Botulinum Toxin Injection for OAB: Indications & Technique

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General Secretary of International Continence
President of Pan Arab Continence Society

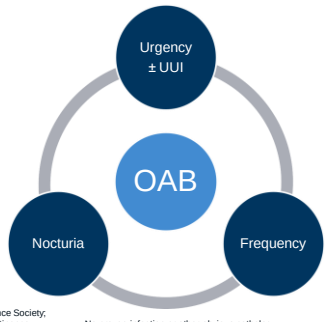
Classification of LUTS

Storage	Voiding	Post-micturition
• Urgency • Urinary incontinence • Increased day-time frequency • Nocturia	• Slow stream •Splitting/spraying • Intermittency • Hesitancy • Straining • Terminal dribbling	• Post-micturition dribbling • Feeling of incomplete emptying

Abrams P et al. *Neurourol Urodyn* 2002;21:167–78

ICS definition of OAB

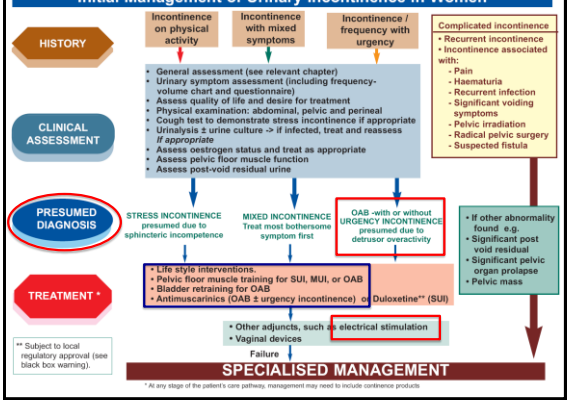
Abrams P et al. Neurourol Urodyn 2002;21:167-78



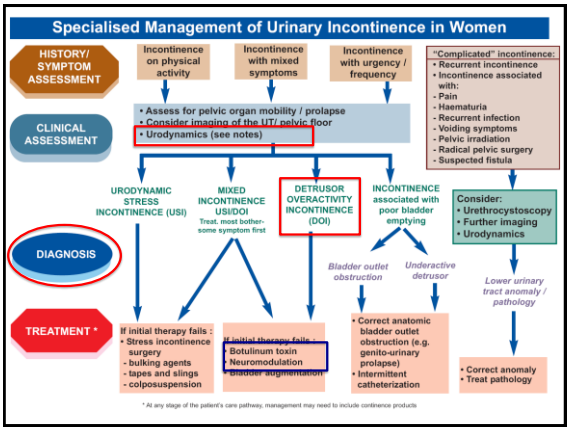
ICS: International Continence Society;
UUI: urgency urinary incontinence

No proven infection or other obvious pathology

Initial Management of Urinary Incontinence in Women



Specialised Management of Urinary Incontinence in Women

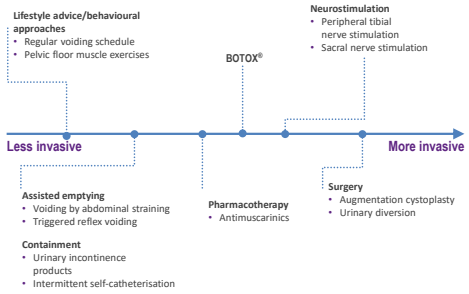


European guidelines for the treatment of NBD

- International Consultation on Incontinence (ICI) 2013[1]
- European Association of Urology (EAU) 2013[2]

NBD, neurogenic bladder dysfunction
1. Abrams P, et al. eds. From the 5th IC. Health Publication Ltd; 2013.
2. Pannek J. European Association of Urology. Guidelines on neurogenic lower urinary tract dysfunction. 2011. Available from http://www.uroweb.org/gls/pdf/17_Neurogenic%20LUTS.pdf. Last accessed June 2011..

