Let’s Talk About Managing “Refractory Overactive Bladder”

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Mayo Clinic
90th Annual Clinical Reviews
November 2nd, November 16th 11 AM

No Industry COI
Objectives:

• Definitions, Prevalence, Diagnosis
• Evaluation and Management of OAB
• Cure rates
• Understand that “Refractory OAB” is usually not what you think!
What is OAB?

- *Medical* condition referring to urgency without or without urge incontinence, usually with frequency and nocturia *in the absence* of other pathological factors. ICS 2003
  - Normal urines!
  - *Outside of norms of bladder function*
    - Not habitual polydipsia
  - Not 2° to lack of cortical inhibition of bladder contractions that continue at a low level throughout our days and nights.
BACH study: Prevalence and CRP Kuperian 2011

FIG. 1. Prevalence of overactive bladder by gender, age and C-reactive protein (CRP) levels.
Impacts of OAB

- 2% of health care costs (!)
- Major impact on QOL; worse than diabetes, particularly OAB-wet
  Irwin DE BJU Int 2008
- Concomitant conditions:
  - Constipation, asthma, diabetes, HBP
  Coyne KS BJU Int 2008
  - Depression
  Zorn BH J Urol 1999
- 20 conditions:
  - Chemical dermatitis, UTIs
  - Falls, fractures
  - Sleep disruption
Evaluation: “Do you have trouble getting to the bathroom because of compelling need to void?

- **Hx** should include bladder, bowel, bulges and sexual function
- **PE**, particularly gait, memory, PFM, rectal
- **Bother**: “What does this keep you from doing?”
- **Urines!**
- **Bladder diary for two consecutive days**
Bladder Diary at 1st visit! : why volumes, not just time…

<table>
<thead>
<tr>
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<th>Volume (cc)</th>
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<td>3:00am</td>
<td>800</td>
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</table>
Primary treatment of OAB is behavioral

1. Education on normal physiology
2. Fluid intake, fruits, vegetables leading to fluid schedules
3. Maintain/restore general health, weight, and bowel function
4. Cognitive and mobility issues: Timed and prompted voiding
5. Pelvic floor muscle re-education: especially Quick Flicks for urge suppression +/- formal biofeedback
Setting Realistic Expectations

• Understanding Bladder Physiology and their own bladder

• Cure Rates with OAB
  • Studies report mean change, not cure
  • In best practices, ex. TAURUS and SCORPIO trials, “% of responders incontinence at baseline and became dry post-baseline was numerically (although not statistically significantly) higher for mirabegron 50 and tolterodine than for placebo” (emphasis mine)

• Commitments over time, multiple modalities, costs

• Demonstrable Changes: Use of validated Questionnaires and bladder diaries
Diagnosis & Treatment Algorithm: AUA Guideline on Non-Neurogenic Overactive Bladder in Adults

**History and Physical; Urinalysis**
- Signs/symptoms of OAB, (-) urine microscopy

**Patient education:**
- Normal urinary tract function
- Benefits/risks of treatment alternatives
- Agree on treatment goals

**Behavioral Treatments***
(consider adding anti-muscarinic if partially effective)

**Anti-muscarinics*** with active management of adverse events; consider dose modification or alternative medication if initial medical treatment is effective but adverse events or other considerations preclude continuation

**Reassess and/or refer:** consider urine culture, post-void residual, bladder diary, symptom questionnaires, other diagnostic procedures as necessary for differentiation

**Follow-up for efficacy and adverse events**
- In extremely rare cases, consider urinary diversion or augmentation cystoplasty

**1st**
- Treatment goals met
- Patient desires treatment and/or treatment is in patient’s best interests

**2nd**
- Treatment goals not met; Patient desires further treatment and/or further treatment in patient’s best interests

**Consider in carefully-selected patients**
(multiple therapies may be tried but they should not be combined):
- Sacral neuromodulation (SNS) or Intradetrusor onabotulinumtoxinA
- Peripheral tibial nerve stimulation (PTNS) or

