Methods to Improve SUD Treatment Adherence

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NIDA

Biarritz, Wednesday Oct. 10, 2017 10:30 (30')

National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

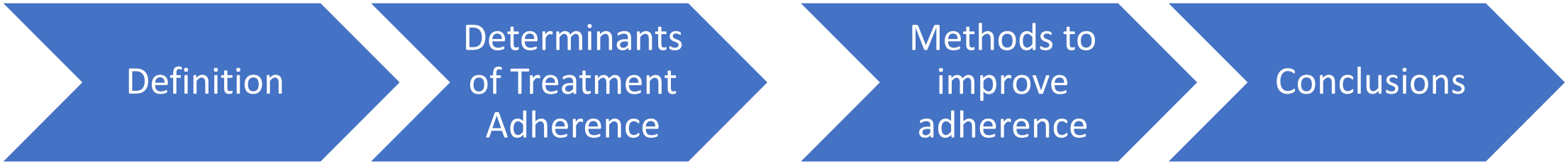
Disclosures

No conflict of Interest

Generic names of medications will be used

FDA unapproved medications will be mentioned

Outline



- Non-pharmacological
- Pharmacological
- Devices

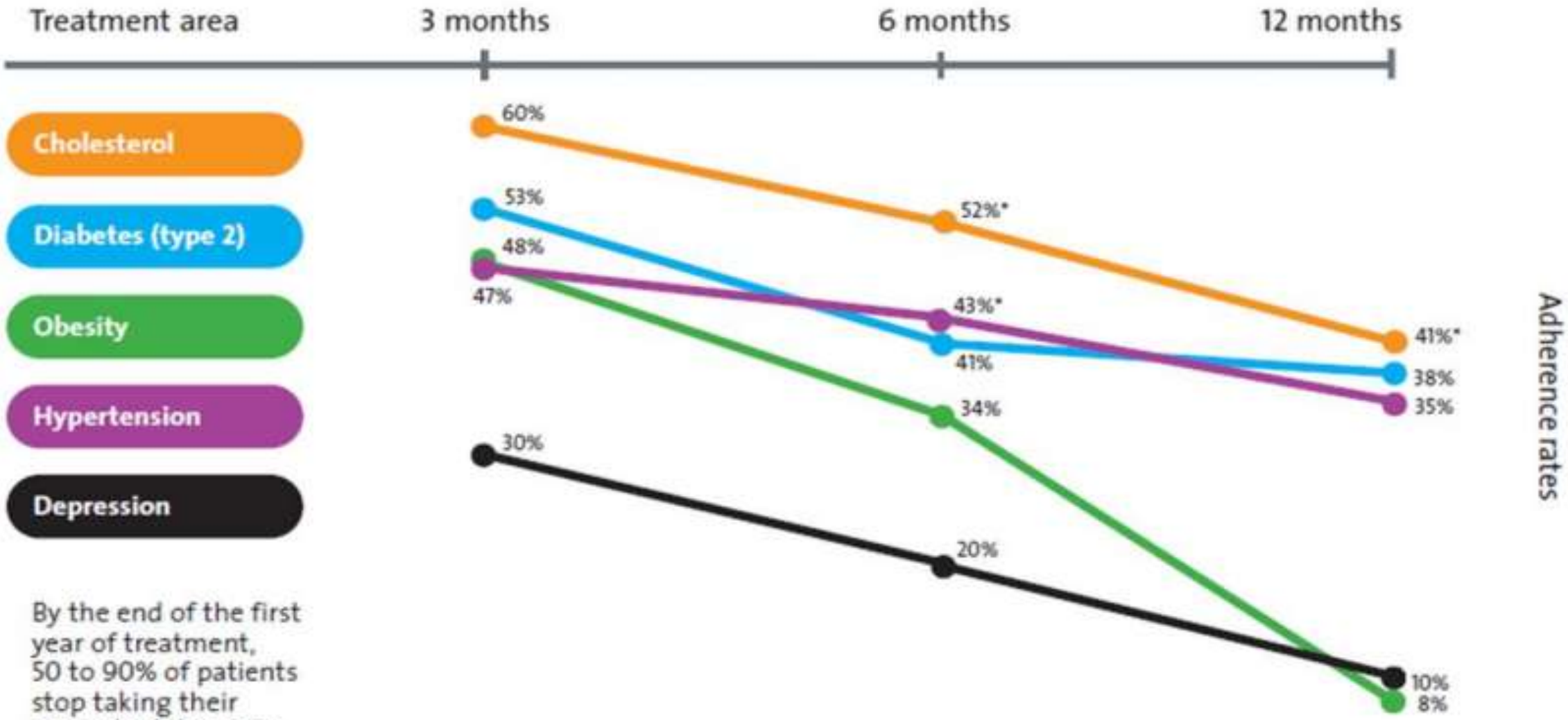
Definition

Treatment Adherence

- Extent to which patients follow the treatment as prescribed by their health care providers
- Adherence is the preferred term because “compliance” suggests that the patient is passive and not in a therapeutic alliance
- Measure: % of the prescribed treatment taken by the patient over a specified period

Osterberg, NEJM 2005

Adherence rates plummet in just a few months

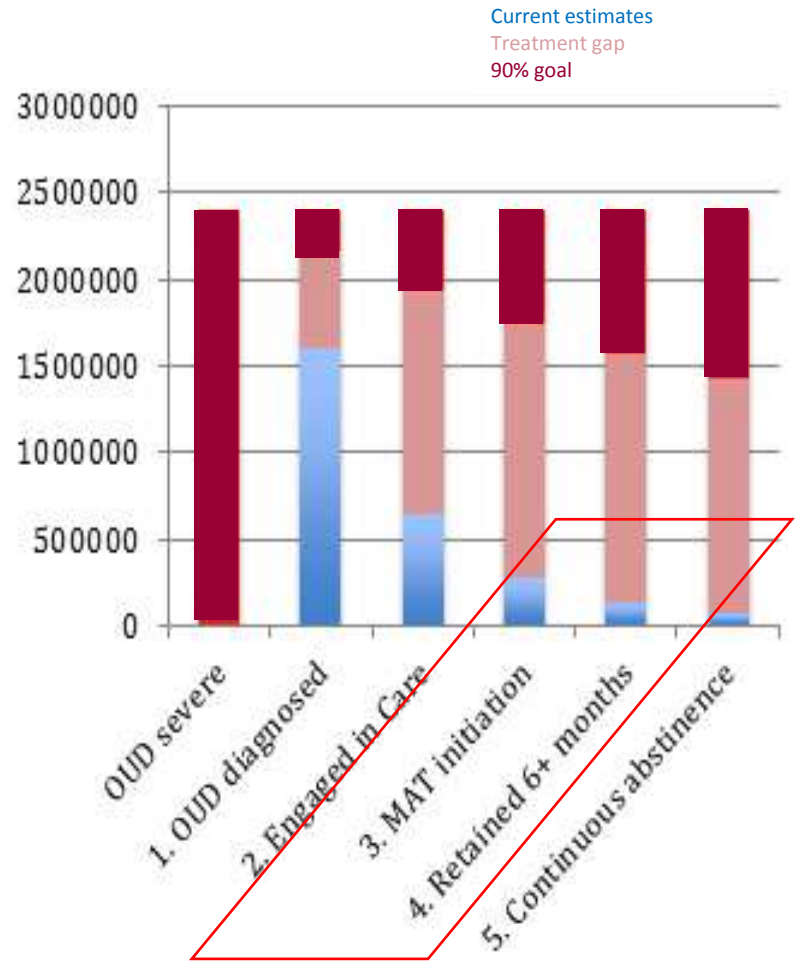


By the end of the first year of treatment, 50 to 90% of patients stop taking their prescribed therapies.

