Tabriz University of Medical Sciences

Research center for EBM

Update on Management of Refractory Overactive bladder:

Nerve stimulation

Sakineh Hajebrahimi, MD

Professor of Urology & Neurourology

Department, Research center for EBM, TUMS, Tabriz, Iran

Tabriz University of Medical Sciences

Research center for EBM

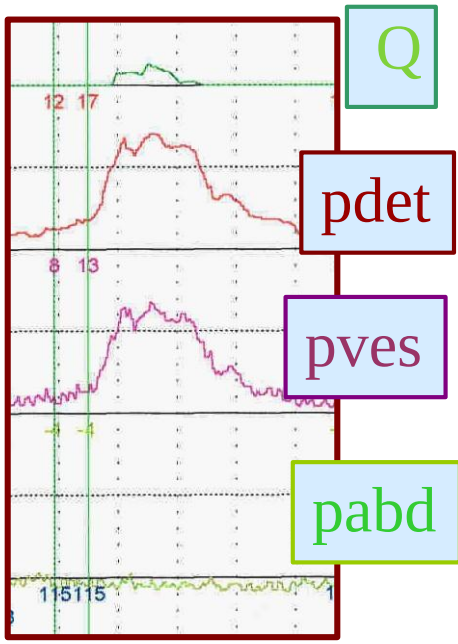
Terminology

Neurogenic
OAB and DO
NLUTD

- Overactive bladder (OAB)
  - A symptomatic diagnosis defined as urinary urgency, usually with daytime frequency or/and nocturia with urinary incontinence(OAB wet), or without(OAB dry), in the absence of urinary infection or any other detectable disease

- Detrusor overactivity (DO)

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



Haylen BT, et al. *Neurourol Urodyn.* 2010;29:4-20.

Tabriz University of Medical Sciences

Research center for EBM

Treatment Priority

1. Protection of the upper urinary tract
2. Improvement of urinary continence
3. Restoration of (parts of) the LUT function
4. Improvement of the patient’s quality of life.

Tabriz University of Medical Sciences

Research center for EBM

Current treatments for Overactive Bladder

- Behavioral therapies & Physical Therapy
- Drugs: anticholinergic, B3- Agonists
- Minimally invasive interventions
  - Intravesical Botox
  - Neurostimulation: Sacral, PTNS
- Surgery
  - Augmentaton cystoplasty
  - Urinary diversion

AUA/SUFU OAB Guidelines 2019
EAU Female LUTS Guideline 2021

Tabriz University of Medical Sciences

Research center for EBM

EAU Female LUTS Guideline 2021

Recommendations	Strength rating
Offer prompted voiding for adults with overactive bladder (OAB) who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with OAB/urgency urinary incontinence (UUI).	Strong
Ensure that pelvic floor muscle training programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for improvement of OAB/UUI in women who have not benefited from anticholinergic medication.	Strong

Recommendations	Strength rating
Offer anticholineric drugs to adults with overactive bladder (OAB) who fail conservative treatment.	Strong
Consider extended release formulations of anticholinergic drugs, whenever possible.	Strong
If an anticholinergic treatment proves ineffective, consider dose escalation or offering an alternative anticholinergic formulation, or mirabegron, or a combination.	Strong
Encourage early review (of efficacy and side effects) of patients on anticholinergic medication for OAB.	Strong

Table 1: Summary of cure rates and discontinuation rates of anticholinergic drugs from RCTs which reported these outcomes [147]

Drug	No. of studies	n	RR (95% CI) (of curing UI)	NNT (95% CI) (to achieve one cure of UI)
Cure of incontinence				
Fesoterodine	2	2,465	1.3 (1.1–1.5)	8 (5–17)
Oxybutynin (includes IR)	4	992	1.7 (1.3–2.1)	9 (6–16)
Propiverine (includes IR)	2	691	1.4 (1.2–1.7)	6 (4–12)
Solifenacin	5	6,304	1.5 (1.4–1.6)	9 (6–17)
Tolterodine (includes IR)	4	3,404	1.2 (1.1–1.4)	12 (8–25)
Trospium (includes IR)	4	2,677	1.7 (1.5–2.0)	9 (7–12)
Discontinuation due to adverse events				
			RR (95% CI) (of discontinuation)	NNT (95% CI) (for one discontinuation)
Darifenacin	7	3,138	1.2 (0.8–1.8)	
Fesoterodine	4	4,433	2.0 (1.3–3.1)	33 (18–102)
Oxybutynin (includes IR)	5	1,483	1.7 (1.1–2.5)	16 (8–86)
Propiverine (includes IR)	2	1,401	2.6 (1.4–5)	29 (16–77)
Solifenacin	7	9,080	1.3 (1.1–1.7)	78 (39–823)
Tolterodine (includes IR)	10	4,466	1.0 (0.6–1.7)	
Trospium (includes IR)	6	3,936	1.5 (1.1–1.9)	56 (30–228)

CI = confidence interval; IR = immediate release; n = number of patients; NNT = number to treat; UI = urinary incontinence; RR = relative risk.


Review

Nocebo Response in the Pharmacological Managen
Overactive Bladder: A Systematic Review and Meta-

