



## Network for Investigation of Delirium: Unifying Scientists

US Deprescribing Research Network

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 preconferences)

Visit <u>deprescribingresearch.org</u> 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 <u>deliriumnetwork.org</u> 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: <u>nidus@hsl.harvard.edu</u> @sharon\_inouye





#### **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

















#### **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





#### **Neurotransmitter Hypotheses of Delirium**





#### Proposed Neurotransmitter Targets





#### **Medications and Delirium**

• Ever implicated in etiology, seldom the exclusive answer

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

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



Inouye SK, et al. *Lancet* 2014;383(9920):911-922. Martinez JA, et al. *BMJ Open* 2012;2(5). van den Boogaard M, et al. *BMJ* 2012;344:e420.





#### **Medications and Delirium**

• Ever desired as a primary mode of treatment, but not consistently appropriate



Cochrane Database of Systematic Reviews

Pharmacological interventions for the treatment of delirium in critically ill adults (Review)

Burry L, Hutton B, Williamson DR, Mehta S, Adhikari NKJ, Cheng W, Ely EW, Egerod I, Fergusson DA, Rose L



Comparative Effectiveness Review Number 219

Antipsychotics for the Prevention and Treatment of Delirium







## **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
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#### Trial 1: eCHAMP

- Evaluate the efficacy of screening and CDSS at reducing exposure to potentially inappropriate anticholinergics, urinary catheters, and physical restraints
- <u>Outcomes:</u>
  - Orders for geriatric consult
  - D/C orders for anticholinergics
  - D/C orders for restraints and catheters









#### **Example CDS: Promethazine**

C	MS-DOS Prompt					- 🗆 🗙
1	ESTS, PATIENT	99999-5 F	DAILY ORDERS O	rd 211K .22s	y 02/18/09	10:03AM
,	1) ORDER 2) REVISE * 3) OMIT	Ondanset Ondanset Ondanset chemothe	eron ron is the prefe ron 24 mg po may rapy-induced nau	rred 5-HT3 ant; be preferred ; sea and vomitin	agonist at WHS. for highly emet ng prophylaxis	ogenic
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	3. OMIT Original order	Ondansetr	on Inj 4 mg IV	every 12 hours	as needed	
	4. OMIT	Promethaz	ine			
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#### **Results**

	CDSS	Usual Care	P value
	N = 199	N = 225	adjusted*
% Patients with ACE consult order			
- First 48 hours of hospital stay	42%	36%	0.40
- Entire hospital stay	56%	49%	0.28
% Patients with a FC discontinuation order			
- First 48 hours of hospital stay	4.5	4.4	0.97
- Any time during hospital stay	18.6%	22.7%	0.48
% Patients with a PR discontinuation order			
- First 48 hours of hospital stay	0%	0%	1.00
- Any time during hospital stay	0.5%	0%	0.95
% Patients with a AC discontinuation order			
- First 48 hours of hospital stay	1.0	0.4	0.41
- Any time during hospital stay	11.6%	6.7%	0.05
AMERICAN DELIRIUM Adjusted for Age, Gender, Race, SPMSQ	, and Chan	l Ison comorbidi	
DS SOCIETY			INDIAN



## 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 prehospital 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





#### **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 RICAN

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	Pı	e-Randomizat	ion	Post	-Randomizati	0 <b>n</b>
	<b>PMD</b> <sup>a</sup> (N=170)	Usual Care (N=176)	P-value	PMD (N=170)	Usual Care (N=176)	P-value
Haloperidol						
Exposed n (%)	29 (17.1)	32 (18.2)	0.888	116 (68.2)	56 (31.8)	< 0.001
Median daily Dose (IQR)	0 (0-0)	0 (0-0)	0.723	0.5 (0-0.9)	0 (0-0.3)	< 0.001
Benzodiazepines						
Exposed n (%)	122 (71.8)	118 (67.0)	0.353	97 (57.1)	116 (65.9)	0.098
Median daily Dose (IQR)	1.3 (0 – 13.1)	1.0 (0-10.5)	0.466	0.1 (0-2.0)	0.3 (0-3.2)	0.079
Anticholinergic Burden						
Exposed n (%)	30 (17.6)	29 (16.5)	0.777	44 (25.9)	54 (30.7)	0.342
Median daily score (IQR)	0 (0-0)	0 (0-0)	0.706	0 (0-0.1)	0 (0-0.2)	0.248
AMERICAN	Khan, et al. JAGS 2019					TER FOR NG RESEAR



Khan, et al. JAGS 2019 Campbell, et al. JAGS 2019 CENTER FOR AGING RESEARCH INDIANA UNIVERSITY



## Study 2 (PMD): Lessons Learned

- Deprescribing
  - Rates of initiation unchanged, slight reduction in duration
  - Continued poor provider interaction with alerts
  - No manipulation of prehospital exposure to deliriogenic
    AMERIME dications

- 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**





## 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



Nation DA, et al. Nat Med 2019; 25(2): 270-276. Montagne A, et al. Nature 2020; 581(7806:71-76.





#### **Justification for Pre-Hospital Assessment**

#### Association between ACh & Dementia

Strong ACh over 6 yrs
 OR: 1.54 (1.21-1.96)

Campbell NL et al. Neurology. 2010; 75(2):152-159.

Strong ACB total score OR: 1.36 (1.17-1.58)

Campbell NL et al. *Pharmacotherapy*. 2016; 36(2):196-202.

- Strong ACh for ≥ 3/10 yrs
   OR: 1.54 (1.21-1.96)
   Gray SL et al. JAMA Intern Med. 2015; 175(3):401-407.
- 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)

Campbell NL et al. Pharmacotherapy. 2018; 38(5):511-519.







#### **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

Rose L, et al. *BMC Med*. 2021 Jun 18;19(1):143.







## Justification for Improvement in Deprescribing Methods

Prior work does <u>Not</u> 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



Dolan, et al. *J Econ Psychiatry* 2012; 33(1):264-277.







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64 0.2 0.0 0.0

0.0 0.0



#### **Development Phase (Executed)**

#### Physician/Provider-focused support

R

ADS SOCIETY

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#### **Development Phase**

#### Staff/MA-focused support

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#### **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:
   ➢ Intervention Dates: 4/1/2019-3/31/2020
   ➢ Comparison Dates: 4/1/2018-3/31/2019





#### **Evaluation**

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



Regenstrief Institute

Campbell, Holden, et al. JAGS 2021

#### **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**

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

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Extracted from:

Valvona, et al. *Proc Int Symp Hum Fact Erg Health Care* 2020





#### 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

#### <u>R2D2</u>

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
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#### **Deprescribing and Delirium**

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