

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

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- Employed by the University of Connecticut
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Agenda

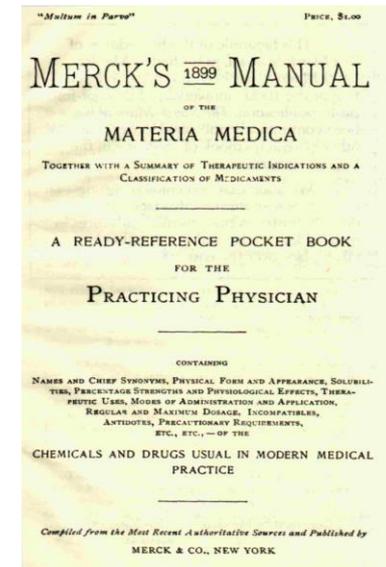
- Multimorbidity and UI: A Clinical-Research Disconnect
- UI and sleep problems viewed in context of delirium (2014)
- Cognitive issues and UI viewed in context of sleep (2015)
- Path to new and better interventions via multifactorial complexity:
 - Addressing risk factors: which and how many?
 - Addressing 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...”



Bladder, Irritable.
See also, Cystitis, Dysuria, Enuresis, Lithiasis, Calculi, Urinary Disorders.

Acid, Benzoic: in large prostate, and alkaline urine.

Alkalies: vegetable salts, especially of potassium when the urine is acid.

Ammonium Benzoate: like benzoic acid.

Aqua-puncture.
Arbutin.

Belladonna: in the irritable bladder of children, more especially when causing nocturnal incontinence.

Buchu: in combination with the vegetable salts of potassium, when urine is very acid.

Cannabis Indica.

Cantharides: in women without acute inflammation or uterine displacement; also in irritable bladder produced by chronic enlargement of the prostate.

Copaiba: in chronic irritability.

Cubebs: like copaiba.

Eucalyptol.

Gelseminine.

Hops.

Hyoscyamus.

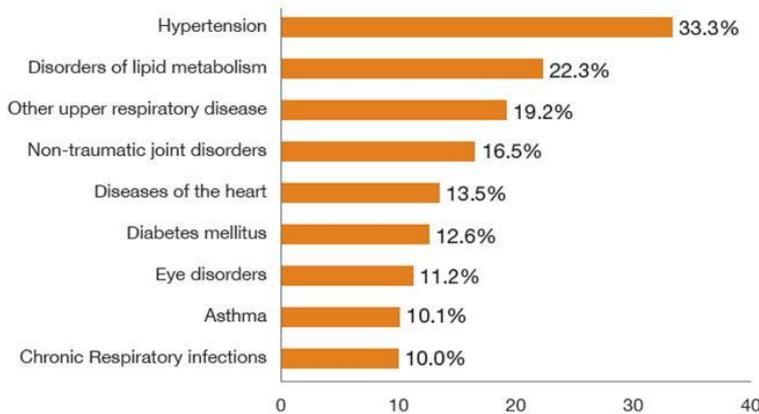
Indian Corn Silk (Stigmata Maydis): a mild

“Cutting-Edge” UI
Therapy since 1899

Multimorbidity and UI: A Clinical-Research Disconnect

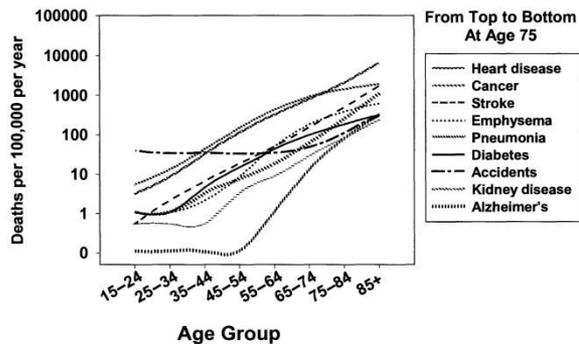
Mystery #3: Why is UI Ignored as a contributor to multimorbidity?