* Adherence rate ranges were averaged. **Source:** Various sources; A.T. Kearney analysis

*Snow, David. The Case for Smarter Medicine: How Evidence-Based Protocols Can Revolutionize Healthcare. 2010. Medco Healthcare Solutions

OUD Cascade of Care in USA



Williams AR, Nunes E, Olfson M. Health Affairs Blog, 2017

Tx Adherence and SUD Patients

Expected to be low due to…

- SUD clinical manifestations
- Tx: Frequent clinic visits
- Some meds can be diverted or misused
- Meds have limited efficacy and side effects
- HCP reluctant to prescribe meds for risks

Low Treatment Adherence

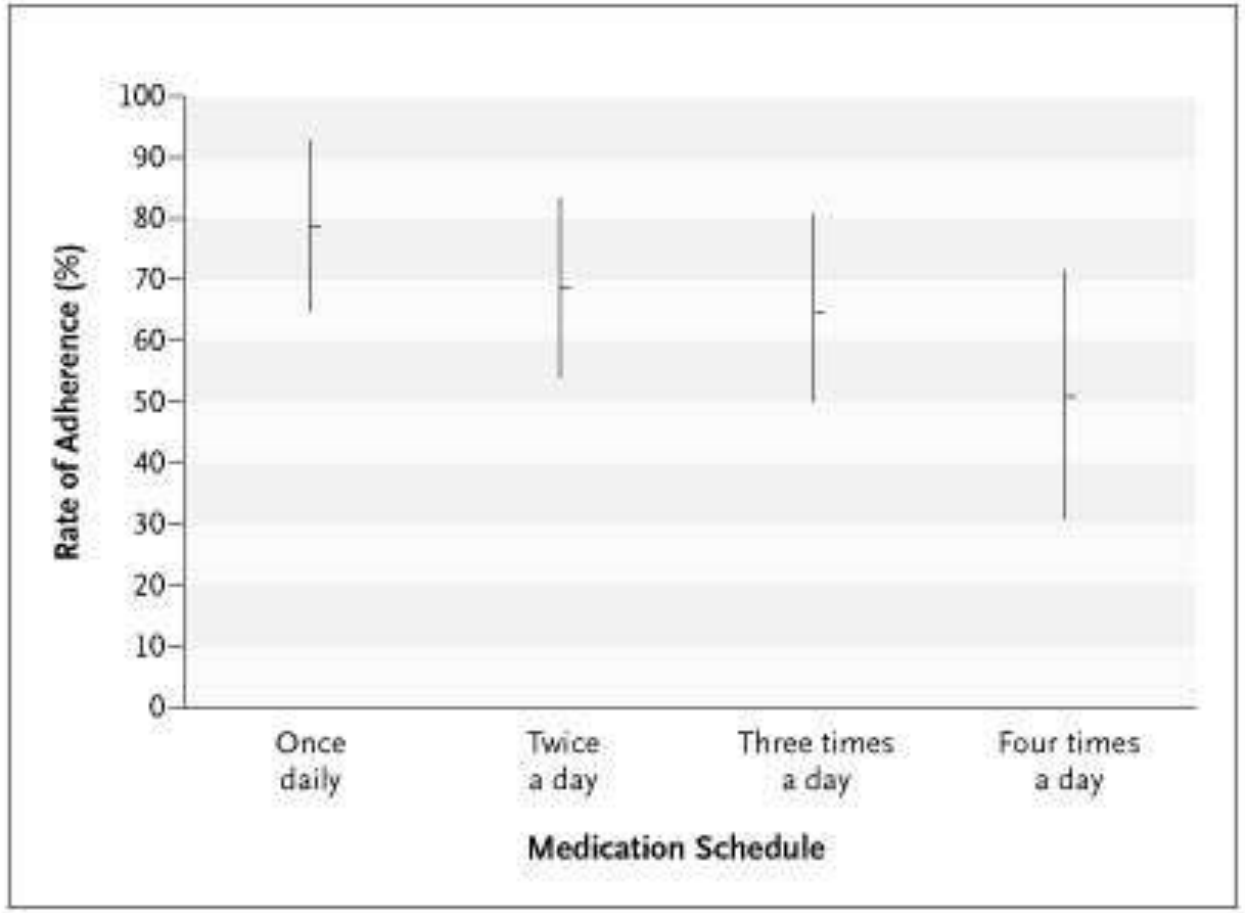
- Associated with:
  - Treatment failure
  - Substantial worsening of disease
  - Increased health care costs
  - Mortality

- *"Of all medication-related hospital admissions in the United States, 33 to 69 percent are due to poor medication adherence, with a resultant cost of approximately $100 billion a year"* (Osterberg, NEJM 2005)

Determinants of Treatment Adherence

- Socioeconomic: basic needs, health insurance, prescription coverage
- Access to treatment
- Education
- Cultural beliefs, values, practices
- Cognitive factors: memory
- Psychological factors: depression, anxiety
- Patient's perception of risk/benefit
- Patient-Doctor relationship
- Confidentiality
- SUD severity
- Previous experience with Tx ...
- Complexity of the tx …

Adherence to Medication According to Frequency of Doses.



Osterberg L, Blaschke T. N Engl J Med 2005;353:487-497.

Strategies to Promote SUD tx Adherence

1

Non-pharmacological

2

Pharmacological

- Biomarkers
- Medication levels
- Formulations
- New medications

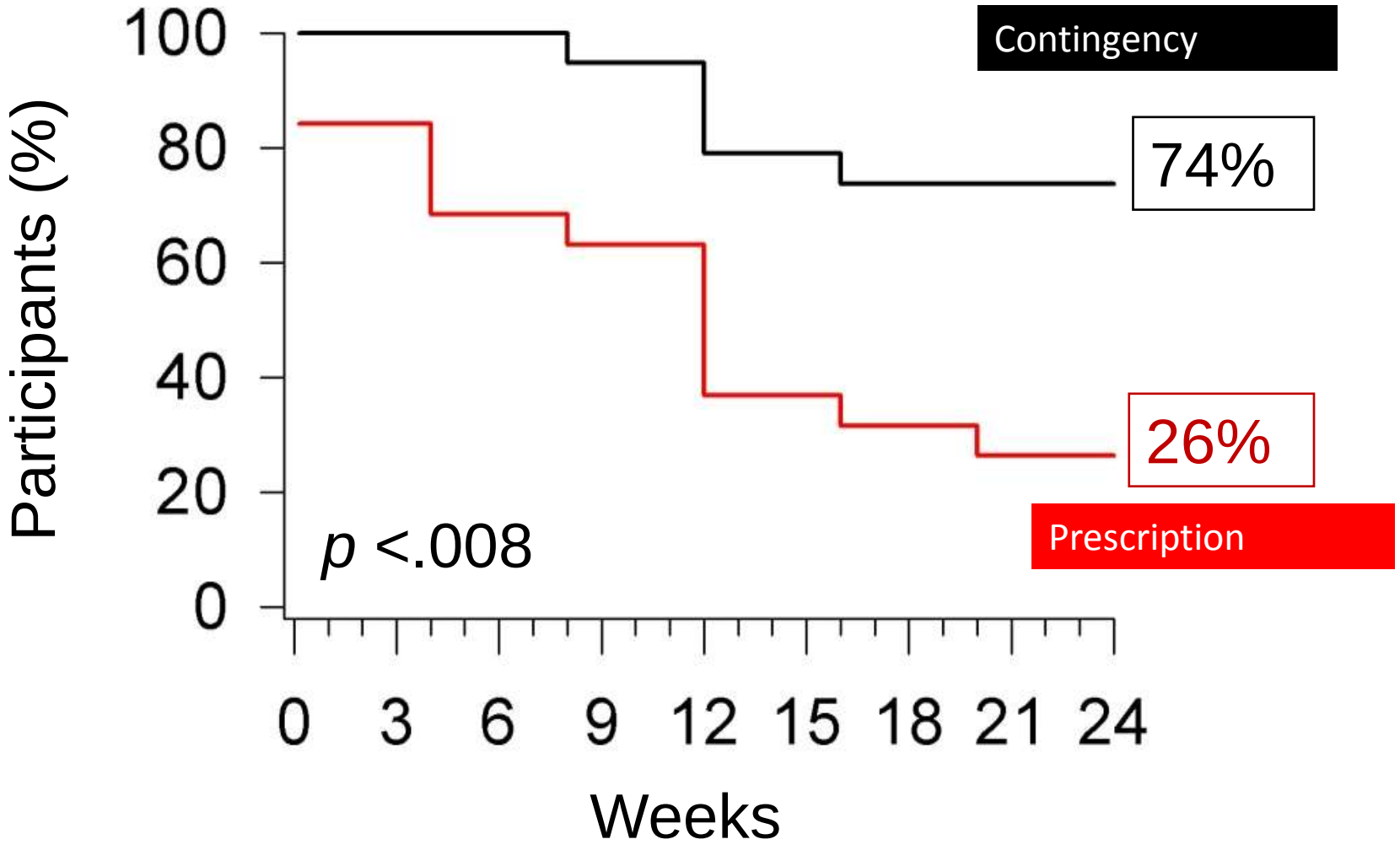
3

Devices

Non-Pharmacological Strategies

- Easy access to treatment
- Flexible schedule
- Clearly explain treatment plan
- Education about disease and realistic tx expectations
- Establish empathic patient-provider relationship
- Engage family, friends, and community
- Recognize importance of tx adherence
- Incentives for adherence

Retention in VIVITROL ® Treatment



DeFulio et al. (2012). Drug and Alcohol Dependence,120, 48-54.