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*As of June 28, 2012, β3-agonist class of medications (i.e., mirabegron) has been approved by the FDA for OAB treatment. This class of medications was not reviewed by this guidelines panel, as it has been FDA-approved since the Guideline publication. Prescribing clinicians are advised to educate themselves regarding the cost-benefit and adverse event profile for those pharmaceutical agents they prescribe.
In those best of all possible worlds pharmacotherapy trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cont. attributable events per 1,000, n (range)</th>
<th>Cont. number needed to treat (NNT), n (range)</th>
<th>Clinically meaningful improvement—attributable events per 1,000, n (range)</th>
<th>Improvement NNT, n (range)</th>
<th>Discontinuation for adverse events compared to placebo (%)</th>
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<td>Darifenacin</td>
<td>NA</td>
<td>NA</td>
<td>117 (57–177)</td>
<td>9 (6–18)</td>
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<tr>
<td>Fesoterodine</td>
<td>130 (58–202)</td>
<td>8 (5–17)</td>
<td>100 (56–145)</td>
<td>10 (7–18)</td>
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<tr>
<td>Oxybutynin</td>
<td>114 (64–163)</td>
<td>9 (6–16)</td>
<td>167 (95–240)</td>
<td>6 (4.0–11)</td>
<td>10/5.0</td>
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<td>Propiverine</td>
<td>163 (86–239)</td>
<td>6 (4–12)</td>
<td>192 (132–252)</td>
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<td>96 (42–149)</td>
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<td>Trosplum</td>
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<td>9 (7–12)</td>
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The figures relate to available anticholinergic agents and head-to-head comparisons with placebo or other anticholinergics. Attributable events represent the difference between placebo response and active drug response.

Neurology and Urodynamics DOI 10.1002/nau
Continued: Mirabegron in BPW trials

SCORPIO: Achieving Zero incontinence @12 wks:

- Mirabegron 50 mg 45.1%
- Tolterodine 4 mg 47.3%
- Placebo 40.5%

TAURUS: 1 yr,

- Not designed to demonstrate differences, efficacy “appears maintained”
- A safety study
Pharmacotherapy Trials: These are “BPW” results

• Motivation of the patient is high
• Intensive follow-ups are required
• Generally of moderate severity for entry
• Excluded comorbidities including diseases with failure to concentrate, frailty, immobility, psychiatric disorders, polydipsia…

These results will not be achieved in our patients!
So what is Refractory OAB?

Is refractory OAB simply the failure to be cured with another line therapy?
Refractory OAB

I. Polydipsia

II. Noncompliance

III. Cortical Function

IV. True Nonresponsiveness to first several therapies
**Bladder/Voiding Diary**

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<td>1800</td>
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<td>oz</td>
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*Total Daily Intake: 176 oz*

*Total Daily Output: 264 oz*

- How many times did you urinate in 24 hours? **19**

**Polydipsia**
I. “OAB” $2^0$ to polydipsia

- Miss the diagnosis without a bladder diary!
- Often very refractory
  - Cultural meme
  - Provider distrust
  - Psychiatric disorders

Few patients accept this…
NO scientific studies…
Including no studies of these common myths:
1. “Relief of constipation”
2. “Thirst is too late”
3. “Dark urine means dehydration”
4. “High fluid intake maintains GFR”
5. Promote weight loss
6. Prevent bladder, colorectal cancers
7. Prevent CAD
IIa. OAB and the non-compliant patient

• This is shared decision-making at its core!
• “What are you willing to do?”

“Not doing my bladder diary, I’m wet all the time…”

https://www.google.com/search?q=crabby+old+lady&biw=1124&bih=806&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjAh__W8s9fKAhXjtYMKHSHvCokQ_AUIBigB#imgrc=c7c86A7d7R6tnM%3A
IIb. OAB and non-compliance with drugs

Drug Discontinuation:

1. Lack of efficacy
2. TEAEs
3. Cost

Response:

a. Duration of use
b. Switch
c. Start and/or continue behavioral tx!