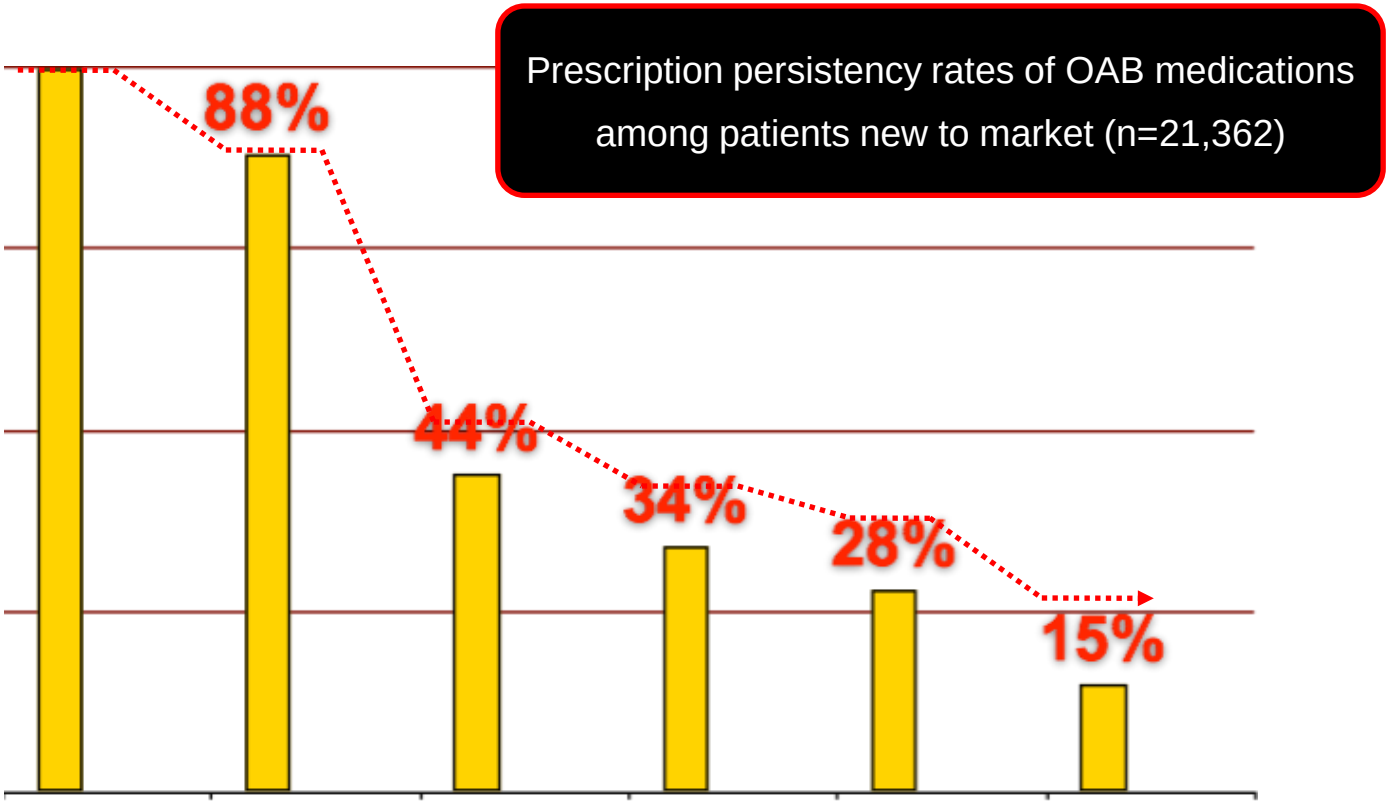
Hadi Mostafaei [a,*], Keiichiro Mori [a,b], Fahad Quhal [a,c], Noriyoshi Miura [a,d], Benjamin Pradere [a,e], Ekaterina Laukhtina [a,f], Ivan Lysenko [a], Sajjad Ghaffa Sakineh Hajebrahimi [g], Shahrokh F. Shariat [a,f,h]


Review

Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis

Hadi Mostafaei [a,b], Florian Janisch [a,c], Keiichiro Mori [a,d], Fahad Quhal [a,e], Benjamin Pradere [a,f], Sakineh Hajebrahimi [b], Claus G. Roehrborn [g], Shahrokh F. Shariat [a,g,h,i,j,k,l,m,*]

How Likely Are Patients To Continue With Their Drug Therapy?



