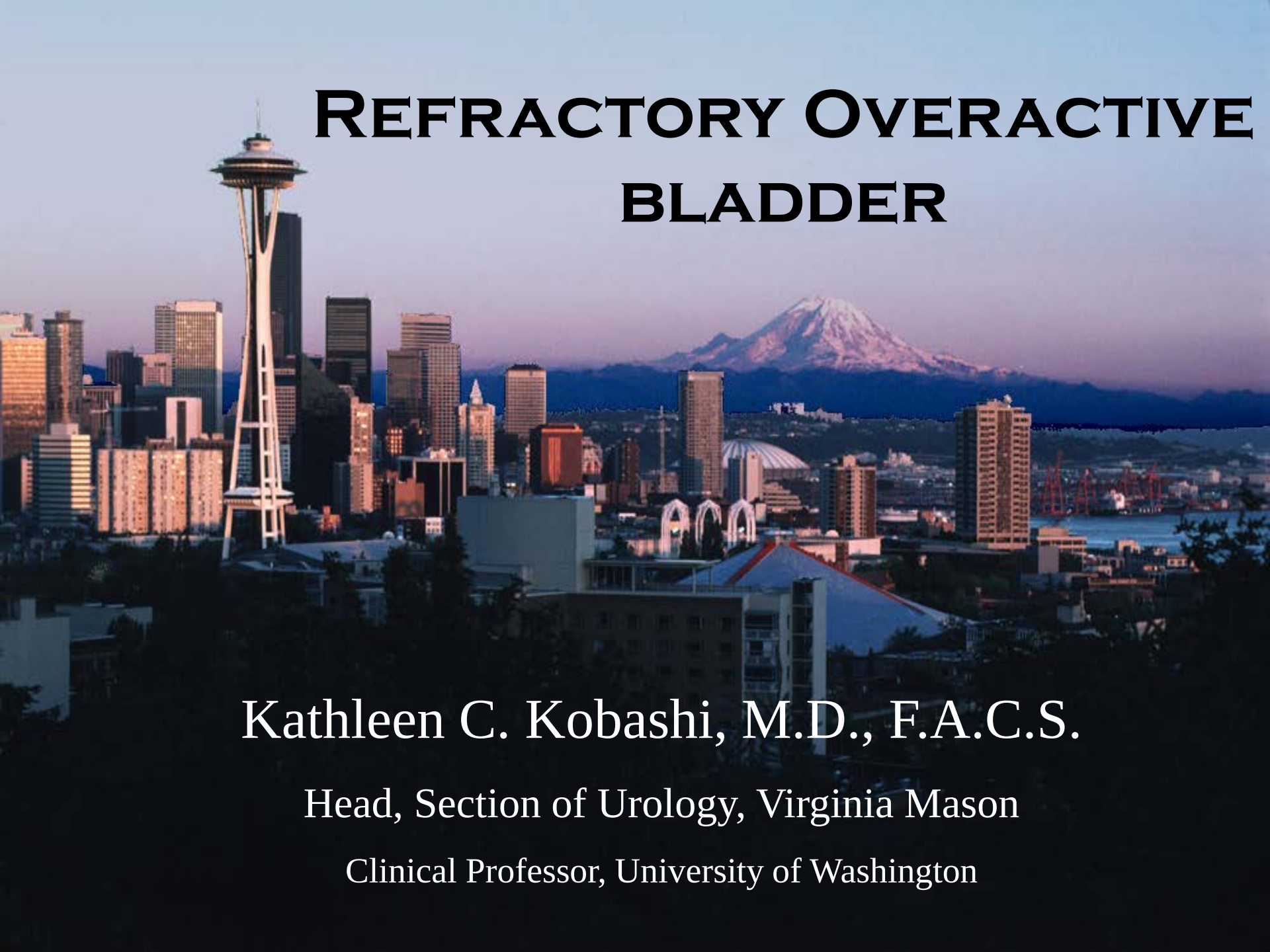


Refractory Overactive bladder

Kathleen C. Kobashi, M.D., F.A.C.S.

Head, Section of Urology, Virginia Mason

Clinical Professor, University of Washington

Disclosures

- Advisory Board and/or Speaker
  - Allergan
  - Medtronic
  - Astellas
- AUA Guidelines
  - Urodynamics, Member 2011-2014
  - Stress incontinence, Chair, 2015-current

All honoraria go to Virginia Mason

Prevalence

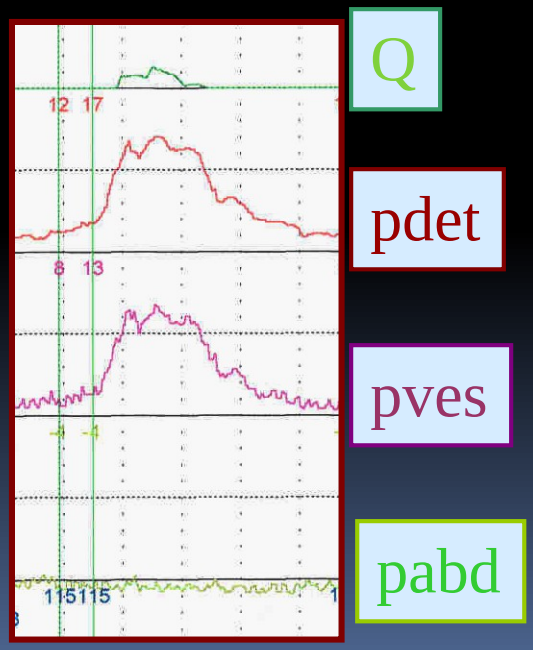
- Up to 100 million worldwid
- 16.6% of adult population in
  - OAB dry: 13.6% men, 7.6% wom
  - OAB wet: 2.4% men, 9.3% women
- <40% seek treatment

Wein AJ. *Urology.* 2002;60(Suppl 5A):7-12.
Merkelj I. *Southern Med J.* 2001;94:952-957.
Johnson TM. *J Amer Geriatr Soc.* 2000;48:894-902.
Stewart WF, et al: *World J Urol* 2003;20:327-36.

