Überaktive Blase und Beckenschmerz
BOTULINUMTOXIN und NEUROMODULATION

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BOTULINUMTOXIN

Botulinumtoxin bei überaktiver Blase

- Geschichtliches
  - 1988 Dykstra
    - Detrusor-Sphinkter-Dyssynergie bei Rückenmarksverletzten
  - 2000 Schürch
    - Neurogene Detrusor-Überaktivität und Neurogene Dranginkontinenz bei Rückenmarkverletzten
  - FDA-Zulassung
    - Neurogene Detrusorüberaktivität 2011 (3 Zulassungsstudien)
    - Idiopathische Detrusorüberaktivität 2013 (3 Zulassungsstudien)

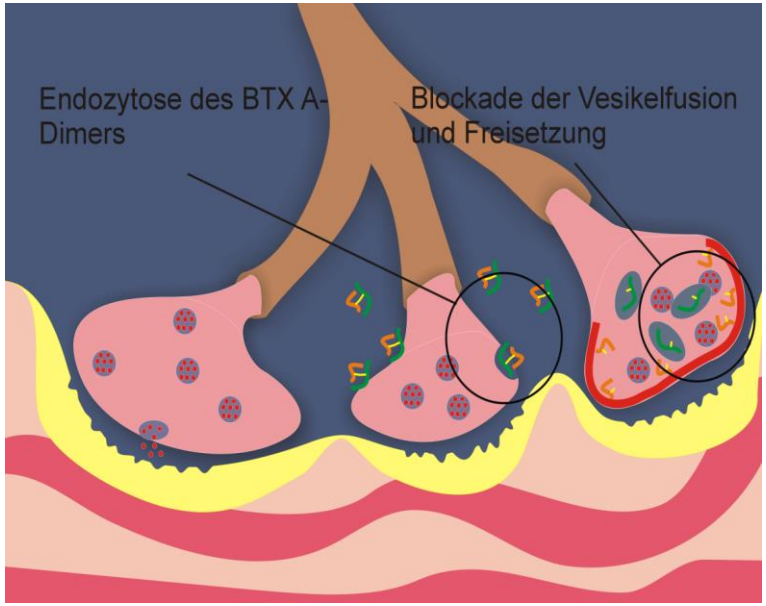
Dykstra D, et al. J Urol 1988;139:919-22

Botulinumtoxin Typ A-Injektion

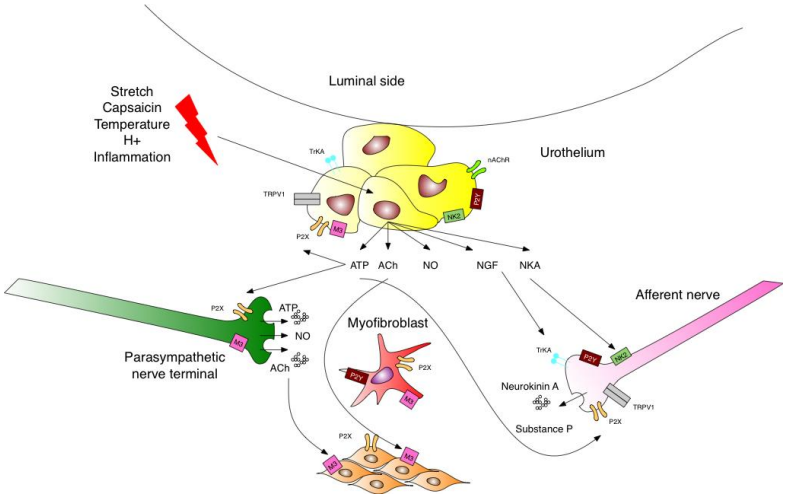
- Anwendungsbereiche
  - Idiopathische überaktive Blase (IDO)
    - Mit/ohne Dranginkontinenz
    - Zugelassen und kassenpflichtig (CH)
  - Neurogene überaktive Blase (NDO)
    - Mit/ohne Dranginkontinenz
    - Zugelassen und kassenpflichtig (CH)
  - Blasenschmerzsyndrom (?)

Botulinumtoxin Wirkmechanismus

Blockiert die cholinerge Transmission der neuromuskulären Endplatte und Verursacht eine temporäre Muskeldenervation



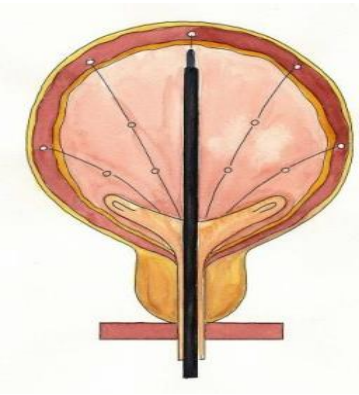
Vermutlich reduziert es die Freisetzung von ATP und Substanz P durch die Reduktion der Expression von purinergen und vanilloiden Rezeptoren

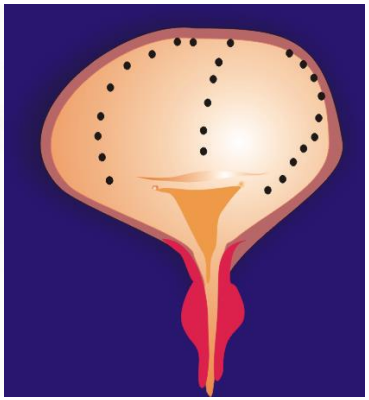


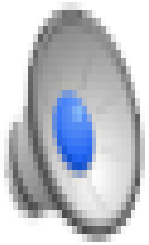
Sun Y, et al. J Urol 2001;166:1951–1956

Botulinumtoxin-Injektion in den Detrusor

- Prinzip:
  - Injektion des Botulinumtoxin A in den Blasenmuskel
  - Verteilung über insgesamt 30 Injektionsorte
  - Kann in ambulant, in Lokalanästhesie und mit flexiblem Intrumentarium gemacht werden



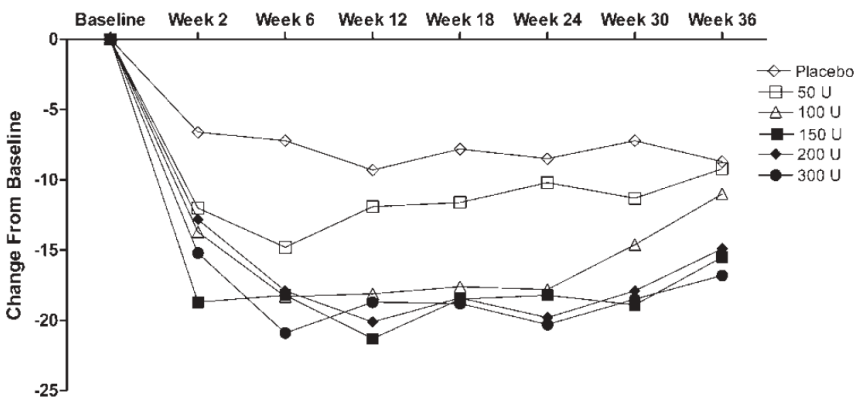




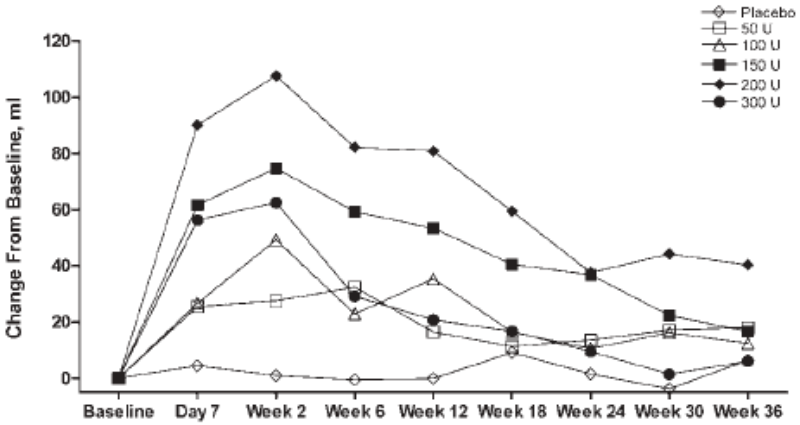
Botulinumtoxin bei idiopathischer überaktiver Blase