56% of patients chose not to refill their prescription a second time

Only 15% of patient continued with their therapy

Tabriz University of Medical Sciences

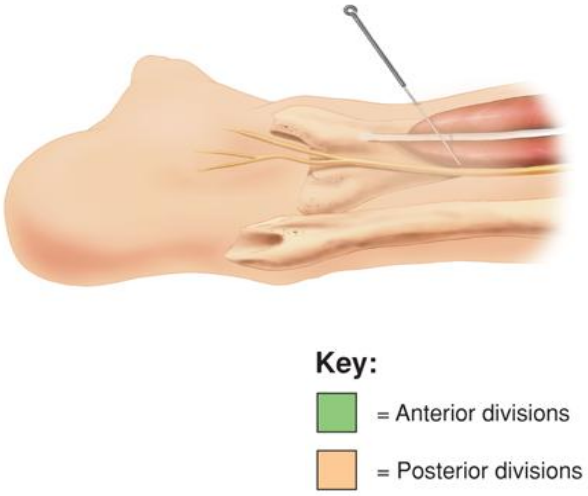
Research center for EBM

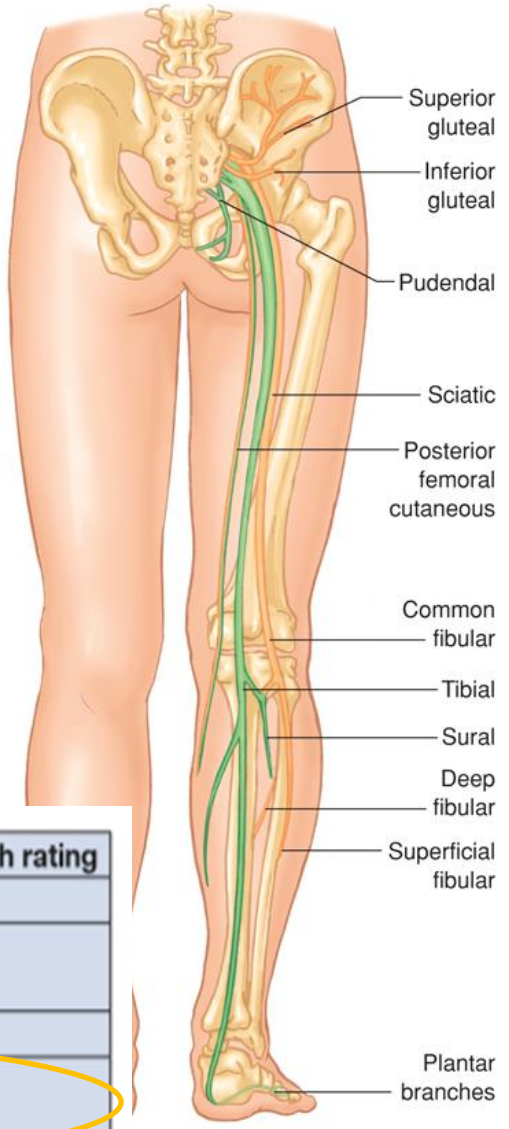
Nerve Stimulations

Tabriz University of Medical Sciences

Research center for EBM

Percutaneous Tibial Nerve Stimulation



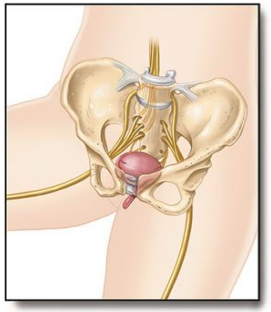


Recommendations	Strength rating
Offer prompted voiding for adults with overactive bladder (OAB) who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with OAB/urgency urinary incontinence (UUI).	Strong
Ensure that pelvic floor muscle training programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for improvement of OAB/UUI in women who have not benefited from anticholinergic medication.	Strong

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: 58.3vs 21.9%
- Response at 12weeks, not at 6weeks
- Improved QOL, frequency, urgency, UUI, nocturia

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



Tabriz University of Medical Sciences

Research center for EBM

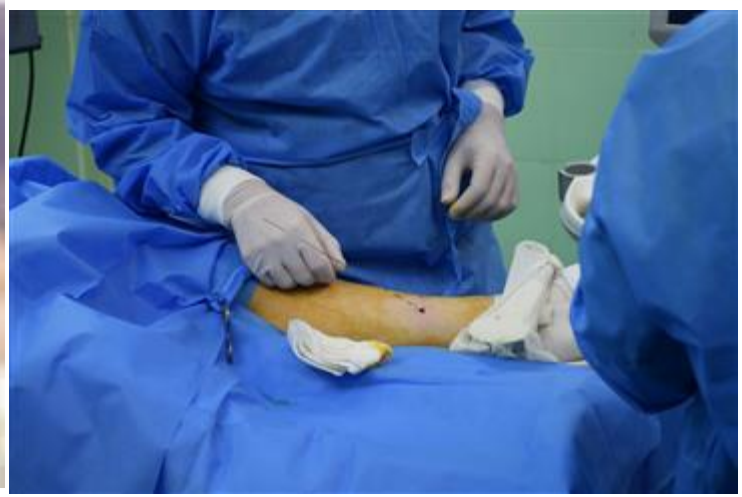
OrBIT trial

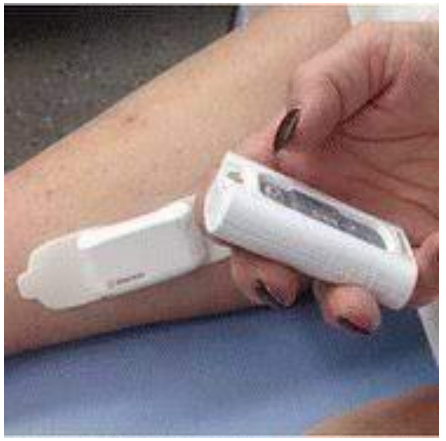
- ***O***veractive ***B***ladder ***I***nnovative ***T***herapy
- PTNS versus tolterodine[1]
- Improvement per GRA:
  - 79.5% vs 54.8%
- PTNS vs solifenacin with cross over[2]
  - Bladder specific assessment
  - Both groups showed improvement

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]

TIBIAL NERVE IMPLANTS (TTNS)

