BOTULINUM TOXIN IN LOWER URINARY TRACT

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Botulinum neurorotoxin (BoNT)
Clinical applications

- Cosmetics
- Focal hyperhydrosis
- Excessive sweating in axilla and palms
- Hyperlacrimation
- Vocal cord dysfunctions
- Migrain and headaches
- Strabismus
- Muscular spasms and dystonia
- Pelvic floor problems
- Vaginusmus
- Lower Urinary Tract Problems

Naumann M, et al. Neurology 2008

Botulinum Toxin Applications in Urology

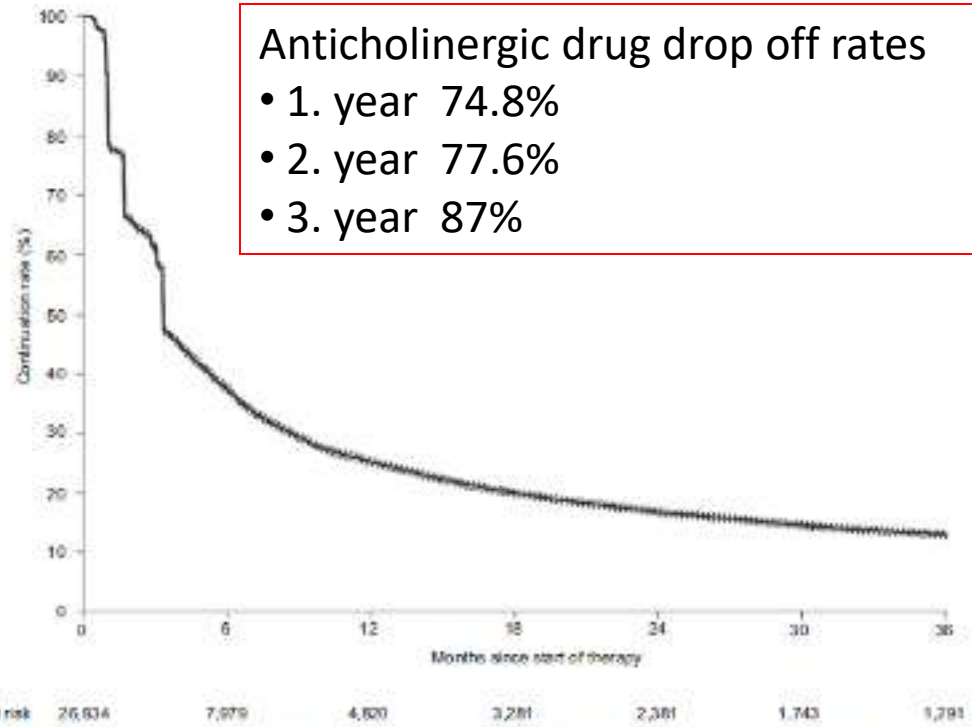
OAB
DSD
Idiopathic and Neurogenic detrusor overactivity
BPH
Chronic pelvic pain syndromes / Interstitial cystitis
Voiding dysfunction in children
Pelvic floor diseases

Discontinuation of Treatment Using Anticholinergic Medications in Patients With Urinary Incontinence

Matthias Kalder, MD, PhD, Konstantinos Pantazis, MD, Konstantinos Dinas, MD, PhD,