- Dosisfindungsstudie
  - Doppelblind, randomisiert, placebokontrolliert (Total N=313)

King's Health Questionnaire



Restharn

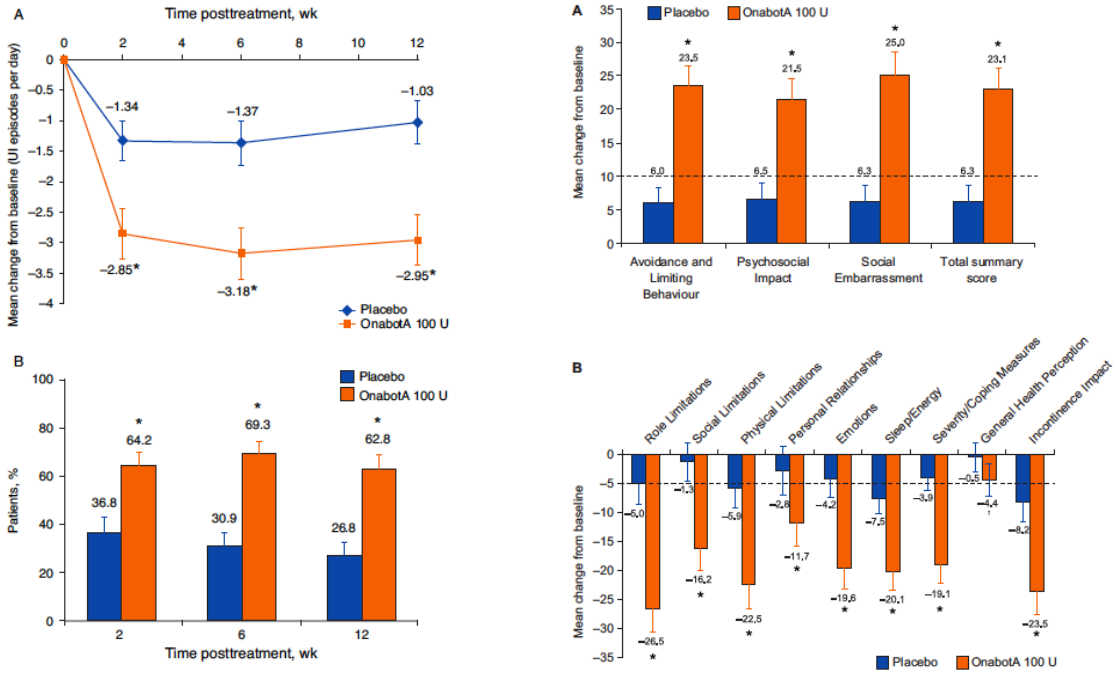


➢ Bestes Wirkungs-/Nebenwirkungsverhältnis für Dosis von 100 Units

Dmochowski R., et al. J Urol 2010; 184:2416-2414

Botulinumtoxin bei idiopathischer überaktiver Blase

- Phase 3 Studie
  - Doppelblind, randomisiert, placebokontrolliert (Total N=548)



➢ Gute Effektivität in sämtlichen relevanten Parametern für Dosis von 100 Units

Chapple C.., et al. Eur Urol 2013; 64:249-256

Botulinumtoxin bei idiopathischer überaktiver Blase

- Phase 3 Studie
  - Doppelblind, randomisiert, placebokontrolliert (Total N=548)

Adverse event	First 12 wk		Entire treatment cycle	
	Placebo, *n* = 270	OnabotA 100 U, *n* = 274	Placebo, *n* = 270	OnabotA 100 U, *n* = 274
AEs with incidence ≥3%, no. (%)				
UTI	14 (5.2)	56 (20.4)	26 (9.6)	66 (24.1)
Dysuria	10 (3.7)	16 (5.8)	11 (4.1)	16 (5.8)
Bacteriuria	6 (2.2)	10 (3.6)	9 (3.3)	17 (6.2)
Urinary retention	1 (0.4)	16 (5.8)	1 (0.4)	16 (5.8)
Haematuria	1 (0.4)	10 (3.6)	2 (0.7)	10 (3.6)
Leukocyturia	2 (0.7)	7 (2.6)	2 (0.7)	10 (3.6)
Residual urine volume	1 (0.4)	8 (2.9)	2 (0.7)	9 (3.3)
Discontinuations, no. (%)	15 (5.6)	9 (3.3)	23 (8.5)	18 (6.6)
Due to AEs	2 (0.7)	2 (0.7)	2 (0.7)	4 (1.5)

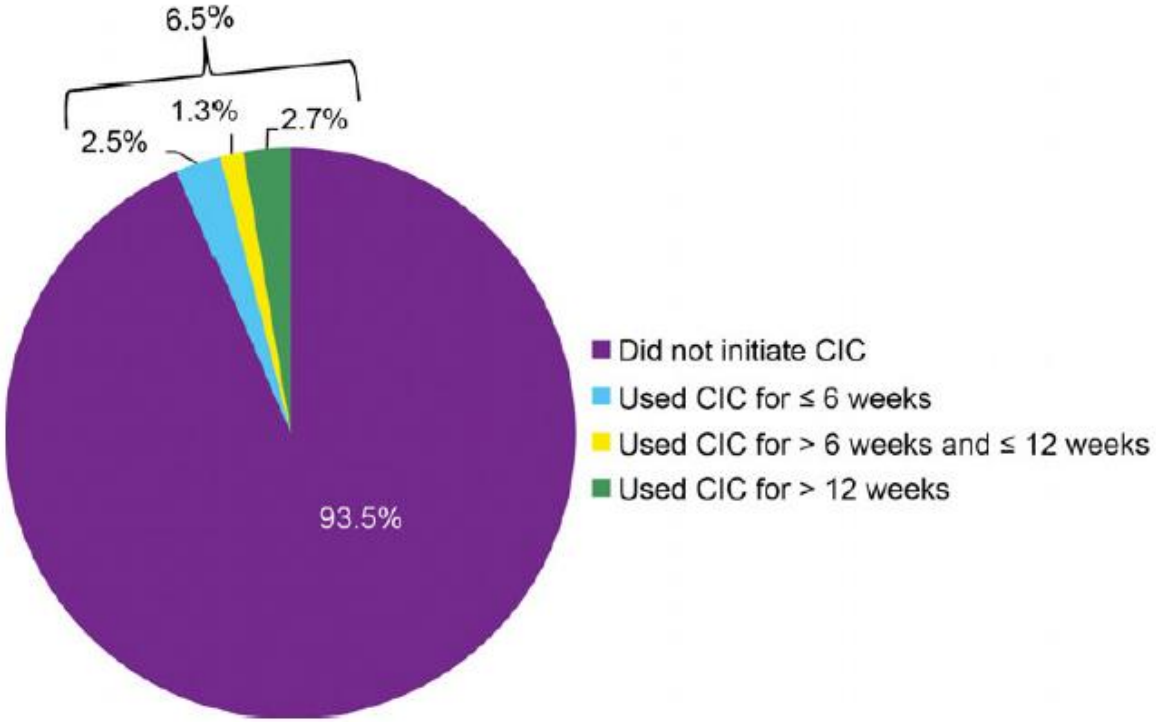
AE = adverse event; OnabotA = onabotulinumtoxinA; UTI = urinary tract infection.