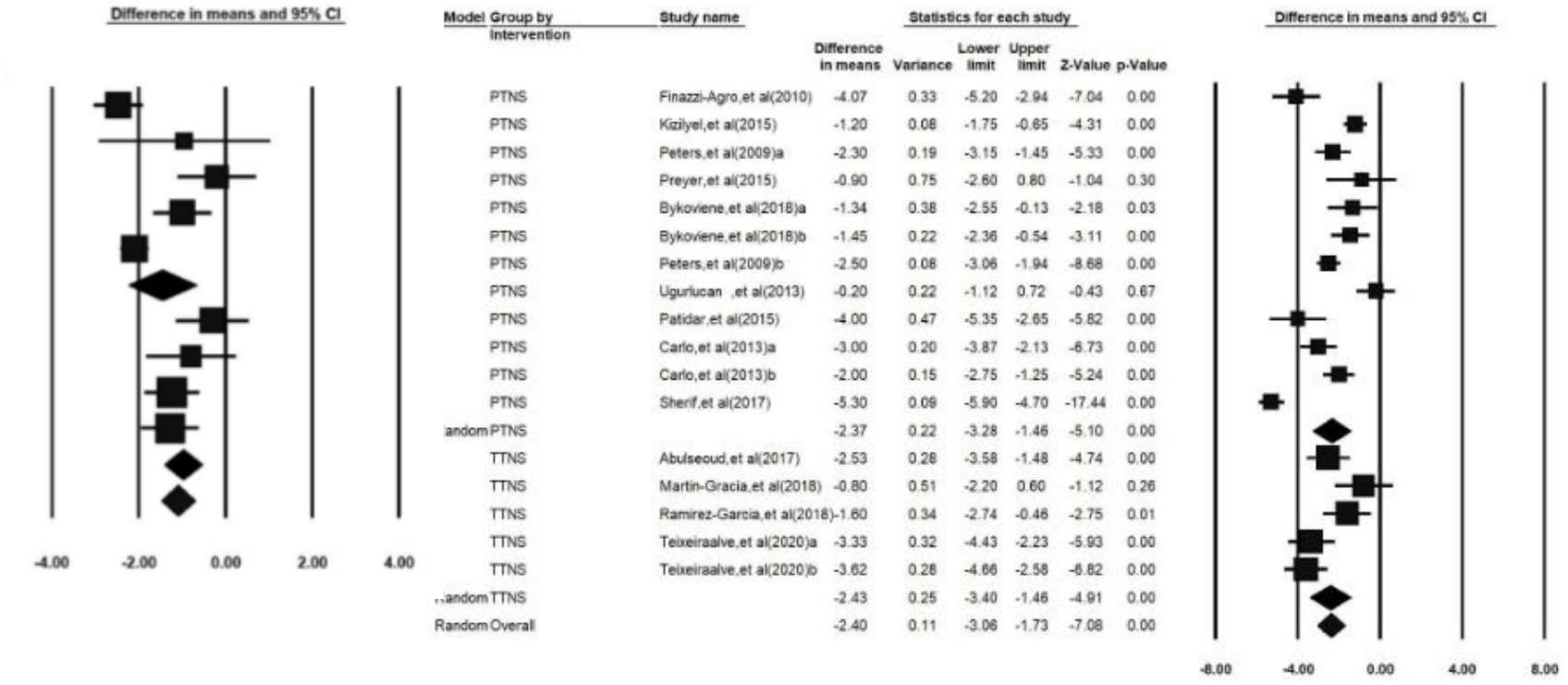




Tabriz University of Medical Sciences

Research center for EBM

Day time frequency and incontinence episodes



Model	Group by intervention	Study name	Difference in means	Variance	Lower limit	Upper limit	Z-Value	p-Value
	PTNS	Finazzi-Agro,et al(2010)	-4.07	0.33	-5.20	-2.94	-7.04	0.00
	PTNS	Kizilyel,et al(2015)	-1.20	0.08	-1.75	-0.65	-4.31	0.00
	PTNS	Peters,et al(2009)a	-2.30	0.19	-3.15	-1.45	-5.33	0.00
	PTNS	Preyer,et al(2015)	-0.90	0.75	-2.60	0.80	-1.04	0.30
	PTNS	Bykoviene,et al(2018)a	-1.34	0.38	-2.55	-0.13	-2.18	0.03
	PTNS	Bykoviene,et al(2018)b	-1.45	0.22	-2.36	-0.54	-3.11	0.00
	PTNS	Peters,et al(2009)b	-2.50	0.08	-3.06	-1.94	-8.68	0.00
	PTNS	Ugurlucan ,et al(2013)	-0.20	0.22	-1.12	0.72	-0.43	0.67
	PTNS	Patidar,et al(2015)	-4.00	0.47	-5.35	-2.65	-5.82	0.00
	PTNS	Carlo,et al(2013)a	-3.00	0.20	-3.87	-2.13	-6.73	0.00
	PTNS	Carlo,et al(2013)b	-2.00	0.15	-2.75	-1.25	-5.24	0.00
	PTNS	Sherif,et al(2017)	-5.30	0.09	-5.90	-4.70	-17.44	0.00
andom	PTNS		-2.37	0.22	-3.28	-1.46	-5.10	0.00
	TTNS	Abulseoud,et al(2017)	-2.53	0.28	-3.58	-1.48	-4.74	0.00
	TTNS	Martin-Gracia,et al(2018)	-0.80	0.51	-2.20	0.60	-1.12	0.26
	TTNS	Ramirez-Garcia,et al(2018)	-1.60	0.34	-2.74	-0.46	-2.75	0.01
	TTNS	Teixeiraalve,et al(2020)a	-3.33	0.32	-4.43	-2.23	-5.93	0.00
	TTNS	Teixeiraalve,et al(2020)b	-3.62	0.28	-4.66	-2.58	-6.82	0.00
..andom	TTNS		-2.43	0.25	-3.40	-1.46	-4.91	0.00
Random	Overall		-2.40	0.11	-3.06	-1.73	-7.08	0.00

Hajebrahimi et al, 2021

Tabriz University of Medical Sciences

Research center for EBM

	GEKO [14▪▪]	Stimrouter [18,19]	eCoin [21▪▪]	Bluewind RENOVA [15▪▪,16]	Stimguard [22,23,24]
Size	15 cm	15 cm	2.3 cm	2.5 cm	12 cm
Duration of stimulation	Daily or weekly	Up to 12 h/day	30 min/2–15 days,	30 min t.i.d.	8 h/day
Pulse width (μs)	70–560	7–500		50–800	50–500
Pulse amplitude (mA)	27		0.5–15	0–9	0–15
Pulse rate (Hz)	1	1–200		0–40	2–1500
External component	TENS – External pulse generator with adhesive surface electrodes	Adhesive external pulse transmitter Patient programmer	No external component.	Wearable unit with leg band	External device in a sleeve at the ankle
Energy transfer	Transcutaneous	Electrical field through surface electrodes.	Battery powered.	Magnetic resonance 6.78 MHz ISM band Closed-loop	Magnetic resonance 915 MHz ISM band Open-loop
Advantage	1. No surgery	1. Eight treatment programs 2. Computerized feedback on use 3. No implanted battery	1. Operates automatically2. Leadless	1. Tailored settings 2. No migration 3. Computerized feedback on use 4. Leadless 5. No implanted battery	1. Treatment overnight 2. Tailored settings 3. No implanted battery
Disadvantage	1. Fixed amplitude and frequency 2. High impedance 3. No computerized feedback	1. Loss of energy because of use of surface gel pads 2. Long lead requiring tunneling	1.Nonrechargeable battery 2.Fixed stimulation parameters 3. Requires replacement surgeries 4. No computerized feedback on use	1. Open-procedure	1. No anchoring system 2. Long lead requiring tunneling

CURRENT OPINION IN UROLOGY

Tibial nerve stimulation in the treatment of overactive bladder syndrome: technical features of latest applications

te Dorsthorst, Manon; van Balken, Michael; Heesakkers, John

Current Opinion in Urology30(4):513-518, July 2020.
doi: 10.1097/MOU.0000000000000781

we can conclude the ideal implant is not yet found. Demonstration of the safety and efficacy on the long-term and in larger scale trials is needed

