An Interdisciplinary Approach to Safe Opioid Treatment
Reducing Potential for Opioid Mishaps
Presented at CBI’s 3rd Abuse Deterrent Formulations Summit

Dr. Fudin’s Disclosures
- Astra Zeneca (Speakers Bureau)
- Clarity (Consultant)
- Eschito SanBio (Advisory Board)
- Depomed (Advisory Board, Speakers Bureau)
- Endo (Consultant, Speakers Bureau)
- Iroko Pharmaceuticals (Speakers Bureau)
- Kalisio (Speakers Bureau, Advisory Board)

Objectives
- Describe the impact of the opioid overdose problem and how pharmacist as clinicians can effectively collaborate with the healthcare team to prevent unforeseen risks
- Discuss roles for pharmacists to become more active on the pain management interdisciplinary team citing specific examples in an advanced practice
- Illustrate weaknesses and potentials harms of a universally accepted MEDD as outlined in the CDC Guidelines and describe the pseudoscience on which they are based
- Recognize new software technologies that integrate comprehensive risk assessments into the patient record to evaluate and mitigate risks, including quantification of OIRD, urine monitoring interpretation, and naloxone access

But first, how has opioid OD problem impacted OUR profession?
Something for everyone...

Practical Daily Issues
- New Limitations
  - MEDD and the pseudoscience
    - Add team members in calculating dose
    - Maximum tablet/capsule units per RX fill
    - Maximum days supply
- Logistical and Time Constraints (Community Setting)
  - Counseling patients on regulation/3rd party pay changes
  - Paperwork (Schedule II vs III)
  - Qualifying patients for in-home naloxone & documentation
- Patient Hardships
  - Multiple copays
  - Repetitive dispensing fees
  - PBM conflicts of interest
  - Patient travel to clinics and pharmacies

Product Development

- Abuse Deterrent Formulations
  - Physical barrier
  - Viscosity management
  - Sequestered opioid antagonist
  - Aversive agent

- Who will pay for these?
  - Prior authorizations
  - No accountability for third party payers

Incorporating Pharmacists into an Advanced Practice Setting

Provider Status vs Reimbursement

What could PHARMACISTS do?

What do I do?

What should CONGRESS do?

Urine Drug Testing (UDM) Rationale

- Guidelines recommend UDM as standard of care when prescribing chronic opioid therapy, especially for CNCP1-5
- Helps to ensure compliance and mitigate risk1-5
  - Detects presence of illicit substances
  - Detects absence of prescribed medication
- Helps to justify continual prescriptions
- Supports clinician decision to discontinue controlled substance medication

References collectively on slide #15

Dr. Jeffrey Fudin
Addressing Unexpected Results

- **False or Unexpected Positive**
  - Discuss findings with patient
    - Confirm false positive (as a true negative) to support and document patient’s integrity and compliance
  - Confirm unexpected positive to justify
    - ADT products, and or other RX adjustments
    - Substance abuse counseling
    - Alternative and other behavior health intervention
- **False Negative**
  - Confirm false negative (as a true positive) to support and document patient’s integrity and compliance
  - **DO NOT FALSELY ACUSE PATIENTS WITHOUT EVIDENCE!**

References collectively on slide #15

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Case Study | Chronic Back Pain

What do these results mean?

<table>
<thead>
<tr>
<th>IA In-Office Results</th>
<th>Chromatography [send out] Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td><strong>Result</strong></td>
</tr>
<tr>
<td>Opiate</td>
<td>Negative</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Negative</td>
</tr>
<tr>
<td>Benzoylecgonine (cocaine metabolite)</td>
<td>Positive</td>
</tr>
<tr>
<td>PCP</td>
<td>Positive</td>
</tr>
<tr>
<td>PCP</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Venlafaxine (Effexor®) 250mg PO QAM
Fentanyl (Duragesic®) 50mcg/hrchanged Q72 hours
Hydrocodone + APAP (Lortab®) 5/325, 1 PO Q4H PRN
Alprazolam 0.5mg PO TID

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Unexpected Results

- **Negative for Prescribed Medications**
- **Positive for unprescribed and illicits**
  - Lack of hydrocodone PRN use
  - Pharmacokinetics (when was urine collected?)
  - Noncompliance (illegally obtained drugs)
  - Test is not specific for the drug tested (opiate vs. synthetic, in this case fentanyl)
  - False positive PCP
  - Drug-drug, drug-disease, drug-food/supplement interactions
  - Genetic polymorphism

