Methods to Improve SUD Treatment Adherence

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

No conflict of Interest

Generic names of medications will be used

FDA unapproved medications will be mentioned
Outline

Definition

Determinants of Treatment Adherence

Methods to improve adherence

• Non-pharmacological
• Pharmacological
• Devices

Conclusions
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

OUD Cascade of Care in USA

Current estimates
Treatment gap
90% goal

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.

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

<table>
<thead>
<tr>
<th>Acetazolamide</th>
<th>Quinine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbonic Anhydrase Inhibitor</strong></td>
<td><strong>Antimalarial (&amp; Tonic Water)</strong></td>
</tr>
<tr>
<td><strong>Half-life</strong> = 4-8 h (per label)</td>
<td><strong>Half-life</strong> = 10-12 h</td>
</tr>
<tr>
<td><strong>100% Bioavailable</strong></td>
<td><strong>80% Bioavailable</strong></td>
</tr>
<tr>
<td>Therapeutic dose: 125 mg-1 g/day</td>
<td>Therapeutic Dose: 650 mg/day</td>
</tr>
<tr>
<td>Testing at 15 mg/day</td>
<td>Testing at 80 mg/day</td>
</tr>
<tr>
<td></td>
<td>(equivalent to ~1.1 liters of tonic water)</td>
</tr>
</tbody>
</table>
The Rate of Elimination of Acetazolamide Is Predictable and Prolonged

Rate of ACZ Elimination in Urine

3 days since last dose is distinct from 1 day (ie “not yet today”)

15 mg ACZ administered
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
Pharmacological

- Medication levels
- New Formulations
- New Medications
New Formulations

“We combined all your medications into ONE convenient dose.”
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>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Administration</th>
<th>Dosing frequency</th>
<th>Indications</th>
<th>Company</th>
<th>Country/region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oil-based injections</strong></td>
<td></td>
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<tr>
<td>Haloperidol decanoate</td>
<td>Halodol Decanoate</td>
<td>IM</td>
<td>once a month</td>
<td>Schizophrenia</td>
<td>Ortho-McNeil Pharm</td>
<td>US</td>
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<tr>
<td>Flupenthixol decanoate</td>
<td>Fluapex Depot</td>
<td>IM</td>
<td>every 2–4 weeks</td>
<td>Schizophrenia</td>
<td>Lundbeck</td>
<td>Europe</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Fluphenazine Decanoate</td>
<td>IM</td>
<td>every 2–4 weeks</td>
<td>Schizophrenia</td>
<td>APP Pharm</td>
<td>US</td>
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<tr>
<td>Fluphenazine decanoate</td>
<td>Moderate</td>
<td>IM</td>
<td>every 2–5 weeks</td>
<td>Schizophrenia</td>
<td>sanofi-aventis</td>
<td>Europe</td>
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<td>Zoledronate decanoate</td>
<td>ClizaCal Depot</td>
<td>IM</td>
<td>every 2–4 weeks</td>
<td>Schizophrenia</td>
<td>Lundbeck</td>
<td>Europe</td>
</tr>
<tr>
<td>Penthotozine palmitate</td>
<td>Poperil Depot</td>
<td>IM</td>
<td>every 4 weeks</td>
<td>Schizophrenia</td>
<td>sanofi-aventis</td>
<td>Europe</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Delatrate</td>
<td>IM</td>
<td>every 2–4 weeks</td>
<td>Hormone therapy</td>
<td>Endo Pharma</td>
<td>US</td>
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<td>Estradiol valerate</td>
<td>Belestrone</td>
<td>IM</td>
<td>every 4 weeks</td>
<td>Hormone therapy</td>
<td>Monarch Pharm</td>
<td>US</td>
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<tr>
<td>Testosterone cypionate</td>
<td>Depo-Testosterone</td>
<td>IM</td>
<td>every 2–4 weeks</td>
<td>Hormone therapy</td>
<td>Pfizer</td>
<td>US</td>
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<tr>
<td>Estradiol cypionate</td>
<td>Depo-Estradiol</td>
<td>IM</td>
<td>every 3–4 weeks</td>
<td>Hormone therapy</td>
<td>Pfizer</td>
<td>US</td>
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<td><strong>Injectable drug suspensions</strong></td>
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<td>Paliperidone palmitate</td>
<td>Invega Sustenna</td>
<td>IM</td>
<td>once a month</td>
<td>Schizophrenia</td>
<td>Jansen</td>
<td>US</td>
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<tr>
<td>Olanzapine</td>
<td>Zypla Rex/revv</td>
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<td>every 2–4 weeks</td>
<td>Schizophrenia</td>
<td>Eli Lilly</td>
<td>US</td>
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<tr>
<td>Medroxyprogesterone acetate</td>
<td>Depo-Provera</td>
<td>IM</td>
<td>every 3 months</td>
<td>Hormone therapy</td>
<td>Pfizer</td>
<td>US</td>
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<td>Medroxyprogesterone acetate</td>
<td>Depo-Subq Provera 104SC</td>
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<td>every 3 months</td>
<td>Hormone therapy</td>
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<td>US</td>
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<td><strong>Supersaturated drug solution</strong></td>
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<td>Lanreotide acetate</td>
<td>Somatuline Depot</td>
<td>deep SC</td>
<td>once a month</td>
<td>Acromegaly</td>
<td>Tercica</td>
<td>US</td>
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<td><strong>Microspheres</strong></td>
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<td>Risperidone</td>
<td>Risperidol Const</td>
<td>IM</td>
<td>every 2 weeks</td>
<td>Schizophrenia</td>
<td>Jansen</td>
<td>US</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Vivitrol</td>
<td>IM</td>
<td>once a month</td>
<td>Alcohol dependence</td>
<td>Alkermes</td>
<td>US</td>
</tr>
<tr>
<td>Somatostatin (DNA origin)</td>
<td>Nutropin Depot</td>
<td>SC</td>
<td>every 2–4 weeks</td>
<td>Hormone therapy</td>
<td>Genentech</td>
<td>US</td>
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<td>Leuprolide acetate</td>
<td>Lupron Depot</td>
<td>IM</td>
<td>every 1–3 months</td>
<td>Advanced prostate cancer</td>
<td>Abbott</td>
<td>US</td>
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<tr>
<td>Triptorelin pamoate</td>
<td>Testodir</td>
<td>IM</td>
<td>every 1–6 months</td>
<td>Advanced prostate cancer</td>
<td>Watson Pharma</td>
<td>US</td>
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<tr>
<td>Olsnitroide acetate</td>
<td>Sandostatin LAR Depot</td>
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<td>every 4 weeks</td>
<td>Acromegaly</td>
<td>Novartis</td>
<td>US</td>
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<tr>
<td>Laronidox acetate</td>
<td>Somatuline LA</td>
<td>IM</td>
<td>every 2 weeks</td>
<td>Acromegaly</td>
<td>Ipsen</td>
<td>US</td>
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<tr>
<td><strong>In situ forming implants</strong></td>
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</tr>
<tr>
<td>Leuprolide acetate</td>
<td>Eligard</td>
<td>SC</td>
<td>every 1–6 months</td>
<td>Advanced prostate cancer</td>
<td>sanofi-aventis</td>
<td>US</td>
</tr>
</tbody>
</table>