Biomarkers

Desired Characteristics Of An Adherence Marker

- Well-behaved PK (once or twice a day dosing) with low variability
- No drug-drug interactions
- Urinary excretion (saliva acceptable, especially for on-site assay)
- Not commonly found in dietary sources, supplements, or pharmaceuticals
- FDA approved for use (and low toxicity)/GRAS
- Bioavailability should not be substantially affected by food

Sounds like a molecule with drug-like characteristics!

Candidate Markers

Acetazolamide

Carbonic Anhydrase Inhibitor

Half-life = 4-8 h (per label)

100% Bioavailable

Therapeutic dose: 125 mg-1 g/day
Testing at 15 mg/day

Quinine

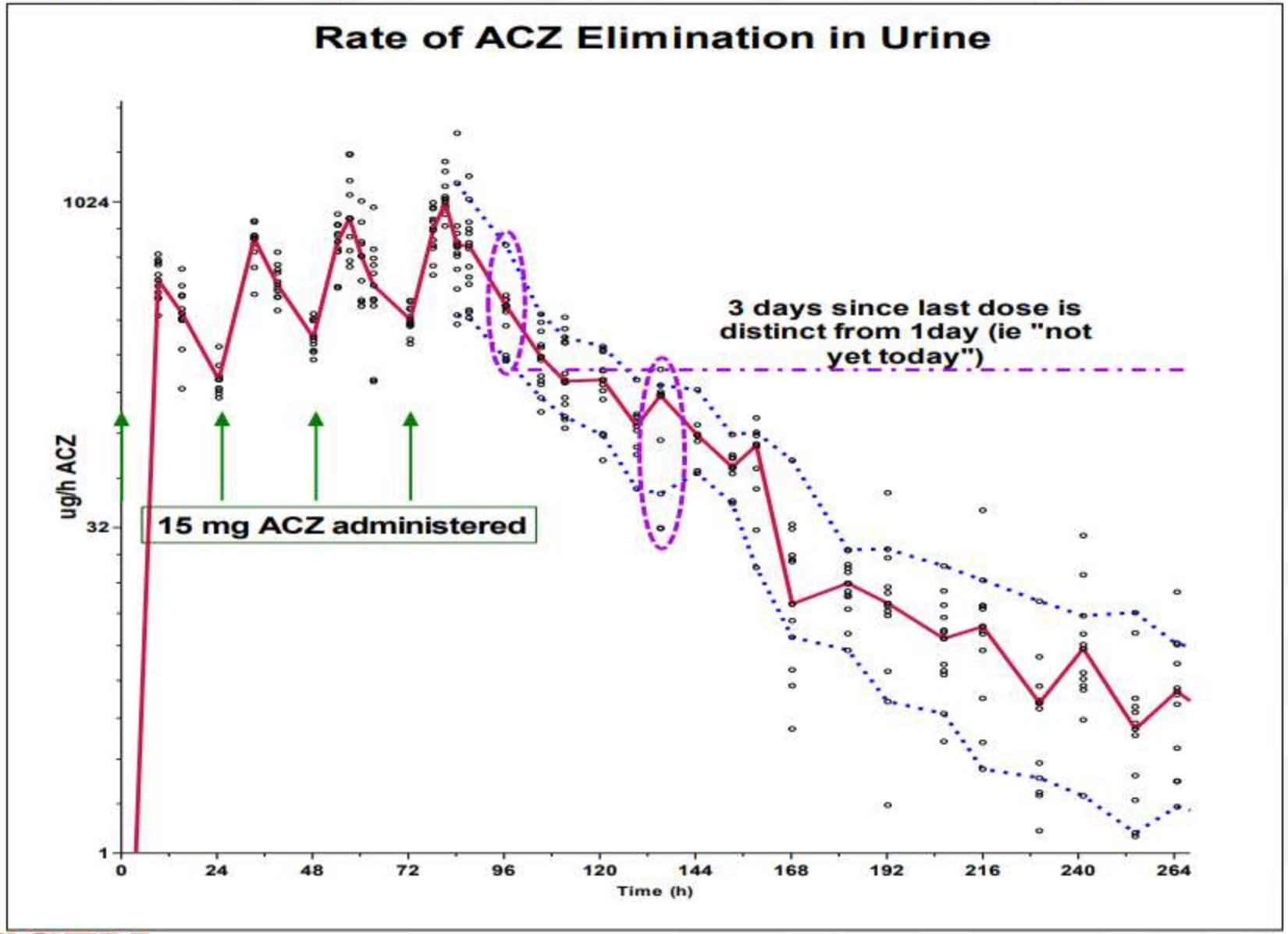
Antimalarial (& Tonic Water)

Half-life = 10-12 h

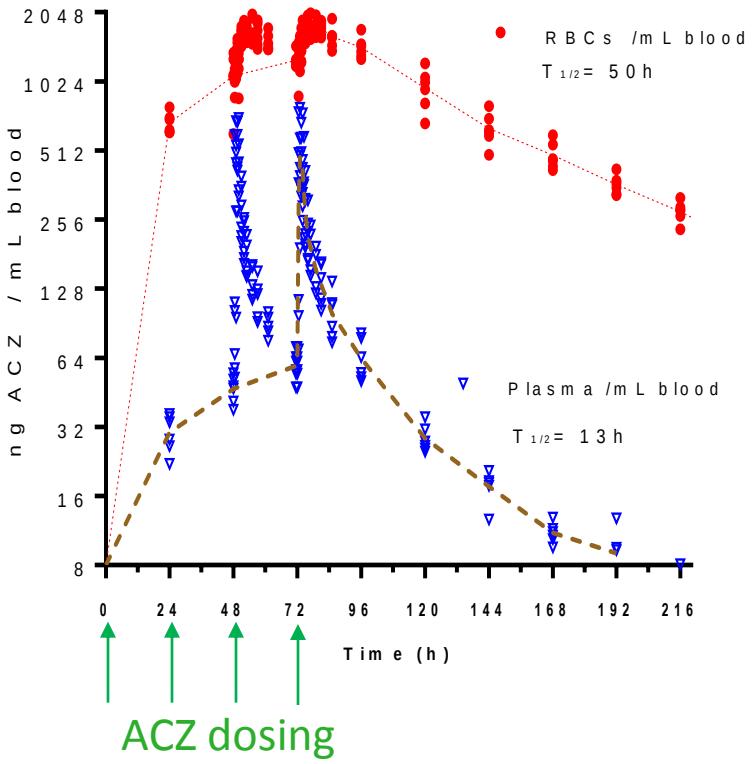
80% Bioavailable

Therapeutic Dose: 650 mg/day
Testing at 80 mg/day
(equivalent to ~1.1 liters of tonic water)

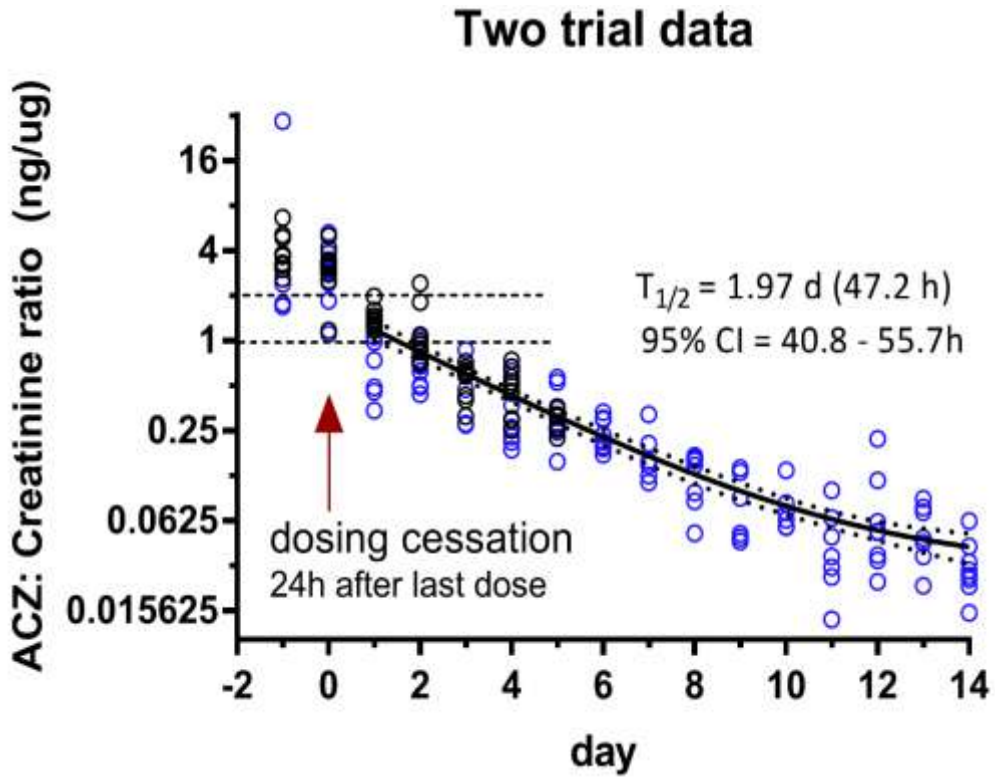
The Rate of Elimination of Acetazolamide Is Predictable and Prolonged