➢ Mehr HWI und Urinretention für Dosis von 100 Units verglichen mit Placebo

Chapple C.., et al. Eur Urol 2013; 64:249-256

Notwendigkeit des intermittierenden Selbstkatheterismus bei idiopathischer Detrusorüberaktivität nach Botulinumtoxin 100 U

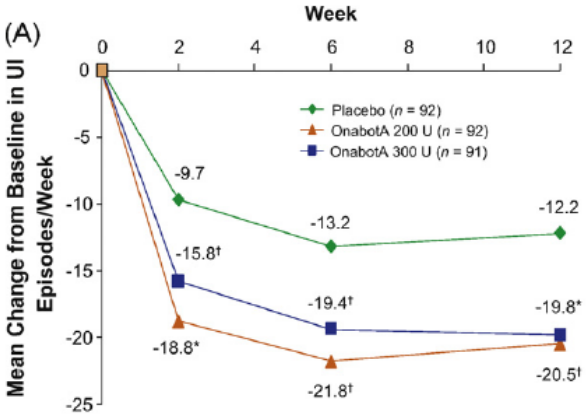
Poolung zweier Zulassungsstudien (N= 552)



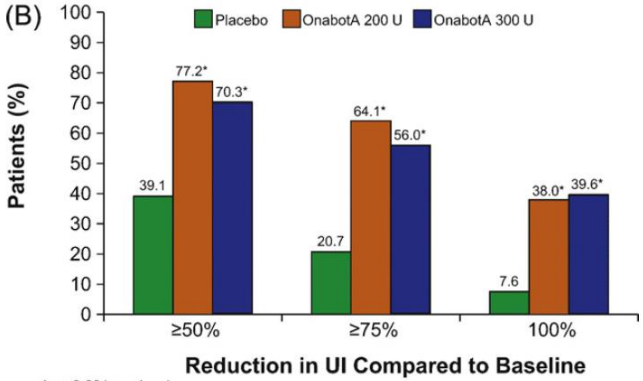
Sievert K.D., et al. Int J Clin Pract 2014; 68:1246-56

Botulinumtoxin bei neurogener überaktiver Blase

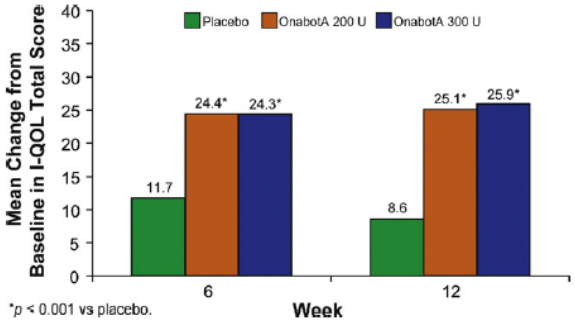
- Multizentrische, doppelblinde, randomisiert, placebokontrolliert
  - Total Placebo N=92, 200 U N=92, 300 U N=91
  - NDO (Multiple Sklerose N=154, Rückenmarksverletzung N=121)



*p < 0.001; †p < 0.01 vs placebo.



*p < 0.001 vs placebo.



*p < 0.001 vs placebo.

Cruz F., et al. Eur Urol 2011; 60:742-50

Botulinumtoxin bei neurogener überaktiver Blase

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  - Total Placebo N=92, 200 U N=92, 300 U N=91
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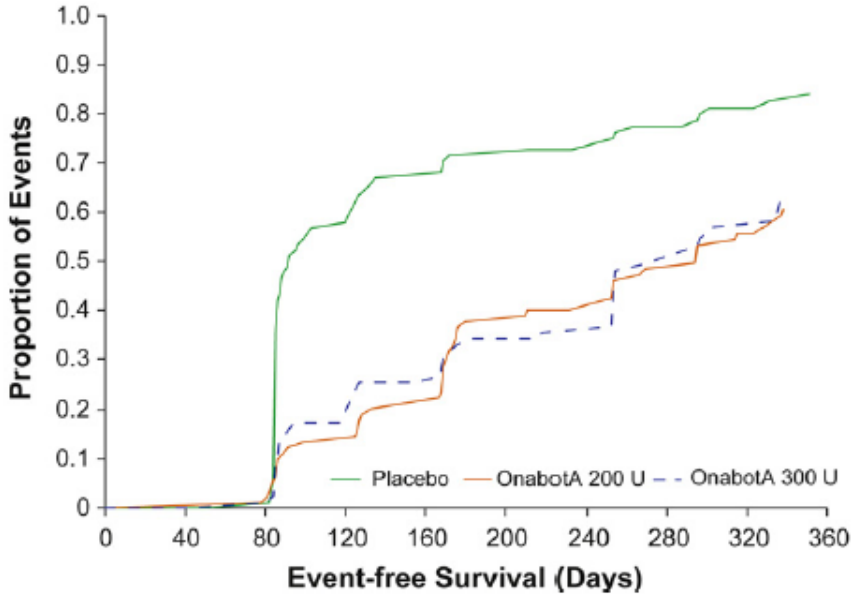
Wunsch der erneuten Behandlung



Cruz F., et al. Eur Urol 2011; 60:742-50

Botulinumtoxin bei neurogener überaktiver Blase

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  - Total Placebo N=92, 200 U N=92, 300 U N=91
  - NDO (Multiple Sklerose N=154, Rückenmarksverletzung N=121

Adverse events

	MS Patients			SCI Patients		
	Placebo ($n = 50$)	OnabotA 200 U ($n = 53$)	OnabotA 300 U ($n = 50$)	Placebo ($n = 40$)	OnabotA 200 U ($n = 38$)	OnabotA 300 U ($n = 39$)
UTI and urinary retention AEs by aetiology, n (%)						
UTI	16 (32.0)	31 (58.5)†	35 (70.0)†	20 (50.0)	20 (52.6)	22 (56.4)
Urinary retention	2 (4.0)	16 (30.2)†	27 (54.0)†	1 (2.5)	2 (5.3)	1 (2.6)

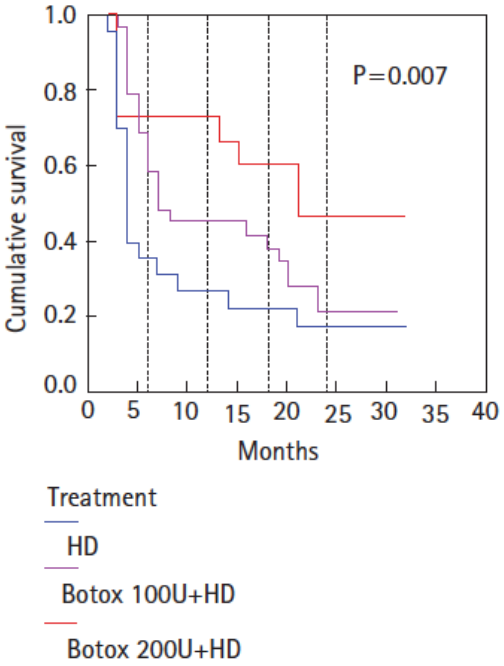
AE = adverse event; MS = multiple sclerosis; OnabotA = onabotulinumtoxinA; SCI = spinal cord injury; UTI = urinary tract infection.
* Placebo-controlled phase.
† $p < 0.05$ compared with placebo; chi-square test, or Fisher exact test,.

