Somato-Visceral Connections Neuromodulation and Related Therapies

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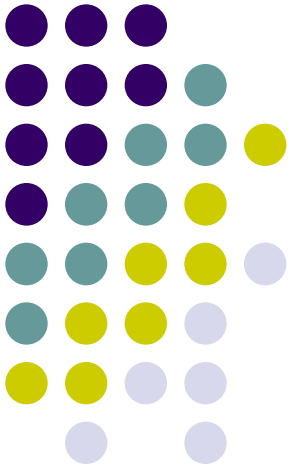

Disclosures

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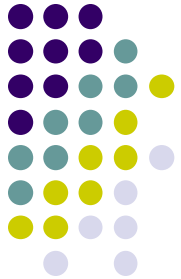
Educational Objectives

- Review translational research on bladder dysfunction (ischemia / progression model)
- Discuss options for treatment of OAB based on evidence-based guidelines
- Discuss bladder neuromodulation and chemodenervation treatments
- Review clinical outcomes in geriatrics
- Highlight role of multimodal therapy and shared decision making

Progression Model of Lower Urinary Tract Symptoms (LUTS)

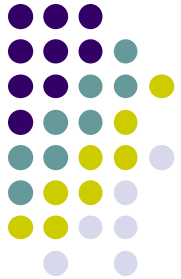


- Ultrastructural changes occur with aging and ischemic change / reperfusion injury
  - Disruption of muscle integrity
  - Increased collagen to smooth muscle ratio
  - Decreased bladder capacity (some increased)
  - Increased muscle overactivity
  - Subsequent loss of muscle contractility

Progression Model of LUTS

- Range of symptoms may overlap
  - Urinary urgency, frequency, urge incontinence
  - Obstructed voiding symptoms
  - Other urinary incontinence
  - Incomplete emptying (? Overflow)
- Bladder overactivity may be an early sign
- Repetitive ischemia and reperfusion injury
- Ultrastructural changes and neurodegeneration
- Potential progression to underactive bladder

Bladder Ischemia – Translational Research



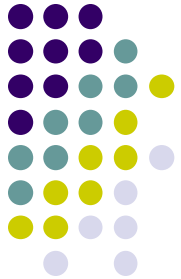
- Bladder outlet obstruction
- Animal model (Sprague-Dawley rats)
  - Ischemia and reperfusion injury
  - Increased free radical (superoxide) expression
  - Increased nitric oxide (NO)
  - Pelvic nerve stimulation led to reduced NO levels

Yildrim A, et al: Int Urol Nephrol 2008; 40: 71-77

Bladder Changes with Aging

- Partial denervation of detrusor may lead to microcontractions
- Decreased suprapontine inhibition may lead to detrusor overactivity
- Excess production of acetylcholine in bladder tissues may increase excitatory activity
- Alterations in muscle and connective tissue structures

Clinical Guideline Recommendations



AUA Clinical Guideline (OAB)

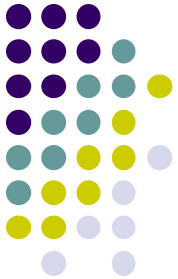
- Available free online at www.AUAnet.org
- Under **'Clinical Guidance'** tab
  - Evidence-based guide diagnosis and therapy
  - Peer-reviewed resource
  - Provides recommendations and levels of evidence

Gormley EA, et al: AUA Guidelines on OAB, 2012

Clinical References – OAB

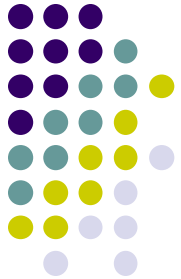
- Urology Care Foundation (of AUA)
  - www.urologyhealth.org
  - Dedicated to advancing research and education to improve patients' lives
- ***'It's Time to Talk About OAB'***
  - Set of resource materials on OAB
  - Includes provider and patient materials
  - Includes *'Voices of OAB'* – patient social media

Clinical Guidelines Overactive Bladder (OAB)



- First line therapies
  - Behavioral modifications / diet / voiding habits
  - Pelvic floor muscle exercises
- Second line therapies
  - Pharmacotherapies
    - Antimuscarinics / anticholinergics
    - β-3 agonist medications
- Third line therapies
  - Neuromodulation (various forms)
  - Chemodenervation
- Fourth line therapies
  - Surgeries (augmentation / diversion)