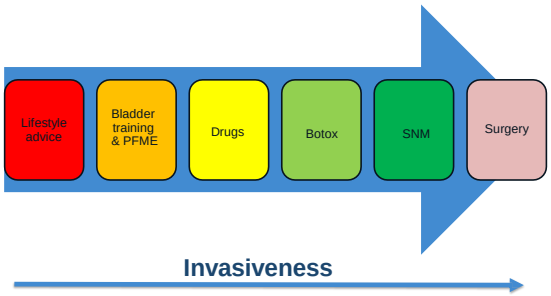
Spectrum of Treatments for NBD

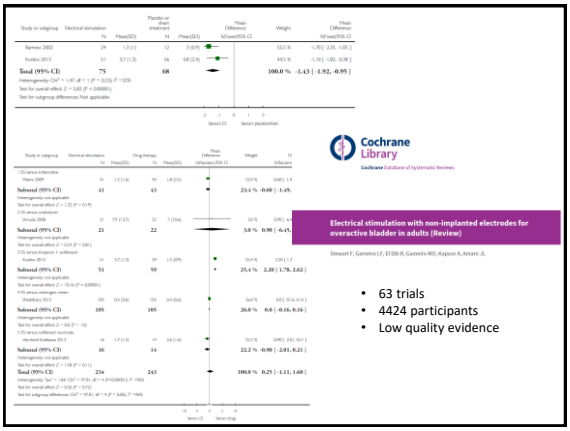


NBD, neurogenic bladder dysfunction

Panmek J. European Association of Urology. Guidelines on neurogenic lower urinary tract dysfunction. 2011. Available from: http://www.uroweb.org/gls/pdf/17_Neurogenic%20LUTS.pdf. Last accessed June 2011.

Spectrum of OAB treatment





Cochrane Library

Cochrane Database of Systematic Reviews

Electrical stimulation with non-implanted electrodes for overactive bladder in adults (Review)

Stewart F, Gameiro LF, El Dib R, Gameiro MO, Kapoor A, Amaro JL

- 63 trials
- 4424 participants
- Low quality evidence

Table 1. Pharmacologic Agents for Treatment of Urge Urinary Incontinence

Drug (Brand)	Usual Dosage and Route	Dosage Adjustment	Additional Comments
Anticholinergics/Antimuscarinics			
Oxybutynin IR (Ditropan)	5 mg po 2-4 times daily. Elderly patients: 2.5 mg	NA	NA
Oxybutynin XL (Ditropan XL)	5-10 mg po once daily	NA	Swallow whole. Increase in weekly 5-mg increments. Max 30 mg/day
Oxybutynin TDS (Rx, Oxytrol, OTC, Oxytrol for Women)	3.9 mg/day patch applied topically twice weekly	NA	Apply every 3-4 days. Rotate sites. Available OTC
Oxybutynin gel 10% (Gelnique)	One sachet (100 mg/g) applied topically once daily	NA	Rotate application sites daily
Tolterodine IR (Detrol)	1-2 mg po twice daily	1 mg twice daily if patient taking strong CYP3A4 inhibitor or has renal/hepatic impairment	NA
Tolterodine LA (Detrol LA)	2-4 mg po once daily	2 mg once daily if patient taking strong CYP3A4 inhibitor or has renal/hepatic impairment	Swallow whole. Avoid in patients with CrCl <10 mL/min
Trospium IR (Sanctura)	20 mg po twice daily. Patients ≥75 y: 20 mg po once daily	Reduce to 20 mg daily in CrCl <30 mL/min	Take 1 h before meals or on empty stomach. Patients aged ≥75 y: Take at bedtime
Trospium ER (Sanctura XR)	60 mg po once daily	NA	Take 1 h before meals or on empty stomach. Swallow whole. Avoid in patients with CrCl <30 mL/min
Solifenacin (Vesicare)	5-10 mg po once daily. Initial dosage: 5 mg po once daily	5 mg once daily if patient taking strong CYP3A4 inhibitor or has CrCl <30 mL/min or moderate hepatic impairment	Swallow whole. Avoid in severe hepatic impairment
Darifenacin ER (Enablex)	7.5-15 mg po once daily. Initial dosage: 7.5 mg po once daily	7.5 mg once daily if patient taking strong CYP3A4 inhibitor or has moderate hepatic impairment	Titrate dose after at least 2 wk. Swallow whole. Avoid in severe hepatic impairment
Fesoterodine ER (Toviaz)	4-8 mg po once daily. Initial dosage: 4 mg po once daily	4 mg once daily if patient taking strong CYP3A4 inhibitor or has CrCl <30 mL/min or moderate hepatic impairment	Prodrug that is metabolized to 5-hydroxymethyl tolterodine. Swallow whole
Beta-3 Adrenergic Agonist			
Mirabegron ER (Myrbetriq)	25-50 mg po once daily. Initial dosage: 25 mg po once daily	25 mg once daily if patient taking strong CYP2D6 substrate or has CrCl 15-29 mL/min or moderate hepatic impairment	Swallow whole. Avoid in CrCl <15 mL/min or severe hepatic impairment

CrCl, creatinine clearance; ER, extended-release; IR, immediate-release; LA, long-acting; max, maximum; min, minute; NA, not applicable; TDS, transdermal system; XL, extended-release; XR, extended-release.
Source: References 1, 11-17.