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



Source: Medical Expenditure Panel Survey, 2006

Main Causes of Death in USA, 1997

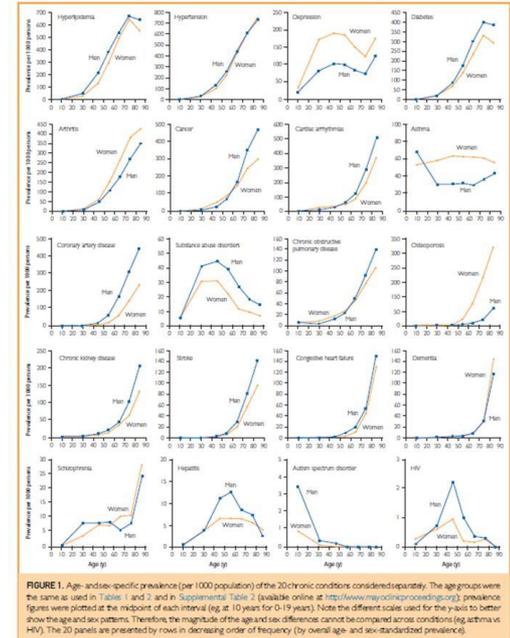


ORIGINAL ARTICLE



Prevalence of Multimorbidity in a Geographically Defined American Population: Patterns by Age, Sex, and Race/Ethnicity

Walter A. Rocca, MD, MPH; Cynthia M. Boyd, MD, MPH; Brandon R. Grossardt, MS; William V. Bobo, MD, MPH; Lia J. Finney Rutten, PhD, MPH; Véronique L. Roger, MD, MPH; Jon O. Eibert, MD, MSc; Terry M. Therneau, PhD; Barbara P. Yawn, MD, MSc; and Jennifer L. St. Sauver, PhD, MPH



SPECIAL ARTICLES

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*

J Am Geriatr Soc 60:1957-1968, 2012.

Key words: multimorbidity; guiding principles; comorbidity; older adults

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?

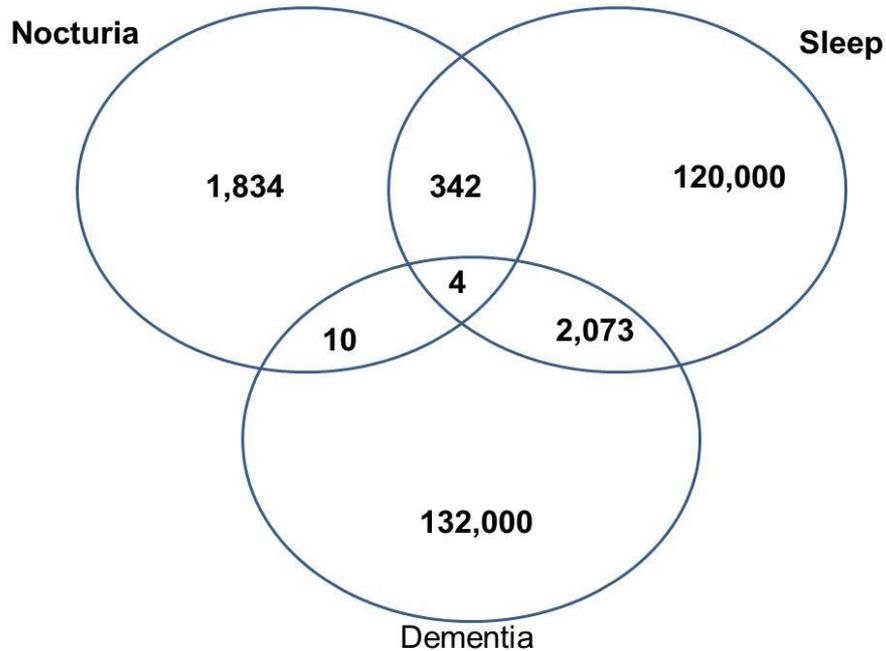
AGS 2013 Annual Meeting: Raise your hand if you commonly see older patients with co-existing problems involving cognition, sleep and voiding as part of your clinical practice.....