Terminology

- Overactive bladder (OAB)
  - A symptomatic diagnosis defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia
- Detrusor overactivity (DO)

  A urodynamic observation characterized by involuntary detrusor contractions (IDC) during the filling phase



Abrams P, et al. *Neurourol Urodyn.* 2002;21:167-178.
Sahai A, et al. *Expert Opin Pharmacother.* 2006;7(5):509-527.

AUA/SUFU OAB Guidelines

- Based on 151 articles
- Based on evidence strength
- AUA nomenclature linked to LOE
- Statements divided into three tiers
  - First line treatments
  - Second line treatments
  - Third line treatments

Gormley EA, et al.: J Urol 2012;188(6 Suppl):2455-63.
Gormley EA, et al.: J Urol 2015;193(5):1572-80.

OAB Guidelines Statements
Treatment

- First line
  - Behavioral therapies (Standard)
  - Above may be combined with pharmacotherapy (Recommendation)

Gormley EA, et al.: J Urol 2012;188(6 Suppl):2455-63.
Gormley EA, et al.: J Urol 2015;193(5):1572-80.

OAB Guidelines Statements
Treatment

- Second line
  - Oral antimuscarinics (Standard)
  - B-3 agonist (Standard)
  - Extended release should be preferentially offered (Recommendation)
  - Transdermal oxybutynin (Recommendation)
  - Change dose or agent as necessary (Clinical principle)

Gormley EA, et al.: J Urol 2012;188(6 Suppl):2455-63.
Gormley EA, et al.: J Urol 2015;193(5):1572-80.

OAB Guidelines Statements
Treatment

- Third line
  - Sacral neuromodulation (Recommendation)
  - Percutaneous Tibial Nerve Stimulation (PTNS) (Recommendation)
  - OnabotulinumtoxinA (Standard option)

Gormley EA, et al.: J Urol 2012;188(6 Suppl):2455-63.
Gormley EA, et al.: J Urol 2015;193(5):1572-80.

OAB Guidelines Statements
Treatment

- Additional treatments
  - Indwelling catheters as last resort (Expert opinion)
  - Augmentation cystoplasty/diversion (Expert opinion)
    - Severe, refractory complicated cases only
- Follow up recommended to assess compliance, efficacy, side effects, to offer alternatives
  - No data available

Gormley EA, et al.: J Urol 2012;188(6 Suppl):2455-63.
Gormley EA, et al.: J Urol 2015;193(5):1572-80.

Treatment Options for Urinary Incontinence

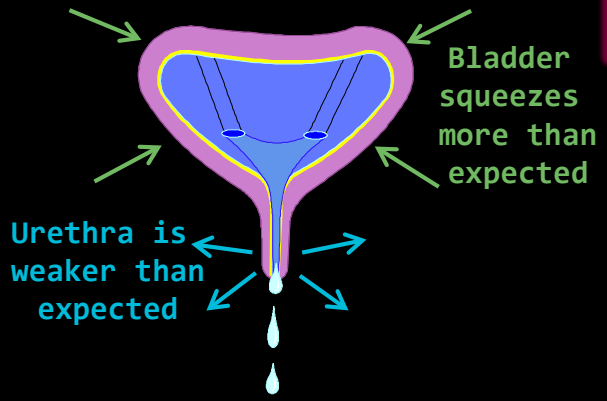
Stress Incontinence
Leakage with laughing, coughing, physical activity

Non-Surgical
- Pelvic floor muscle training
- Pelvic floor physical therapy
- Incontinence pessary
- Urethral inserts

Surgical
- Urethral bulking
- Sling
  - •Autologous fascia (your own tissue)
  - •Mesh (retropubic or transobturator approach)
- Retropubic suspension (Burch)

Clinical Trials

Mixed Incontinence



Reduce Risk Factors
- Patient education
- Weight loss
- Stopping smoking

Overactive Bladder
Urinary frequency, urgency, and/or incontinence associated with urgency

1st line: Behavioral Therapy
- Bladder control strategies & bladder training
- Fluid management & avoidance of bladder irritants
- Pelvic floor physical therapy

2nd line: Non-Surgical
- Overactive bladder medications
- Vaginal estrogen

3rd line: Minor Procedure or Surgical
- Botox® injections into the bladder
- Peripheral tibial nerve stimulation
- Sacral neuromodulation (Interstim®)

Clinical Trials

*If you are not improving and still experiencing bothersome symptoms, please call your physician and schedule a follow up appointment

Options

- “Conservative measures”
- Pharmacotherapy
- Neuromodulation
  - Electrical or biological
- Reconstruction
  - Augmentation cystoplasty
  - Urinary diversion
  - Sling-lysis/urethrolysis