ACZ elimination from plasma and Red Blood Cells following cessation of 15 mg/day dosing (Hampson et al 2016)



Creatinine normalized ACZ in urine following cessation of 15mg/day dosing data from two trials (in prep)



- Plasma values rise and fall rapidly within 24h of dosing, RBCs release slowly
- After dosing cessation, RBC sequestered ACZ controls urine concentration

A Pharmacokinetic Study Examining Acetazolamide as a Novel Adherence Marker for Clinical Trials. Hampson AJ et al (2016) J.Clin.PsychoPharmacol (36) 324-32

Pharmacological

- Medication levels
- New Formulations
- New Medications

New Formulations

Long Acting Formulations

- Reproducible sustained delivery of a drug at a target site for more than one week by controlled drug-delivery systems.
  - Oil-based injectable solutions
  - Injectable drug suspensions
  - Supersaturated drug solutions
  - Polymer-based microspheres
  - in-situ forming implants

Table II. Commercially available injectable sustained-release drug-delivery systems.

Drug	Brand name	Administration	Dosing frequency	Indications	Company	Country/region
Oil-based injections						
Haloperidol decanoate	Haldol Decanoate	IM	once a month	Schizophrenia	Ortho-McNeil Pharm	US
Flupenthixol decanoate	Fluanxol Depot	IM	every 2–4 weeks	Schizophrenia	Lundbeck	Europe
Fluphenazine decanoate	Fluphenazine Decanoate	IM	every 2–4 weeks	Schizophrenia	APP Pharm	US
Fluphenazine decanoate	Modecate	IM	every 2–5 weeks	Schizophrenia	sanofi-aventis	Europe
Zuclopenthixol decanoate	Clopixol Depot	IM	every 2–4 weeks	Schizophrenia	Lundbeck	Europe
Pipothiazine palmitate	Piportil Depot	IM	every 4 weeks	Schizophrenia	sanofi-aventis	Europe
Testosterone enanthate	Delatestryl	IM	every 2–4 weeks	Hormone therapy	Endo Pharma	US
Estradiol valerate	Delestrogen	IM	every 4 weeks	Hormone therapy	Monarch Pharm	US
Testosterone cypionate	Depo-Testosterone	IM	every 2–4 weeks	Hormone therapy	Pfizer	US
Estradiol cypionate	Depo-Estradiol	IM	every 3–4 weeks	Hormone therapy	Pfizer	US
Injectable drug suspensions						
Paliperidone palmitate	Invega Sustenna	IM	once a month	Schizophrenia	Janssen	US
Olanzapine	Zyprexa Relprevv	IM	every 2–4 weeks	Schizophrenia	Eli Lilly	US
Medroxyprogesterone acetate	Depo-Provera	IM	every 3 months	Hormone therapy	Pfizer	US
Medroxyprogesterone acetate	Depo-Subq Provera 104	SC	every 3 months	Hormone therapy	Pfizer	US
Supersaturated drug solution						
Lanreotide acetate	Somatuline Depot	deep SC	once a month	Acromegaly	Tercica	US
Microspheres						
Risperidone	Risperdal Consta	IM	every 2 weeks	Schizophrenia	Janssen	US
Naltrexone	Vivitrol	IM	once a month	Alcohol dependence	Alkermes	US
Somatropin (rDNA origin)	Nutropin Depot	SC	every 2–4 weeks	Hormone therapy	Genentech	US
Leuprolide acetate	Lupron Depot	IM	every 1–3 months	Advanced prostate cancer	Abbott	US
Triptorelin pamoate	Trelstar	IM	every 1–6 months	Advanced prostate cancer	Watson Pharma	US
Octreotide acetate	Sandostatin LAR Depot	IM	every 4 weeks	Acromegaly	Novartis	US
Lanreotide acetate	Somatuline LA	IM	every 2 weeks	Acromegaly	Ipsen	Europe
***In situ* forming implants**						
Leuprolide acetate	Eligard	SC	every 1–6-months	Advanced prostate cancer	sanofi-aventis	US

IM is intramuscular. SC is subcutaneous. Genentech was acquired by Roche in 2009.

Yun-Seok Rhee, Chun-Woong Park, Patrick P. DeLuca, Heidi M. Mansour
Pharmaceutical Technology
Volume 2010 Supplement, Issue 6

Long Acting Formulations for SUD: Advantages

- Better treatment adherence
- Better tx outcomes
- Reduce morbidity and mortality
- Improved systemic availability by avoidance of first-pass metabolism
- A predictable drug-release profile
- Reduced dosing frequency (i.e., fewer injections) without compromising the effectiveness of the treatment
- Reduce risk of
  - Inappropriate prescribing
  - Unintentional overdose
  - Diversion (sharing/selling prescribed doses)
  - Misuse (Snorting or injecting to “get high”)
  - AEs during peak blood med levels (drowsiness)
  - Withdrawal symptoms during trough blood med levels
  - Tolerance and require higher doses (“self-titration”)
- Accidental exposure of children or opioid naïve individuals (overdose)
- Reduce fetal effects of peak and trough blood med levels of pregnant mother (?)

Long Acting Formulations for SUDs: Disadvantages

- AEs once administered are hard to control
- Less contact with tx program → Less SUD monitoring
- Application risk of local inflammation or infection
- Allergy to slow release chemicals (e.g., polymers)
- Risk of med-med interactions
- Unintended effects (e.g., blockade of analgesic effect)
- Unintentional overdose
- FDA's Risk Evaluation and Mitigation Strategy (REMS) program

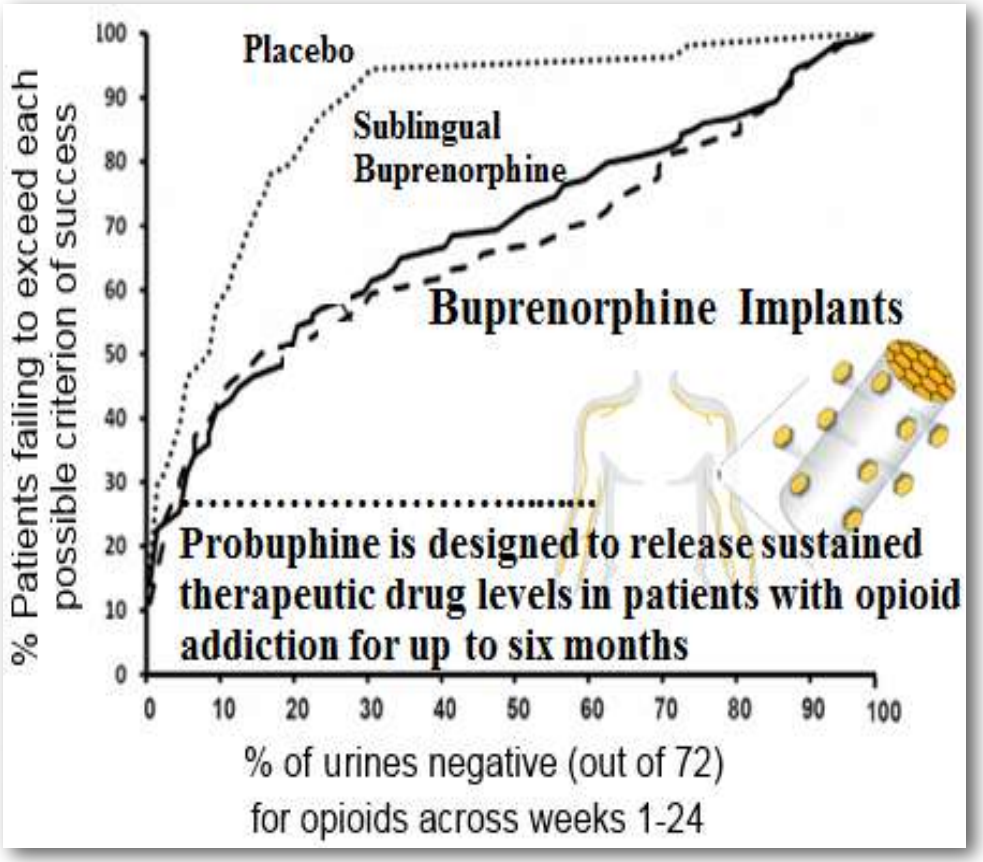
Long Acting Meds for SUDs

		Route	Frequency	Pros	Cons
Buprenorphine	RBP-6000 (Indivior®)	SC	1 month	Positive pivotal PIII trial results	Site pain
	CAM2038 (Camurus®/ Braeburn®)	SC	Weekly/monthly	Positive PII multisite	Site pain
	Probuphine (Titan®/ Braeburn®)	Implant	6 months	FDA-approved	Site AEs, implant expulsion, migration, protrusion

