Prof. Martin Michel, MD

- Professor of Pharmacotherapy at Johannes Gutenberg Univ., Germany
- Post-doctoral training at Univ. of Essen (1985-1987 and 1990-1993), Univ. of California San Diego (1987-1990).
- Head of Nephrology and Hypertension Research Laboratory, Univ. of Essen (1993-2002)
- Head of Department of Pharmacology & Pharmacotherapy, Univ. of Amsterdam, Netherlands (2003-2011)

Prof. Martin Michel, MD (Cont'd)

- Global Head of Product & Pipeline Scientific Support at Boehringer Ingelheim (2011-2016)
- Editor of several international journals, e.g. Pharmacol Rev, N-S Arch Pharmacol, Mol Pharmacol
- Published more than 500 articles in peer-reviewed journals, mostly in urogenital and cardiovascular pharmacology

TITLE

Future directions in the treatment of overactive bladder syndrome

Future directions in the treatment of overactive bladder syndrome

Martin C. Michel, MD, MAE, FBPhS
Dept. of Pharmacology
Johannes Gutenberg University, Mainz, Germany

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Conflict of interest

- Public grant support
  - Deutsche Forschungsgemeinschaft
- Consultant
  - Apogepha
  - Astellas
  - Ferring
  - Velicept
- Travel support
  - Apogepha
  - Ferring
- Share holder
  - Velicept

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Overactive bladder syndrome (OAB)

- The International Continence Society defines OAB by the presence of "urgency, with or without urge incontinence, usually with frequency and nocturia"
- Urgency is defined as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer"
- OAB is highly prevalent among adults
  - 12-16% in overall adult population, increasing with age
- Major adverse effects on quality of life of patient and partner
- Huge economic loss to society

Abrams et al. (2002) Neurourol Urodyn 21: 167-178
Coyne et al. (2014) J Managed Care Pharm 20: 130-140

Times (and diapers) are changing …

In 2014, for the first time more diapers were sold in Europe for adult than for infant use

What is the medical need (tolerability)?

- Little tolerance for tolerability issues in non-life-threatening condition
- Muscarinic receptor antagonists
  - Largely good tolerability
  - Mild frequent issues (dry mouth), more serious, less frequent issues (impaired cognition)
  - Probably minor room for improvement within drug class
- β_3-Adrenoceptor agonists
  - Tolerability generally close to placebo
  - Rare cardiovascular side effects with mirabegron
    - Class effect?
  - Probably very minor room for improvement within drug class

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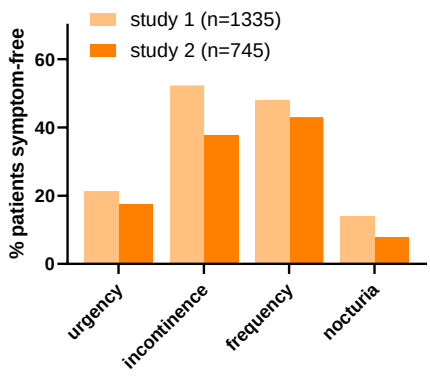
Maman et al. (2014) Eur Urol 65: 755-765
Michel & Gravas (2016) Exp Opin Drug Safety 15: 647-657

What is the medical need (efficacy)?

- Efficacy
  - How many become free of a given symptom?
  - Based on real world evidence with propiverine
  - Room for improvement
    - Incontinence
    - Frequency
  - Major room for improvement
    - Urgency
    - Nocturia
  - Possibly applicable to all muscarinic antagonists
  - Possibly also applicable to β_3-agonists



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Michel et al. (2018) Neurourol Urodyn 37 Suppl 5: S401-S402

Why is efficacy limited?

- Have we not yet identified the right drug class?
  - Question implies two assumptions
    - Is pathophysiology at time of diagnosis fully reversible?