Anticholinergics vs Non-Drug Therapies

- 23 trials; 3685 participants
- More symptomatic improvement when
  - Anticholinergics were compared with bladder training alone

Cochrane Library

Cochrane Database of Systematic Reviews

Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults (Review)

Rai BP, Cody JD, Alhasso A, Stewart L

Anticholinergics vs Other Drug Therapies

- Only a few, small-scale randomised trials found
- Many drugs are no longer used clinically e.g. Flavoxate
- Inadequate evidence to assess whether or not available alternative drugs are better or worse than anticholinergics

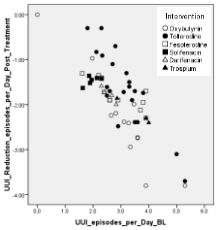
Cochrane Library

Cochrane Database of Systematic Reviews

Anticholinergic drugs versus other medications for overactive bladder syndrome in adults (Review)

Roxburgh C, Cook J, Dublin N

Anticholinergics vs Anticholinergics



- No compelling evidence for differential efficacy across medications
- ER better than IR in terms of SE profile
- Solifenacin better than Tolterodine IR
- Fesoterodine better than Toleterodine ER
- Patients with more severe symptoms, on average, experienced greater symptom reductions

AUA/SUFU Guideline

DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFU GUIDELINE

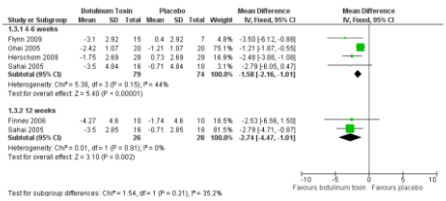
Cochrane Library

Which anticholinergic drug for overactive bladder symptoms in adults (Review)

Botox vs Placebo

Cochrane Library

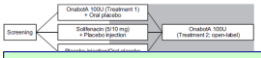
Botulinum toxin injections for adults with overactive bladder syndrome (Review)



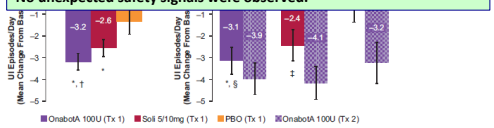
Botox vs Solifenacin

The Efficacy and Safety of OnabotulinumtoxinA or Solifenacin Compared with Placebo in Solifenacin-Naive Patients with Refractory Overactive Bladder: Results from a Multicenter, Randomized, Double-Blind, Phase 3b Trial

Sender Herschorn , Alfred Kohan , Philip Aliotta , Kurt McCammon , Rajagopalan Sriram , Steven Abrams , Wayne Lam , Karel Everaert



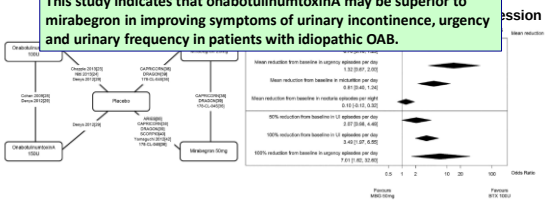
The efficacy of onabotulinumtoxinA and solifenacin was significantly higher than that of placebo.
However, onabotulinumtoxinA showed significantly greater decreases in urinary incontinence than solifenacin with a third of patients achieving a 100% incontinence reduction.
No unexpected safety signals were observed.



Botox vs Mirabegron

Patients improved, on average, by 1.32 (CrI 0.67, 2.00) and 1.49 (CrI 0.80, 2.16) episodes more per day on onabotulinum toxin A 100 U compared with mirabegron 50 and 25 mg.

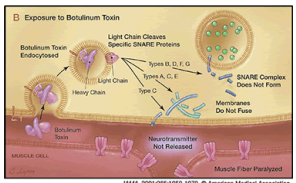
This study indicates that onabotulinumtoxinA may be superior to mirabegron in improving symptoms of urinary incontinence, urgency and urinary frequency in patients with idiopathic OAB.