13 trials, 1.8K, drugs better than retraining alone, but both better than drugs alone. Alhasso et al, Cochrane, 2006

Use extended release, treat AE
Use inexpensive generics
III. OAB and cortical function

- **OAB is defined as idiopathic**
- Frontal micturition center normally suppressive but is known to be deactivated in many forms of OAB
- NB- requires excellent higher brain function to have socially acceptable bowel and bladder & to get out of diapers

https://www.studyblue.com/notes/n/6526141
The Standard Mini-Cog Test (Clock Drawing)

- Normal: Score 10
- Mild Cognitive Impairment (Numbers error and placement of hands): Score 8
- Moderate Cognitive Impairment: Score 4
- Severe Cognitive Impairment: Score 2

Sunderland, 1989
“Refractory” OAB:

• Polydipsia

• Noncompliance (which includes poor drug therapeutic efficacy, etc.)

• Medically complicated comorbidities, including renal, cardiovasc disease, loss of higher cortical function, TEAE of medications

*By definition, appropriately determined expectations but unresponsiveness to behavioral and medical management*
Refractory OAB in a normal healthy patient

Sudden Bothersome Urge
Concentrates urine
Normal intake
Normal FBC
Low PVR
*NOTHING neurologic*

Treatment:
- Reassure
- Dietary irritant trial
- Timed and prompted
- Quick Flicks
- Menopausal? +/- intravaginal estrogens (no human data)
- +/- meds

https://www.google.com/search?q=scarce+as+hen%27s+teeth&biw=1169&bih=737&sou rce=lnms&tbm=isch&sa=X&ved=0ahUKEwiYg5Tv-77PAhULw4MKHdhqCFkQ_AUIBygC#tbm=isch&q=hen%27s+teeth&imgc=6nIYV0A qD06xdM%3A
Beware of Medicalization of OAB

- Voiding and continence are a learned social behavior.
  - Some patients perceive the symptom *as an disease* to be “fixed”, rather than what can be 2° symptoms, requiring regulation of behaviors
  - Obviates responsibility *to change social expectations of fluids, of weight, of bowel programs, of pelvic floor exercises*, simply, of good health…
  - Success rate for these patients?
Truly Refractory OAB

- Realistic treatment goals not met
- Highly bothersome
- Compliant with cares & in their best interest
- Willing and able

What can we offer these people?

1. Sacral neuromodulation
2. Peripheral tibial nerve stimulation
3. Intradetrusor onabotulinumtoxinA
   (Augmentation cystoplasty, diversion)
Sacral Nerve Stimulation for Neuromodulation:

- Also modulation of bowel and pelvic floor
- Stimulation can be performed at the sacral level or more peripherally
So what’s truly refractory OAB?

• Remember the urines and the bladder diary!
• While significant & bothersome in most people…
• …Compliance of patient is critical: “what are you willing to do?”
• Age, comorbidities & frailty impact treatment options, reducing QOL is essential
Thanks!
How many recurrent stone formers will consume 4.9 l a day to avoid another stone?
Predictors of (drug) noncompliance:

- Smokers
- Poor establishment of realistic expectations
- Lack of education on TEAE
- High degree of bother from urgency \(^{\text{Coyne et al 2008}}\)
- Costs
- Lack of benefit
- TEAE themselves

http://1.bp.blogspot.com/q4I01L1A9us/UzBlg0brR7I/AAAAAAAAI8I/IQT1D2eY1IM/s1600/rock+hard+place.jpg
Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation (SNM) with ________ therapy compared to standard medical therapy (SMT) at 6-months in subjects with mild symptoms of overactive bladder. Siegel, Noblett et al. 2015

- InSite study, ongoing over 5 years
- >2 leaks in 72 hours, > 8 voids/d
- 93% females

- @ 6 mo
  - ITT analysis 61% for SNM vs 42% for drugs
  - Of UI, continence in 39% for SNM vs 21% for drugs

- 100 U, muscarinic failures with UI >3/d and/or > 12 voids/d

- No placebo

- Obj/Subj Success at 3 months in 60%
  - Global urgency scores<2
  - UI decreased to 5 in 72 hours
  - Voids decreased to <10/d

- Female gender, younger, lower symptom bother, and OAB-wet c/w better success

- Other points: % dry; UTIs, retention; duration of response
Medicalizing urgent bladder behaviors has consequences

- Costs, drugs, AEs, medical products, interventions
- Patients perceive this as an *disease* that can be “fixed”, rather than regulating choice of behaviors
- Obviates responsibility to change social expectations of fluids, of weight, of bowel programs, of pelvic floor exercises, simply, of good health...