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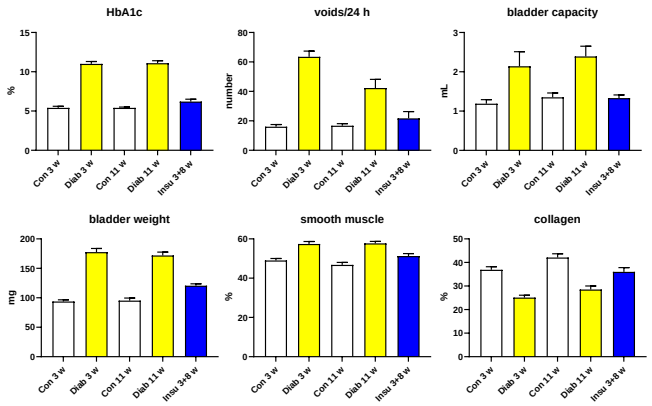
Reversability: bladder dysfunction in diabetes

- Experimental type 1 diabetes (streptozotocin injection in rats) changes bladder morphology and function
- Insulin treatment starting after established changes largely reverses this
- Similar data also for removal of bladder outlet obstruction



Xiao et al. (2015) Int J Urol 22: 410-415

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Why is efficacy limited?

- Have we not yet identified the right drug class?
  - Question implies two assumptions
    - Is pathophysiology at time of diagnosis fully reversible?
      - Possibly yes
    - Is there a “master switch” to do so?
      - Possibly yes, at least when cause is removed/eliminated
      - Master switch not necessarily the same in all patients

Why is efficacy limited?

- Have we not yet identified the right drug class?
  - Question implies two assumptions
    - Is pathophysiology at time of diagnosis fully reversible?
      - Possibly yes
    - Is there an unidentified “master switch” to do so?
      - Possibly yes, at least when cause is removed
      - Master switch not necessarily the same in all patients
- Is it too much to expect that one drug class can “cure” OAB?
  - OAB is a symptom complex, not a disease entity
  - Multiple risk factors and causes may lead to/present as OAB
    - each possibly requiring a specific treatment
  - Individual natural history is unpredictable

Multiple risk factors of OAB

- Age
- Lifestyle
  - Smoking
  - Fluid, alcohol and caffeine intake
- Metabolic disease
  - Obesity and diabetes
- Cardiovascular disease
  - Hypertension, atherosclerosis
- Neurological disease
- Urological disease

Unreasonable to assume
that each patients has the same pathophysiology

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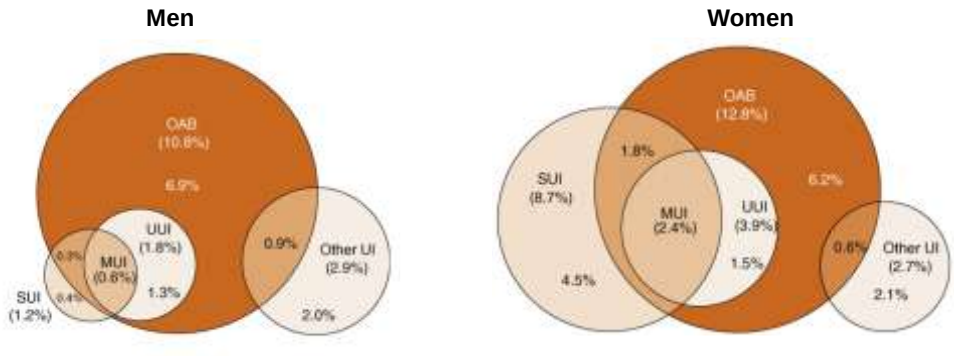
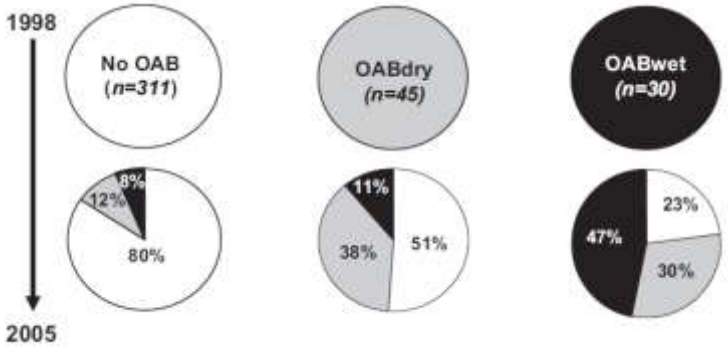
OAB and other Lower Urinary Tract Symptoms



