Vaccines for Opioid Use Disorder: Focusing on the Fentanyl Epidemic

Thomas R. Kosten, MD
Waggoner Professor in Psychiatry, Pharmacology and Neuroscience
Baylor College of Medicine

Fang Yang, MD, PhD
Addiction Psychiatry Fellow
Baylor College of Medicine

Tuesday, May 28, 2019
PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

<table>
<thead>
<tr>
<th>American Academy of Family Physicians</th>
<th>American Psychiatric Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Neurology</td>
<td>American Society of Addiction Medicine</td>
</tr>
<tr>
<td>Addiction Technology Transfer Center</td>
<td>American Society of Pain Management Nursing</td>
</tr>
<tr>
<td>American Academy of Pain Medicine</td>
<td>Association for Medical Education and Research in Substance Abuse</td>
</tr>
<tr>
<td>American Academy of Pediatrics</td>
<td>International Nurses Society on Addictions</td>
</tr>
<tr>
<td>American College of Emergency Physicians</td>
<td>American Psychiatric Nurses Association</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>National Association of Community Health Centers</td>
</tr>
<tr>
<td>American Dental Association</td>
<td>National Association of Drug Court Professionals</td>
</tr>
<tr>
<td>American Medical Association</td>
<td>Southeastern Consortium for Substance Abuse Training</td>
</tr>
<tr>
<td>American Osteopathic Academy of Addiction Medicine</td>
<td></td>
</tr>
</tbody>
</table>
Webinar Housekeeping

Minimize or maximize the webinar panel by selecting the orange arrow.

To be recognized, type your question in the “Question” box and select send.
Disclosures

• Dr. Thomas Kosten serves as a consultant for Alkermes US World Pharma.
• Dr. Fang Yang has no disclosures.
The overarching goal of PCSS is to train a diverse range of healthcare professionals in the safe and effective prescribing of opioid medications for the treatment of pain, as well as the treatment of substance use disorders, particularly opioid use disorders, with medication-assisted treatments.
Educational Objectives

At the conclusion of this activity participants should be able to:

• Identify the extent and greatest geographic concentration of fentanyl overdoses and abuse in the current USA opioid epidemic.

• Define how and why current treatments with naltrexone, methadone and buprenorphine may be ineffective for fentanyl abuse.

• Identify the mechanism of action for fentanyl vaccines in preventing overdoses and abuse through the production of anti-fentanyl antibodies.
Geographic Concentration of Fentanyl Overdoses and Abuse
Highly Potent Synthetic Opioids

A class of full agonists of $\mu$-opioid receptor that include:

- **Fentanyl** – developed by Janssen in 1963; highly lipophilic opioid agonist
- **Fentanyl analogues** – Sufentanil, alfentanil, remifentanil, carfentanil, lofentanil, thiofentanil
National Annual Estimates of Fentanyl Reports in NFLIS-Drug, January 2009–December 2017
Mortality Rates from Unintentional Drug Overdoses

Jalal H, et al, Science 2018; 361
Items Identified & Reported to National Forensic Laboratory Information System by Region: 2017

National Drug Early Warning System (NDEWS) State of Texas Sentinel Community Site (SCS) Drug Use Patterns and Trends, Maxwell 2018
Mexican Black Tar Heroin

Mexican Brown ("Cheese")
Black Tar mixed with Benedryl or Tylenol or coffee creamer, etc.

South American Heroin & “new” SA Mexican White Heroin. Easy to mix in fentanyl powder.
Category of Drug Deaths and Mentions of Tramadol or Fentanyl on Texas Death Certificate: 2017

1. Psychostimulants
   - Total Deaths: 813
   - Tramadol: 63
   - Fentanyl: 180

2. Benzodiazepines
   - Total Deaths: 572
   - Tramadol: 23
   - Fentanyl: 71

3. Cocaine
   - Total Deaths: 849
   - Tramadol: 31
   - Fentanyl: 99

4. Heroin
   - Total Deaths: 591
   - Tramadol: 22
   - Fentanyl: 52

5. Other Opiates
   - Total Deaths: 578
   - Tramadol: 15
   - Fentanyl: 56

Provisional Reports, DSHS
Percentage Change in Carfentanil Reports in NFLIS-Drug in the United States by State: 2016–2017
Why were there so many overdose deaths?

- Fentanyl is substantially more potent than natural opioids or semi-synthetics:
  - Fentanyl is approximately **50-100 times** more potent than morphine
  - Rapidly acting
  - Carfentanil is approximately **10,000 times** more potent than morphine, 100 times more potent than fentanyl
Low Community Awareness

- People who use drugs may not be aware that they are using fentanyl
  - Survey of syringe exchange program participants in NYC found most people buying heroin were not intentionally seeking fentanyl and were not aware if they had used it.
- Street sellers may not know their drug products contain fentanyl
- Therefore, these people are at increased risk of overdose
- The need to educate users on harm reduction measures: using less of the substance, not using alone, taking turns when using, avoiding mixing drugs, having naloxone on hand

AAAP, 2018
Current Treatments May be Ineffective for Fentanyl Abuse
What should clinicians do?