Wolters Kluwer

Tabriz University of Medical Sciences

Research center for EBM

SACRAL NEUROMODULATION

Tabriz University of Medical Sciences

Research center for EBM

EAU Female LUTS Guideline 2021

4.1.4.3.2.1 Summary of evidence and recommendation for sacral nerve stimulation

Summary of evidence	LE
Sacral nerve stimulation is more effective than continuation of failed conservative treatment for OAB/ UUI, but no sham controls have been used.	1b
Sacral nerve stimulation is not more effective than onabotulinumA toxin 200 U injection at 24 months.	1b
In patients who have been implanted 50% improvement of UUI is maintained in at least 50% of patients and 15% may remain cured at four years.	3
The use of tined, permanent electrodes in a staged approach results in more patients receiving the final implant than occurs with temporary test stimulation.	4

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have overactive bladder/urgency urinary incontinence refractory to anticholinergic therapy.	Strong

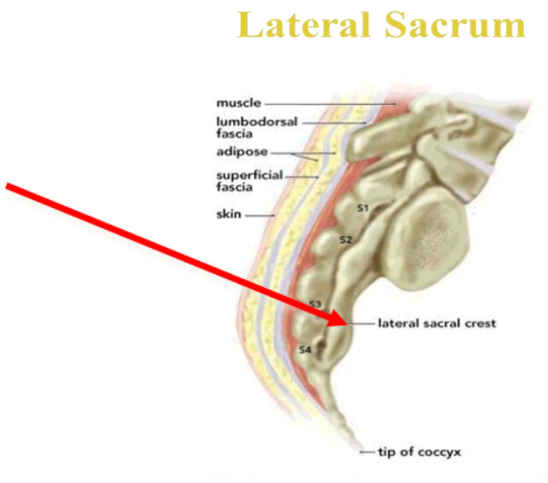
Tabriz University of Medical Sciences

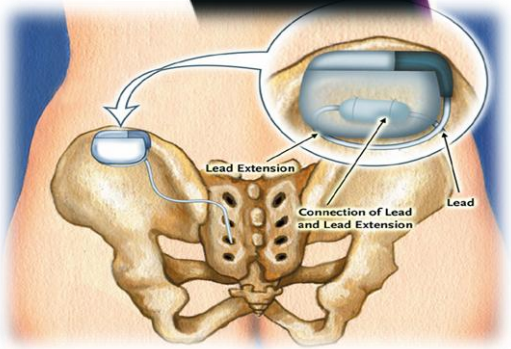
Research center for EBM

SNM - Therapy

Definition:

An implantable system that stimulates the sacral nerves modulating the neural reflexes that influence the bladder, sphincter, and pelvic floor.



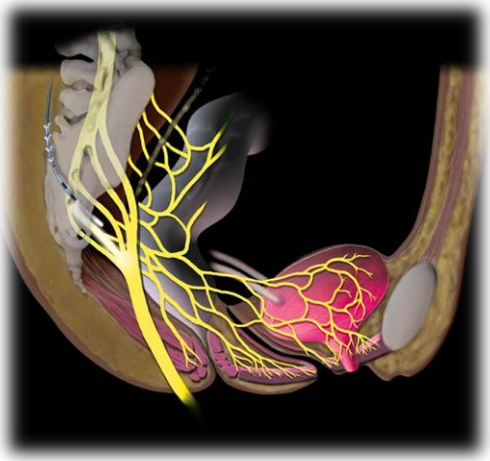


Mechanism of Action

- Not a bladder specific therapy

  Central afferent modulation

  Targets reflex centers in cord and pons



- Treats both OAB and retention

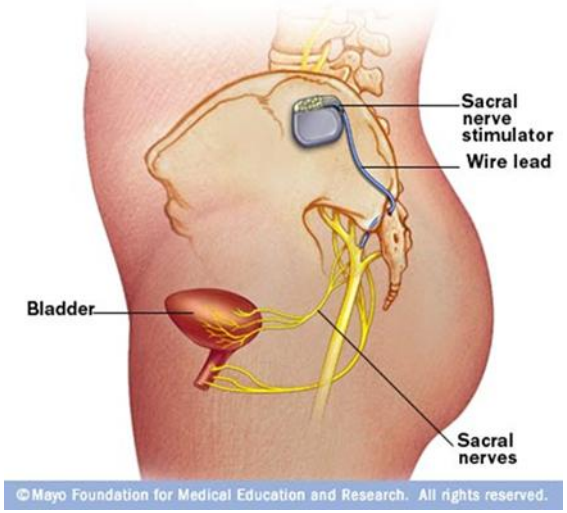
  Blocks ascending sensory pathway inputs

- Turns on voiding reflexes by suppressing the guarding reflex pathways

Leng WW - Urol Clin North Am - 01-FEB-2005; 32(1): 11-8

All inclusive!!!

- Urinary retention
- Overactive bladder (OAB),
- Painful bladder syndrome
- Fecal incontinence
- Sexual function improves
- Quality of life improves
- Psychosocial outlook
  - Depression improves
  - Optimism is not a predictor of success
- Long-term safety in Medicare beneficiaries