Freemantle N, Ginsberg DA, McCool R, et al. Comparative assessment of Onabotulinum toxin A and mirabegron for overactive bladder: an indirect treatment comparison. BMJ Open 2016;6:e009122. doi:10.1136/bmjopen-2015- 009122

Botulinum Toxin and Mechanism of Action

- BoNT exerts its activity by prohibiting the release of neurotransmitters from autonomic and somatic nerve endings.
- Translocation of the toxin is correlated with synaptic activity and, thus, the most active nerves are preferentially affected.

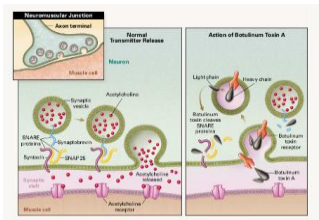


Montecucco et al, 2004
Chapple 7 Patel, 2006
Dykstra et al, 1988

Mechanism of action

- BoNT-A cleaves synaptosomal-associated protein (SNAP-25), which is necessary for fusion of synaptic vesicles at the cellular membrane, thus specifically **preventing the SNARE-mediated release of neurotransmitters** into the synaptic cleft.

Montecucco et al, 2004
Chapple 7 Patel, 2006
Dykstra et al, 1988



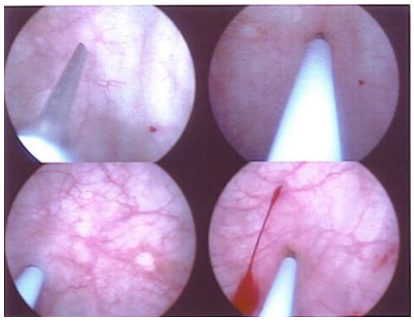
Mechanism of action

- BoNT does not cause neuronal death, and the effect is temporary as the toxin is inactivated and degraded with time.
- The commercially available BoNT-A preparations are
  - **Botox**® (onabotulinumtoxin A, Allergan Pharmaceuticals, Parsippany-Troy Hills, NJ, USA)
  - **Dysport**® (abobotulinumtoxinA, Ipson Biopharm, Paris, France),
  - **Xeomin**®(IncobotulinumtoxinA, Merz Pharmaceuticals, Frankfurt am Main, Germany). Mangera, 2011

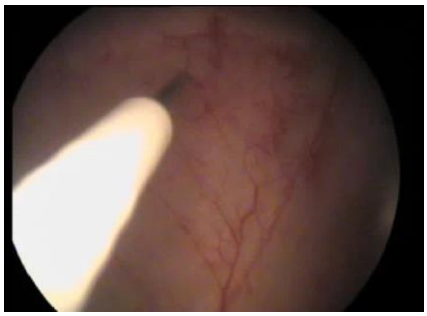
Administration and Injection Technique

- BoNT-A is administered via intradetrusor injection under **local**, **regional** or **general anesthesia** using a **rigid or flexible cystoscope**.
- While **no protocol** regarding the location and number of injections is universally accepted.

Injecting Botulinum Toxin



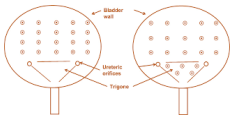
BOTOX INJECTION



Administration and Injection Technique

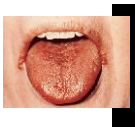
- Food and Drug Administration approved indications, 100 U onaBoNT-A diluted in 10 mL preservative-free saline or 200 U onaBoNT-A diluted in 20 mL preservative-free saline are then injected 1 mL /site separated by a distance of 1 to 1.5 cm.
- Injections to the trigone have traditionally been spared out of concern for producing vesicoureteral reflux (VUR).
- **Despite this, several studies have shown trigonal injections to be safe and effective without evidence of VUR**.

Kuo, 2007 – Karsenty et al, 2007



Safety and Adverse Effects

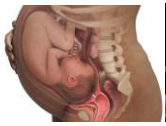
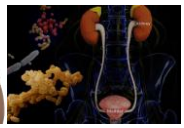
- Despite the incredible potency of BoNT, the toxin is highly specific for peripheral nerves and **does not spread** from its site of local injection in significant quantities to cause systemic symptoms.
- Systemic BoNT toxicity is **rare**, often associated with higher doses or underlying disease.
- Signs include impaired vision, extremity weakness, dry mouth, dysphagia, and constipation.



