Joint Webinar:
Deprescribing and Delirium
Speaker: Noll Campbell, PharmD, MS
Moderator: Sharon Inouye, MD, MPH
Hosts: Jennifer Tija, MD, MSCE and Ken Boockvar, MD
USDeN Announcements

Junior Investigator Intensive Program

• Application deadline: February 1

USDeN Annual Meeting

• Wednesday, May 11 in Orlando
• Adjacent to AGS meeting
• Register on AGS meeting page (under pre-conferences)

Visit deprescribingresearch.org for more information
What is NIDUS? Network for Investigation of Delirium: Unifying Scientists!
- NIA-funded research network dedicated to advancing the study of delirium through collaborative studies, use of NIDUS research resources, career development opportunities, and dissemination of delirium science.

How to be involved:
- Apply to attend the Delirium Boot Camp – 2.5-day workshop on delirium research, Nov. 13-15 2022 (tentative) in Chapel Hill, NC
  - Application open February 1
  - Applications due July 22
  - Join a junior faculty working group—email us!
- Participate in the American Delirium Society Meeting, June 12-14, 2022 (Indianapolis)
- Register for website deliriumnetwork.org to access our blog, resources and receive NIDUS newsletter and announcements, pilot and collaboration awards, webinars.

Follow NIDUS online!
Twitter: @nidus_delirium ● Facebook: NIDUSDelirium ● Email: nidus@hsl.harvard.edu
@sharon_inouye
Figure 3. Organizational Structure of NIDUS II

**Administrative Core**
- MPIs: SK Inouye, MD, MPH; RN Jones, ScD

**Executive Committee**
- MPIs and Core Leaders

**Scientific Advisory Board**

**Measurement & Harmonization Core**
- RN Jones, ScD

**Research Resources Core**
- ER Marcantonio, MD, SM

**Pilot & Exploratory Studies Core**
- M Avidan, MD

**Career Development & Outreach Core**
- J Devlin, PharmD
- J Busby-Whitehead, MD

**Working Groups (4)**
Deprescribing and Delirium

Noll Campbell, PharmD, MS
Assistant Professor, Purdue University College of Pharmacy
Faculty Associate, Purdue Center for Aging and the Life Course
Investigator, IU Center for Aging Research @ Regenstrief
Scientist, IU Center for Health Innovation and Implementation Science
Aging Brain Clinical Pharmacist, Sandra Eskenazi Center for Brain Care Innovation

@nollcampbell
Conflict of Interest

• No Financial Conflicts to Report

• Support for work presented received from:
  ➢ National Institutes of Health/National Institute on Aging
  ➢ Agency for Healthcare Research and Quality
  ➢ Healthcare Resources & Services Administration
Objectives

• Discuss existing literature summarizing the relationship between medications and delirium outcomes
• Describe prior trials attempting to deprescribe deliriogenic medications in the acute care setting
• Identify opportunities for deprescribing research that can add value to delirium care
Medications and Delirium

• **Ever implicated** in etiology, seldom the exclusive answer

<table>
<thead>
<tr>
<th>Use as prescribed</th>
<th>Recreational use</th>
<th>Adverse clinical effects</th>
<th>Withdrawal States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives &amp; Hypnotics</td>
<td>Alcohol</td>
<td>Valproic Acid (hyperammonemia)</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>Heroin</td>
<td>Antidepressants</td>
<td>Cholinesterase inhibitors</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Hallucinogens</td>
<td>(Serotonin syndrome)</td>
<td></td>
</tr>
<tr>
<td>Non-prescription (OTC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics/Antivirals</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Among the strongest risk factors for delirium in hospitalized and critically ill older adults
• Toxicities represent a small proportion of reversible cases

Medications and Delirium

- **Ever desired** as a primary mode of treatment, but not consistently appropriate
Objectives

• Discuss existing literature summarizing the relationship between medications and delirium outcomes

• Describe prior trials attempting to deprescribe deliriogenic medications in the acute care setting

• Identify opportunities for deprescribing research that can add value to delirium care
Trial 1: eCHAMP

• Evaluate the efficacy of screening and CDSS at reducing exposure to potentially inappropriate anticholinergics, urinary catheters, and physical restraints

• Outcomes:
  ➢ Orders for geriatric consult
  ➢ D/C orders for anticholinergics
  ➢ D/C orders for restraints and catheters
Example CDS: Promethazine