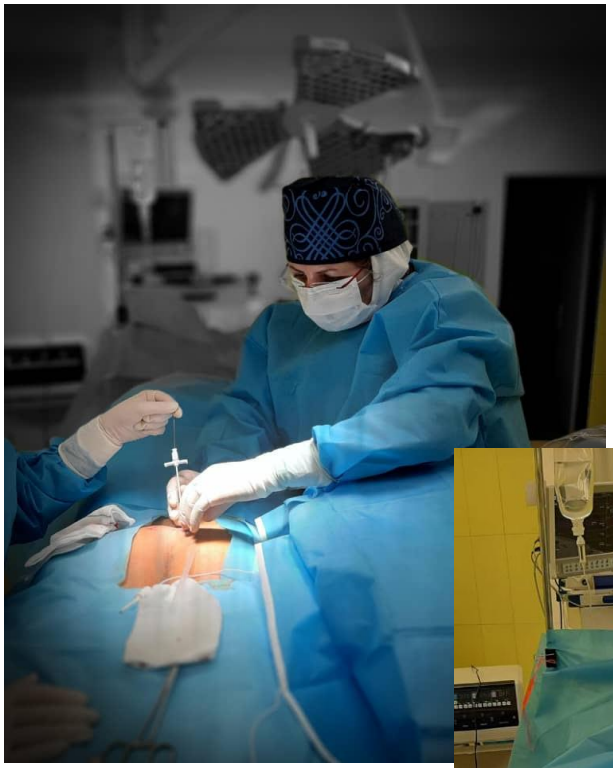


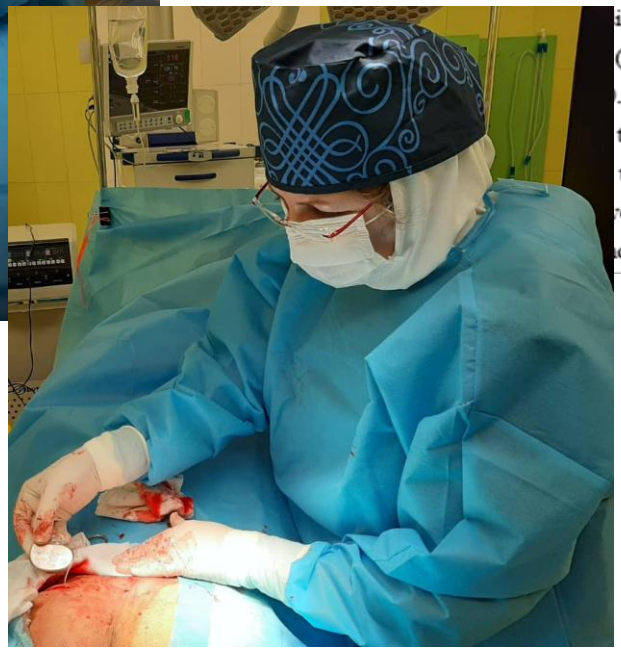
Chungtai, 2014, Levin 2014

Tabriz University of Medical Sciences

Our experience

Research center for EBM





Sacral Neuromodulation in Patients with Underactive Bladder: The Outcomes of a Multicenter Case Series

Abstract

Introduction and objections: We report the long-term outcomes of sacral neuromodulation (SNM) in detrusor underactivity (DU) and chronic non-obstructive urinary retention.

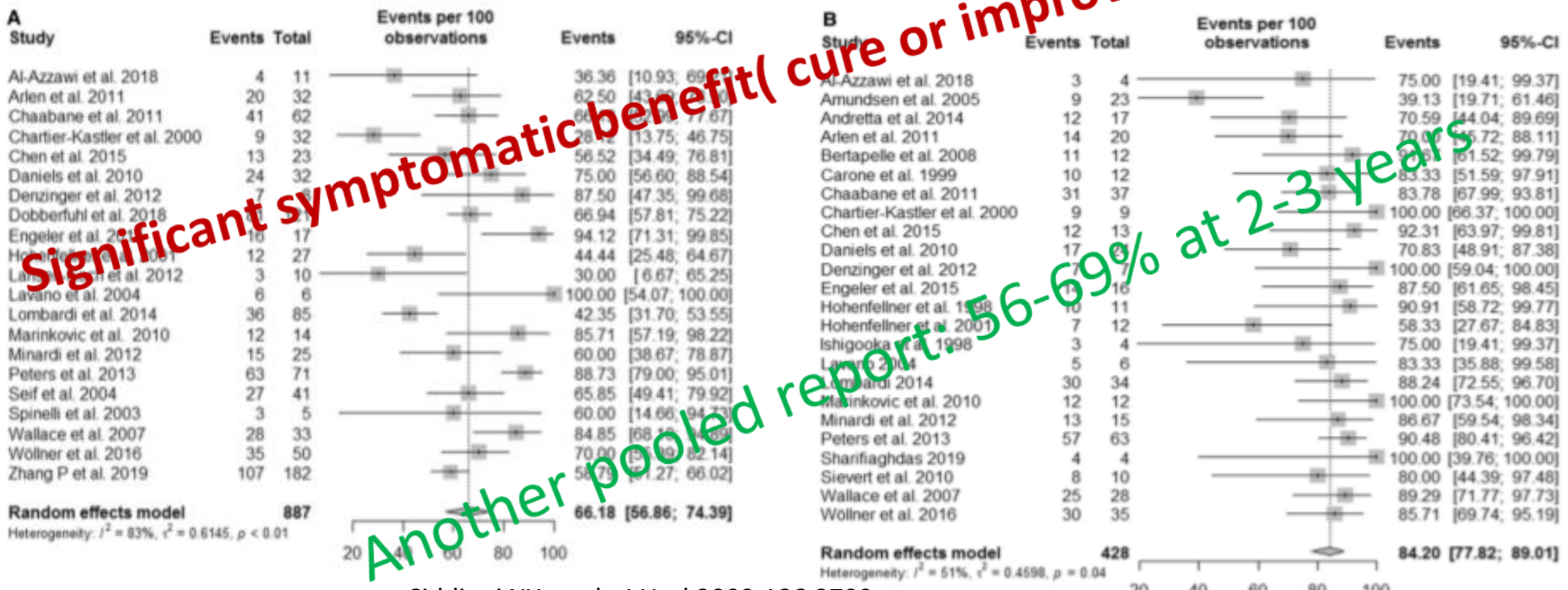
Materials and methods: A total of forty-six cases underwent SNM between March 2017 and October 2020. To assess patients' response to treatment (stage I), temporary percutaneous stimulation was used prior to permanent implantation. Patients were observed for two weeks following surgery, and if treatment response was 50 percent or more, the implantable pulse was placed in stage II of the study.