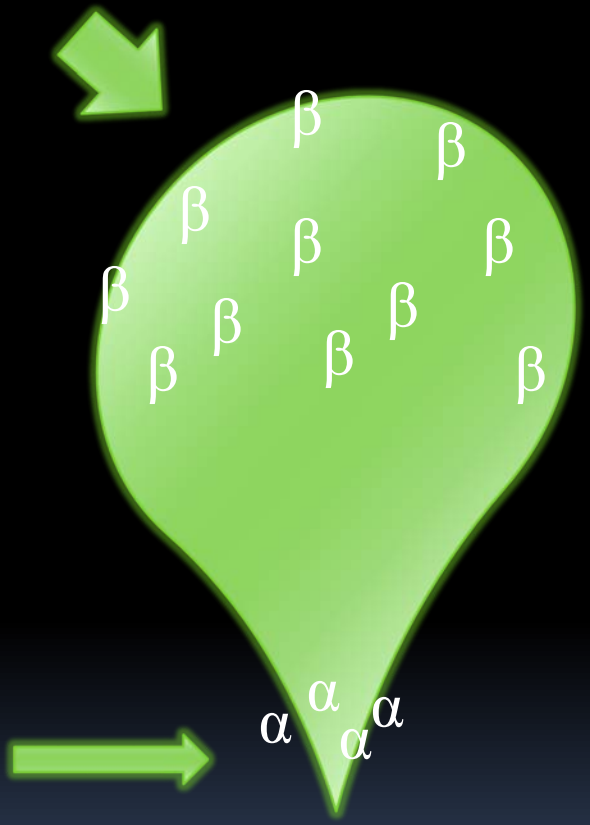
Conservative measures

- Dietary modification
- Bladder drills and retraining
- Pharmacotherapy
  - Antimuscarinics
  - Beta-3 adrenergics
  - Combination therapy
- Local hormone replacement therapy

WHEN DOES IT BECOME “REFRACTORY”?

Beta-3 adrenergic agonist MOA

- Increase bladder capacity
- *Without* effect on voiding parameters
  - Qmax
  - PdetQmax
  - Residual volume



Nitti VM, et al.: J Urol 2013:190;1320-7.

Symphony: Combination therapy

- Monotherapy
  - Mirabegron, solifenacin, placebo
- 6 combinations mirabegron + solifenacin
  - 25 or 50mg AND 2.5, 5, or 10mg
- Combo therapy efficacy greater than solifenacin 5mg
  - Mean volume voided/micturition, frequency/24 hours, urgency
- All combos tolerated well

Abrams P, et al.: Eur Urol 2015;67:577-88

MILAI: Combination therapy

- Multicentre, open-label phase IV study
- Patients on solifenacin (2.5 or 5mg)
- Add mirabegron 25mg x16 weeks
- Measures
  - Safety
  - Efficacy

Yamaguchi O, et al.: BJUI 2015;116:612-22.

Outcomes

- Safety
  - Adverse events
  - Labs
  - Vital signs
  - Electrocardiogram
  - QT interval
  - Post void residual
- Efficacy
  - OAB-SS, OAB-q-SF
  - Micturitions
  - Urgency
  - Urgency incontinence
  - Mean voided volume
  - Nocturia

Yamaguchi O, et al.: BJUI 2015;116:612-22.

Results/Conclusions

- Add on therapy well-tolerated
- AE 23% - mostly mild-moderate
  - Constipation most common
  - No retention
  - QT, heart rate, blood pressure, PVR changes NOT clinically significant
- Significant improvements all groups

Yamaguchi O, et al.: BJUI 2015;116:612-22.

But what if meds don't work?

Neurourology and Urodynamics 29:658–661 (2010)

CONTROVERSIAL TOPIC

What Treatment Should We Use If Drugs Fail for OAB; and, What Really Works After Drugs?

J.L.H.R. Bosch,[1]* C. Kelleher,[2] P.E.V. van Kerrebroeck,[3] and B. Schurch[4]
[1]Department of Urology, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Department of Obstetrics and Gynaecology, Guys and St Thomas' NHS Foundation Trust, London, UK
[3]Department of Urology, Maastricht University Medical Centre, Maastricht, the Netherlands
[4]Department of Neuro-Urology, University Hospital Balgrist, Zürich, Switzerland

Alternative Options

- “Conservative measures”
- Pharmacotherapy
- Neuromodulation
  - Electrical or biological
- Reconstruction
  - Augmentation cystoplasty
  - Urinary diversion
  - Sling-lysis/urethrolysis

PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS)

Percutaneous tibial nerve stimulation

- 34-gauge needle
- 3-5 cm cephalad to medial malleolus
- Placement confirmed
  - Great toe plantar flexion
  - Sensation on plantar aspect of foot
- 6-12 weekly treatments
- Maintenance (?)

PTNS: SUmiT Trial

- ***S***tudy of ***U***rgent PC vs Sham Effectiveness of ***T***reatment of Overactive Bladder Symptoms
- Improvement in global response assessment (GRA)
  - PTNS vs sham: 58.3 vs 21.9%
- Response at 12 weeks, not at 6 weeks
- Improved QOL, frequency, urgency, UUI, nocturia

Peters KM, et al.: J Urol 2010;183(4):1438-43.

OrBIT trial

- ***O***veractive ***B***ladder ***I***nnovative ***T***herapy
- PTNS versus tolterodine[1]
- Improvement per GRA:
  - 79.5% vs 54.8%
- PTNS vs solifenacin with cross over[2]
  - Bladder specific assessment
  - Both groups showed improvement

[1]Peters KM, et al.: J Urol 2009;182(3):1055-61.
[2]Veccioli-Scaldazza C, et al.: Gyneocol Obstet Invest 2013;75(4):230-4.