**Recommended Blocking Orders**

DO NOT USE IF CHILD LESS THAN 2 YEARS OLD. FDA has issued a safety alert reporting at least 7 deaths in children less than 2 years old using promethazine. Use with caution in pediatric pts over 2 years old. Your patient has/had DELIRIUM due to a deficit in her/his cholinergic system. Promethazine has central ANTICHOLINERGIC activities. Although this reminder does not serve as a substitute for clinical judgment, a local panel of geriatric pharmacology experts cautions that its use may place your patient at higher risk for continuous delirium, mortality, hospital acquired complications and prolonged ICU and hospital stay. In its place, consider prescribing:

1. **OMIT** Ondansetron 8 mg PO every 12 hours as needed
2. **OMIT** Metoclopramide 5 mg orally every 6 hours as needed
3. **OMIT** Ondansetron 1 mg IV every 12 hours as needed
4. **OMIT** Promethazine

**Action**

1. ORDER
2. REVISE
3. OMIT
# Results

<table>
<thead>
<tr>
<th></th>
<th>CDSS N = 199</th>
<th>Usual Care N = 225</th>
<th>P value adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients with ACE consult order</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- First 48 hours of hospital stay</td>
<td>42%</td>
<td>36%</td>
<td>0.40</td>
</tr>
<tr>
<td>- Entire hospital stay</td>
<td>56%</td>
<td>49%</td>
<td>0.28</td>
</tr>
<tr>
<td>% Patients with a FC discontinuation order</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- First 48 hours of hospital stay</td>
<td>4.5</td>
<td>4.4</td>
<td>0.97</td>
</tr>
<tr>
<td>- Any time during hospital stay</td>
<td>18.6%</td>
<td>22.7%</td>
<td>0.48</td>
</tr>
<tr>
<td>% Patients with a PR discontinuation order</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- First 48 hours of hospital stay</td>
<td>0%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>- Any time during hospital stay</td>
<td>0.5%</td>
<td>0%</td>
<td>0.95</td>
</tr>
<tr>
<td>% Patients with a AC discontinuation order</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- First 48 hours of hospital stay</td>
<td>1.0</td>
<td>0.4</td>
<td>0.41</td>
</tr>
<tr>
<td>- Any time during hospital stay</td>
<td>11.6%</td>
<td>6.7%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Adjusted for Age, Gender, Race, SPMSQ, and Charlson comorbidity*
Study 1 (eCHAMP): Lessons Learned

- **Deprescribing**
  - Low rates of deprescribing in general
  - Low rates of provider engagement with alerts
  - Alerts followed existing template, but design not user friendly

- **Delirium**
  - Unable to determine impact of deprescribing alerts on delirium outcomes
  - No influence on pre-hospital use of deliriogenic medications
“It’s fine to celebrate success but it is more important to heed the lessons of failure.”

“Success is failure in progress.”

“Accept failure as a gift that helps you learn how to do it better next time.”
Study 2: PMD

- Determine the impact of a multicomponent pharmacologic intervention on delirium outcomes

Khan, et al. JAGS 2011
PMD Intervention

- PMD: haloperidol 0.5 or 1 mg TID x 7 days

- Anticholinergic reduction:
  - Similar alerts in EMR as in eCHAMP for 20 strong anticholinergics
  - Twice-daily, pharmacist surveillance throughout hospital stay

- Benzodiazepine reduction
  - Pharmacist surveillance (only)
  - Dose reduction following standard recommendations
<table>
<thead>
<tr>
<th></th>
<th>Pre-Randomization</th>
<th></th>
<th></th>
<th>Post-Randomization</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PMDa (N=170)</td>
<td>Usual Care (N=176)</td>
<td>P-value</td>
<td>PMD (N=170)</td>
<td>Usual Care (N=176)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td><strong>Haloperidol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed n (%)</td>
<td>29 (17.1)</td>
<td>32 (18.2)</td>
<td>0.888</td>
<td>116 (68.2)</td>
<td>56 (31.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Median daily Dose (IQR)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.723</td>
<td>0.5 (0-0.9)</td>
<td>0 (0-0.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed n (%)</td>
<td>122 (71.8)</td>
<td>118 (67.0)</td>
<td>0.353</td>
<td>97 (57.1)</td>
<td>116 (65.9)</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td>Median daily Dose (IQR)</td>
<td>1.3 (0 – 13.1)</td>
<td>1.0 (0-10.5)</td>
<td>0.466</td>
<td>0.1 (0-2.0)</td>
<td>0.3 (0-3.2)</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergic Burden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed n (%)</td>
<td>30 (17.6)</td>
<td>29 (16.5)</td>
<td>0.777</td>
<td>44 (25.9)</td>
<td>54 (30.7)</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>Median daily score (IQR)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.706</td>
<td>0 (0-0.1)</td>
<td>0 (0-0.2)</td>
<td>0.248</td>
<td></td>
</tr>
</tbody>
</table>
Study 2 (PMD): Lessons Learned