Results: The mean age of patients was 37.46 ± 13.58 years, with a male to female ratio of 1:1. The etiology of disease in 32 patients (69.6%) was idiopathic, while the others had neurogenic conditions. Thirty-two (69.6 %) patients responded to stage I, of which **75% either** experienced a reduction in CIC frequency, PVR, or void spontaneously , or were fully treated by the end of iopathic, 7 neurologic) showed no response to stage I. The mean (2-46) months. Voided volume improved significantly, from a .0) to 226.50 (range 0.0-550.0) ($p < 0.001$). The median PVR was to 1000.0) to 170 ml (range 0 to 800) ($p < 0.001$), and the median to 12 (range 0 to 21) ($p < 0.001$). Idiopathic DU cases showed rement in their urodynamic study results for voided volume d PVR (P=0.040) as compared to neurogenic patients.In addition,

Tabriz University of Medical Sciences

Research center for EBM

This meta-analysis supports not only the benefits of permanent SNM for various nLUTDs but also high overall success rates, similar to idiopathic patients in over 20 Years' Experience



Significant symptomatic benefit(cure or improvement >70%

Another pooled report: 56-69% at 2-3 years

Arndt van Ophoven et al 2021

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

Adverse events

Table 4 Adverse events with permanent SNM

Adverse event	No. of patients with adverse event/total no. of permanently implanted patients	Percentage of adverse events	No. of studies reporting type of AE
Infection	18/494	3.6%	8
Pain at implant	16/494	3.2%	8
Adverse stimulation	10/494	2.0%	5
Lead migration	16/494	3.2%	7
Lead breakage	6/494	1.2%	4
Hardware issues	14/494	2.8%	6
Adverse change in bowel function	2/494	0.4%	1
Loss of effectiveness	23/494	4.7%	9
Other	9/494	1.8%	6

Arndt van Ophoven et al 2021

- The FDA's approval of Axonics Sacral Neuromodulation System—a system that is MRI-compatible. The FDA has approved the system to treat overactive bladder syndrome as well as fecal incontinence (for similar uses as InterStim from Medtronic).

Cumulative 3-year costs

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

Tabriz University of Medical Sciences

Research center for EBM

Cost effectiveness

- BTX was more cost-effective in 2 years follow up
- BTX and SNM similar cost effectiveness in 5 years follow up

JAMA (2016; 316:1366-74).

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

Treatment Options

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

Augmentation cystoplasty / Urinary diversion

Augmentation cystoplasty

- Implanting ileum into bladder
- Significant morbidity
- Detrusor myectomy (auto-augmentation)
- Denervation, deafferentation, neurostimulation, neuromodulation

Urinary diversion

- Ileal conduit
- Total cystectomy may be indicated with this
- Complications

The Last Resort…

ENLARGE THE BLADDER!

Bowel segment to enlarge bladder

Lowers intravesical pressure

Increases capacity

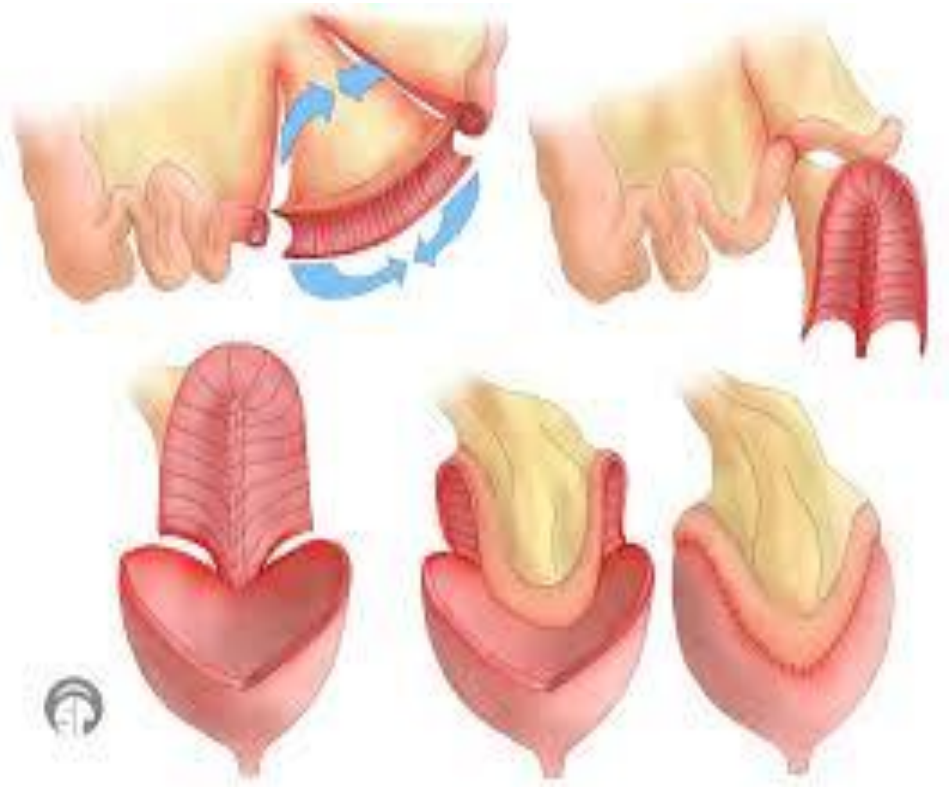
>80% must catheterize

A big operation, but…it works!

Tabriz University of Medical Sciences

Research center for EBM

Augmentation cystoplasty



Current indications

when conservative management, pharmacological methods and minimally invasive treatments have been unsuccessful and exhausted

High satisfaction rates

Tabriz University of Medical Sciences

earch center for EBM

An Adapted Enhanced Recovery Protocol for Adult Augmentation Cystoplasty in limited sources countries: A pilot clinical trial

Abstract

Objective: To investigate an adapted ERAS protocol in adult augmentation cystoplasty in limited sources countries.

Material and methods: A total of 33 consecutive cases with a history of refractory idiopathic detrusor overactivity (IDO) or neurogenic bladder (NGB) referred to the urology department of our teaching hospital between March 2016 and October 2020 were enrolled in the current study. Postoperative morbidity and hospital stay duration were analyzed using SPSS version 21.

Results: A total of 33 adults were operated. Twenty-two patients had IDO, and the remained cases were NGB, or had low bladder capacity or compliance. The mean (SD) age of patients in the IDO group was higher than that in NGB cases (P=0.020). Following the adapted ERAS protocol implementation, more than two-third of patients returned to a regular diet on the second-day post-operation in both groups. The mean (SD) hospital stay duration was 7.68 (1.50) days. Postoperative fasting time mean was 8.81 ± 3.67 hours, and bowel function was returned one-day post-operation in 82% of patients. Only 33.3% of adults need post-procedure apotel for two days, and in 11 cases it prescribed one day. All subjects except paraplegic patients had early mobilization one-day post-operation.