Extended Release Medications Improve Tx Adherence

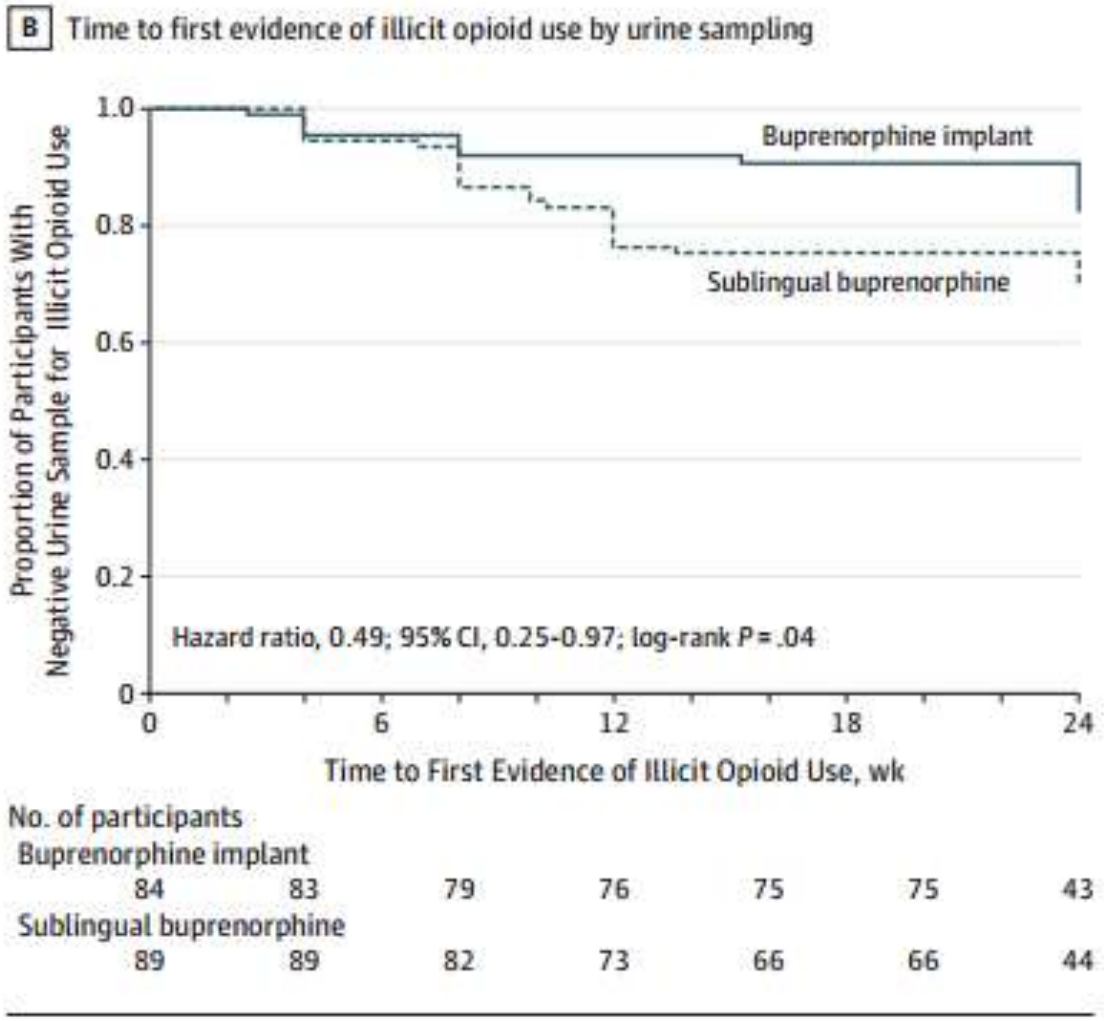
- Implantable buprenorphine
  - Trial: buprenorphine implants
    vs. placebo for 6 months

FDA approval – May 26, 2016



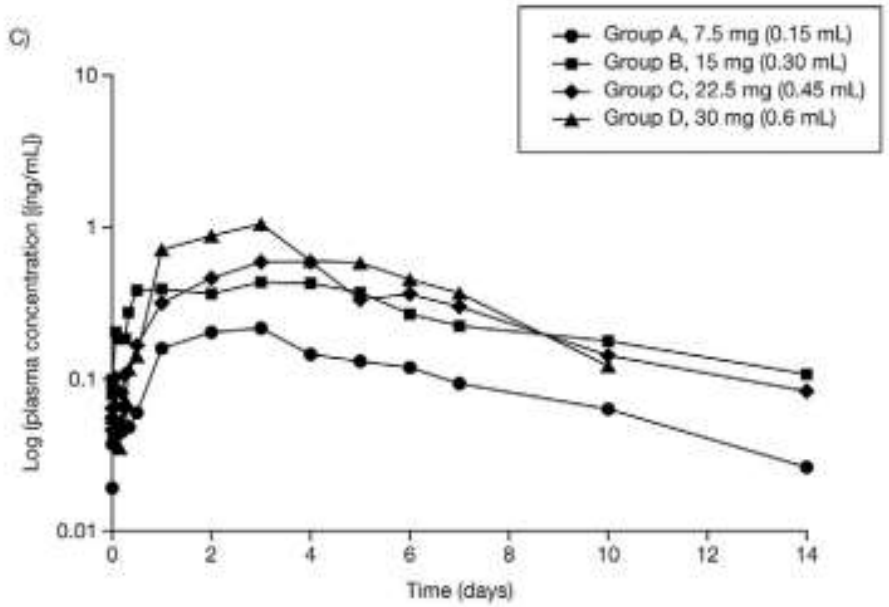
Rosenthal et al., Addiction 2013;105.