• Deprescribing
  ➢ Rates of initiation unchanged, slight reduction in duration
  ➢ Continued poor provider interaction with alerts
  ➢ No manipulation of pre-hospital exposure to deliriogenic medications

• Delirium
  ➢ Unable to determine impact of deprescribing (alone) on clinical outcome
  ➢ Sample size too small to evaluate outcomes among those receiving ‘high dose’ of intervention
Objectives

- Discuss existing literature summarizing the relationship between medications and delirium outcomes
- Describe prior trials attempting to deprescribe deliriogenic medications in the acute care setting
- Identify opportunities for deprescribing research that can add value to delirium care
Medication Relationships of Interest

- Pre-hospital period
- Hospital period
- Post-hospital period

Time:
- Admission
- Delirium Onset
- Delirium Resolution
- Discharge

Immediate post-D/C Cognitive Outcomes

Delayed Cognitive outcomes (Dementia)

Medication as a predisposing factor?

Medication as a precipitating factor?

Medication with delayed benefit
Relevant Phases of Medication Use in Delirium Research

• Pre-hospital use
  ➢ precipitating vs. predisposing factor?

• In-hospital, pre-delirium use
  ➢ Does initiation vs. continuation vs. discontinuation influence delirium outcomes

• Post-delirium use
  ➢ Does initiation vs. continuation vs. discontinuation in the recovery phase influence LTCI/Dementia
Relevant Deprescribing Opportunities

• Pre-hospital medication use
  ➢ Can pre-hospital deprescribing reduce risk of delirium?

• In-hospital, pre-delirium use
  ➢ Does deprescribing in the acute environment (if conducted effectively) result in harm or benefit?

• Post-delirium use
  ➢ Does deprescribing at discharge influence delirium recovery or long-term cognitive impairment

Justification for Pre-Hospital Assessment

- Medications with central activity known to compromise cognition
  - BBB prevents certain medications from crossing into CNS
- BBB is compromised in APOE4 carriers regardless of cognitive status (evident in cognitively normal, more prominent in cognitive impairment)
- ARB theorized to stabilize the BBB
- Timeline for pharmacologic impact on BBB needs to be tested

Justification for Pre-Hospital Assessment

• Association between ACh & Dementia
  ➢ Strong ACh over 6 yrs
    OR: 1.54 (1.21-1.96)
  ➢ Strong ACB total score
    OR: 1.36 (1.17-1.58)
  ➢ Strong ACh for ≥ 3/10 yrs
    OR: 1.54 (1.21-1.96)
  ➢ Strong ACh for ≥ 4/20 yrs
    OR: 1.40 (1.30-1.50)
    Richardson K et al. BMJ. 2018; 361:k1315.

• Association between ACh & MCI
  (Transitions between normal cognition and MCI)
  ➢ All Strong ACB (Norm to MCI)
    OR: 1.15 (1.01-1.31)
  ➢ Musc ACB (Norm to MCI)
    OR: 1.34 (1.09-1.65)
  ➢ Musc ACB (MCI to Norm)
    OR: 0.63 (0.40-0.99)
Relevant Outcomes of Interest

• Each link between medication and delirium outcomes should evaluate:
  ➢ Delirium Incidence
  ➢ Delirium Severity
  ➢ Delirium Duration
  ➢ Long-term cognition
  ➢ Emotional distress
  ➢ Health-Related Quality of life

Justification for Improvement in Deprescribing Methods

Prior work does **Not** represent failure,
Just negative results:
Study 3: Outpatient Anticholinergic Deprescribing

• Prevent potential harms to brain health by reducing the use of medications with anticholinergic adverse cognitive effects

• Context:
  - Prior attempts to reduce exposure have failed in inpatient studies
  - Majority of prescriptions coming from primary care
Design/Development: Ideation

Brainstorm interventions for multiple targets, without constraints.
Deprescribing as Behavior Change

- Behavior that is:
  - Infrequent
  - Complicated
  - Lacks immediate feedback
  - Benefits delayed

- May be influenced by behavioral economic principles

Development Phase (Executed)