Cruz F., et al. Eur Urol 2011; 60:742-50

Detrusorinjektion von Botulinumtoxin A bei Blasenschmerzsyndrom

- Hydrodistention+-Botulinumtoxin A
  - Kuo 2009 (N=67)
    - Signifikante Besserung
  - Manning 2014 (N=50)
    - Relevanter Effekt nur in Subgruppen/-Scores
    - Underpowered?

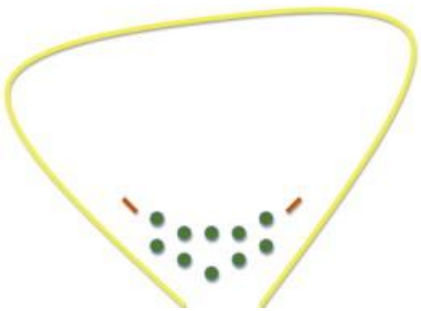
Behandlungserfolg

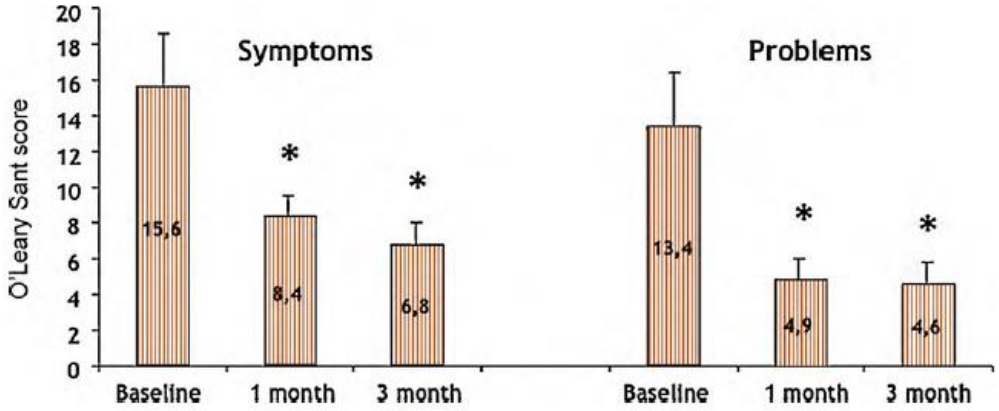


Kuo HC, et al. BJUI 2009;104:657-61
Manning J, et al. Int Urogynecol J 2014;25:593-9

Detrusorinjektion von Botulinumtoxin A bei Blasenschmerzsyndrom

- Pinto 2010: Trigonale Injektion?





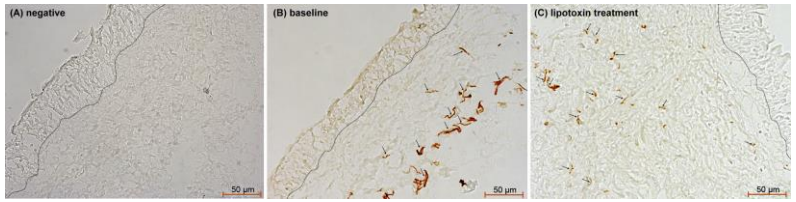
Pinto R, et al. Eur Urol 2010; 58:360-5

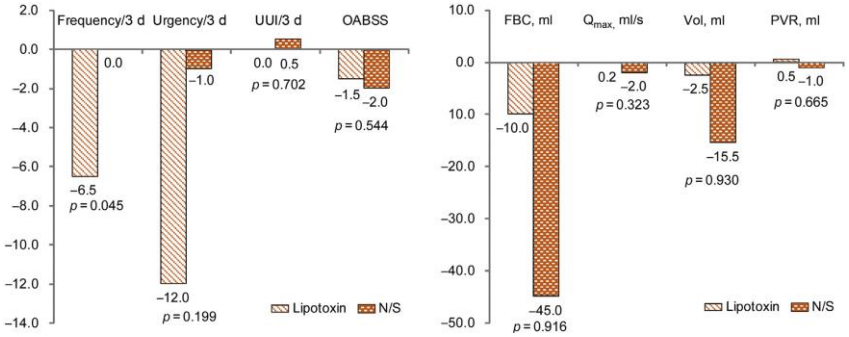
Zukunft?

Liposome-encapsulated Botulinumtoxin A (Lipotoxin) - LipoBoNT

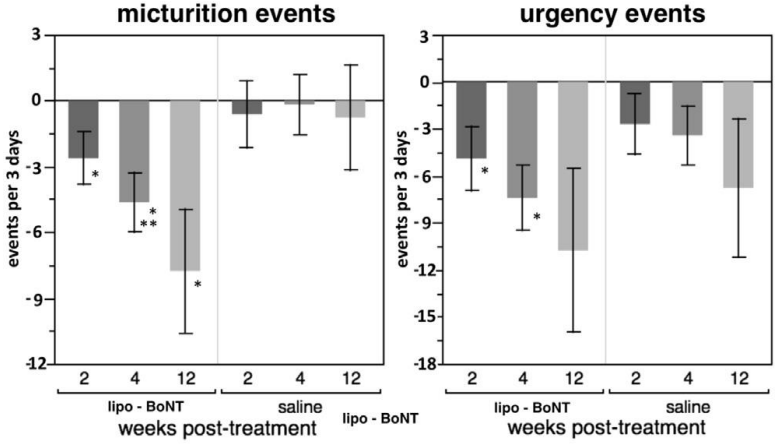
- Randomisierte placebokontrollierte Pilostudie (N=24)

SNAP25 Immunhistochemie





- Phase 2 Studie (N=62)



∗ p < 0.05 Wilcoxon matched-pair signed-rank, effect vs. baseline
∗∗ p < 0.05 ANOVA, effect vs. placebo

Kuo H.-C.., et al. Eur Urol 2014; 65:1117-24

Langzeitstudie

- Teilnehmer der 3 Zulassungsstudien eingeladen für Langzeitstudie
  - Nach 3.5 Jahren oder 6 Behandlungszyklen
  - Konstante Wirkung (Dranginkontinenz) 12 Wochen nach jeder Behandlung
  - Mediane Wirkdauer 7.6 Monate
  - Hohe Zufriedenheit bei 70-90%
  - Keine respiratorischen Probleme
  - Keine Antikörperentwicklung