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U DM References


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Opioid Chemistry and Cross-sensitivity

[Diagram showing opioid chemistry and cross-sensitivity]

**DO NOT FALSELY ACUSE PATIENTS WITHOUT EVIDENCE!**
Software Help!

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Presumptive testing (immunoassays)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Panel:</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>Neg</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Neg</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Neg</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Neg</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Neg</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Neg</td>
</tr>
<tr>
<td>FOP (Phenylpropanolamine)</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Typical Add-ons or Special Order:
- Opioids
- Benzodiazepines
- Antibiotics
- Amphetamines
- Cannabis
- Cocaine
- FOP (Phenylpropanolamine)

Recommendations

<table>
<thead>
<tr>
<th>Opioids Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative result not unexpected because total dose of synthetic opioids may be too low for detection. Clinical recommends discussing finding with patient, using clinical judgement, and if indicated, definitive testing by quantitative confirmation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benzodiazepines Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative result not unexpected because total dose of synthetic benzodiazepines may be too low for detection. Clinical recommends discussing finding with patient, using clinical judgement, and if indicated, definitive testing by quantitative confirmation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amphetamines Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative result not unexpected because total dose of synthetic amphetamines may be too low for detection. Clinical recommends discussing finding with patient, using clinical judgement, and if indicated, definitive testing by quantitative confirmation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cannabis Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative result not unexpected because total dose of synthetic cannabis may be too low for detection. Clinical recommends discussing finding with patient, using clinical judgement, and if indicated, definitive testing by quantitative confirmation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cocaine Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative result not unexpected because total dose of synthetic cocaine may be too low for detection. Clinical recommends discussing finding with patient, using clinical judgement, and if indicated, definitive testing by quantitative confirmation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FOP (Phenylpropanolamine) Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative result not unexpected because total dose of synthetic FOP (Phenylpropanolamine) may be too low for detection. Clinical recommends discussing finding with patient, using clinical judgement, and if indicated, definitive testing by quantitative confirmation.</td>
</tr>
</tbody>
</table>

Dr. Jeffrey Fudin
Recent CDC Guidelines:  
Who Should I Target for In-Home Naloxone?

Variability in Opioid Equivalence Survey

What Do You Think Were the Most Outrageous Conversions?

Available Online Opioid Conversion Calculators

Dr. Jeffrey Fudin
The higher the dose of morphine (or “equivalent”), the less methadone is needed to replace it.

Equianalgesic Dose of Morphine to Methadone

<table>
<thead>
<tr>
<th>Methadone (mg)</th>
<th>Morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg Morphine = 60 mg Methadone</td>
<td></td>
</tr>
<tr>
<td>302.5 mg Morphine = 30 mg Methadone</td>
<td></td>
</tr>
</tbody>
</table>

An Actual Example from CDC Smart Phone App

<table>
<thead>
<tr>
<th>Guideline Resources: CDC Opioid Guideline Mobile App</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Morphine Equivalent” (mg)</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>168</td>
</tr>
<tr>
<td>320</td>
</tr>
<tr>
<td>410</td>
</tr>
</tbody>
</table>

https://www.cdc.gov/drugoverdose/prescribing/app.html
Comparison of Proposed Morphine to Methadone Equivalents

Ripamonti et al, 1998

<table>
<thead>
<tr>
<th>Morphine dose (mg/day)</th>
<th>Morphine: Methadone EDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90</td>
<td>3.70:1</td>
</tr>
<tr>
<td>91-300</td>
<td>7.75:1</td>
</tr>
<tr>
<td>301+</td>
<td>12.25:1</td>
</tr>
</tbody>
</table>

Ayonrinde et al, 2000

<table>
<thead>
<tr>
<th>Morphine dose (mg/day)</th>
<th>Morphine: Methadone EDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>˂100</td>
<td>3:1</td>
</tr>
<tr>
<td>101-300</td>
<td>5:1</td>
</tr>
<tr>
<td>301-600</td>
<td>10:1</td>
</tr>
<tr>
<td>601-800</td>
<td>12:1</td>
</tr>
<tr>
<td>801-1000</td>
<td>15:1</td>
</tr>
<tr>
<td>˃1001</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Mercadante et al, 2001