Implant versus Sublingual Buprenorphine

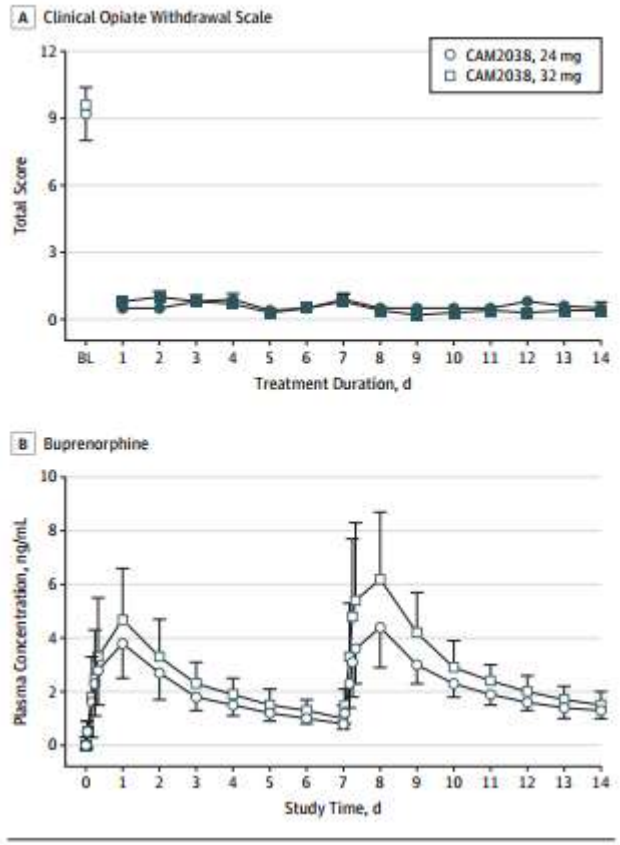


Rosenthal, 2016

CAM2038



Haasen C, Linden M, Tiberg F., J Subst Abuse Treat. 2017

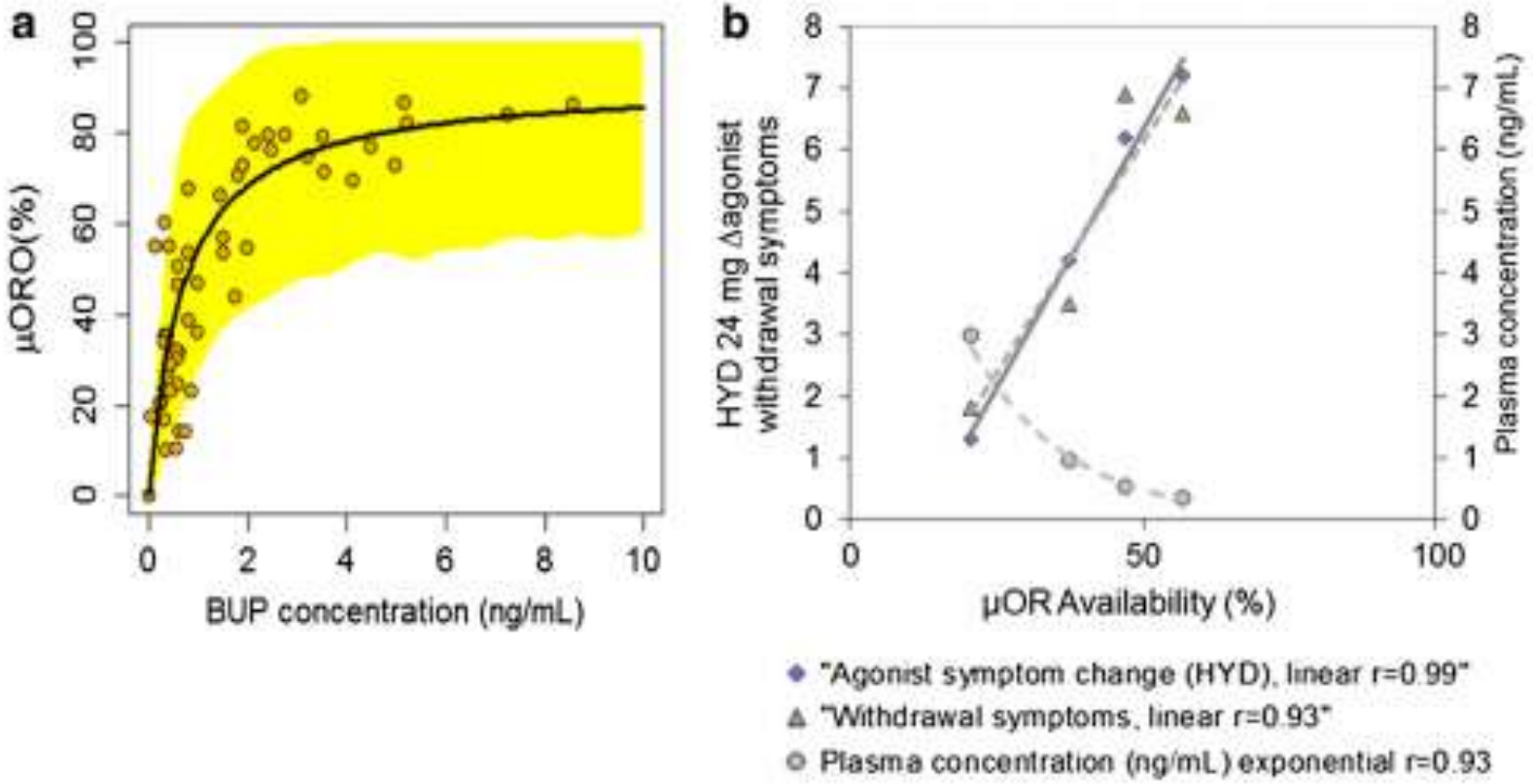


Walsh SL, Comer SD, Lofwall MR, et al JAMA Psychiatry. 2017 Sep

CAM2038

- Phase 3, double-blind, double-dummy study randomized
- N= 428 adults with moderate-to-severe Opioid Use Disorder
- Flexible dosing with weekly and monthly CAM2038 or daily sublingual (SL) buprenorphine/naloxone (BPN/NX).
- Primary endpoints were non-inferiority in proportion of opioid-negative urine samples (EMA) and responder rate (FDA).
- A responder had no evidence of illicit opioid use at nine pre-specified time points. Superiority for the cumulative distribution function (CDF) of the percentage of opioid-negative urine samples was also evaluated.
- Results:
  - Non-inferiority was demonstrated
  - Positive treatment difference of 3.4% (95% CI: -3.5–10.4%; P<0.001) for responder rate
    - 6.7% (95% CI: -0.1–13.6%; P<0.001) for the mean percent opioid-negative urine samples.
    - Superiority of CAM2038 versus daily SL BPN/NX was demonstrated for the CDF for the percentage of illicit opioid-negative urines plus self-reports during treatment weeks 4–24 (P=0.004).

RBP-6000



Laffont CM, Gomeni R, Heidbreder C, Jones JP 3rd, Nasser AF. J Clin Pharmacol. 2016

Camurus Announces that FDA Grants Priority Review of NDA for Weekly and Monthly CAM2038 Buprenorphine Depots for Treatment of Opioid Use Disorder

Lund, Sweden – 18 September 2017 — Camurus (NASDAQ STO: CAMX) announces that the U.S. Food and Drug Administration (FDA) has accepted the New Drug Application (NDA) for weekly and monthly CAM2038 buprenorphine depots for the treatment of adults with opioid use disorder (OUD) and granted a Priority Review. The NDA for CAM2038 was submitted on July 19, 2017 by Camurus' U.S. partner Braeburn Pharmaceuticals and comprises data from seven clinical trials, including two Phase 3 trials.

Indivior RBP-6000 NDA Acceptance with Priority Review Designation

07.31.2017 | PDF Version

Indivior PLC Announces FDA Acceptance with Priority Review Designation of RBP-6000 Buprenorphine Monthly Depot New Drug Application (NDA) for the Treatment of Opioid Use Disorder

braeburn

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September 18, 2017

FDA Acceptance of NDA for CAM2038 for Opioid Use Disorder

Braeburn Announces FDA Acceptance with Priority Review of New Drug Application for CAM2038 Buprenorphine Depot for the Treatment of Opioid Use Disorder

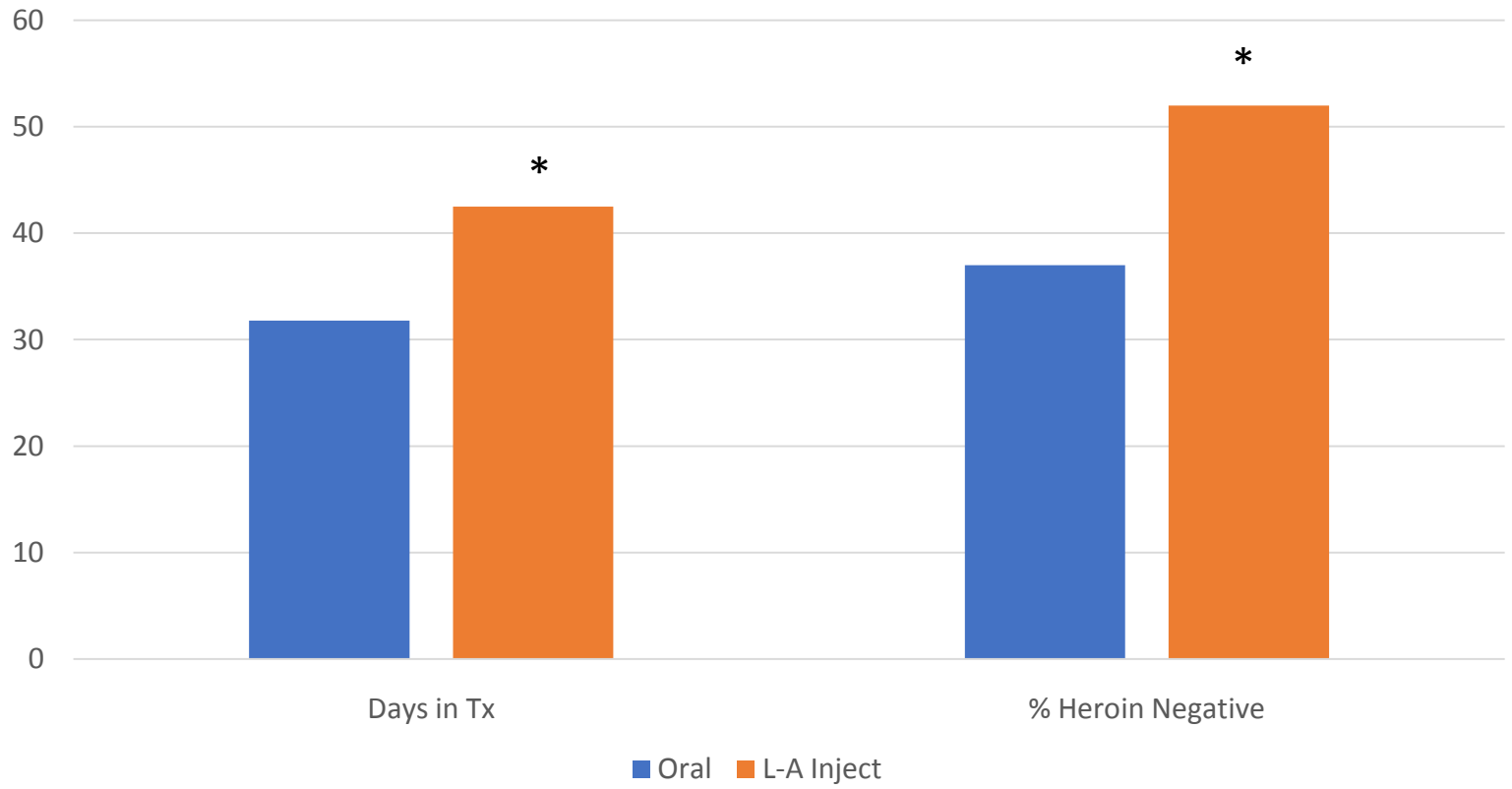
- If approved, CAM2038 will provide patients and HCPs with weekly and monthly dosing options for the treatment of opioid use disorder, with the goal of improving treatment adherence and reducing the burdens associated with the daily medication.
- The FDA has assigned a Prescription Drug User Fee Act (PDUFA) target date of January 19, 2018