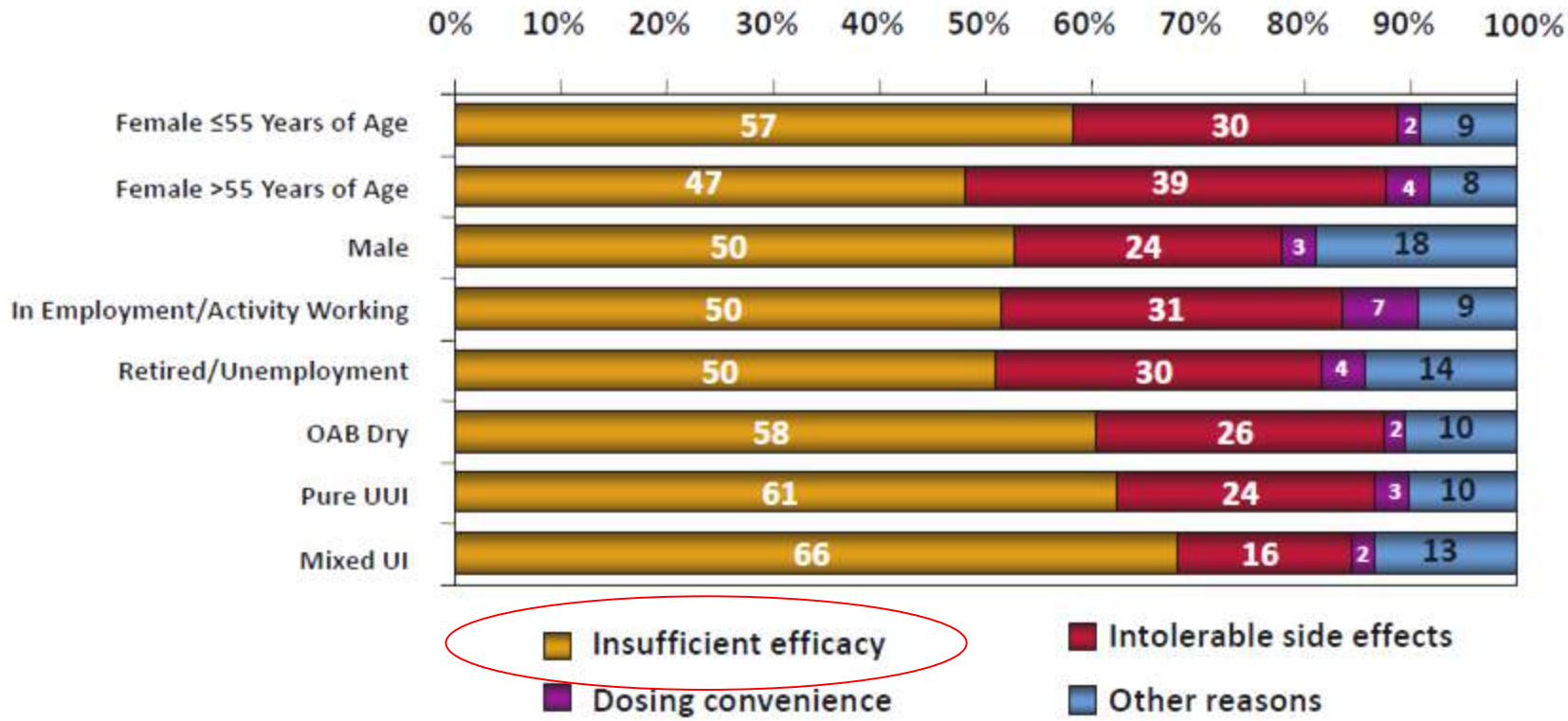
Anticholinergic drug drop off rates

- 1. year 74.8%
- 2. year 77.6%
- 3. year 87%



2. Kaplan–Meier curves for continuation over 36 months in patients with urinary incontinence treatment

The Reasons for Anticholinergic Treatment Drop Off



Guidelines on

Urinary Incontinence

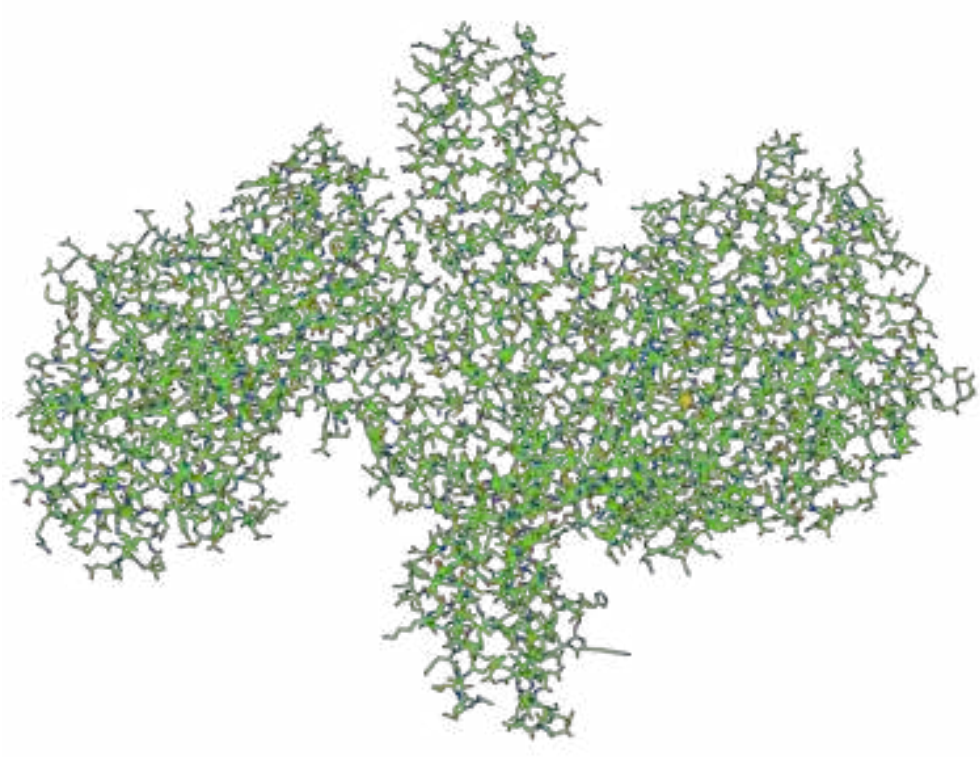
V.G. Lucas (Chair), D. Bedretdinova (Guidelines Associate),
[illegible]

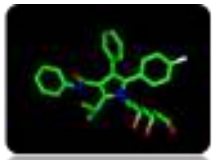
Evidence summary	LE
A single treatment session ofl onabotulinum toxin A (100U) injected in the bladder wall is more effective than placebo at curing and improving UUI and QoL for up to 12 months.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy.	3
There is a high risk of increased PVR when injecting elderly frail patients.	3
The risk of bacteruria after onabotulinum toxin A (100U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A 100 U is superior to solifenacin for cure of UUI.	1a
Long-term treatment with of onabotulinum toxin A may be associated with a high discontinuation rate.	2

Recommendations	GR
Offer bladder wall injections of onabotulinum toxin A (100 units) to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to selfcatheterise (ensure that they are willing and able to do so) and risk of UTI.	A

BoNT is huge and a very complex 3D protein[1]

BoNT/A (core)
149,500 Da[1,2]
$C_{6763}H_{10452}N_{1744}O_{2011}S_{33}Zn$





***Lipitor*® (Atorvastatin)[3]**
559 Da
$C_{33}H_{35}FN_2O_5$

1. Lacy DB et al. *Nat Struct Biol.* 1998;5:898-902.
2. Lacy DB, Stevens RC. *J Mol Biol.* 1999;291:1091-1104.
3. DrugBank http://www.drugbank.ca/drugs/DB01076 . Accessed April, 2011.
4. Schantz EJ, Johnson EA. *Perspect Bio Med.* 1997;40:317-327.