Nuanthaisong et al, 2014

Safety and Adverse Effects

- **Absolute contraindications** to BoNT use include active urinary tract infection and hypersensitivity to the toxin or its components.
- **Relative contraindications** to BoNT injection include pregnancy, motor neuropathies, and concomitant use of drugs that affect the neuromuscular junction (*i.e.*, aminoglycosides). Nuanthaisong et al, 2014


Sacral Neuromodulation

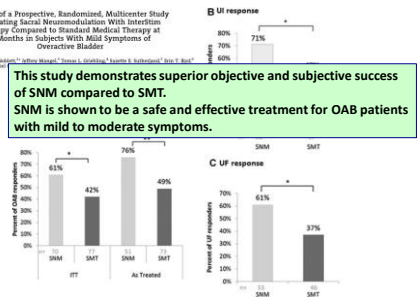
- Sacral Neuromodulation (SNM)
  - Objective: Re-balancing the micturition with electric stimulation of the sacral nerve roots (S3) on patients with chronic micturition troubles
  - Principle: raise the inhibitor mechanisms of the micturition reflex with electric stimulation

- Exact mechanism is still poorly understood
- Need expertise in every phase (Test, IPG, follow up)

SNM vs Anticholinergics

Results of a Prospective, Randomized, Multicenter Study Evaluating Sacral Neuromodulation With InterStim Therapy Compared to Standard Medical Therapy at 6-Months in Subjects With Mild Symptoms of Overactive Bladder

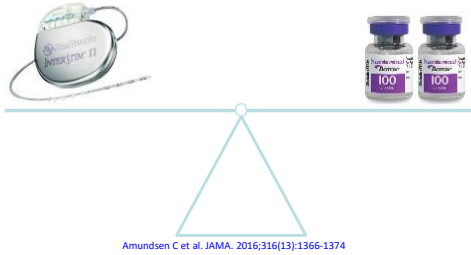
This study demonstrates superior objective and subjective success of SNM compared to SMT.
SNM is shown to be a safe and effective treatment for OAB patients with mild to moderate symptoms.



SNM vs Botox

JAMA | Original Investigation

OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women
A Randomized Clinical Trial



Amundsen C et al. JAMA. 2016;316(13):1366-1374

ROSETTA Design

- Women with UUI (OAB wet) **refractory to medical therapy**, N=386 (randomized); n=364 (ITT)
- At least 6 incontinence episodes/3d

- Interstim® versus Botox®200 U
- Evaluated at 6 months

Amundsen C et al. JAMA. 2016;316(13):1366-1374

ROSETTA Design

- The rate of clinical response — **defined as a reduction of at least 50% in urgent urinary incontinence episodes on a 3-day bladder diary** — was similar in the injection and neuromodulation groups (83% vs 84%).
- This was measured at 1 month in the injection group and during the test phase in the neuromodulation group.

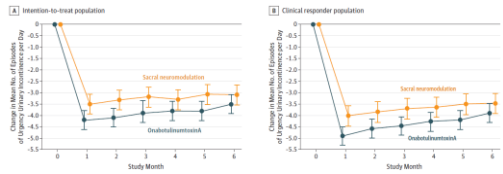
Amundsen C et al. JAMA. 2016;316(13):1366-1374

ROSETTA Design

- In the intention-to-treat analysis at 6 months, the change in the mean number of **daily incontinence episodes from baseline** — the primary outcome — was greater in the injection group than in the neuromodulation group (–3.9 vs –3.3 episodes/day; *P* = .01).
- More patients in the injection group than in the neuromodulation group achieved **complete symptom resolution at 6 months** (20% vs 4%; *P* < .0001) and a reduction of at least 75% in episodes per day (46% vs 26%; *P* = .0002).

Amundsen C et al. JAMA. 2016;316(13):1366-1374

Rosetta Results



Amundsen C et al. JAMA. 2016;316(13):1366-1374

ROSETTA Design

- Overactive bladder symptom bother scores, measured with the **ICI-OAB-SF**, were significantly better in both groups after treatment, but the change from baseline was greater in the injection group than in the neuromodulation group (–46.71 vs –38.5; *P* = .002).
- **Treatment satisfaction** was better in the injection group than in the neuromodulation group (*P* = .01), as was endorsement, assessed with the Overactive Bladder Satisfaction of Treatment Questionnaire (*P* = .0009).