Conclusion: Our findings revealed adapted ERAS protocol could be safe, practical, and effective in adult augmentation cystoplasty in limited sources countries. It accompanied by few complications, reduced intestinal motility problems, and a short length of hospital stay.

Tabriz University of Medical Sciences

Research center for EBM

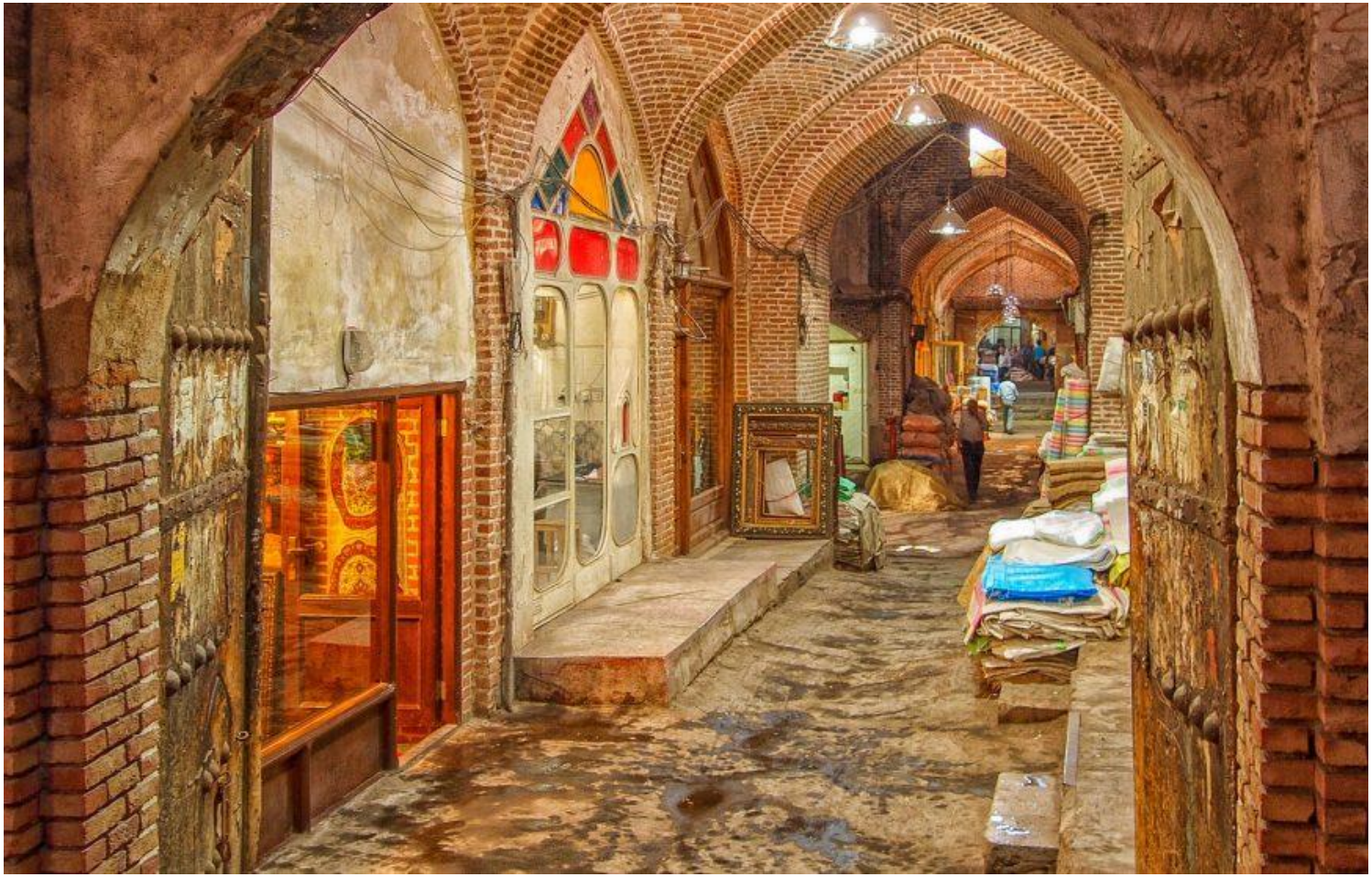
complications

- Early complications (<1 month after surgery)
  - Alterations of bowel transit
    - Adynamic ileus
    - Mechanical obstruction
  - Urinary leakage from anastomosis of ureter and conduit or reservoir
  - Fluid collections
    - Urinoma
    - Abscess
    - Lymphocele
    - Hematoma
  - Wound infection
  - Sepsis
  - Fistula
  - Urinary obstruction
- Late complications (≥1 month after surgery)
    - Urinary infection
    - Ureteral stenosis
    - Parastomal herniation
    - Lithiasis
    - Tumor recurrence

Tabriz University of Medical Sciences

Research center for EBM

Take home message



Tabriz University of Medical Sciences

Research center for EBM

Current treatments for Overactive Bladder

- Behavioral therapies & Physical Therapy
- Drugs, anitcholinergic
- Intravesical Botox
- Neuromodulation
  - Sacral
  - PTNS
- Surgery
  - Augmentaton cystoplasty
  - Urinary diversion

From a practical standpoint…

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

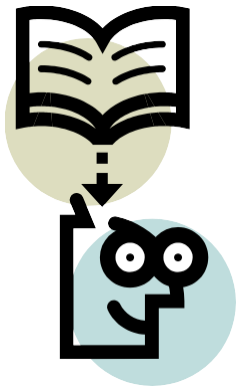
Tabriz University of Medical Sciences

Research center for EBM

Take Home Messages

- OAB" multifactorial
- Conservative measures first
- Stepwise progression
- Successful options available

(*Patients must be made aware*)



Tabriz University of Medical Sciences

Research center for EBM

Any Questions?