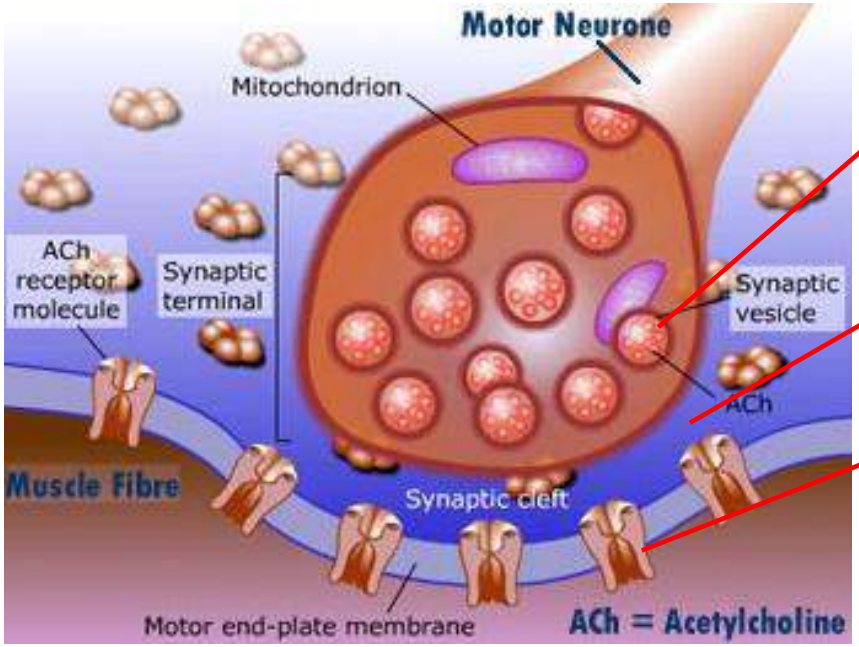
BoNT Types

- A-G: 7 different serotypes
- BoNT- A (Botox® ve Dysport®)
- BoNT- B (Neurobloc® ve Myobloc®)
- Effective on striated muscles for 3-4 months and smooth muscles for 6- 9 months

  (Reformation of presynaptic molecules and regrowth in terminal nerves endings)

BoNT: Mechanism of effect

Neuromuscular Junction



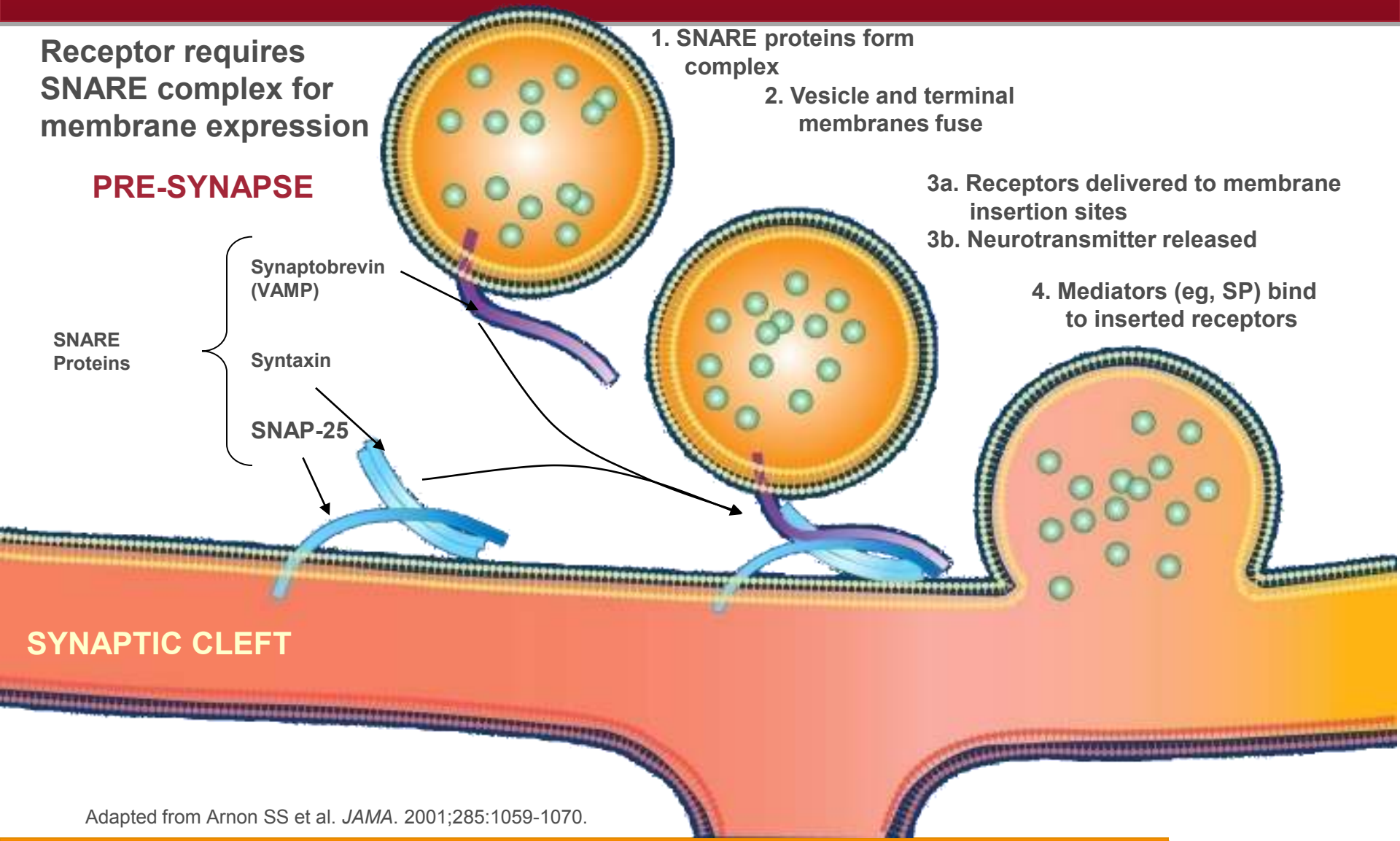
Synaptic vesicles with acetylcholine (Ach)