Neuromodulation (Sacral Nerve)



- FDA approved in 1998 – urge incontinence
- Subsequently expanded indications
  - Urinary urgency and frequency
  - Idiopathic nonobstructive urinary retention
  - Fecal incontinence

- Therapy has evolved over time
  - Less invasive
  - Easier to operate / program

Neuromodulation

- Surgically implanted in 2-stage outpatient procedure
  - Awake patient (sedation and local)
  - Fluoroscopic guidance
  - Target is the S3 nerve root
    - Bellows response of gluteal cleft
    - Flexion of ipsilateral great toe
    - Vibratory sensation in perineum / vagina / scrotum

Ammi M, et al: Int Urogynecol J 2014, 25: 1065-1069

Neuromodulation

- Patient tests device
  - 1-2 weeks
  - Possible bilateral testing (one side at a time)
  - Keep bladder diaries pre- and post-operatively
  - 50% reduction in urinary urgency / frequency or urge incontinent episodes
  - 50% improvement in spontaneous voiding
- Generator implant or system removal
- Battery life ~ 5-7 years

Neuromodulation

- Programmable generator
  - Interactive therapy
  - Requires adjustment and reprogramming
    - Based on symptoms
    - Variety of setting and parameters that can be changed
  - Requires baseline cognitive function and ability to gauge symptoms
  - Caregivers can potentially help
    - Presents unique challenges in some cases

Neuromodulation

- Mechanisms of action
  - Works to normalize neural control
  - Exact mechanisms ‘unknown’
    - Inhibition of preganglionic neurons
    - Relaxation of detrusor smooth muscle
    - Inhibition of central inhibitory pathways (A-delta fibers)
    - May also block c-afferent fibers (pain response variable)
    - Inhibits micturition reflex arc

    - Inhibits guarding reflex
    - Enhances ‘rebound’ phenomenon

Neuromodulation

- Clinical outcomes in older adults
  - Overall results have been promising, although studies are limited in geriatric cohorts
  - Emerging data from FDA long-term trials

  - Initial studies showed success in 50% + of geriatrics patients tested with ongoing success at 7.8 months in all subjects with full implant

Amundsen & Webster Am J Obstet Grynecol 2002; 187: 1462

Neuromodulation

- Increase in use in Medicare population has been observed in past 10 years
  - Overall increase from 0.03% to 0.91% ($p < 0.001$)
  - Younger patients (< 65 years) still more likely to be treated
  - Higher use in females and in Caucasians
  - Geographic differences in use across USA

Laudano et al: J Urol 2015; 194: 449-453

Neuromodulation

- Clinical outcomes
  - Medicare population dataset research
    - Overall explant rate of 11.3%
    - Mean followup of 60.5 months
      - Loss of efficacy / Infection / Pain at generator site
      - Desire to change therapy
    - Reprogramming common
  - Cohort studies have not shown age-dependent changes in efficacy

Cameron et al: Neurourol Urodyn 2013; 32: 238-241
Peters et al: Neurourol Urodyn 2013; 32: 30-36
White et al: J Urol 2009; 182: 1449-1452

Neuromodulation

- Efficacy in patients with neurologic comorbidity has been widely variable
  - Parkinson's disease
  - Stroke
  - Multiple sclerosis
    - Dependent on status of neurologic disease
    - May change with time and treatments
  - Contraindicated in complete spinal cord injury

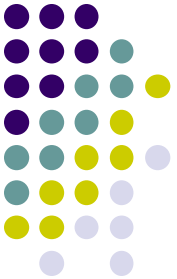
Kabay et al: Neurourol Urodyn 2009; 28: 62-67

Neuromodulation

- Pudendal nerve stimulation
- Undergone research and clinical investigation
- Not currently commercially available

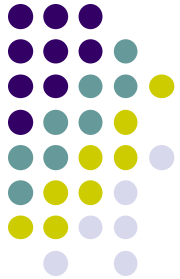
- Theoretically may have different efficacy
  - More direct neural action
  - Smaller device
  - ? More challenging to implant
  - Promising in clinical trials