Nitti V. et al. J Urol 2015;193 (4 Suppl) e719-20

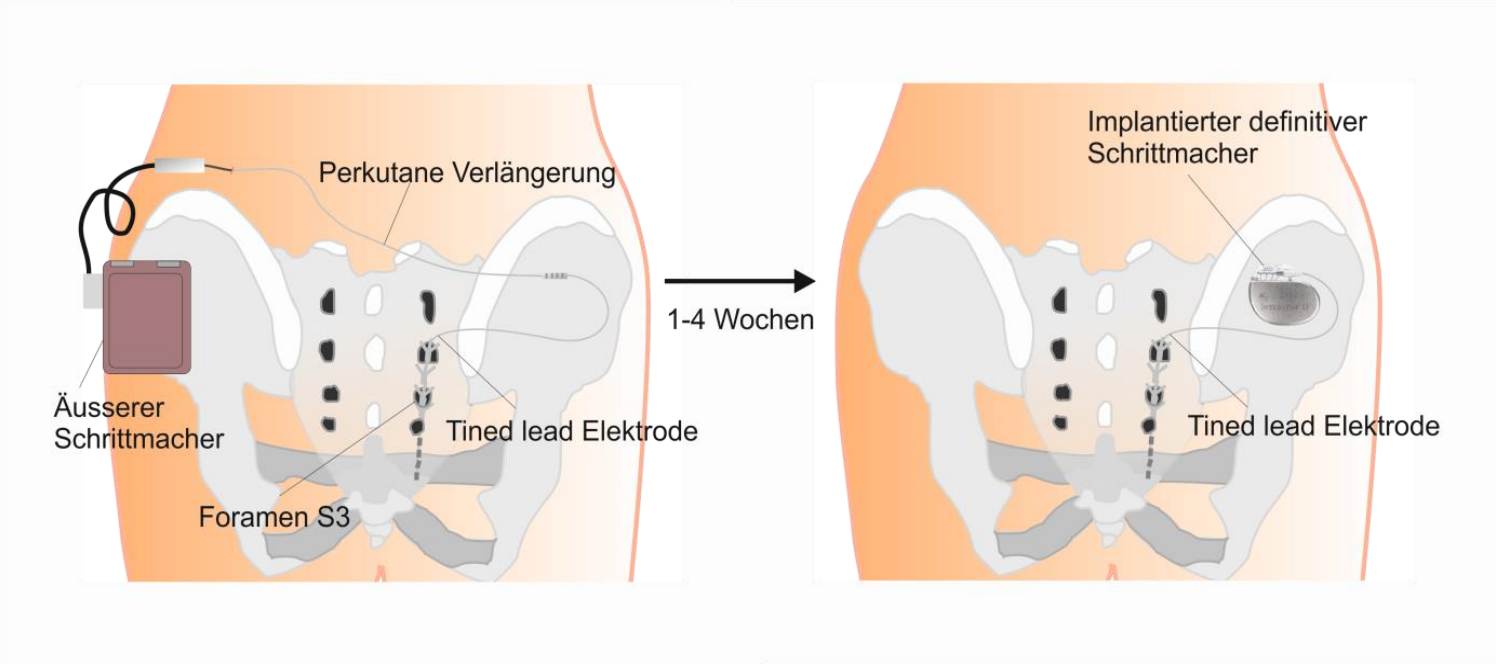
NEUROMODULATION

- SNM
- PTNS

Sakrale Neuromodulation (SNM) bei überaktiver Blase

- Geschichtliches
  - 1988 Tanagho & Schmidt
    - Erstes SNS Implantat bei einem urologischen Patienten
  - 1985-92 Multizenterstudie von Urosystems, Inc.
  - 1997 FDA-Zulassung für Dranginkontinenz
  - 1999 FDA-Zulassung Überaktive Blase und Harnretention
  - 2000 Markteinführung Europa
  - 2003 Erstes SNM-Implantat SG