Synaptic cleft

ACh Receptor molecule

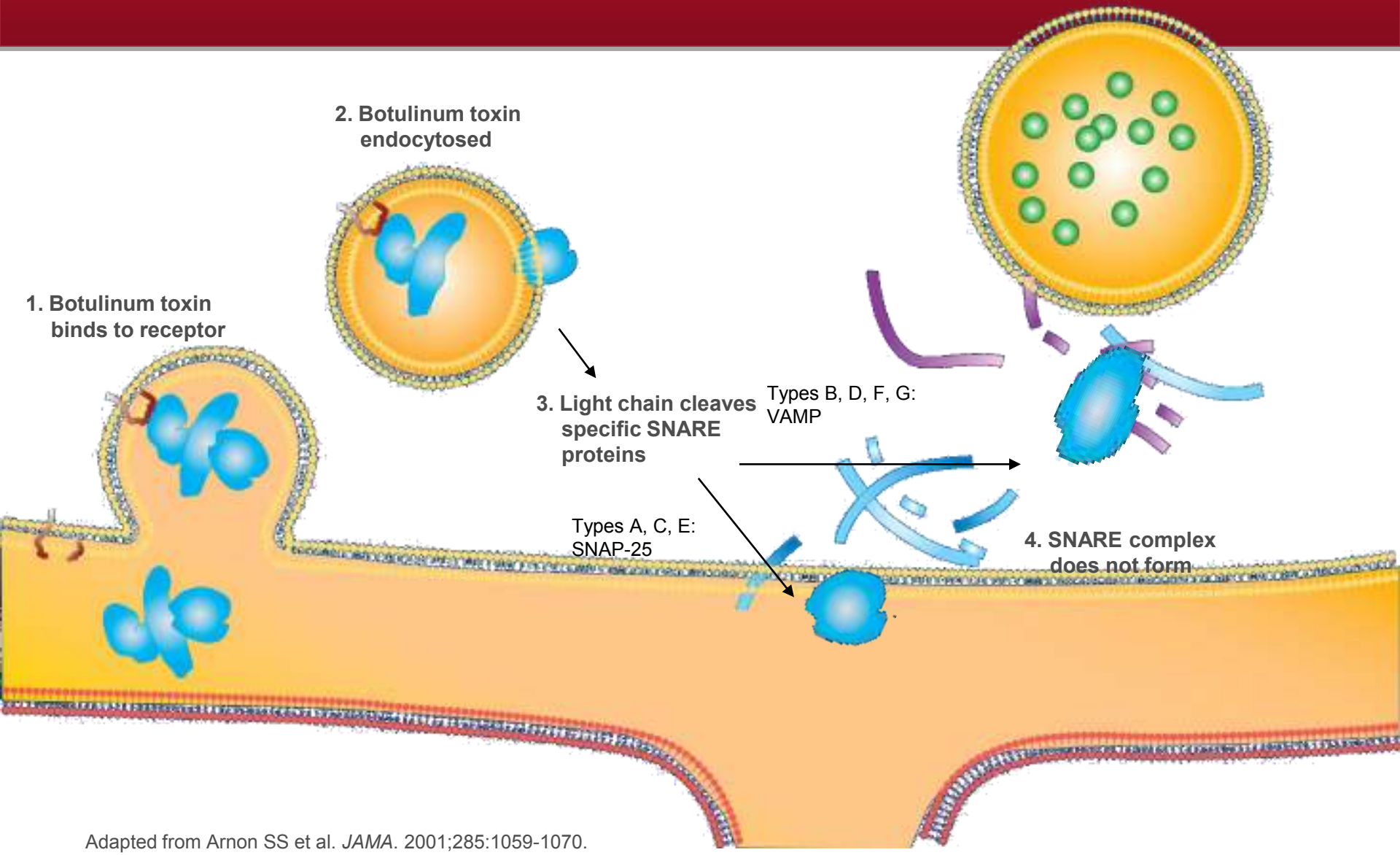
CONTRACTION

Release of ACh from motor nerve terminal



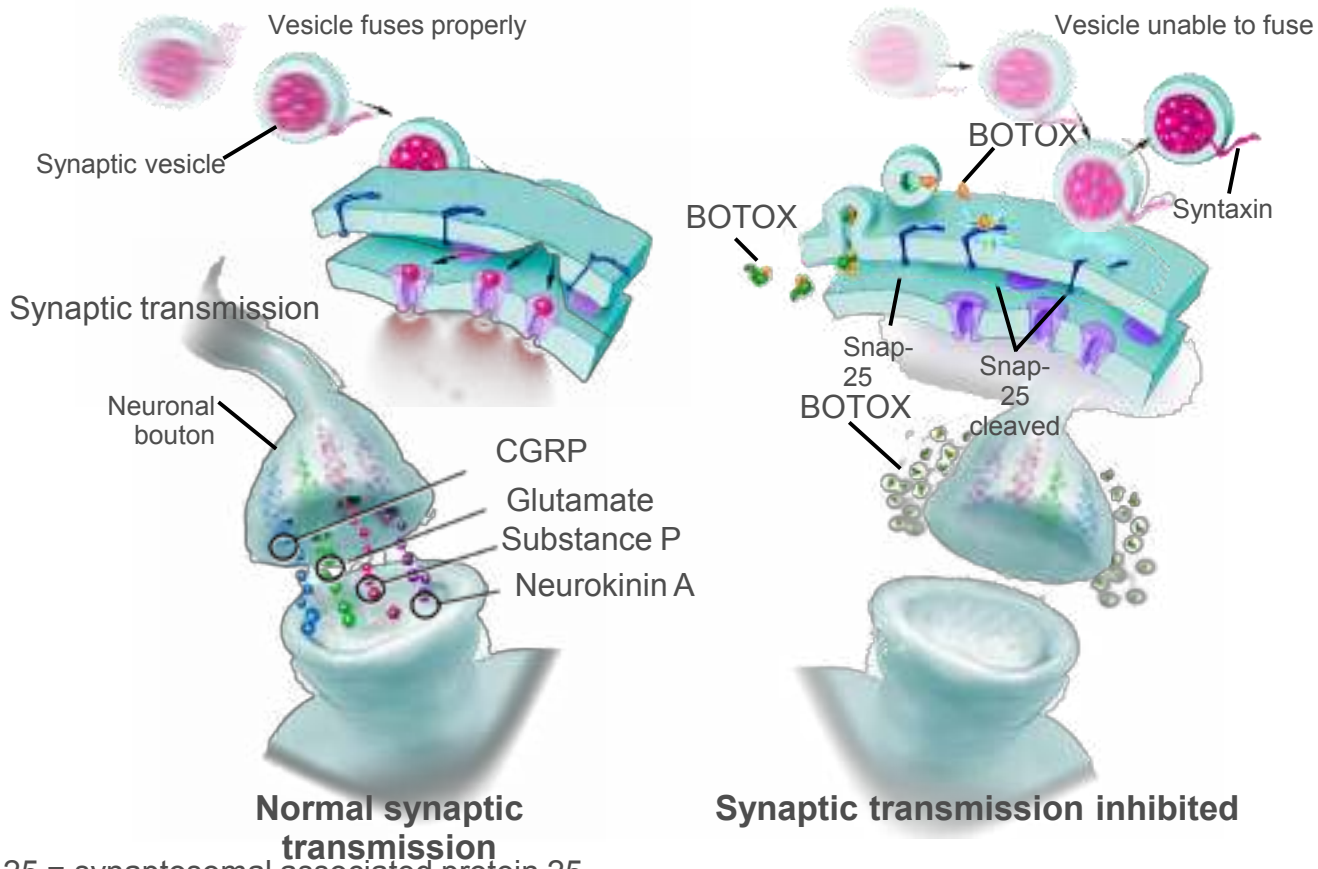
Adapted from Arnon SS et al. *JAMA*. 2001;285:1059-1070.

BoNT: Mechanism of effect



Adapted from Arnon SS et al. *JAMA*. 2001;285:1059-1070.

BoNT inhibits neurotransmitter transmisson



SNAP-25 = synaptosomal associated protein 25

Arnon SS et al. *JAMA*. 2001;285:1059-1070.

NDO and IDO/OAB: Indications and technique

IDO/OAB	
Use BoNTA to treat refractory IDO in patients willing to use CISC.	A
Use caution because the risk of voiding difficulty as well as the duration of effect has not been accurately evaluated to date. Future studies should address the benefit-risk ratio for the best minimal dosage.	
All patients should accept in writing the possible need to perform CISC following treatment.	A
Residual volumes should be measured regularly for the first month starting at the first week.	A
Patients should be told that the treatment does not last indefinitely but has a mean duration of 6 mo.	A
Comparison of injection techniques	
The dilution of Botox should be 10 U/ml per site; thus, the number of injection sites depends on the total dosage being administered (ie, 30 sites for a dosage of Botox 300 U in NDO). The optimum dose for dilution of Dysport has yet to be established.	B
The choice of flexible or rigid cystoscope should be left to local expertise.	C
The depth and location for injections should be within the detrusor muscle outside the trigone.	C

Refractory means no response at least for 3 months and at least to 2 different anticholinergic agents

Apostolidis A, et al. Eur urol 2009

Patient informed consent should include

- Relatively low effective time
- Requirement for re-injections
- Does not cure the pathology
- Need for CIC