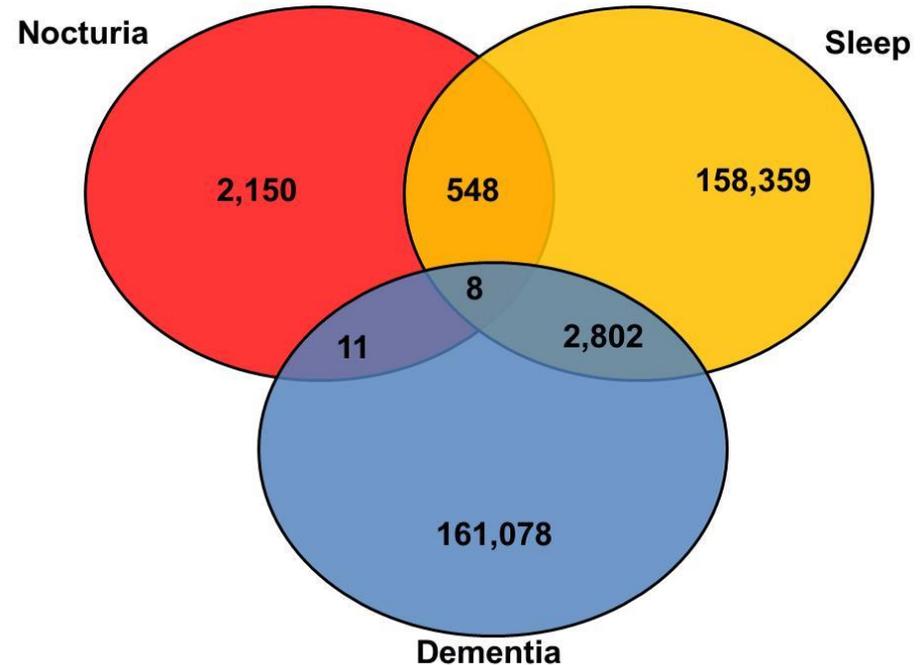
Multimorbidity and UI: A Clinical-Research Disconnect

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

PubMed Hits
2013



PubMed Hits
2016



UI and sleep problems viewed in context of delirium (2014)

SPECIAL ARTICLE

The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults

AGS/NIA Delirium Conference Writing Group, Planning Committee and Faculty

J Am Geriatr Soc 63:843-852, 2015.

Key words: delirium; Geriatric syndromes; cognition; measurement; pathophysiology; interventions

The American Geriatrics Society, with support from the National Institute on Aging and the John A. Hartford Foundation, held its seventh Bedside-to-Bench research conference, entitled "Delirium in Older Adults: Finding Order in the Disorder" on February 9-11, 2014, to provide participants with opportunities to learn about cutting-edge research developments, draft recommendations for future research involving translational efforts, and opportunities to network with colleagues and leaders in the field. This meeting was the first of three conferences that will address delirium, sleep disorders, and voiding difficulties and urinary incontinence, emphasizing, whenever possible, the relationships and potentially shared clinical and pathophysiological features between these common geriatric syndromes (Figure 1).

BACKGROUND

Delirium can be thought of as acute brain failure that occurs when stressors exceed the brain's homeostatic reserve (Figure 2). Celsus initially described delirium in the 1st century CE (i.e., 47 CE, Aulus Cornelius Celsus, *De Medicina*, 2:728), but little in the way of progress was made until the early 1980s, when delirium first appeared in the

Public Policy, American Geriatrics Society, New York, New York.

AGS/NIA Delirium Conference Writing Group, Planning Committee and faculty members are listed in Appendix.