Princeton, N.J. — September 18, 2017 — Braeburn Pharmaceuticals, Inc.

Long Acting Meds for SUDs

		Route	Frequency	Pros	Cons
Biologics	Vaccines	IM	~weekly	No CNS	Under evaluation
	Butirylcholinesterase	IM	~weekly	No CNS	Under evaluation
Methadone		Implant	1 month	Methadone serum levels adequate	1 study in mice (2004). Implant too big for clinical use
Naltrexone	Injectable	IM	Monthly	FDA approved for AUD and opioid relapse prevention	Site pain, inflammation, opioid tx resist, loss opioid tolerance
	Implant (Prodetoxon®)	Surgical Abdomen	2-3 months	Approved in Russia	Implant site AEs
	Implant (O'Neil)	SC	6 months	Australia	Site infection, necrosis, implant leaking

Long-Acting versus Oral Naltrexone



Two concurrent RCTs
Oral n=69
L-A injectable n=42

* <.05

Brooks at al, 2010

Implant versus Oral Naltrexone

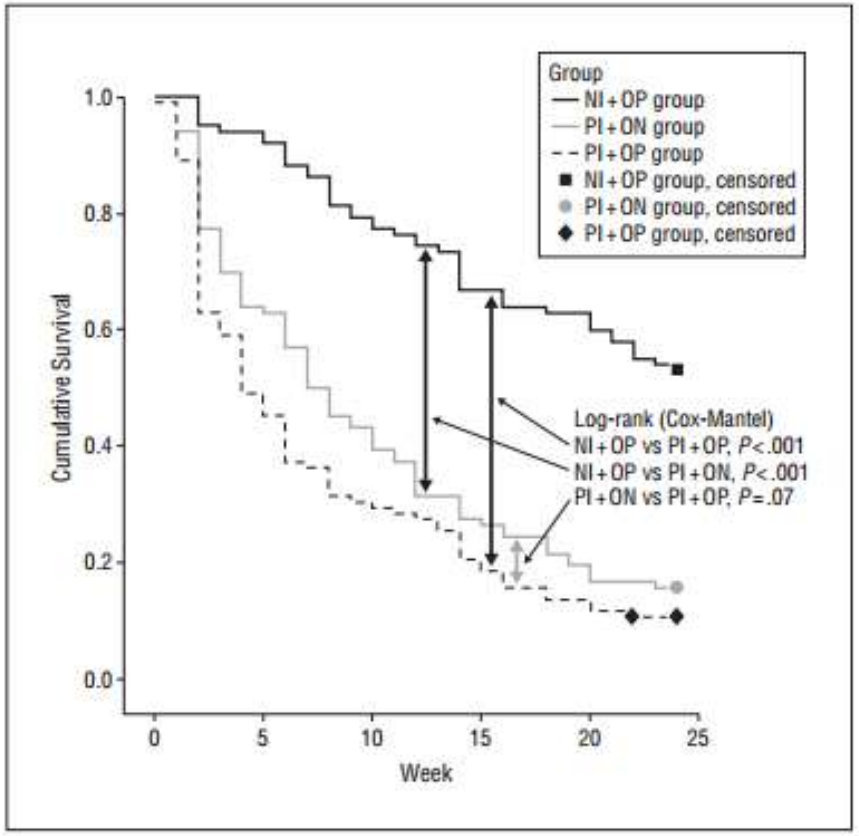


Figure 2. Kaplan-Meier survival evaluating treatment dropout and relapse. NI+OP indicates 1000-mg naltrexone implant and oral placebo (n=102); PI+NO, placebo implant and 50-mg oral naltrexone hydrochloride (n=102); PI+OP, placebo implant and oral placebo (n=102).

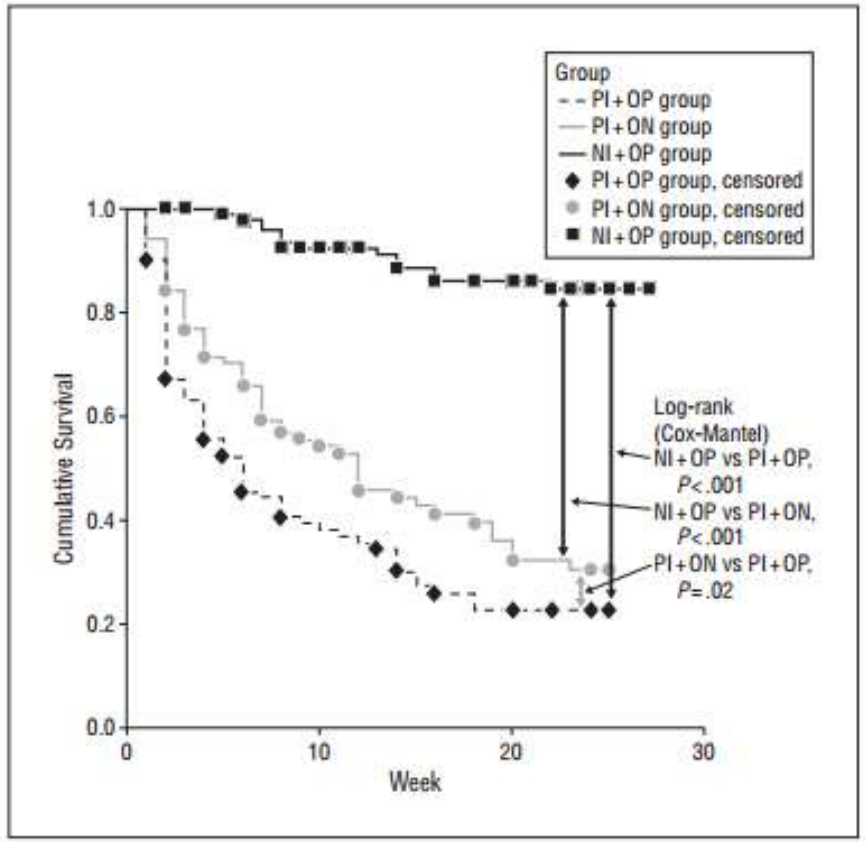


Figure 3. Kaplan-Meier survival evaluating verified relapse. NI+OP indicates 1000-mg naltrexone implant and oral placebo (n=102); PI+NO, placebo implant and 50-mg oral naltrexone hydrochloride (n=102); PI+OP, placebo implant and oral placebo (n=102).