BoNT: Application technique Bladder

- Dosage (100 IU-300 IU ?)
- Dilution ratio

  (1 mL, 3 mL, 10 mL)
- Injection site

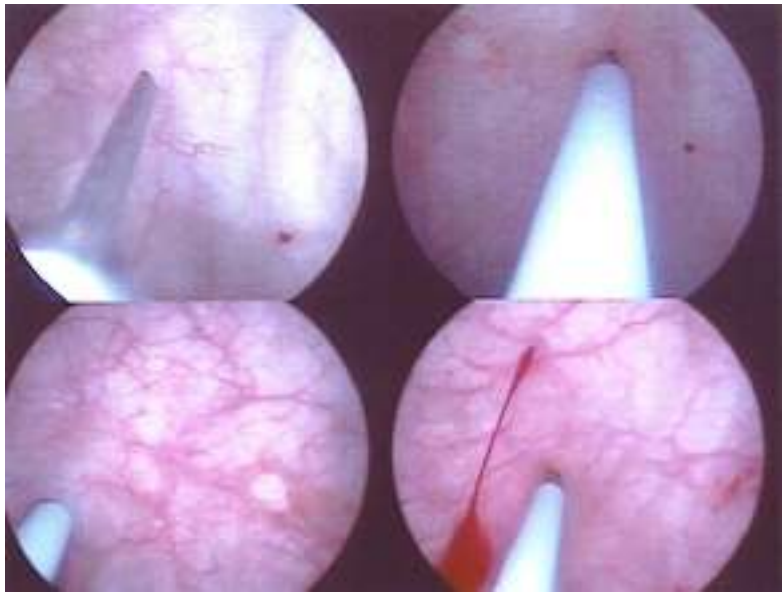
  (10-20- 30 site)
- Application site

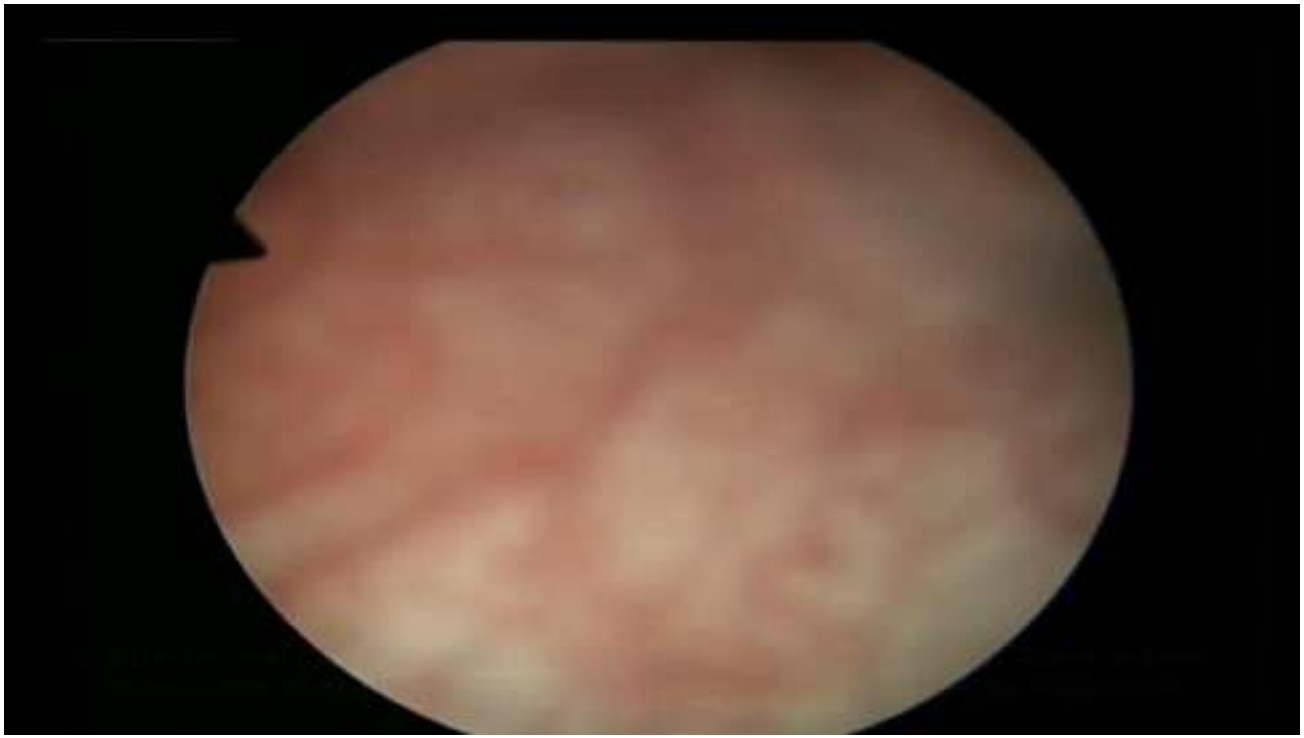
(trigon Preservation / Unpreserved

detrusor / suburothelium)

BoNT: Application tips

- AUA guidelines: Antibiotic prophylaxis (prebtx and post: 1-3 days)
- Local or general anesthesia (2% lidocain, 20 min)
- No Shake No pressure (mind the disulfide bonds)
- Conserve at 2 - 8C
- CIC training
- Partially full bladder (100-150mL)
- Flexible/rigid cystoscope





Botox A Industry Manual:
100 IU is diluted U in 10 mL and injected 0.5 ml at 20 sites
For NDO : 200 IU / 30 ml inj 1 ml at 30 sites

Neurourology and Urodynamics 33:S26–S31 (2014)

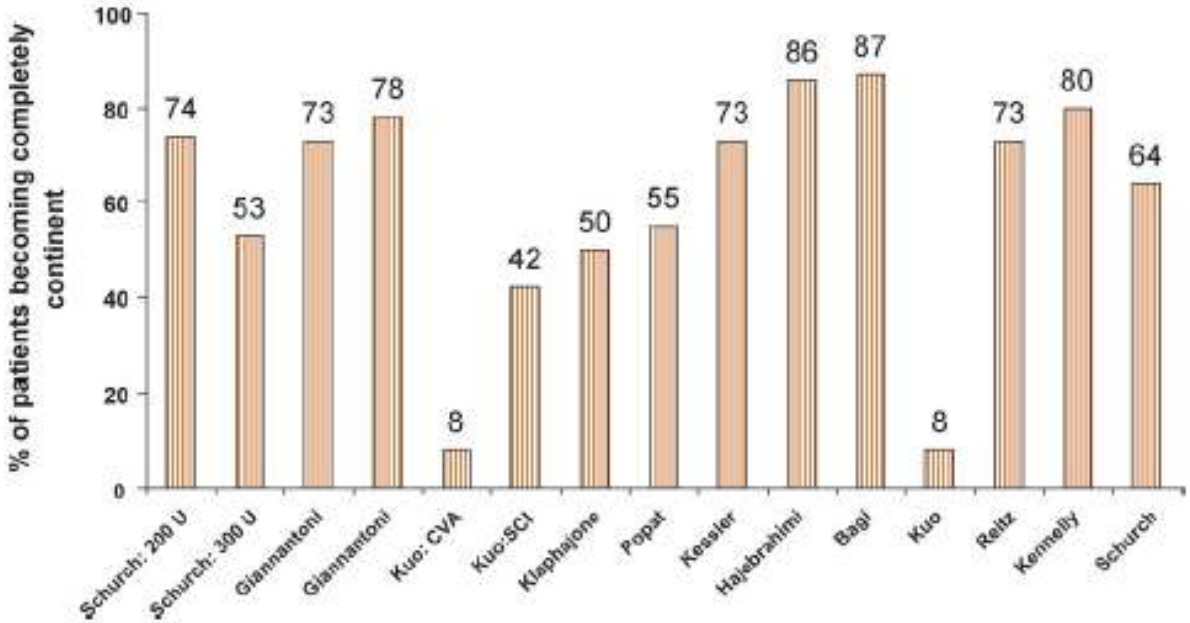
Chapter 5: Clinical Data in Neurogenic Detrusor Overactivity (NDO) and Overactive Bladder (OAB)