Amundsen C et al. JAMA. 2016;316(13):1366-1374

ROSETTA Design

- At 6 months, the rate of **UTIs** was higher in the injection group than in the neuromodulation group (35% vs 11%; *P* < .0001).
- In addition, in the injection group, **IC** was required by 8% of patients at 1 month, by 4% at 3 months, and by 2% at 6 months.
- In the neuromodulation group, 3% of patients required **surgical revision or removal**.

Amundsen C et al. JAMA. 2016;316(13):1366-1374

ROSETTA results

- 83% (n=192) and 84% (n=189) of Botox and SNMs clinical responders
- In ITT population, Botox had

– a greater reduction (-3,9 vs. – 3,3)
– complete resolution in 20% vs. 4%
– 75% reduction of episodes in 46% vs. 26%

– more UTI's (35% vs. 11%)
– CISC: 8%, 4% and 2% @ 1, 3 and 6 months
– Interstim: 3% revision rate

Real life consequences?

- Both treatments have high response rate
- Higher "cure rate" for BoNTA 200 U vs SNM in women with UUI
- UTI/CISC rate versus revision rate

But:
100 U is approved dose for OAB 'wet'
? Same results in men
? Long-term follow-up in terms of cost-effectiveness

ROSETTA Study

- Onabotulinum Toxin A Injection & Sacral Neuromodulation are both third-line therapies for overactive bladder, to be used after therapies such as behavior modification, pelvic floor exercises, and medication
- There's really been no clear-cut guidance on whether you should do one or the other.
- 200 Units (100 Units).

(Nitti, AUA 2016)

VALUE IN HEALTH 14 (2011) 219–228

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Cost-Effectiveness of Sacral Neuromodulation Compared to Botulinum Neurotoxin A or Continued Medical Management in Refractory Overactive Bladder

Treatment	Improvement, %	Total per-patient costs, €	QALYs	ICER (cost/QALYs gained), €	Episodes	ICER (costs/episode avoided), €
5 years						
SNM	72.1	19,156	3.69		9561	
BoNT-A	68.6	18,235	3.45		9790	
OMT	0.0	15,932	2.75		16,529	
Incremental: SNM vs. BoNT-A year 5		921	0.24	3775	229	4.02
Incremental: SNM vs. OMT year 5		3223	0.94	3412	6968	0.46
7 years						
SNM	68.8	26,019	5.03		12,976	
BoNT-A	62.9	22,597	4.68		13,389	
OMT	0.0	21,593	3.74		22,486	
Incremental: SNM vs. BoNT-A year 7		3422	0.35	9830	413	8.29
Incremental: SNM vs. OMT year 7		4426	1.29	3433	9509	0.47
10 years						
SNM	62.1	29,166	6.89		17,765	
BoNT-A	55.2	29,458	6.38		18,498	
OMT	0.0	29,370	5.12		30,787	
Incremental: SNM vs. BoNT-A year 10		−292	0.51	Dominant	733	Dominant
Incremental: SNM vs. OMT year 10		−204	1.77	Dominant	13,021	Dominant

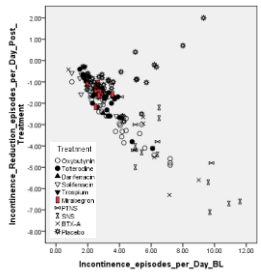
BoNT-A, botulinum neurotoxin A; ICER, incremental cost-effectiveness ratio; OMT, optimized medical treatment; QALY, quality-adjusted life-year; SNM, sacral neuromodulation.

So which is most effective in UUI?

No Consensus!

Depends on:

- baseline symptomatology
- magnitude of placebo effect



How to choose?

– Guidelines
– Experience
– Clinical practice and setting
– Patients preference

- Predictive factors?
- Doctors preference?
- Patient information?
- Reimbursement/Cost benefit?

ICS

INTERNATIONAL CONTINENCE SOCIETY

www.ics.org

International Continence Society (ICS)

- The ICS strives to improve the quality of life for people affected by urinary, bowel and pelvic floor disorders by advancing basic and clinical science through education, research and advocacy.

- Membership Society - £80 GBP per yea
- Online access to Neurourology and Urodynamics
- Annual Meeting discount
- Research and Membership database
- Access to travel grants, fellowships and research grants

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Lori Birder
Scientific Co-Chair


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