OAB overlaps with various other LUTS – gender dependent

Irwin et al. (2006) Eur Urol 50: 1306-1315

Course of OAB not predictable in individuals



Heidler et al. (2011) Neurourol Urodyn 30: 1437-1441

Implications of OAB heterogeneity

- A hypothetical example (best case scenario)
  - 60% of OAB patients have pathophysiology A, fully responsive to drug X
  - 30% of OAB patients have pathophysiology B, fully responsive to drug Y
  - 10% of OAB patients have pathophysiology C, fully responsive to drug Z
- The optimal drugs X, Y and Z can “cure” 60%, 30% and 10% of patients
- In a broad OAB population
  - X will reduce symptoms by 60% (current standard of care of incontinence and frequency)
  - Y will reduce symptoms by 30% (would not look promising)
    - But would be highly efficacious in group B!
  - Z will reduce symptoms by only 10% (probably cannot be differentiated from placebo)
    - But would be highly efficacious in group C!

Resulting research needs

- Identify subsets of OAB patients based on pathophysiology and biomarkers
  - May preferentially exhibit one symptom (e.g. nocturia)
  - Example:
    - Early placebo-controlled phase III studies with desmopressin included only responders to open-label desmopressin
    - Strong enrichment for patients with desmopressin-responsive pathophysiology (nocturnal polyuria)

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Resulting research needs

- Identify subsets of OAB patients based on pathophysiology and biomarkers
- Create better understanding of pathophysiology subsets
  - Example:
    - Strong increase in urinary NGF in some but not other patients
    - Is NGF master switch for such patients?

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Ochodnicky et al. (2011) Neurourol Urodyn 30: 1227-1241

Resulting research needs

- Identify subsets of OAB patients based on pathophysiology and biomarkers
- Create better understanding of pathophysiology subsets
- Identify treatments addressing master switches of subsets

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If it was that easy

- Bladder function is controlled by a complex system of multiple tissues and cell types

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Multiple tissues and cell types as target

- Bladder
  - Smooth muscle
  - Urothelium
  - Interstitial cells
- Afferent nerves and ganglia
- Brain and spinal cord
- Kidney

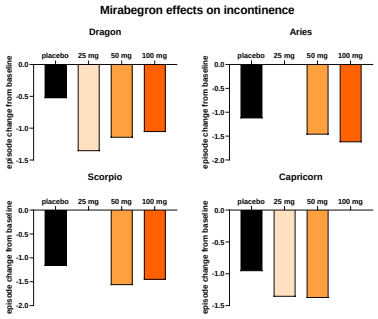
Receptors and effectors in urothelium

- Will addressing a single tissue/target be sufficient?
  - Only if is a master switch
- The most promising target may depend on patient subset

Michel (2015) Annu Rev Pharmacol Toxicol 55: 269-287

If it was that easy

- Bladder function is controlled by a complex system of multiple tissues and cell types
- The large placebo component in any existing OAB treatment makes it difficult to obtain clear signals
  - Probably even more difficult for urgency and nocturia



Chapple et al. (2014) Neurourol Urodyn 33: 17-30

Conclusions

- Room for improvement of tolerability is limited for oral OAB treatments
- The greatest medical need in OAB is increased efficacy
  - Greatest need for urgency and nocturia
  - Both have major adverse impact on QoL
- Major efficacy gains may not come from new drug classes if the overall OAB population is targeted
- Major research needs
  - Identify subsets of OAB patients with specific pathophysiology/biomarkers
  - Understand pathophysiology of such subsets
  - Identify treatments addressing master switches of such pathophysiology

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