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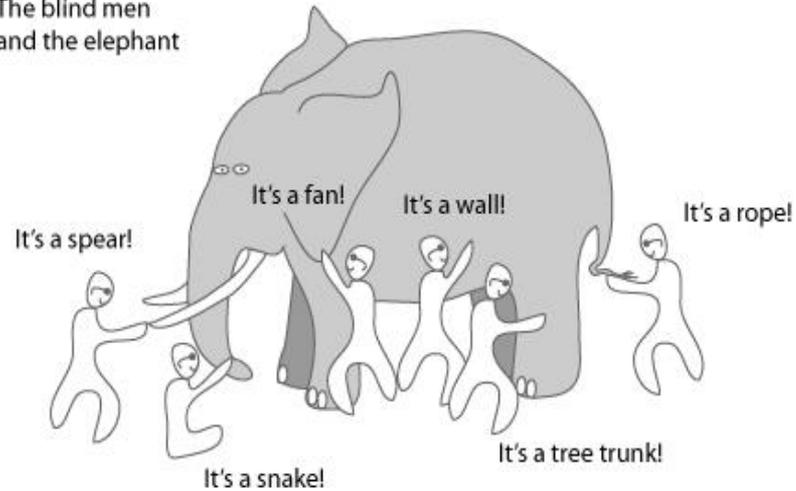
JAGS 63:843-852, 2015
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Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM III). The most current definition of delirium was recently published in the 5th edition of the DSM and includes a disturbance in attention and awareness; a change in cognition that is not better accounted for by a preexisting, established, or evolving dementia; that the disturbance develops over a short period and tends to fluctuate during the course of the day, and that there is evidence that a direct physiological consequence of a general medical condition, an intoxicating substance, medication use, or more than one etiology causes the disturbance.¹ The DSM definition can be difficult to operationalize or quantify in certain settings. Although a number of approaches exist, the diagnostic approach most commonly used is the Confusion Assessment Method (CAM) four-item diagnostic algorithm, which trained physicians and nurses and other allied health personnel can apply;² the use of the CAM format for delirium evaluation has expanded widely, and valid and reliable forms are now in use in numerous healthcare settings (e.g., b-CAM for "bed" emergency medicine evaluations,³ p-CAM intensive care unit (ICU) for pediatric use,⁴ and CAM-ICU for intensive care unit use).⁵ Different clinical phenotypes have been described, including the psychomotor variants of hyperactive and hypoactive delirium, frank hallucinations or delusions, and abnormal levels of consciousness. The incidence of delirium varies widely depending upon the population studied, ranging from approximately 15% after some types of elective surgery to as high as 80% in ICU populations.⁶ Delirium is associated with a variety of poor outcomes, including cognitive and functional decline, longer hospital stay, greater healthcare use, and long-term morbidity and mortality. The number of indexed articles in standard bibliographic databases on delirium has increased from fewer than 50 per year in the 1960s to more than 350 per year in 2012, highlighting increased efforts to differentiate delirium from other cognitive disorders and the impetus for developing novel treatment strategies.

DELIRIUM-INTERFACE WITH OTHER GERIATRIC SYNDROMES

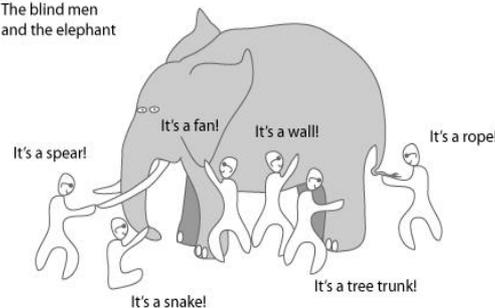
The relationships between delirium and other geriatric syndromes such as sleep disorders, voiding dysfunction, and

The blind men and the elephant

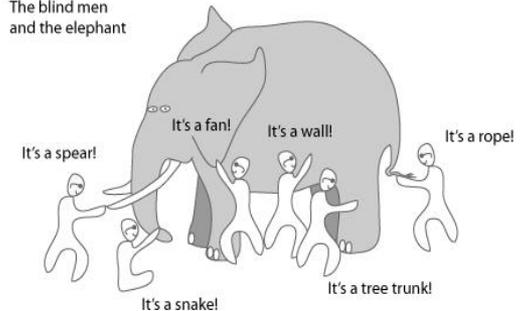


The Delirium Elephant

The blind men and the elephant



The blind men and the elephant



UI and sleep problems viewed in context of delirium (2014)

- 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



UI and sleep problems viewed in context of delirium (2014)

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....