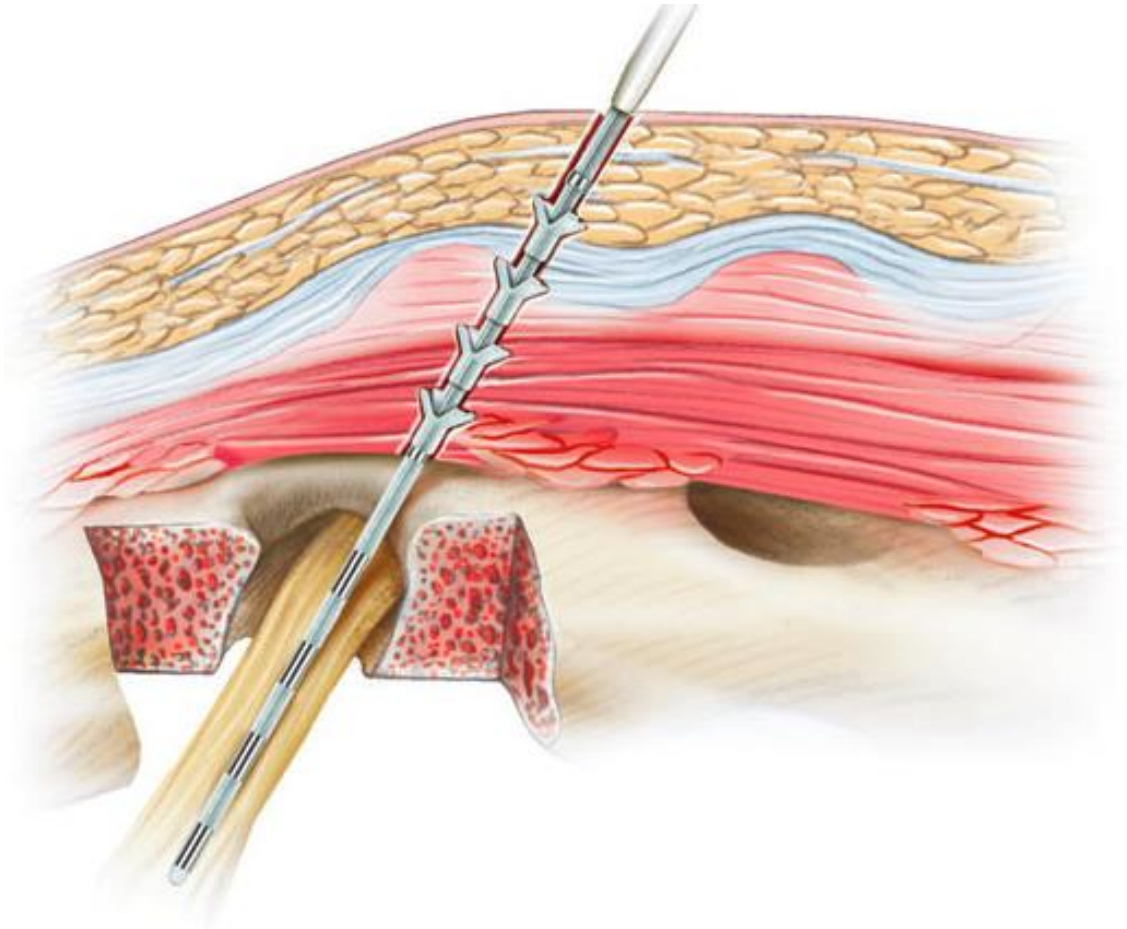
Sakrale Neuromodulation



Testphase

Einbau des Pulsgenerators

Implantation der quadripolaren Elektrode

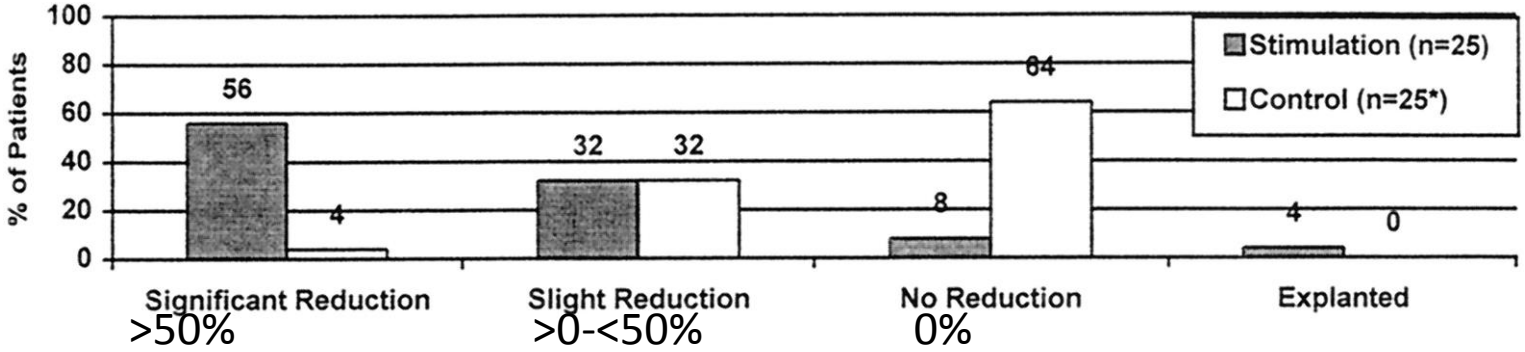


Wöllner J., et al. BJU Int 2012;110:146–59

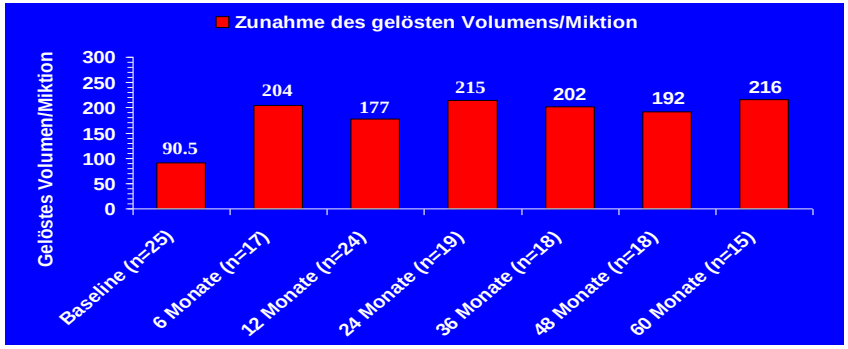
SNM bei idiopathischer überaktiver Blase

- Verschieden RCT's u.a. Hassouna 2000

Reduktion der Anzahl Miktionen pro Tag



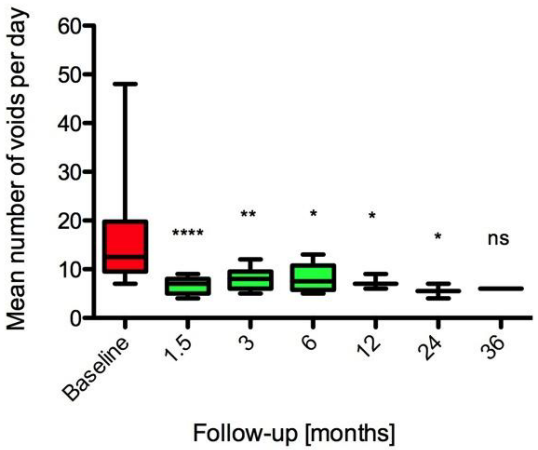
- Langzeitverlauf : van Voskuilen 2004

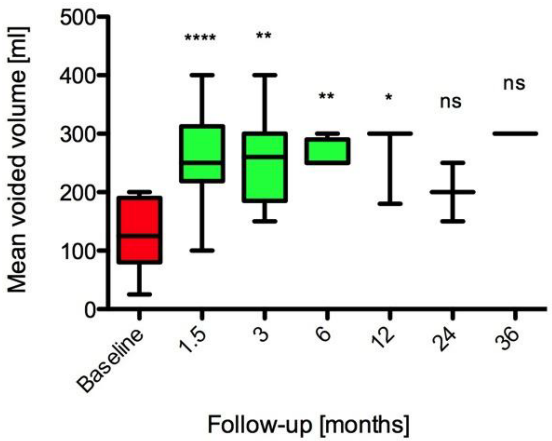


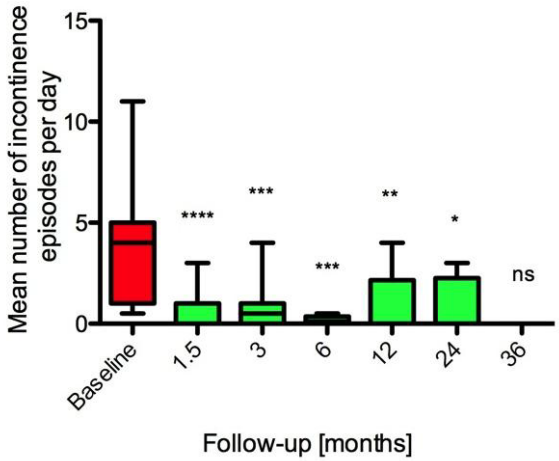
Hassouna M.M.., et al. J Urol 2000;163:1849-54
Van Voskuilen A., et al. J Urol 2004;171(4suppl):328

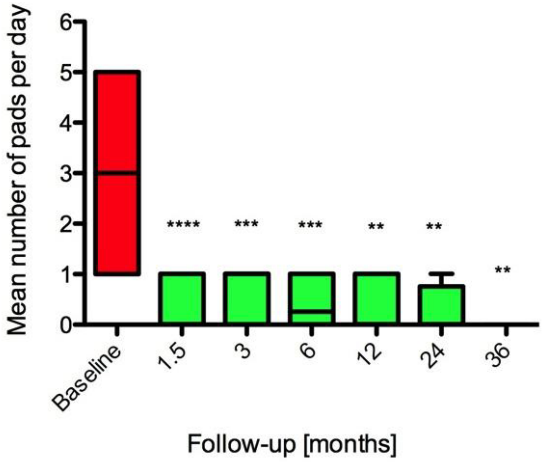
Eigene Erfahrungen bei überaktiver Blase

N=36









SNM bei neurogener überaktiver Blase

- Nur Fallserien

Testphase

	No. with success/total no. of tested patients	Success rate, %
LUTD resulting from:*		
MS	36/43	84
Parkinson's disease	4/6	67
Myelomeningocele	2/4	50
CVA	5/12	42
CP	2/2	100
Pelvic surgery	19/23	83
Disk disease	18/30	60
Spinal cord injury:	11/31	35
Complete	2/5	40
Incomplete	5/17	29
Unknown	4/9	44
Other neurologic disease or injury	48/80	60
Type of LUTD:**		
Chronic urinary retention	67/119	56
Urgency–frequency syndrome	6/8	75
Urgency incontinence	46/77	60
Combination†	26/29	90

Letzter Follow-up

	No. of patients with success/total no. of permanently implanted patients	Success rate, %
LUTD resulting from:*		
MS	46/50	92
Parkinson's disease	6/6	100
Myelomeningocele	1/2	50
CVA	6/10	60
CP	2/2	100
Pelvic surgery	14/23	61
Disk disease	10/18	56
Spinal cord injury:	47/61	77
Complete	10/12	83
Incomplete	30/37	81
Unknown	7/12	58
Other neurologic disease or injury	38/52	73
Type of LUTD:**		
Chronic urinary retention	65/89	73
Urgency–frequency syndrome	12/14	86
Urgency incontinence	62/84	74
Combination†	31/37	84

Kessler T.M., La Framboise D., Trelle S., Fowler C.J., Kiss G., Pannek J., Schurch B., Sievert K.D., Engeler D.S. Eur Urol 2010; 58:865-74