Krupitsky, 2012

Opiant Pharmaceuticals collaborate to explore a new approach to opioid use disorder treatment

Reuters Staff

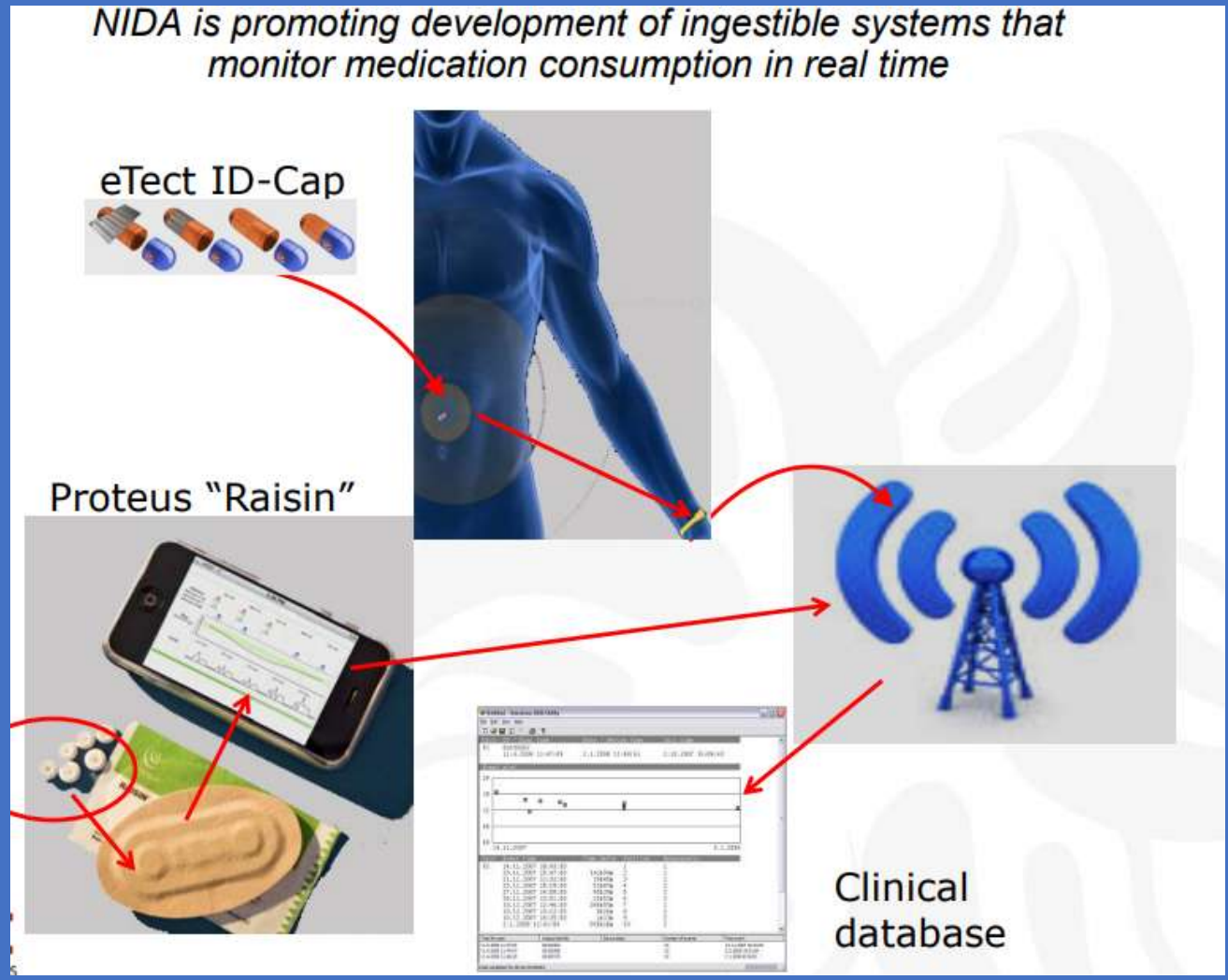
1 MIN READ

Oct 2 (Reuters) - Opiant Pharmaceuticals Inc

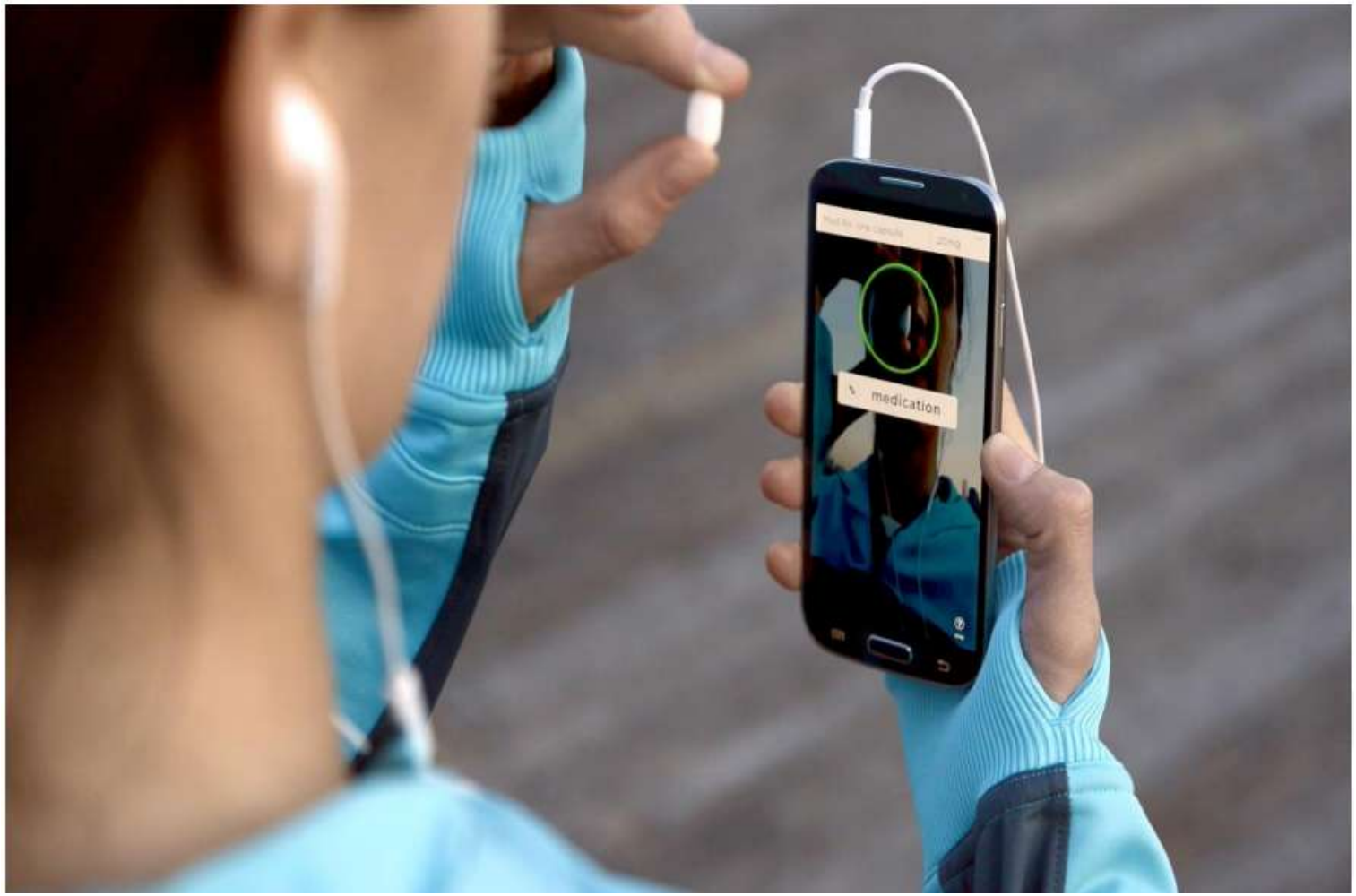
* Titan Pharmaceuticals and Opiant Pharmaceuticals collaborate to explore a new approach to opioid use disorder treatment

* Titan Pharmaceuticals - companies will conduct feasibility assessment of subcutaneous implant using Titan's ProNeura sustained release technology to administer an opioid antagonist Source text for Eikon:

Devices


NIDA is promoting development of ingestible systems that monitor medication consumption in real time
eTect ID-Cap
Proteus "Raisin"
Clinical database

AiCure: Facial Recognition



Capsula releases a taggant (uniquely coded material, ~ fingerprint) to a volatile breath marker that is analyzed

Xhale

Adherence Technologies

- **Proteus Biomedical:** Microchip attached to the pill communicates with a patch on the body
- **e-tect:** ID-Cap, a microchip in a capsule that communicates with a wearable hub

National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

Summary

Treatment adherence is a significant concern in SUD treatment

Efforts to improve it

- Behavioral
  - Psychosocial support
  - Contingency management
- Pharmacological
  - Biomarkers - acetazolamide
  - New long-acting formulations
  - New Medications
- Devices

HOW MANY PSYCHOTHERAPISTS DOES IT TAKE TO CHANGE A LIGHTBULB?

ONLY ONE, BUT THE BULB MUST GENUINELY WANT TO CHANGE.