- Physician/Provider-focused support

1) Identifies risk
2) Indication-specific alternative
3) Auto-populated titration to alternative
Development Phase

- Staff/MA-focused support
Implementation Phase

• Cluster-randomized trial of 10 primary care clinics within Eskenazi Health
• Eskenazi Health is one of the nation’s largest safety net health systems, and includes 10 FQHC’s
• Pre-post comparison by group:
  ➢ Comparison Dates: 4/1/2018-3/31/2019
## Evaluation

<table>
<thead>
<tr>
<th>Target Anticholinergics</th>
<th>Order Type*</th>
<th>Intervention</th>
<th>Control</th>
<th>p-value: difference by time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of pre-intervention d/c orders, n (% of all orders)</td>
<td>21 (7.3%)</td>
<td>34 (9.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of post-intervention d/c orders, n (% of all orders)</td>
<td>23 (7.8%)</td>
<td>29 (8.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>2</td>
<td>-5</td>
<td>0.7736</td>
</tr>
<tr>
<td>Recommended Alternatives</td>
<td>Number of pre-intervention active orders, n (% of all orders)</td>
<td>672 (94.9%)</td>
<td>1019 (93.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of post-intervention active orders, n (% of all orders)</td>
<td>913 (94.9%)</td>
<td>979 (94.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>241</td>
<td>-40</td>
<td>0.3066</td>
</tr>
</tbody>
</table>
Evaluation

• Process Measures:
  ➢ 259 alerts directed towards providers
    ▪ 15% opened
    ▪ Order changed in 1.2% of all alerts
    ▪ NNR = 86

  ➢ 276 alerts directed towards MA
    ▪ 4.7% confirmed action taken
Study 3 (BSL): Lessons Learned

• Deprescribing
  ➢ Complex interventions in EMR have multiple opportunities to fail
  ➢ EMR-based deprescribing interventions risk inability to evaluate clinical impact

• Delirium
  ➢ Unable to evaluate clinical outcome without change in process/fidelity measure
## Performance of EPIC CDS

<table>
<thead>
<tr>
<th>Topic</th>
<th>% Compliant</th>
<th>Active</th>
<th>Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing anticoag d/c instructions</td>
<td>90.9</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Foley cath 24-48 hrs w/out order</td>
<td>64.5</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>No level of care on admit</td>
<td>61.8</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>No ACE/ARB order for BP 12 h after admission</td>
<td>21.3</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Suicide Precautions Rec</td>
<td>20.9</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Foley without order</td>
<td>20.3</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pressure Ulcer on Admit</td>
<td>12.3</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Suicide Precautions Rec</td>
<td>7.1</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Swallow Eval Rec</td>
<td>6.3</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>No Code 12 hrs after admission</td>
<td>1.9</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Foley Cath &gt; 48hrs</td>
<td>1.4</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>NPO x 72 hrs</td>
<td>1.2</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Summary

• It remains unknown if deprescribing during hospitalization influences delirium outcomes

• Deprescribing methods need to be enhanced in order to evaluate the impact on clinical outcomes

• Potential deprescribing opportunities exist in the pre-, peri-, and post-delirium journey that could improve outcomes
Brain Safety Lab

R2D2
Funding: NIA R01AG061452
PI: Noll Campbell
Cluster-randomized trial to determine whether pharmacist-based deprescribing improves clinical outcomes in primary care older adults

Brain Safe
Funding: NIA R01AG056926
PI: Rich Holden
Randomized trial to determine if a mobile health application reduces use of anticholinergics and improves clinical outcomes among primary care older adults
Research Team

- Chris Callahan, MD
- Dan Clark, PhD
- Rich Holden, PhD
- Malaz Boustani, MD, MPH
- Nan Kong, PhD
- Zhouyang Lou, PhD student
- NiCole Keith, PhD
- Michael Weiner, MD
- Kim Trowbridge
- Christian Vallejo
- Allie Carter
- Alexxus Knight
- Jordan Hill, PhD
- Sarah Vitelli
- Wanzhu Tu, PhD
- Qing Tang, MS
- Fred Unverzagt, PhD
- Sujuan Gao, PhD
- Chris Steinmetz, MD
- Mohammed Zawahiri, MD
- Philip Adeoye
- Preethi Srinivas, PhD
- Kunal Bodke
- Youngbok Hong, MFA
- C. Thomas Lewis, MFA
- Jaichi Liu
- Addison Harrington
- Gracen O’Neal
- Ricardo Tellez