Percutaneous Tibial Nerve Stimulation (PTNS)



- FDA approved 2000 for urinary urgency, frequency and urge incontinence
- Marketing started again in 2005
- FDA expanded indications for overactive bladder (OAB)

Percutaneous Tibial Nerve Stimulation (PTNS)



- Minimally invasive
- Outpatient
- Potential home therapy
- Need repeat treatments about every 2 weeks
- Typically start with 6 treatments (12 weeks)
- Then tailored to patient needs

PTNS in Geriatrics

- Pilot study in residential care
- 30 subjects – 12 treatments (30 minutes) versus sham control
- Improved objective and subjective measures in those treated with PTNS
- Limitations
  - Relatively short term study
  - Motivation and continued therapy

Booth et al: JAMDA 2013; 14: 270-274

PTNS in Geriatrics

- Use in patients with neurologic comorbidity has been promising
  - Parkinson's disease
  - Stroke
  - Multiple sclerosis
- Small cohort studies with limited followup
- Appears to improve urinary urgency, frequency and urge incontinence

Kabay et al: Neurourol Urodyn 2009; 28: 964-968
Kabay et al: Urology 2015 (in press)
Gobbi et al: MSJ 2011; 17: 1514-1519

Acupuncture

- Acupuncture and/or electroacupunture compared to pelvic floor muscle exercise and antimuscarinic medications
- Also examining role in stress incontinence
- Small pilot studies reported
- High dropout rates
- Studies are ongoing

Liu et al: BMC Comp Alt Med 2014; 14: 301
Solberg et al: Acupunct Med 2016; 34: 7-13
Su et al: Trials 2015; 16: 45

Acupuncture

- Randomized controlled trial
  - 240 women randomized
    - 118 acupuncture (weekly)
    - 122 pharmacotherapy (tolterodine)
  - 4 weeks
  - Both groups improved – subjective measures and voiding diaries
  - No adverse events
  - Similar outcomes between groups

Yuan et al: World J Urol 2015; 33: 1303-1308

Chemodenervation

- Botulinum toxin-A injection
  - Approved (2011) by FDA only for neurogenic voiding dysfunction (spinal cord, spina bifida, MS)
  - Subsequent approval (2013) for idiopathic urinary urgency, urge incontinence (OAB)
  - Data suggest improvement durability 6-12 months
  - Outpatient, minimally invasive, repeatable
  - Risk of urinary retention requiring clean intermittent self-catheterization (CIC) – 5%

Dmochowski R, et al: J Urol 2010, 184: 2416-2422

Chemodenervation

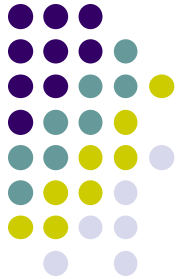
- Botulinum toxin blocks presynaptic release of acetylcholine
- Irreversible process
- Leads to muscular relaxation and a partial flaccid paralysis

Chemodenervation

- Clinical outcomes in geriatrics
  - Studies have been limited in this population
  - Cohort studies have shown efficacy similar to younger populations
  - ? Concern for increased risk of urinary retention
    - Role of detrusor underactivity
    - Preoperative urinary retention and postvoid residual

White et al: J Urol 2008; 180: 2522-2526

Setting Treatment Expectations



- Identify goals for patient and caregivers
- Review expected improvements associated with each therapy
- Acknowledge multimodal therapy may be required to achieve improvement
- Discuss that changes in therapy may be necessary over time
- Recognize wide outcome variability for individual patients and importance of shared decision making

Conclusions

- A wide variety of OAB treatments
  - Behavioral, pharmacological
  - Neuromodulation and chemodenervation
  - Surgery (augmentation and diversion)
  - Published evidence-based guidelines (AUA)
- Treatment tailored to each patient
- Goals of therapy important
- Need to follow adherence / persistence
- Shared decision making is crucial

Future Implications

- Neuromodulation and chemodenervation may be viable treatment options for select older adult patients with voiding dysfunction
- Additional research is needed to delineate best practice in geriatrics
  - Patient selection
  - Specific procedures
  - Role of multimodal therapy
  - Cost effectiveness
- Ongoing translational research

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