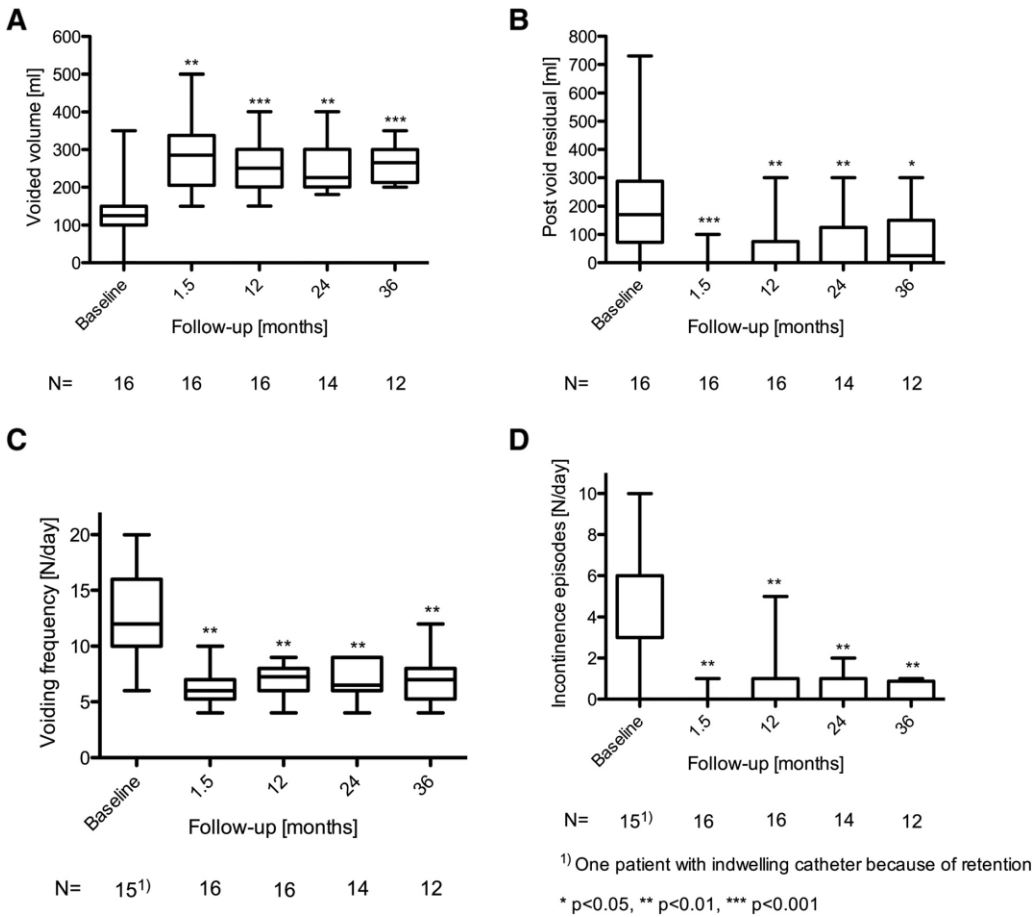
Adverse Events SNM bei neurogener Blase

	No. of patients with adverse events/total no. of permanently implanted patients	Adverse event rate, %
Type of adverse event (one event per patient):		
Lead migration	15/224	7
Pain at lead site	2/224	1
Infection at lead site	4/224	2
Lead fracture	3/224	1
Migration of permanent neuromodulator	1/224	1
Pain at site of permanent neuromodulator	12/224	5
Infection at site of permanent neuromodulator	11/224	5
Hypersensitivity to stimulation	9/224	4
Neuromodulator malfunction	3/224	1
Other	9/224	4
Type of surgical intervention resulting from an adverse event (one event per patient):		
Explantation of both lead and permanent neuromodulator	25/224	11
Explantation of lead only	8/224	4
Drainage/evacuation of seroma/haematoma/abscess	2/224	1
Other	10/224	4

Kessler T.M., La Framboise D., Trelle S., Fowler C.J., Kiss G., Pannek J., Schurch B., Sievert K.D., Engeler D.S. Eur Urol 2010; 58:865-74

SNM bei Überaktiver Blase wegen Multipler Sklerose

- Eigene Erfahrungen bei 16 konsekutiven Patienten (17 Tests)



Engeler DS, et al. BMC Urol 2015;15:105

SNM bei Blasenschmerzsyndrom

Systematische Review über publizierte Daten von Resultaten von SNM bei chronischem Beckenschmerz: 10/12 Papers über Blasenschmerzsyndrom

Published data on the outcome of sacral neuromodulation for BPS/IC

References	Technique	No. Pts	Duration of Test Stimulation	% Success PNE	% Success 2-Staged Procedure	% Permanent Implant	Mean Mos Followup	Treatment Success After Implant
Maher et al[22]	Unilat PNE S3	15	7–10 Days	73	—	—	—	—
Chai et al[21]	Bilat PNE S3	6	5 Days	Not available	—	—	—	—
Peters KM: Rev Urol 2002; **4**: 536	PNE + staged S3	33	2 Wks	67 (14/21)	92 (11/12)	67	5	Pain moderately improved in 35% + markedly improved in 30%
Comiter[25]	Bilat PNE S3 + unilat staged S3	25	9 Days	40 (4/10)	87 (13/15)	68	14	Mean reduction in VAS pain scores by 72%
Whitmore et al[23]	Bilat PNE S3	33	7–14 Days	78	—	52	—	—
Steinberg AC: Urology 2007; **69**: 441	Staged S3	15	Not available	—	—	Not available	14	Reduction in Urinary Distress Inventory 44%: mean decrease in posttreatment medication use of 1.4
Peters et al[24]	Pudendal vs S3 stimulation	22	7 Days	—	—	77	6	Mean VAS pain scores decreased 49% for SNM & 29% for PNS
Powell and Kreder[26]	PNE + staged S3	39	1–3 Wks	40 (13/33)	81.8 (9/11)	56	60	Long-term success in 77%, 65% free of pain symptoms
Marinkovic et al[27]	Staged S3	34	Not available	—	88	88	87	Mean reduction in VAS pain scores by 63%
Gajewski and Al-Zahrani[28]	Unilat PNE S3	78	5–7 Days	67	—	59	62	Long-term success in 72%

Schlussfolgerung

Vielversprechende Resultate bei kleinen Serien, aber insgesamt Evidenz ungenügend, um Rolle der SNM zu klären➔ Grössere kontrollierte Studien mit Langzeitverlauf benötigt

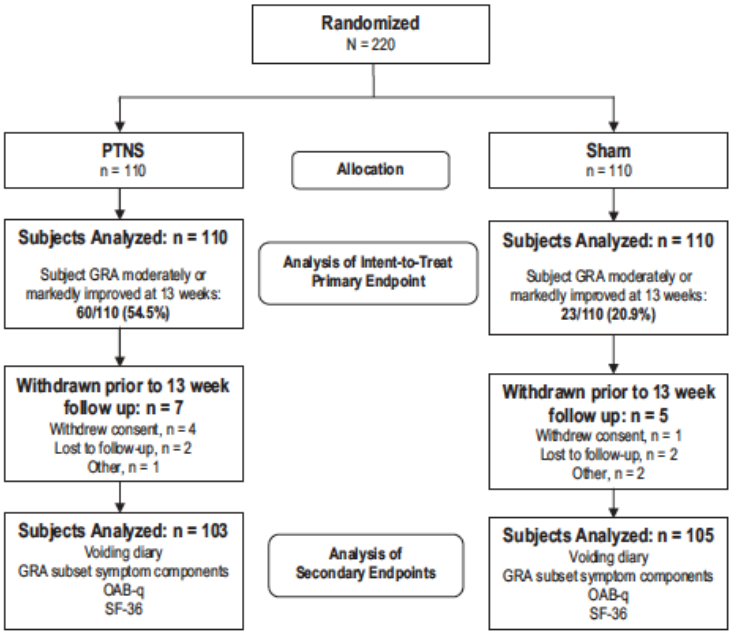
Marcelissen et al. 2011; 183:971-9

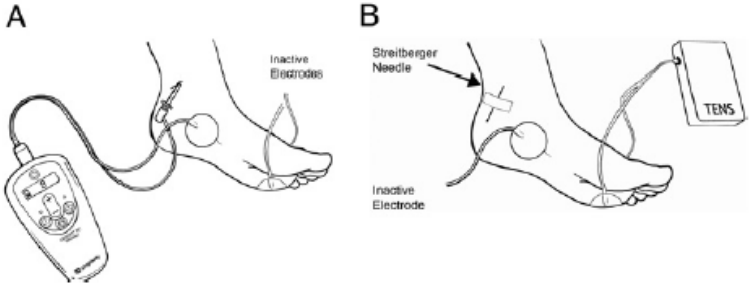
Perkutane tibiale Nervenstimulation (PTNS)

