WHEN HAVE CONSERVATIVE MEASURES FAILED ?

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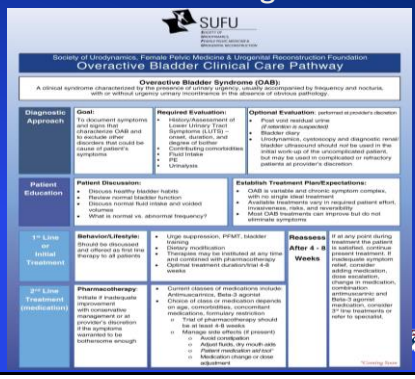
POTENTIAL COI

- Advisor/Consultant to
- Avadel
- Axonics
- Allergan
- Medtronic
- Roivant
- Serenity
- Valencia

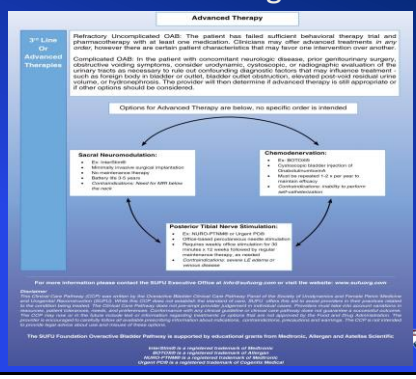
Refractory Detrusor Overactivity (RDO)

- Usual definition
  - Persistent urgency / frequency / incontinence
  - Still bothersome
  - Despite therapy (oral pharmacologic + behavior modification)
- Implications
  - More recalcitrant OAB syndrome
  - Relatively few options

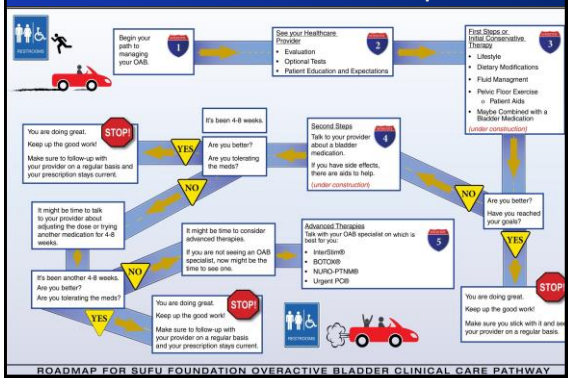
CCP Flow Diagram



CCP Flow Diagram



CCP Patient Road Map



Etiologies of Failure of OAB Rx

- Did not take the drug at all
- Did not take the drug as directed
  - Half dose
  - No titration
- Did not add drug as directed

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Etiologies of "Failure" of OAB Rx

- Practical reasons/ Missed Diagnosis:
  - Excessive fluid intake
  - Urinary retention (overflow)
  - UTI/prostatitis
  - Radiation cystitis, tuberculous cystitis
  - Sexually transmitted diseases (GC, chlamydia, etc)
  - Interstitial cystitis, sensory urgency syndromes
  - Bladder cancer
  - Bladder stones

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Etiologies of "Failure" of OAB Rx

- Practical reasons/ Missed Diagnosis:
  - Pelvic mass (GI, GU, GYN, vascular, etc)
  - GYN problem:
    - » Vaginitis, endometriosis, GYN malignancy, etc
    - » Postmenopausal atrophic vaginitis
    - » Prolapse: cystocele, etc
  - Neurological condition: multiple sclerosis, CVA, back injury, s/p APR, etc
  - Bladder outlet obstruction (BPH, prostate cancer, etc)
  - Severe stress incontinence
  - Medical illness: diabetes, CHF, etc
  - Urethral disease
  - Other

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Etiologies of Failure of Pharmacologic Treatment

- Theoretical reasons:
  - Atropine resistance (NANC)
    - May be increased in:
      - Obstruction
      - Aging
      - Some neurogenic conditions
  - Non-M_3 cholinergic-mediated phenomena
  - Upregulation of M_3 receptors
    - And / Or other M receptors
    - Myogenic etiology of OAB
  - Genetic (pharmacogenomic)

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Options for "Failure" of OAB Rx

- WaWa, reassurance
- Assess patient motivation
- Redo behavior modification
- D/C drug
- Change drug
- Add additional drug
- Increase dose of drug
- Add another type of therapy or change therapy

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Options for "Failure"

- The Big Two(No order intended)

1. Chemodenervation

2. Neuromodulation
   a. PTNS
   b. Sacral
   c. Pudendal

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OTHER OPTIONS

- AUGMENTATION
- DIVERSION
- ? FUTURE: TISSUE ENGINEERING

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ARE WE DONE ?