STEP Study

- Carryover effect of PTNS
- Patients who had effect at 12 weeks
- 14 week tapering
  - 2 treatments over 14 days
  - 2 treatments over 21 days
  - q 28 days

Peters KM, et al.: J Urol;189(6):2194-2201.

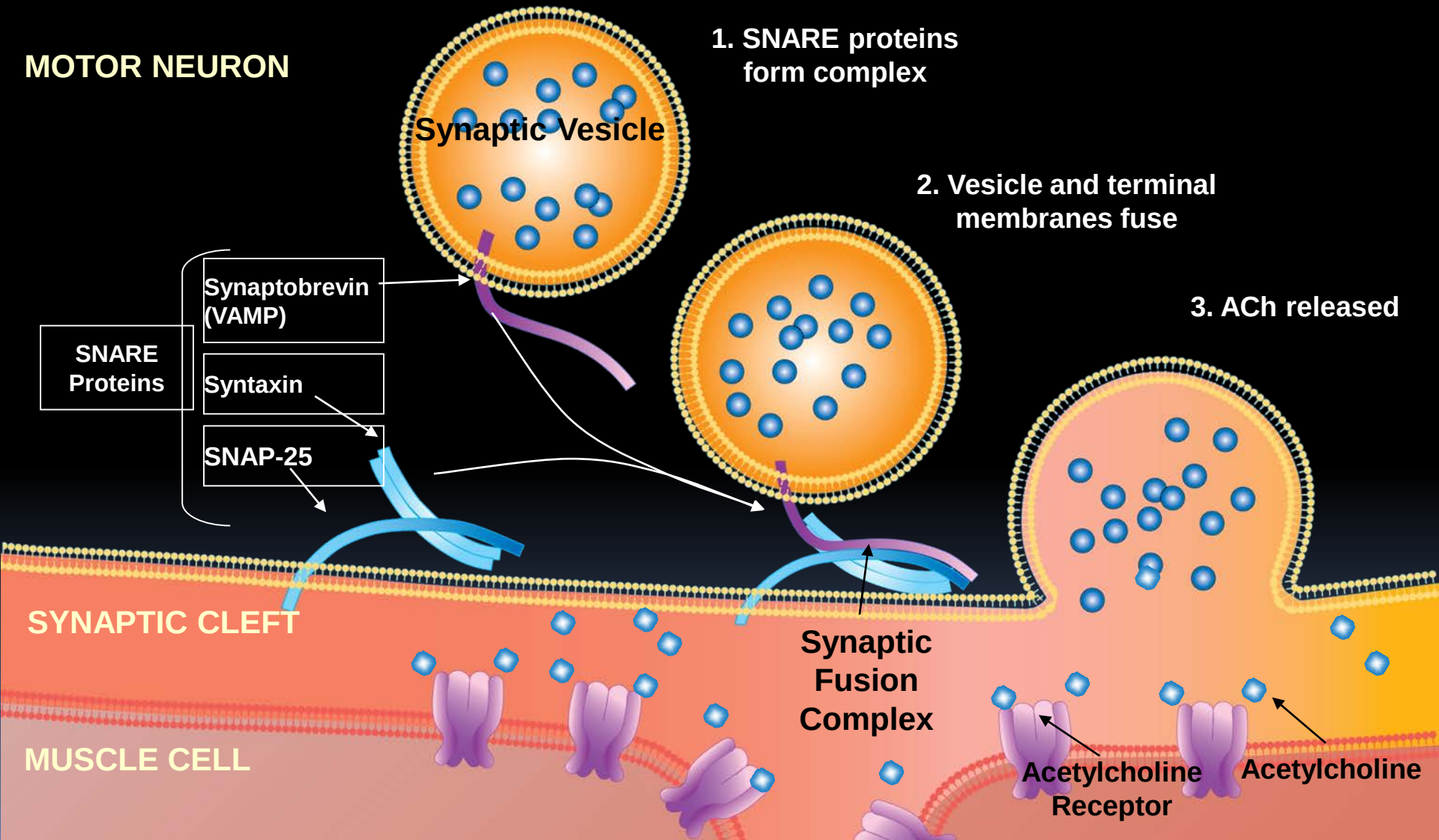
STEP Study results

- At 36 months 77% had sustained moderate/marked improvement[1]
  - All domains tested
- Over 36 months, average 1.1 treatments/month
- OrBIT phase 2 similar carryover noted[2]