- We have essentially no data to guide pharmacotherapy management for fentanyl overdose deaths in the US.
- Need to educate patients, families, and other clinicians of the new risk of using opioids as well as other illicit drugs.
- Need to adjust urine toxicology procedures:
  - Major labs have MS/GC panels for fentanyl and its analogues.
  - ELISA dip sticks for rapid information.
Naloxone for Opioid Overdose Fentanyl

- Naloxone is short-acting MOR antagonist which can rapidly reverse MOR agonist effects
- However, Naloxone is NOT effective at usual dose for fentanyl overdoses
- Multiple doses of naloxone were required to reverse fentanyl overdose
- Time between fentanyl use and death is shorter. This led to unsuccessful attempts to revive overdose patients despite of multiple and escalating doses of naloxone
- Some programs began to provide more than the standard 2 doses of naloxone, and others begun using higher dose devices
- It is not clear whether these approaches are effective

AAAP, 2018
Buprenorphine

• No clinical trial data
• Higher dose of buprenorphine may required to provide protection against override and maintain higher opioid tolerance
Methadone

• No clinical data
• Unknown if the standard methadone doses are protective
Naltrexone XR

- No clinical data
- Induction:
  - Longer wait time to start naltrexone
  - More difficult induction; consider aggressive adjunctive medication for withdrawal
  - May require inpatient setting
- Maintenance:
  - May require more frequent administration
Mechanisms of Action for Fentanyl Vaccines in Preventing Overdoses and Abuse
Anti-Drug Vaccine
Mechanism of Action in Anti-Drug Antibodies

Antibodies bind drug in the blood

Drug brain concentrations and activation of target receptors are reduced

Blood-Brain Barrier
Anti-drug Antibodies Keeps Drugs Out of the Brain
Dose Related Reduction of Opioid Brain Levels

Pravetoni et al., JPET 2012;341:225
Entolimod Adjuvant: TLR-5 Agonist

- Peptide derived from flagellin with TLR-5 epitope (Patent pending – Cleveland Biolabs)
- Already given to humans at 100 times greater dose than needed as adjuvant
- Stimulates IL-1 and IL-8 in human CD14+ monocytes.
TT-SNC Vaccine With or Without Entolimod

Entolimod Increases Peak Anti-Coc Antibody 3-Fold
The Role of Entolimod in Antibody Production

- Co-stimulation by Entolimod generated 3-4-fold greater total anti-Cocaine antibodies to the TT-SNC vaccine than to the CTB-SNC + E6020
- TT-SNC+ Entolimod produced 4-fold higher affinity antibodies than TT-SNC alone, expected to reduce brain levels of cocaine
Blood and Brain Fentanyl Levels with Vaccination in Mice

Anti-Fentanyl Antibodies in Response to Different Vaccine Combinations

Anti-fentanyl antibody levels in mice vaccinated at 0, 3 and 6 weeks with either tetanus toxoid-fentanyl (TT-FEN), Alum + TT-FEN or Alum + entolimod + TT-FEN.
Fentanyl Vaccine Blocks Analgesia and Respiratory Depression (rats)

- Blockade of fentanyl analgesia and respiratory depression in rats
- Still responsive to naloxone
Conclusions: Fentanyl Vaccine

- Fentanyl is the leading cause of opioid overdose deaths
  - Poor response to naloxone for OD
  - Poor efficacy of buprenorphine for relapse prevention
- Mechanism of action of addiction vaccines
  - Antibody-fentanyl complex can’t enter the brain
- Lessons learned from clinical trials of anti-cocaine vaccine
  - Entolimod generated 3~4-fold more anti-drug antibodies in rodents
  - With 4-fold higher affinity antibodies in rodents: hold more fentanyl in blood
- Current status of anti-fentanyl vaccine testing
  - High antibody levels that keep more fentanyl out of the brain
  - Block fentanyl analgesia & respiratory depression
• NFLIS Drug Special Release: Tracking Fentanyl and Fentanyl-Related Substances, Jan 2019
• Jalal H, et al., Science 2018; 361
• Maxwell JC., National Drug Early Warning System (NDEWS) State of Texas Sentinel Community Site (SCS) Drug Use Patterns and Trends, 2018
• Bremer PT and Kim D. Janda Pharmacol Rev 2017; 69: 298-315
• Pravetoni et al., JPET 2012; 341: 225
• Bremner PT, Angew Chem Int Ed 2016; 55: 3772–3775
PCSS Mentoring Program

• PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
• PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment.
• 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
• No cost.

For more information visit: https://pcssNOW.org/mentoring/
Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now

http://pcss.invisionzone.com/register
Opioid Response Network (STR-TA)

- **Opioid Use Disorder Virtual Learning Collaborative (VLC)**
  - Play a role in expanding the availability of medical for addiction treatment options for opioid use disorders
  - Each collaborative runs for 12-weeks and is lead by an experienced faculty advisor
  - Participants watch pre-recorded webinars, call into office-hours, engage with a virtual community and complete an individual project
  - Participants will earn up to 12 Continuing Medical Education (CME) credits
  - Fill out our interest intake form at apapsy.ch/OpioidSTR
  - Contact Eunice Maize at emaize@psych.org for more information.

Funding for this initiative was made possible (in part) by grant no. 1H79TI080816-01 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
Session Evaluation and Certificate

- Instructions will be provided in an email sent to participants an hour after the live session.
- Certificates are available to those who complete an evaluation.
- Recordings of today’s webinar can be accessed at www.pcssNOW.org and education.psychiatry.org.
Educate. Train. Mentor

Funding for this initiative was made possible (in part) by grant no. 5U79TI026556-03 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.