Incontinence Interactions with Sleep and Cognition: Insights into Common Geriatric Syndromes and a Translational Path Forwards?

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Agenda

• Multimorbidity and UI: A Clinical-Research Disconnect
• UI and sleep problems viewed in context of delirium (2014)
• Cognitive issues and UI viewed in context of sleep (2015)
• Path to new and better interventions via multifactorial complexity:
  - Addressing risk factors: which and how many?
  - Addressing mechanisms: which and how?
  - Single or Multicomponent Interventions?
  - Targeted, Pleiotropic or Both?
  - Focus on molecule, organ, disease process or functional domains?
  - When is a paradigm worth more than 2 nickels?
Multimorbidity and UI: A Clinical-Research Disconnect

Mystery #1: Why is aim such a big issue?
Multimorbidity and UI: A Clinical-Research Disconnect

Mystery #2: “Plus ça change, plus c'est la même chose...”

“Cutting-Edge” UI Therapy since 1899
Multimorbidity and UI: A Clinical-Research Disconnect

Mystery #3: Why is UI Ignored as a contributor to multimorbidity?

Percentage of Non-Institutionalized People With Specific Chronic Conditions, All Ages

- Hypertension: 33.3%
- Disorders of lipid metabolism: 22.3%
- Other upper respiratory disease: 19.2%
- Non-traumatic joint disorders: 16.5%
- Diseases of the heart: 13.5%
- Diabetes mellitus: 12.6%
- Eye disorders: 11.2%
- Asthma: 10.1%
- Chronic Respiratory infections: 10.0%

Source: Medical Expenditure Panel Survey, 2006

Main Causes of Death in USA, 1997

Patient-Centered Care for Older Adults with Multiple Chronic Conditions: A Stepwise Approach from the American Geriatrics Society

American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity*

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*Clinical management is defined as representing all types of care for chronic conditions, including pharmacological and nonpharmacological treatment and interven-
Multimorbidity and UI: A Clinical-Research Disconnect

Mystery #4: Why dearth of literature at interface of UI-sleep-delirium?

AGS 2013 Annual Meeting: Raise your hand if you commonly see older patients with co-existing problems involving cognition, sleep and voiding as part of your clinical practice.....
Multimorbidity and UI: A Clinical-Research Disconnect

Mystery #4: Why dearth of literature at interface of UI-sleep-delirium?

<table>
<thead>
<tr>
<th>Year</th>
<th>PubMed Hits</th>
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<tbody>
<tr>
<td>2013</td>
<td>1,834 Nocturia, 342 Sleep, 4 Nocturia-Sleep, 132,000 Dementia, 120,000 Total</td>
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<tr>
<td>2016</td>
<td>2,150 Nocturia, 548 Sleep, 8 Nocturia-Sleep, 158,359 Dementia, 161,078 Total</td>
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UI and sleep problems viewed in context of delirium (2014)
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- No discussion of co-existence or interactions of all three
- Talk on UI-Delirium Interactions (N Resnick)
- Both are multifactorial geriatric syndromes
- Risk of either condition reflects interactions between baseline vulnerability and severity of a superimposed stressor (resilience)
- Many risk factors (predisposing & precipitating) are the same
- The “cause” versus “multiple contributors”
- Both challenge the classical disease paradigm seen in young
- Aging, followed by multimorbidity, represents by far the greatest predisposing risk factor
UI and sleep problems viewed in context of delirium (2014)

How may voiding dysfunction promote/influence delirium?

• Overactive and Underactive Bladder’s link to CNS (shared CNS tracts and response mechanisms to stressors)

• Acute urinary retention (6 case reports of Acute Cystocerebral Syndrome; mostly acute on chronic UR)

• Use of anticholinergics for OAB (risk of cognitive decline is small and difficult to objectively measure, but certainly desirable)

• Nocturia via sleep disruption
How may delirium promote/influence voiding dysfunction?