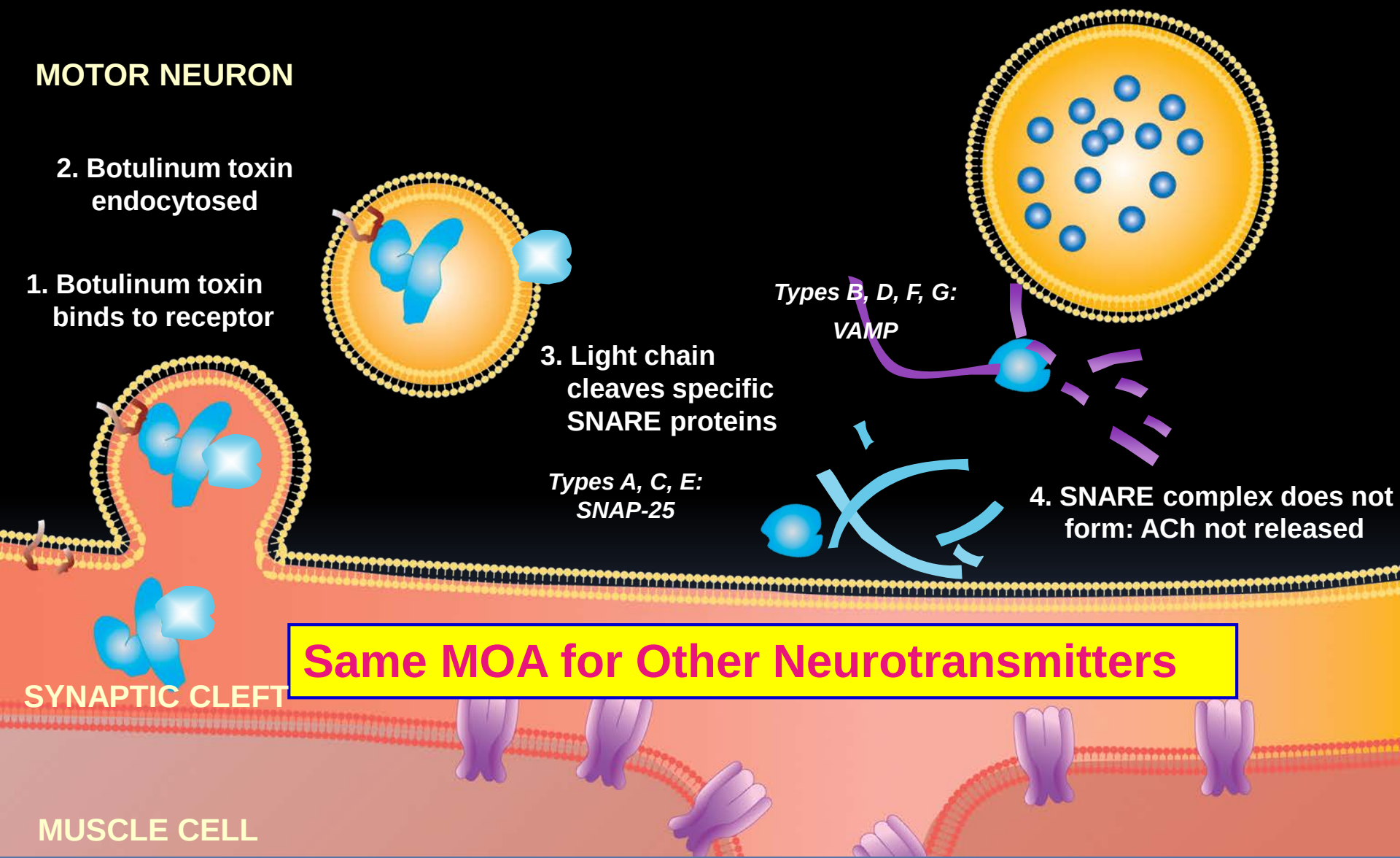
[1]Peters KM, et al.: J Urol;189(6):2194-2201.
[2]MacDiarmad SA, et al.: J Urol 2010;183(1):234-40.

ONABOTULINUMTOXIN-A

Normal ACh release



Botox inhibits Ach release



Same MOA for Other Neurotransmitters

A recent meta-analysis on BoNTA

- n=1320 in 8 publications
  - 6 RCTs
- Incontinence episodes/day: -2.77 vs -1.01
- Voids per day: -1.61 vs -0.87
- MCC 91.39 vs 32.32
- Incontinence-free: 29.20% vs 7.95%

Cui Y, et al., Neurourol UDS 2014

Jury still out…

- Dose
- Injection technique
  - Location
  - Depth
  - Number of injections
- Retreatment interval
- Long term efficacy and safety

Safety

- Systemic effects – unlikely for bladder
- Urinary retention
  - 11-40% depending on study
  - 9-fold higher risk than placebo in meta-analyses
  - 2015 AUA study showed 30%
    - Again definition of AUR was unclear

Anger J, et al. 2009, Dmochowski, et al. 2010, Brubaker, et al. 2008
Milhouse and Siegel, AUA 2015

Challenges in literature

- Lack of uniformity in:
  - Definitions
    - Success
    - Retention
  - Follow up
  - Management
    - Recurrent symptoms
    - Retention

Repeat injections OK?

- 3-year extension study
- Multiple injections on prn basis
- Assessments
  - Mean change in UI/day
  - Median time to request Rx
  - AEs

Nitti et al., AUA 2015

Repeat injections OK?

- n=543, 51% completed study
- Discontinuation
  - AEs: 5.3%
  - Lack of efficacy: 2.8%
- Mean baseline UI/day similar
- Mean reduction 2.9-4.5

Nitti et al., AUA 2015

Repeat injections OK?

- Median time to request retreatment
  - ≤6 months: 34.2%
  - 6-12 months: 37.2%
  - >12 months: 28.5%
- Median efficacy 7.6 months

Nitti et al., AUA 2015

Key considerations

- Safety
- Efficacy
- Ease of performance
- Duration of response
- Sequela
- Cost

ABC

- ***A***nticholinergic vs ***B***otox™ ***c***omparison in women with urgency incontinence
- n=242 randomized to two arms
  - Botox™ and oral placebo
  - Saline and trospium or solifenacin

Visco AG, et al.,: Contemp Clin Trials 2012;33(1):184-96.
Visco AG, et al.,:NEJM 2012;367(19):1803.

“ABC” trial

Parameter	Anticholinergic	OnabotulinumtoxinA	p
UI episodes per day	-3.4	-3.3	0.81
Complete resolution of UI	13%	27%	0.003
Dry mouth	46%	31%	0.02
Catheter use	0%	5%	0.01
UTIs	13%	33%	<0.001

Visco AG, et al, PFDN: NEJM 2012;367(19):1803-13.