Francisco Cruz[1*] and Victor Nitti[2]

TABLE IV. Clinical and Urodynamic Parameters at Week 12 in the EMBARK Trials (OAB)

	Nitti et al.[24]		Chapple et al.[23]	
	Placebo (n = 277)	OnabotulinumtoxinA 100 U (n = 280)	Placebo (n = 271)	OnabotulinumtoxinA 100 U (n = 277)
Mean change from baseline in clinical and urodynamic parameters at week 12				
UI episodes/day (co-primary endpoint)	−0.87	−2.65‡	−1.03	−2.95‡
Micturition episodes/day	−0.91	−2.15‡	−0.83	−2.56‡
Urgency episodes/day	−1.21	−2.93‡	−1.24	−3.67‡
Nocturia episodes/day	−0.24	−0.45*	−0.25	−0.54†
Patients with a positive response on TBS, % (co-primary endpoint)	29.2	60.8‡	26.8	62.8‡
Mean change in I-QOL score[a]				
Total summary	6.8	21.9‡	6.3	23.1‡
Avoidance and limiting behavior	7.3	23.9‡	6.0	23.5‡
Psychological impact	6.1	19.6‡	6.5	21.5‡
Social embarrassment	7.2	22.6‡	6.3	25.0‡

Complete urinary incontinence with BoNT-A



Karsenty G, et al. Eur Urol 2008

Re-Injection

- The duration of symptom relief : 6.3-10.6 months

- Re-injection Period: 12 weeks – 18 months

- Average urodynamic effect: 9 months

- 100-300 IU applied 100 patients avarage re-injection period 10.6 months

Neurourology and Urodynamics 33:S26–S31 (2014)

Chapter 5: Clinical Data in Neurogenic Detrusor Overactivity (NDO) and Overactive Bladder (OAB)

Francisco Cruz[1*] and Victor Nitti[2]

Re-Injection-2

Botox 100 IU application:

- First re-injection period is 36.3 weeks, and further re-injection period is 36.1 weeks

- Decrease in urge incontinence episodes:
- 2.65 vs – 0.87(plasebo)

- Symptom relief is 48 %

Associated anticholinergic use

- Anticholinergics should be quitted after injection

- In anticholinergic non responders no need for associated anticholinergic use following failed BoNT use.

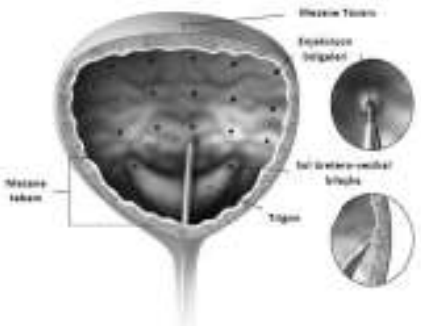
Nonresponse and Antibody Formation

- BoNT is bacterial origin and immune response is conceivable
- Following 1-15 injections (ave. 3.8): 0.49% antibody formation and no hypersenstivity docmentation
- In 1 series with 90 patients: 2.1% antibody formation

-In nonresponders, there is no only and sole factor !!!

-Antibody formation, main pathology, technical problems, BoNT conservation , and so on….

Trigone injection ?



Neurourol Urodyn. 2011 Sep;30(7):1242-8. doi: 10.1002/nau.21054. Epub 2011 May 10.

Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics.

Kuo HC[1].

- No association between trigon injection and VUR

BoNT-A
Side Effects and Complications

- Bleeding, hematoma and allergies
- Urinary retention, infection and pain

- *Possible side effects:*
  - *Muscle weakness,*
  - *dysphagia, upper extremity weakness ,*
  - *Fatal heart block,*
  - *diplopia, accomadation problems,*
  - *Rash,*
  - *Flue like symptoms*

Leippold T, et al. Eur Urol 2003, Abbott J, et al. Obstet Gynecol 2006,

Incidence

- Urinary infection: 6 – 35 %
- Dysuria: 12%
- Retention: 4 – 45%
- Hematuria: 3- 5 %
- CIC rate: 6- 88 %

- Urinary total incontinence and enuresis nocturna: case reports

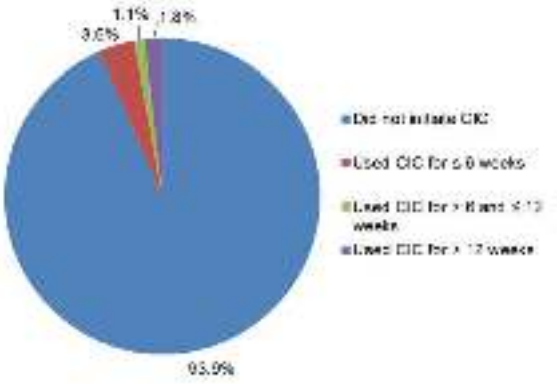
Apostolidis A, Eur Urol 2009

Long-Term Use and Complications

- BoNT-A: 5-10 years or 15 years results
- 7 year use in LUT is very plausible.
- 20 year use for dystonia is very plausible