IM is intramuscular, SC is subcutaneous. Genentech was acquired by Roche in 2009.
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
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Frequency</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>SC</td>
<td>1 month</td>
<td>Positive pivotal PIII trial results</td>
<td>Site pain</td>
</tr>
<tr>
<td>RBP-6000 (Indivior®)</td>
<td>SC</td>
<td>Weekly/monthly</td>
<td>Positive PII multisite</td>
<td>Site pain</td>
</tr>
<tr>
<td>CAM2038 (Camurus®/Braeburn®)</td>
<td>SC</td>
<td>Weekly/monthly</td>
<td>Positive PII multisite</td>
<td>Site pain</td>
</tr>
<tr>
<td>Probuphine (Titan®/Braeburn®)</td>
<td>Implant</td>
<td>6 months</td>
<td>FDA-approved</td>
<td>Site AEs, implant expulsion, migration, protrusion</td>
</tr>
</tbody>
</table>
Extended Release Medications Improve Tx Adherence

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

FDA approval – May 26, 2016

Probuphine®

Probuphine is designed to release sustained therapeutic drug levels in patients with opioid addiction for up to six months.

% of urines negative (out of 72) for opioids across weeks 1-24

Rosenthal et al., Addiction 2013;105.
Implant versus Sublingual Buprenorphine

Rosenthal, 2016
CAM2038

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

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

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

Love, Sweden — 18 September 2017 — Camurus (NASDAQ STX: CAM) 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 comprised 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

9.18.2017

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 burden associated with the daily medication.
• The FDA has assigned a Prescription Drug User Fee Act (PDUFA) target date of January 15, 2018.

Princeton, N.J. — September 18, 2017 — Braeburn Pharmaceuticals, Inc.
# Long Acting Meds for SUDs

<table>
<thead>
<tr>
<th>Meds</th>
<th>Route</th>
<th>Frequency</th>
<th>Pros</th>
<th>Cons</th>
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</thead>
<tbody>
<tr>
<td>Biologics</td>
<td>Vaccines</td>
<td>IM</td>
<td>~weekly</td>
<td>No CNS</td>
</tr>
<tr>
<td>Biologics</td>
<td>ButiryCholinesterase</td>
<td>IM</td>
<td>~weekly</td>
<td>No CNS</td>
</tr>
<tr>
<td>ButiryCholinesterase</td>
<td>IM</td>
<td>~weekly</td>
<td>No CNS</td>
<td>Under evaluation</td>
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<tr>
<td>Methadone</td>
<td>Injectable</td>
<td>IM</td>
<td>Monthly</td>
<td>Methadone serum levels adequate</td>
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<tr>
<td>Naltrexone</td>
<td>Injectable</td>
<td>IM</td>
<td>Monthly</td>
<td>FDA approved for AUD and opioid relapse prevention</td>
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<tr>
<td>Naltrexone</td>
<td>Implant (Prodetoxxon®)</td>
<td>Surgical Abdomen</td>
<td>2-3 months</td>
<td>Approved in Russia</td>
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<tr>
<td>Naltrexone</td>
<td>Implant (O’Neil)</td>
<td>SC</td>
<td>6 months</td>
<td>Australia</td>
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</tbody>
</table>
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).
Opient Pharmaceuticals collaborate to explore a new approach to opioid use disorder treatment

Oct 2 (Reuters) - Opient Pharmaceuticals Inc

* Titan Pharmaceuticals and Opient 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:
NIDA is promoting development of ingestible systems that monitor medication consumption in real time.

- eTect ID-Cap
- Proteus "Raisin"
- Clinical database
Capsula releases a taggant (uniquely coded material, ~ fingerprint) to a volatile breath marker that is analyzed.
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
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.