ROSETTA

- ***R***efractory ***o***veractive bladder: ***S***acron***e***uromodulation vs Bo***t***ulinum ***t***oxin ***A***ssessment
- 380-patient goal met last year
- Initial reports anticipated

Pelvic floor disorders network (PFDN)

SACRAL NEUROMODULATION

SNS vs standard medical therapy

- Inclusion criteria
  - ≥2 urgency leaks/72 hours OR
  - ≥8 voids/day
  - Failed at least one medication
  - At least one medication not tried
- n= 147 randomized, 6 month f/u
  - 70 SNM
  - 77 SMT

Siegel S, et al.: Neurourol UDS 2015;34:224-30.

SNS vs SMT

	SNS	SMT	p
Success ITT As treated	61% 76%	42% 49%	=0.02 =0.002
Improved urinary symptoms interference	86%	44%	<0.001
Complete continence	39%	21%	
Adverse events	30.5	27.3	-0.06

Siegel S, et al.: Neurourol UDS 2015;34:224-30.

SNS: 12 month follow up

- n=341, 272 to implant
- 255 with 12 month follow up
- 220 with baseline *and* 12 month diary
- Baseline
  - UUI/day: 3.1 +/-2.7
  - Frequency: 12.6 +/-4.5

Noblett K, et al.: Neurourol UDS 2014; SOI 10.1002/nau.

SNS: 12 month results

- Success: 85% at 12 months
- UUI/day ↓ 2.2 +/-2.7
- Frequency ↓ 5.1 +/-4.1
- All parameters of ICIQ-OABqol significantly improved ($p<0.0001$)
- 80% had improvement in urinary symptom interference

Noblett K, et al.: Neurourol UDS 2014; SOI 10.1002/nau.

SNS: adverse events

- 16% (56/340) during test
  - 3 serious: Site infection, skin infection, respiratory arrest intra op
- 30% (82/272) post-implant
  - 1 serious: Implant site erosion

Noblett K, et al.: Neurourol UDS 2014; SOI 10.1002/nau.

SNS: Device-specific AEs

	0-3 m #events (#pts)	3-6m #events (#pts)	6-12m #events (#pts)	Events	# pts % (n=272)
Undesireable change in stimulation	20(18)	10(10)	6(6)	36	32(12)
Implant site pain	11(9)	8(8)	7(4)	26	20(7)
Implant site infection	8(7)	1(1)	3(3)	12	9(3)

Siegel S, et al.: Neurourol UDS 2015;34:224-30.

Other tidbits…

- Sexual function improves
- Quality of life improves for FI
- Psychosocial outlook
  - Depression improves
  - Optimism is not a predictor of success
- Long-term safety in Medicare beneficiaries

Banakhar, 2014
Chungtai, 2014
Levin 2014

SNS success rates very good

- Pooled results from multiple publications[1]
- n=234 women
- 45% “cure” at minimum 6 months
- 46% maintained continence at 3 years
- 54% maintained self-reported improvement at 5 years
- Another pooled report: 56-69% at 2-3 years[2]

[1]Siddiqui NY, et al.: J Urol 2009;186:2799.
[2]Chartier-Kastler, et al.: BJU Int 2007;101:417.

Surgical revision low

- Rate: 3-16%
- Explantation
  - 6% due to lack of efficacy
  - 5-11% due to infection

Siddiqui NY, et al.: J Urol 2009;186:2799.

And, though we can't advocate for it…

- MRI may be feasible under controlled conditions
- n=9 underwent 15 MRIs
  - Both 0.6 and 1.5 Tesla machines used
  - IPGs off in all patients
  - IPG magnetic switch turned off in 8
- IPGs functioned in all 8 post MRI
- No complications
- Patients perceived no change

Chermansky CJ, et al.: Neurourol Urodyn 2011;30(8):1586-8.

Overall…

- SNS has a good track record
- Easy, “test-drive” available
- SNS durability more stable than other Rxs
- SNS can also affect bowel and sexual function
- Long-term costs may be lower for SNS

From a practical standpoint...

	"Pros"	"Cons"
SNS	Battery life 5-7 years No retention Global effects on pelvic floor	Implanted device Potential complications 2-staged surgery No MRIs Not for neurogenic bladder
BTX	Nothing implanted Local anesthesia in office Well-tolerated	Risk of retention Risk of UTI Durability of response

Cumulative 3-year costs

Treatment	Cost (US $)
PTNS	7,565
OnabotulinumtoxinA	11,748
Interstim®	24,681
Vaginal POP repair	6,353

Martinson et al.: J Urol 2013
Medicare, CMS

Cost effectiveness

- SNS more expensive ($15,743 vs. $4,392) and more effective (1.73 vs. 1.63 QALYs) than BoNTA
  - SNS was more effective
  - BTX was more cost-effective
- Cost per effectiveness (Incremental Cost Effectiveness Ratio = ICER) may change with longer follow up
  - (At 4 years, SNS becomes more cost effective)