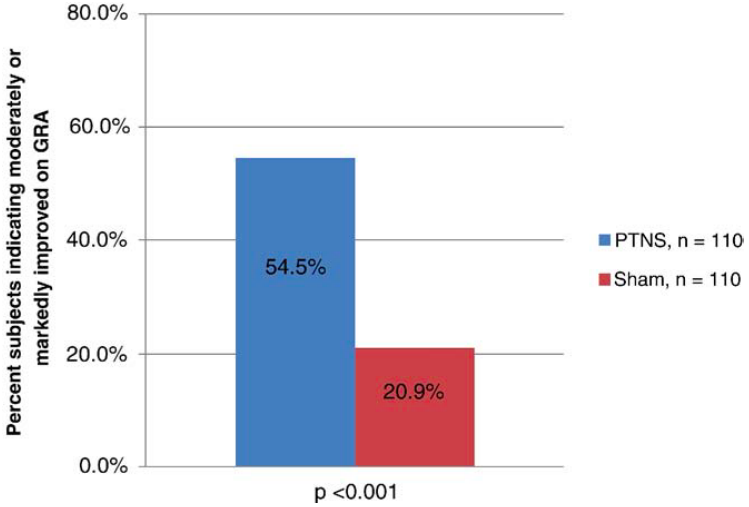
- Stoller 1987
- Neuromodulation über N. tibialis
- 34 Gauge Nadel
- 12 wöchentliche Behandlungen à 30‘
  - Erhaltungstherapie ca. 1/Monat

Perkutane tibiale Nervenstimulation (PTNS)

- Randomisierte, Sham-kontrollierte Studie (SUmiT-Trial)







Peters K.M. et al. 2010; 183:1483-43

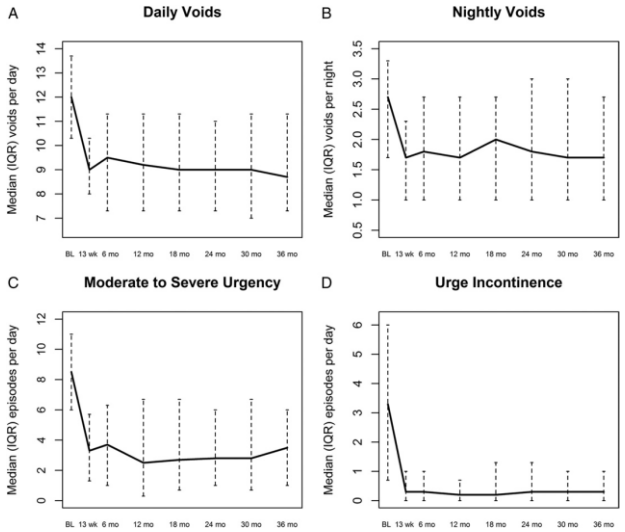
Perkutane tibiale Nervenstimulation (PTNS)

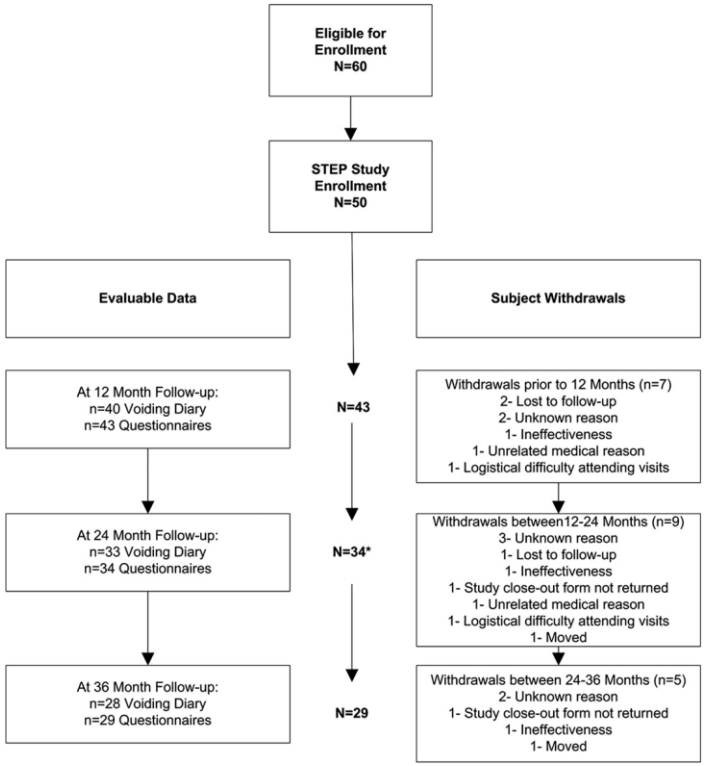
	Baseline	13 Wks	Change From Baseline	p Value	Difference (PTNS − sham)	p Value
Mean ± SD PTNS:						
Frequency*	12.3 ± 3.2	9.8 ± 2.8	−2.4 ± 2.5	<0.001	−0.9 ± 2.5	0.01
Nighttime voids†	2.9 ± 1.6	2.1 ± 1.4	−0.7 ± 1.2	<0.001	−0.4 ± 1.3	0.04
Voided vol‡	169.5 ± 78.9	183.0 ± 75.6	11.4 ± 45.0	0.01	5.5 ± 42.1	0.35
Mean ± SD sham:						
Frequency	12.4 ± 3.0	11.0 ± 3.1	−1.5 ± 2.4	<0.001		
Nighttime voids	2.9 ± 1.7	2.6 ± 1.6	−0.3 ± 1.4	0.02		
Voided vol	168.7 ± 84.0	172.6 ± 90.6	5.9 ± 39.0	0.13		
Median PTNS:						
Moderate to severe urgency§	8.3	3.7	−3.7	<0.0001		<0.001
Urge incontinence‖	3.0	0.3	−1.3	<0.0001		0.002
Median sham:						
Moderate to severe urgency	8.0	5.0	−2.0	<0.0001		
Urge incontinence	1.8	1.0	−0.3	<0.0001		

* Measured by average number of intentional voids per day (day and night in 3-day voiding diary).
† Measured by average number of waking episodes per day (in 3-day voiding diary).
‡ Average voided volume per void (CC) from the 3-day voiding diary (99 for PTNS, 102 for sham due to incomplete diary completion for this measuring parameter).
§ Measured by the median number of voids per day (in 3-day voiding diary).
‖ Measured by median number of incontinence episodes accompanied by moderate to severe urgency per day (day and night in 3-day voiding diary).

Perkutane tibiale Nervenstimulation (PTNS)

- Follow-up Studie des SUmiT-Trials (STEP)
  - 50 Patienten aus SUmiT-Trial
  - Relativ konstante Wirkung für die Patienten , welche das Follow-up beendeten (n=29)





Schlussfolgerungen

- Nach Versagen von konservativen und oralen medikamentösen Therapieansätzen sind sowohl...
  - wiederholte Botulinumtoxininjektion
  - wie auch Neuromodulation

  ...hervorragende Optionen für die Therapie der überaktiven Blase und Dranginkontinenz

  ...mögliche Optionen für ausgewählte Patienten mit einem Blasenschmerzsyndrom

Vielen Dank für Ihre Aufmerksamkeit