33

Urinary Retention



- Generally after 10-15 days

- 100IU BoNT:

  Visco et al. 5% in 2 months, 3 in 4 ms and 1% in 6 ms

- In no retention cases in the first injection, spontaneous voiding in the second injection is 87%

- In retention cases in the first injection, retention rate is 100% in the second injection

Visco AG et al, New Eng J Med, 2012

EMBARK

- 280 pts: 100 IU Botox A
- Infection rate 15.5 % vs 6% placebo
- 2nd, 6th ve 12th PVR: 49 mL, 42 mL ve 32 mL
- In 8.7% pts > 200 mL PVR rise
- CIC beginning rate: 6.1%
- Treatment drop off due to side effects: 1.8%

Nitti VW et al, JUrol, 2013

Risk factors for Urinary Retention

- Kuo HC et al. 217 pts: 100-200 IU Trigone non-preserving

:

Risk factors: *Male patient, İnitial PVR>100 mL*

-Sahai A et al .; Preop urodynamics : *low flow rate, decreased pDetQmax, decreased detrusor contraction*

Kuo HC et al, Eur Urol, 2010, Sahai A, Urology 2008

Evidence summary	LE
A single treatment session of intravesical onabotulinumtoxinA (100-300 U) is more effective than placebo at curing UUI and improving UUI and QoL for up to 12 months.	1a
Doses of onabotulinumtoxinA above 100 U are associated with an increased risk of requiring de novo CIC.	1a
Doses of onabotulinumtoxinA above 100 U do not add additional improvement in QoL.	1b
There is no evidence that repeated injections of onabotulinumtoxinA have reduced efficacy.	3
There is a high risk of increased PVR when injecting elderly frail patients.	3
The risk of bacteruria is high following intravesical injection of botulinum toxin but the clinical significance of this remains uncertain.	1b
There is no evidence that one technique of injecting botulinumtoxinA is more efficacious or harmful than another.	1b
OnabotulinumtoxinA 100 U is superior to solifenacin for cure of UUI.	1a
Repeated injections of onabotulinumtoxinA may be associated with a high discontinuation rate.	2

Recommendations	GR
Offer onabotulinum toxin A (100 units) intravesical injections to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to self-catheterise (ensure that they are willing and able to do so).	A

IDO / OAB: Indications and technique

IDO/OAB	
Use BoNTA to treat refractory IDO in patients willing to use CISC.	A
Use caution because the risk of voiding difficulty as well as the duration of effect has not been accurately evaluated to date. Future studies should address the benefit–risk ratio for the best minimal dosage.	
All patients should accept in writing the possible need to perform CISC following treatment.	A
Residual volumes should be measured regularly for the first month starting at the first week.	A
Patients should be told that the treatment does not last indefinitely but has a mean duration of 6 mo.	A
Comparison of injection techniques	
The dilution of Botox should be 10 U/ml per site; thus, the number of injection sites depends on the total dosage being administered (ie, 30 sites for a dosage of Botox 300 U in NDO). The optimum dose for dilution of Dysport has yet to be established.	B
The choice of flexible or rigid cystoscope should be left to local expertise.	C
The depth and location for injections should be within the detrusor muscle outside the trigone.	C

BoNT-A in IDO/OAB---- A

10U/mL dilution for 20 sites---------- B

Apostolidis A, et al. Eur urol 2009

BoNT: Summary

- Refractory DOA

- At leat 6 months follow-up

-Prior UF and PVR

-Cytology or US ???

-Urodynamics is NOT a must

- Antibiotic surgical prophylaxis and post-op antibiotic
- DON'T USE Aminoglicosides
- Transient effect

Summary

- Infection : Postpone BoNT!
- Don’t shake the bottle too much
- Half full bladder....
- 0.5 -1 cc per injection site
- Prior CIC training is advisable

Summary

- STOP anticoagulants prior injection!
- Anesthesia: Sedation or 2% lidokain + 30 mL 14/1000 HCO3 for bladder instillation
- Needle goes 2-3 mm in depth
- At least 10 sites – at most 30 sites
- İnstill 1 mL of SF after last injection

Summary

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Efficacy and Safety of OnabotulinumtoxinA for Idiopathic Overactive Bladder: A Double-Blind, Placebo Controlled, Randomized, Dose Ranging Trial

Roger Dmochowski*†, Christopher Chapple‡, Victor W. Nitti§, Michael Chancellor||, Karel Everaert¶, Catherine Thompson||, Grace Daniell||, Jihao Zhou||, Cornelia Haag-Molkenteller||

- Post-op PVR > 200ml CIC required
- Benefit risk ratio is best with 100 IU
- Prior retention increases risk of retention in further injections

Summary

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OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3, Randomized, Placebo Controlled Trial

Victor W. Nitti, Roger Dmochowski, Sender Herschorn, Peter Sand, Catherine Thompson, Christopher Nardo, Xiaohong Yan, Cornelia Haag-Molkenteller, EMBARK Study Group

- No cath if no bleeding
- Wait for 15 days for full response
- 25% of pts do not desire second injection

  - no desire for CIC
  - unsatisfactory response.

Summary

- Average urodynamic response is 9 months

- Average injection period is 10.6 months

- Third injection has no effect on compliance