Siddiqui NY et al, Neurourol Urodyn 2010; 29 Suppl 1: S18

Treatment Options

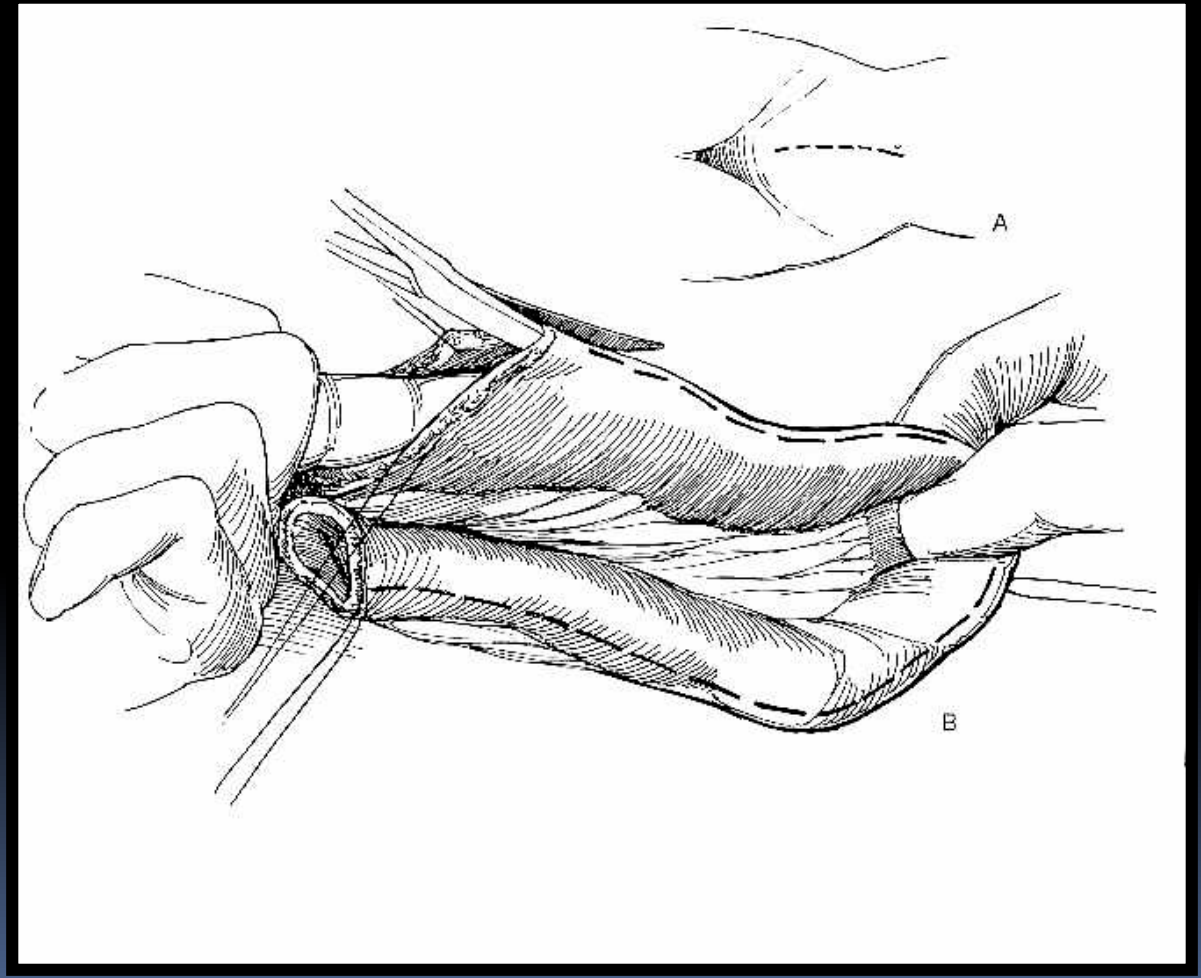
- “Conservative measures”
- Pharmacotherapy
- Neuromodulation
  - Electrical or biological
- Reconstruction
  - Augmentation cystoplasty
  - Urinary diversion
  - Sling-lysis/urethrolysis

