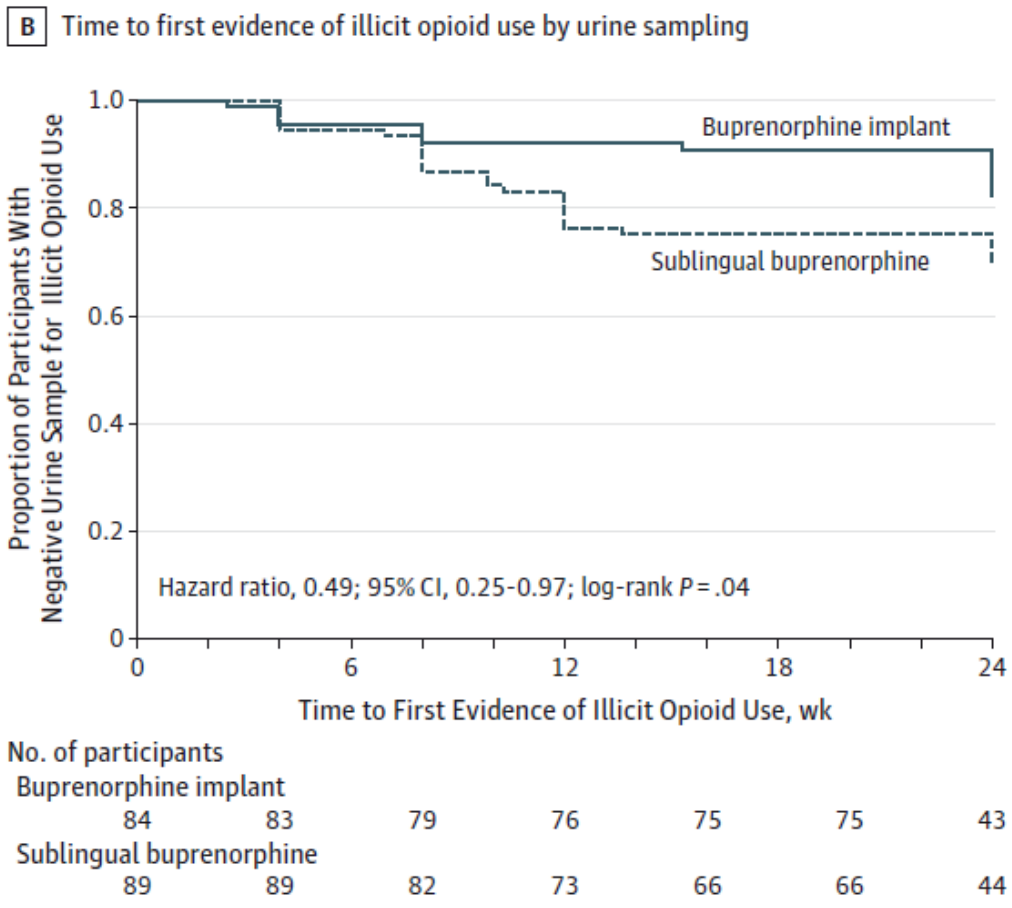
SIXMO® 74.2 mg IMPLANT BUPRENORPHINE





Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ; PRO-814 Study Group. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA. 2016 Jul 19;316(3):282-90

SIXMO® 74.2 mg IMPLANT BUPRENORPHINE

https://www.psychiatrist.com/pcc/delivery/recurrent-use-of-implantable-buprenorphine/

CASE REPORT

Recurrent Use of Implantable Buprenorphine

Michael C. Campbell, MD, FAPA, FAAFP

In October 2019, Mr A received his seventh set of consecutive buprenorphine implants. His would be the first documented case of a patient successfully maintained on buprenorphine implants longer than the FDA-approved 1 year of usage. There were no observed complications from placement of buprenorphine implants in previously used sites with the seventh set of implants. Incisions were made at the approximate insertion scars with no complications. Previous explants were completed as expected. The patient experienced no adverse events from consecutive buprenorphine implants. Implants in a stacked position were easier to explant than the standard fan pattern. Mr A continues in treatment to the present day and did not require the resumption of 2-mg buprenorphine/naloxone film in the summer of 2019.

NEW AGONIST OPIOID FORMULATIONS

TREATMENT

ORAL FORMULATIONS

Methadone* syrup
Methadone* tablets
Buprenorphine° SL tablets
Buprenorphine film

abstinent/user
heroin user/polydrug user
psychiatric comorbidities or not
medical comorbidities or not
married/divorced
first treatment/past treatment
history of misuse/diversion
employed/unemployed
house/homeless
custodial setting or not

EXTENDED-RELEASE FORMULATIONS

Buprenorphine depot
Buprenorphine implant

HARM REDUCTION

*Methadone and levomethadone
°Buprenorphine alone or buprenorphine/naloxone

NEW AGONIST OPIOID FORMULATIONS
WHAT WE NEED TO LEARN

How to use them	Guidelines, manufacturer information, training, clinical experience
When to use them	Which formulation for which patient or which formulation at what stage of disease? Treatment's formulations may change following the evolution of the patient's disease
How to switch from one formulation to another	Guidelines, manufacturer information, training, clinical experience
How to convince our health care systems that our patients' therapeutic adherence is worth	National and international policies, guidelines and….
How to explain them to patients	Clinical experience, training and…
How to introduce them into the care paradigm	Training for all components of OAT services and…

Thanks for your attention