- Well, now that we all agree, what are we talking about ?
- Outcome indicators and setting goals

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Efficacy of OAB Treatments: How Is it Measured? (1)

- Traditional measures of efficacy – primary efficacy variables
  - Change in urinary incontinence episodes
  - Change in micturitions/24 hours
- These do not consider the defining symptom of OAB – urgency
- Data available from registration studies of all compounds

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Efficacy of OAB Treatments: How Is it Measured? (2)

- Traditional measures of efficacy– secondary efficacy variables
  - Voided volume
  - Effect on QOL
- Urodynamic endpoints
  - Early-phase studies
  - Little clinical relevance

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Efficacy of OAB Treatments: How Is it Measured?(3)

- Dry rates or incontinence-free days
  - Usually expressed as percentage of patients with no incontinence episodes over a fixed period of time
  - Different studies have used different time intervals, so be careful
  - Baseline often different, so be careful

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What and How Do We Measure?

All concepts and tables: Wein A, Dmochowski R; The Overactive Bladder, 2007, pp 239-252 (Informa Healthcare)

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EFFICACY MEASURES: OAB

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Parameter	Per Day	Per Week	Mean	Median	Explanation
Urge incontinence episodes	√	√	√	√	
Total incontinence episodes	√	√	√	√	
Frequency (total)	√	√	√	√	Both counting episodes and not absolute and >8
Frequency minus nocturia	√	√	√	√	Same as above
Interval between micturitions			√		1440 (minutes)/# per day [mean]
Interval between micturitions				√	Minutes between each [median]
Delay (warning) time			√	√	Time (minutes) from urgency to void/leak.
Nocturia	√	√	√	√	Awakened from sleep plus go back. Both counting incontinence episodes and not. Absolute and > "normal"
Nocturia/voids	√	√	√	√	# from going to bed until arising. Both counting incontinence episodes and not. Absolute and > "normal"
Volume/void			√	√	Absolute and increase from placebo. Voluntary void only

Efficacy Measures: OAB

Parameter	Per Day	Per Week	Mean	Median	Explanation
Urgency episodes	√	√	√	√	Both counting incontinence and not
Urgency assessment					Visual analog scale or 3- or 5-point
Pad #	√	√	√	√	Different types a problem
Pad weight	√		√	√	Pad test? o/w how to weigh (before or after changing)
Quality of Life					Which tool? KHQ, I-QOL, etc.
% dry (No UUI episodes)					Need baseline: 3 days? 7 days?
% dry (No incontinence whatever)			√	√	As a % of those with incontinence
% dry days for those with incontinence?			√	√	Same as above
% No urgency					3 days, 7 days?
% urge-free days			√	√	
Overall impression					Visual analog scale or 3- or 5-point scale

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Tolerability Measures: OAB

Parameter	Details
Discontinuations	# (%) - Any reason Why? When ?(persistence)
Dry mouth	# (%) Mild/Moderate/Severe (total and %; % of those with dry mouth) % discontinuing because of it Quantitative? (ie, "spit test" or others)
Constipation (Can also term change in bowel habits but need to assess diarrhea, gas, etc. Should do, scale or parameters needed)	Mild/Moderate/Severe (total and %; % of those with constipation) % discontinuing because of it % starting or increasing laxatives Decrease in # of bowel movements, increase in consistency
Dry eyes	% Mild/Moderate/Severe # / % discontinuing because of it
Headache	% Mild/Moderate/Severe # / % discontinuing because of it How measure? subjective/objective

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Safety Measures: OAB

Parameter	Details	
Blurred vision	% Mild/Moderate/Severe # / % discontinuing because of it	
Photophobia	Same as above	
Mental status	Same as above	How measure? subjective/objective
Somnolence, confusion	Same as above	How measure? subjective/objective
Depression, recall	Same as above	How measure? subjective/objective
Dizziness, light-headedness	Same as above	How measure? subjective/objective
Cardiac	Tachycardia/palpitations Arrhythmias QTc interval	
Drug-drug interactions	Liver metabolism issues Renal excretion issues	

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Bladder Diaries

- Often used in clinical trials and in office practice
- Simple to use
- Compliance varies[1]
- Measures dryness or other symptom improvement
- Do not measure quality-of-life improvement[2]
- Electronic diaries
  - Increased placebo rate

1. Wein AJ, *et al. BJU Int.* 2006;99:360-363.
2. Amundsen CL, et al. *Neurourol Urodyn.* 2007;26:341-349.

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There are 10 separate scales for "measuring" URGENCY listed in the ICI book(INCONTINENCE, 2007)

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Urgency Perception Score (UPS)

1. I am usually not able to hold urine
2. I am usually able to hold urine until I reach the toilet if I go immediately
3. I am usually able to finish what I'm doing before going to the toilet

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Cardozo et al, BJU int, 2005; 95:591-596

Indevus Urgency Severity Scale (IUSS)

0. None – no urgency
1. Mild – awareness of urgency but easily tolerated (can continue your usual activity/tasks)
2. Moderate – enough urgency discomfort that it interferes with or shortens usual activity/tasks
3. Severe – extreme urgency discomfort that abruptly stops all activity/tasks

Nixon et al, J.Urol. 2005; 174: 604-607

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Patient Perception of Intensity of Urgency Scale (PPIUS)

0. No urgency: I felt no need to empty my bladder but did so for other reason

1. Mild urgency: I could postpone voiding as long as necessary without fear of wetting myself
2. Moderate urgency: I could postpone voiding for a short while without fear of wetting myself
3. Severe urgency: I could not postpone voiding but had to rush to the toilet in order not to wet myself
4. Urge incontinence: I leaked before arriving to the toilet

Notte et al, BMC Urology, 2012; 12: 26-34

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How does the PATIENT feel about all of this ?