- Hospital risks for delirium (mobility issues, fluid, UTI, impaction, restraints etc.) also contribute to UI
- Impact of CNS on voiding and UI is complex and highly nuanced
- Delirium can have broad effects across nearly all cognitive functions
- This includes high cortical regions and association pathways involved in ability to perform complex tasks such as driving a car, flying a plane .... or being able to sense bladder filling, appropriately process such information, make a suitable decision on what to do in the context of all the other issues and challenges confronting the individual at that time and then implement a successful solution that allows for continence, while also....
Cognitive issues and UI viewed in context of sleep (2015)

- No discussion of co-existence or interactions of all three
- Sleep as a Geriatric Syndrome: Nocturia (D. Bliwise/T. Johnson)
- Nocturia worsens sleep
- Sleep influences nocturia
- Obstructive sleep apnea increases nocturia and may even cause UI
- CPAP reduces nocturia episodes in selected populations
- Behavioral Rx for insomnia may improve nocturia
- “Chicken and Egg” – Did you wake up because of a need to void or did you awaken for some other reason and then noticed bladder sensations that prompted a decision to visit the bathroom?
Addressing risk factors: which and how many?

• Exclusive focus on GU symptoms may have hindered progress
• Historically have targeted risk factors for urgency
• Why not also focus on the manner in which older adults are able to maintain homeostasis in the face of a stressor such as bladder filling?
• Systems-based approach to homeostasis...addressing resilience
• All of a sudden, it is not just about the bladder
• All of a sudden, it is not just about “suppression” of urgency
• All of a sudden it makes sense to study and target:
  - CNS sensory and regulatory pathways
  - CNS capacities involved in decision making and dual tasking
  - Capacities to implement decisions
    (suppressing urgency, making one’s way to the bathroom, disrobing)
Single or Multicomponent Interventions?

• History of great success in geriatrics (T. Johnson’s talk tomorrow)
• High priority area for our field
• Most NIH Study Sections struggle with the concept
• Need for deeper science behind intervention rationale and selection
• Why is polypharmacy inevitably associated with increased risk of adverse events?
• Why is use of suitable multicomponent interventions associated with greater likelihood of improvement and generally without a greater risk of adverse events?
Targeted, Pleiotropic or Both?

• A drug may have targeted effects at the molecular level yet may exert pleiotropic effects across many tissues and processes (e.g. statins are HMG-CoA reductase inhibitors yet effects go beyond mere lipid lowering influencing nearly all tissues)

• An intervention may have highly pleiotropic effects in terms of both molecular targets and tissues influenced (e.g. exercise, weight loss)

• Similarly a drug may also exert highly pleiotropic effects in terms of both molecular targets and tissues influenced (e.g. effects of metformin on glucose reduction, mitochondrial metabolism, inflammatory pathways and mTOR)

• Potential role for all of above in UI prevention and management
Focus on molecule, organ, disease process or functional domains?

As you will hear:

• If a molecule were to be shown to contribute to decreased capacity to sense and adjust to bladder filling in older adults with voiding disorders, then efforts to target that specific molecule might make sense following appropriate preclinical validation.

• There is no age limit of benefits from sling surgery when addressing this organ dysfunction in appropriately selected women.

• Treatment or prevention targeting vascular disease processes contributing to brain white matter disease or atherosclerosis in larger pelvic vessels may help improve voiding and continence.

• Strategies targeting a key functional domain (mobility) may help maintain continence regardless of the cause of urgency.
When is a paradigm worth more than 2 nickels?

Future Priorities:

• We must remain open to different approaches and ideas
• Approaches must be multidisciplinary
• Manpower shortages absolutely critical
• Anticholinergics do play a major role in current UI care
• We MUST escape conceptual constraints of “UI Rx = anticholinergic”
• Role of NIH as funder
• Help in guiding network development as a means of bridging gaps
• Encouraging efforts to address knowledge gaps
• Especially when “Clinical-Research Disconnects” can be identified
• Multimorbidity is not only about AD, CHF, DM, ASHD, cancer etc....
• Geroscience is not only about delaying AD, CHF, DM, ASHD, cancer etc....