<table>
<thead>
<tr>
<th>Morphine dose (mg/day)</th>
<th>Morphine: Methadone EDR</th>
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</thead>
<tbody>
<tr>
<td>30-90</td>
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<tr>
<td>91-300</td>
<td>8:1</td>
</tr>
<tr>
<td>301+</td>
<td>12:1</td>
</tr>
</tbody>
</table>

Fudin et al, 2012

\[ \text{Morphine (mg)} \times \text{EDR} = \text{Methadone (mg)} \]

2% of prescriptions for opioid analgesics are for Methadone.

Methadone accounts for nearly 1 in 3 prescription opioid overdose deaths in the US, 6X the number in 2009.

Ref: Methadone Statistics (CDC2012) http://www.cdc.gov/features/vitalsigns/methadoneoverdoses/

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Ref: Methadone Statistics (CDC2012) http://www.cdc.gov/features/vitalsigns/methadoneoverdoses/

Serum Fentanyl Concentrations Following Multiple Applications of Fentanyl TD 100mcg/h (n=10)

Unanticipated Risks of Opioid-induced Respiratory Depression

Hypothetical Case:
Patient Profile (SR): Pain Clinic Patient

- SR 47-year-old female patient with 3 failed back surgeries and DM type 2
  - 5’6” tall and weighs 200 lbs
- Medication regimen at pain clinic (for last 2 years):
  - Oxycodone ER 30 mg PO q12h and oxycodone IR 10 mg PO q4h PRN
- Do you think this patient is at elevated risk (Low, Med, High)?
  - Medications prescribed by psychiatrist:
    - Lorazepam 0.5 mg q8h for anxiety
- What if the patient:
  - Is placed on pregabalin 75 mg PO TID (Endocrine for DPN)
  - Goes on a grapefruit diet? (Self)
  - Is an ultra-rapid 2D6 metabolizer? (Ohhhh Nooo!!)
  - Develops an URTI?
  - Takes OTC meds?
- She has obstructive sleep apnea

http://www.arupconsult.com/assets/graphics/OpiatesAndOpioidMetabolism.jpg

http://www.arupconsult.com/assets/graphics/OpiatesAndOpiodMetabolism.jpg
PGY Variability & Response

- General population has 40-60% phenotype variability
- CYP450 enzymes most frequently involved
  - CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP1A2, CYP2E1
- Genetic differences impact 25% of all drugs

Phenotypes & Variants

- Allele Variations
  - wild: wild vs variant: wild vs wild: variant

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>citalopram, venlafaxine, tramadol</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>venlafaxine</td>
</tr>
<tr>
<td>Extensive Metabolizer (EM)</td>
<td>tramadol</td>
</tr>
<tr>
<td>Ultra Rapid Metabolizer (UM)</td>
<td>venlafaxine</td>
</tr>
</tbody>
</table>

Real Case
Sally is a 42 year old female with history of depression, anxiety, chronic moderate back pain, mood disorder, and panic attacks

- Venlafaxine XR 225mg PO QAM
  - minimal response + side effects
- Citalopram 60mg PO QAM
  - minimal response
- Tramadol 100mg PO QID
  - minimal benefit
- Carbamazepine 200mg PO BID
- Consider PGT

Case: Sally

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>Ultrarapid metabolizer</td>
<td>venlafaxine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Poor metabolizer</td>
<td>venlafaxine, tramadol</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Reduced activity</td>
<td>carbamazepine</td>
</tr>
</tbody>
</table>
| CYP3A4 | Extensive metabolizer | ????
**Case: Amy**

- Citalopram → Desmethyl-citalopram → Desmethyl-citalopram → Desmethyl-citalopram → Desmethyl-citalopram

**Folate Metabolism**

- Dietary Folate → (not usable) → L-methylfolate → (S-HT, NE, DA)

- COMT

- 50-60% of individuals have reduced or greatly reduced activity


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**Tramadol**

- 2D6 → 2A4, 2B6 → O-desmethyl-Tramadol → inactive metabolites

**Sally – what to do...**

- Change SSRI / SNRI
  - Examples: O-desmethy-venlafaxine, milnicipran, fluvoxamine
- Supplement with L-methylfolate
- Switch tramadol to tapentadol
- Is morphine a possibility?
  - Which opioids don’t depend on CYP metabolism?