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Patient Treatment Goals

- Primary goals in treating OAB are
  - Reduced symptom occurrence
  - Increased patient's HRQL
  - Patient satisfaction with treatment
  - Willingness to continue therapy
- Quality-of-life goals influenced by
  - Personal values
  - Beliefs
  - Age
  - Life Experience

1. Abrams P, et al. *Urology*. 2006;68(suppl 2A):17-28.
2. Kelleher C, et al. *BJOG*. 2006;113 (suppl 2):3-13.
3. Kelleher C, et al. *Br J Obstet Gynaecol*. 1997;104:1374-1379.

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Assessment Versus Patient-Reported Outcomes Instruments (PROs)

Symptom Assessment Instrument (OABSS)[1]	Outcomes Instruments Range of concepts[2]
• Daytime urination episodes	• Physical function
• Nighttime urination episodes	• Activities of daily living
• Reason to urinate (convenience, mild, moderate, severe or desperate urge)	• Psychological well-being (coping, self-esteem, adjustment)
• How long one can postpone	• Global judgments of health
• How often does a sudden urge occur but you do not leak	• Social well-being (family, social contacts)
• How often does a sudden urge occur and you do leak	• Employment
• How good is one's bladder control	• Satisfaction with life
	•Satisfaction with care

OABSS=Overactive Bladder Symptom Score

1. Adapted from: Blaivas JG, et al. *J Urol*. 2007;178:543-547.
2. Adapted from: Brubaker L, et al. *Urology*. 2006;68 (suppl 2A):3-8.

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Overactive Bladder Questionnaire (OABq)

- Important details regarding the 33-item OAB-q
  - Self-administered in approximately 10 minutes
  - Recall period is the previous four weeks
  - Each item is rated on a 6-point Likert scale
  - Designed for use among individuals who are 18+ in age.

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Overactive Bladder Satisfaction (OAB-S) Questionnaire

- Comprehensive instrument to assess OAB treatment satisfaction based on independent scales
- Questionnaire components and number of questions:
  - OAB control expectations (10)
  - Impact on daily living with OAB (10)
  - OAB control (10)
  - Fulfillment of OAB medication expectations(1)
  - Interruption of day to day life due to OAB(1)
  - OAB medication tolerability (6 questions)
  - Satisfaction with OAB control (10)
  - Overall satisfaction with OAB medication (1)
  - Willingness to continue OAB medication(1)
  - Improved life with OAB medication(1)

Piault E, et al. *Neurourol Urodyn*. 2008, 27:179-190

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Patient Perception of Bladder Condition (PBC/PPBC)

My bladder condition[1]:

1. **Does not cause me any problems at all**
2. **Causes me some very minor problems**
3. **Causes me some minor problems**
4. **Causes me (some) moderate problems**
5. **Causes me many severe problems**
6. **Causes me severe problems**

PPBC is a single-item, 6-point global scale that asks patients to rate their subjective impression of current bladder problems.[2]

1. Coyne KS, et al. *Eur Urol*. 2006;49:1079-1086.
2. Mamza J N, et al. *Neurourol Urodyn*. 2006;24:315-320.

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Patient Global Impression of Improvement (PGI-I)

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

- Validated for treatment of Stress Urinary Incontinence (SUI)

Yalcin I, Bump. RC Am *J Obstet Gynecol*. 2003;189:98-101.

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REALLY ?

Is it that complicated ?

EGGS for patient centered outcomes

Linda Brubaker
Bob Shull

Int Urogynecol J, 2005; 16: 171-173

EXPECTATIONS

- Specific expectations about symptom relief
  1. Clarified and coached to be realistic
  2. Extent of improvement for specific symptoms
  3. Possible side effects, complications
  4. Time line

May be readjusted along the way(up or down)

GOAL SETTING

- Typically stated in terms of life style events affected by the problem, ie
- sit through a movie or play
- play tennis without leaking
- Typically realistic and personal

GOAL ACHIEVEMENT

- Can be measured using visual analog scales or Likert type measures
- An important primary goal poorly achieved will adversely affect satisfaction
- Only weakly related to traditional outcome measures
- If more than one goal, each rated

SATISFACTION

- The bottom line
- Captures the phenomenon of VALUE
- Was it worth it ?
- Would you do the same thing again ?
- The overall perception of the health care experience; may be influenced by the doctor-patient relationship
- Traditional outcomes(measurements) are still important, but probably moreso to us than to the patient

A REFRACTORY OVERACTIVE BLADDER IS ONE FOR WHICH SATISFACTION HAS NOT BEEN ACHIEVED

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The patient then decides whether to move ahead with second or third line therapy based on the bother and QOL disruption and a realistic description by the practitioner of what to expect in terms of benefits and risks

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Thank you

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