The Last Resort…

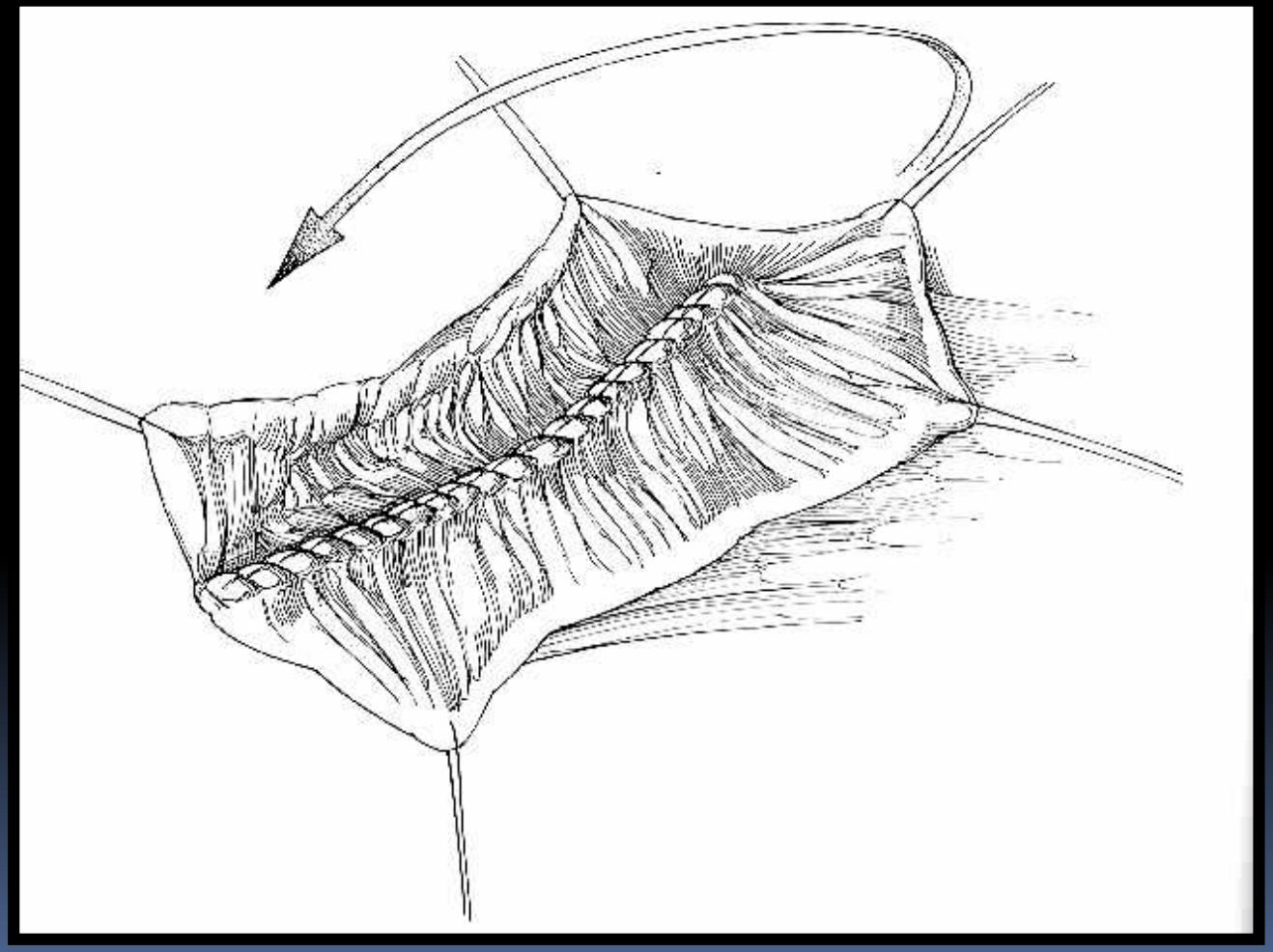
ENLARGE THE BLADDER!

A big operation, but…it works!

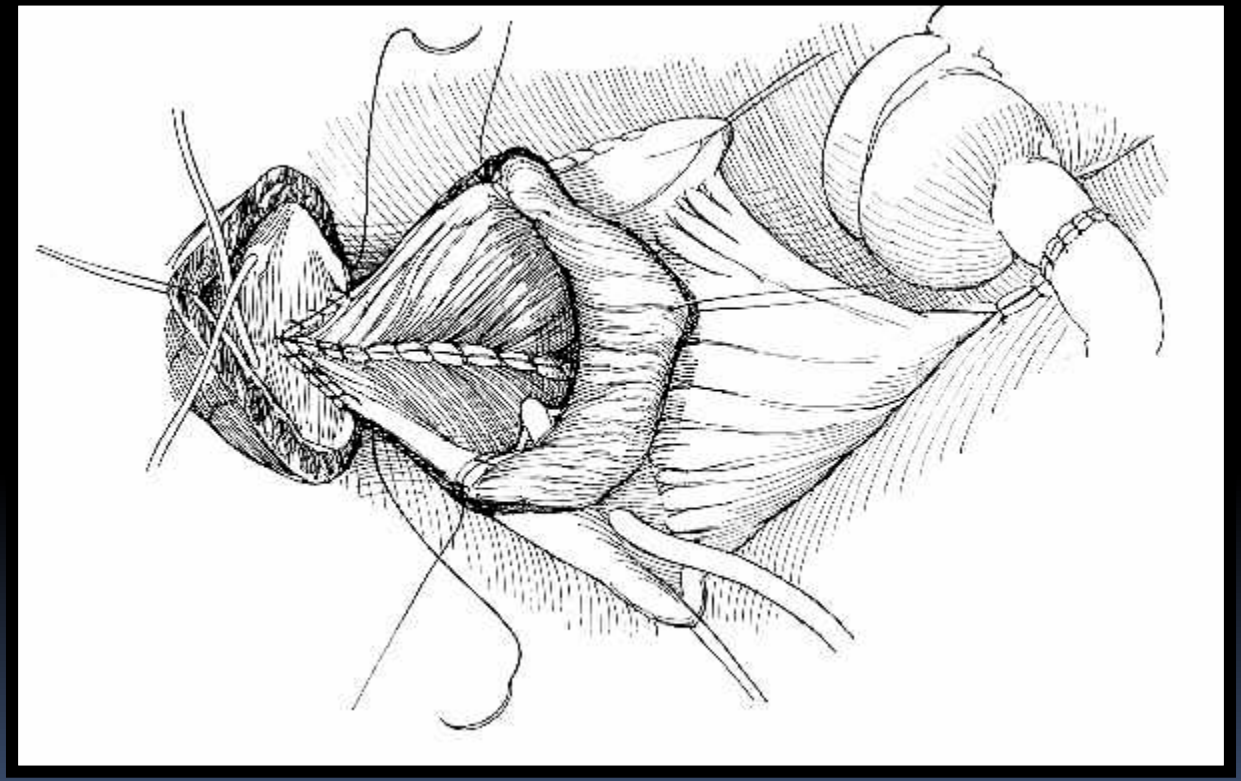
Open a piece of bowel



Flatten it out



Sew it to the bladder…



Augmentation Cystoplasty

- Bowel segment to enlarge bladder
- Lowers intravesical pressure
- Increases capacity
- >80% must catheterize

Take Home Messages

- “OAB” multifactorial
- Conservative measures first
- Stepwise progression
- Successful options available

(Patients must be made aware)