**What could you do for Sally?**

- Change tramadol to tapentadol
- Change carbamazepine to oxcarbazepine

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**Let’s take a break...**

**ARE YOU READY TO SCREAM YET?**

---

Dr. Jeffrey Fudin
NOW WHAT?

Do you think maybe in-home naloxone is a good idea due to unanticipated or unpredictable risks?

Naloxone: Antidote for Life-Threatening Opioid-induced Respiratory Depression (OIRD)

- Non-scheduled opioid antagonist proven to rapidly reverse life-threatening OIRD and other CNS depressant effects
- Displaces opioid agonists at the mu receptor binding site
- Higher affinity for mu-receptors than traditional opioids, except buprenorphine


Naloxone Regulatory Considerations

- Good Samaritan
- Liability protection
- Collaborative practice agreement

Naloxone Access

States with Naloxone Access and Drug Overdose Good Samaritan Laws
States with Drug Overdose Good Samaritan Laws Only
States with Naloxone Access Laws Only


Politics, Practicality, Professionalism, and Pricing

NALOXONE CHOICES

Intranasal (IN) Naloxone Rescue Kit

Dr. Jeffrey Fudin

March 8, 2017

**FDA Approved In-Home Naloxone**

Naloxone HCl for injection

Audio-Injector

(FDA approved in 2014)

**Critical Naloxone Comparisons**


**NALOXONE KIT COMPARISONS**

<table>
<thead>
<tr>
<th>Naloxone Kit</th>
<th>Naloxone Autoinjector</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Nasal</td>
<td>In-Nasal Autoinjector</td>
</tr>
<tr>
<td>(2) Naloxone 0.4 mg/mL (1 mL) vials</td>
<td>(2) Naloxone 1 mg/mL (2 mL) pre-filled needleless syringes</td>
</tr>
<tr>
<td>(2) Syringes, 1 mL with 25G 1-inch needle</td>
<td>(1) Mucosal Atomizer Device (MAD 300)</td>
</tr>
<tr>
<td>(2) Alcohol pads</td>
<td>(1) Laerdal Face shield CPR barrier or equivalent</td>
</tr>
<tr>
<td>(1) Laerdal Face shield CPR barrier or equivalent</td>
<td>(1) Pair of gloves</td>
</tr>
<tr>
<td>(1) Pair of gloves</td>
<td>(1) Overdose Rescue Instructions</td>
</tr>
<tr>
<td>(1) Overdose Rescue instructions</td>
<td>(1) Opioid Safety brochure</td>
</tr>
<tr>
<td>(1) Opioid Safety brochure</td>
<td>(1) Zippered pouch</td>
</tr>
</tbody>
</table>

**Utilizing Pharmacists to Increase Naloxone Access**

National Alliance of State Pharmacy Associations (NASPA) www.ncspa.org


**Results**

<table>
<thead>
<tr>
<th>Questions</th>
<th>Points for VE Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you lead monthly staff education about naloxone and safely administering it?</td>
<td>15</td>
</tr>
<tr>
<td>Are the naloxone kits stocked in all OPD’s in your hospital?</td>
<td>9</td>
</tr>
<tr>
<td>Can you describe how and why you would choose naloxone?</td>
<td>7</td>
</tr>
<tr>
<td>Do you feel your hospital has enough naloxone?</td>
<td>7</td>
</tr>
<tr>
<td>Do you feel your hospital has enough naloxone in the ED?</td>
<td>7</td>
</tr>
<tr>
<td>Do you have a plan for how to handle naloxone?</td>
<td>5</td>
</tr>
<tr>
<td>Do you have a plan for who will administer naloxone?</td>
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</tr>
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Results


NON-VA POPULATION

- Retrospective case-control study of 18,365,497 patients
- IMS PharMetrics Plus integrated commercial health plan opioid claims in the U.S.
- 7,234 patients experience OSORD
- OSORD found to be associated with:
  - ER/IA opioid formulations
  - Daily morphine equivalence dose
  - Interacting medications
  - ED visits and hospital admissions
  - Coexisting health conditions

NON-VA POPULATION

RIOSORD Risk Index for Overdose or Serious Opioid-induced Respiratory Depression

Online Software App to Determine Risk for OIRD

Please select patient demographic:
- General Population
- U.S. Military Veteran

https://www.remitigate.com/saloxoetl/
March 8, 2017

Dr. Jeffrey Fudin

Documented: 10/05/16
Provider: Dr. John Doolittle, Physician
Patient: John Doe, 00/00/0000, ID 666

Prescribed drugs:
- oxycodone 60 mg/day
- hydrocodone 20 mg/day

Total Morphine Dose: 110mg/day

The following parameters were evaluated and identified to elevate risk for opioid-induced respiratory depression in this patient:

- Bipolar disorder or schizophrenia
- Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, tuberculosis)
- Chronic headache (e.g., migraine)

Prescribed Drugs or Drug Classes Identified by RIOSORD:
- An extended-release or long-acting (ER/LA) formulation of any prescription opioid, including the above
- A prescription benzodiazepine (e.g., diazepam, alprazolam)
- A prescription antidepressant (e.g., fluoxetine, citalopram, venlafaxine, amitriptyline)

The following parameters were evaluated and identified to elevate risk for opioid-induced respiratory depression in this patient:

- Within the past 6 months the patient has had a healthcare visit (outpatient, inpatient, or ED) involving the following:
  - Bipolar disorder or schizophrenia
  - Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, tuberculosis)
  - Chronic headache (e.g., migraine)

Predicted Opioid Risk Assessment - 83%

This patient was evaluated for percent risk of opioid-induced respiratory depression using the validated RIOSORD (1,2) analysis tool. This patient was determined to have an 83% risk based on the unique criteria outlined herein.

This patient was determined to have a(n) 83% risk based on the unique criteria outlined herein.

For this reason, naloxone for in-home use is recommended for this patient. This recommendation is consistent with AMA, ASAM, FDA, CDC, SAMHSA and other professional organization recommendations or guidelines to provide in-home naloxone for patients receiving opioids that are at risk for opioid-induced respiratory depression.

This patient was evaluated for percent risk of opioid-induced respiratory depression using the validated RIOSORD (1,2) analysis tool. This patient was determined to have an 83% risk based on the unique criteria outlined herein.

This patient was determined to have a(n) 83% risk based on the unique criteria outlined herein.

For this reason, naloxone for in-home use is recommended for this patient. This recommendation is consistent with AMA, ASAM, FDA, CDC, SAMHSA and other professional organization recommendations or guidelines to provide in-home naloxone for patients receiving opioids that are at risk for opioid-induced respiratory depression.

In the context of these recommendations, naloxone was prescribed for in-home use.

Patient and caregiver were counseled on opioid risk factors, how to minimize such risks, and offered naloxone for in-home use. Based on the overall assessment and understanding of the patient and/or caregiver, it is determined that the best option for this patient is: Evzio auto-injector. This is due to the following reasons:

- Patient has medically documented seasonal or chronic sinusitis with nasal congestion
- Patient has other nasal septal abnormalities, nasal trauma, epistaxis

Patient agrees to fill prescription for naloxone as outlined above. Education about overdose prevention and instructions for use of Evzio auto-injector for opioid overdose reversal were provided to this patient and/or caregiver. Method of contact was In-person. Length of the session was 20 minutes.


Access to Naloxone Varies From State to State

• Media, Governors:
  Naloxone in the state is now “OTC”
• Certain large chain pharmacies:
  “Our pharmacists provide naloxone”
  – Dispensing pharmacist: What?!?!
  – Some payers require prior authorization
• Maine requires naltrexone failure

Patient: Why Should I Have Naloxone Now?

• Why all of a sudden is this an issue?
• Who will pay for it?
• Where should I keep it?
• Documentation in EMR or pharmacy record
• Software application for assessing OIRD risk
  – Yet to come...

OPEN ACCESS
PANIC BUTTON & HOME ALONE

NOverdose

Conclusion

• Encourage the use of risk stratification tools
  (See painedu.org)
• Education for all prescribers & pharmacists
• Slow escalation of opioid doses upon conversion
• Recognize unique population variables
• Realize the value of a PHARMACIST “provider”
  to mitigate drug risks and encourage them to
  be part of YOUR team!
• And when all else fails…
  There’s an app for that!