Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2013-B-024 Mirabegron

Stand: 08.04.2013

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Mirabegron
Symptomatische Therapie von imperativem Harndrang, erhöhter Miktionsfrequenz und/oder Dranginkontinenz bei überaktiver Blase (ÜAB)

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Flavoxat, Oxybutynin, Propiverin, Tolterodin, Solifenacin, Trospiumchlorid, Darifenacin, Fesoterodin
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Beckenbodentraining ist bei Harninkontinenz verordnungsfähig
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	nicht angezeigt

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Mirabegron ATC Name	Symptomatische Therapie von imperativem Harndrang, erhöhter Miktionsfrequenz und/oder Dranginkontinenz, die bei Erwachsenen mit überaktiver Blase (ÜAB) auftreten können.
Flavoxat G04BD02 Spasuret®	Zur symptomatischen Behandlung von Pollakisurie, imperativem Harndrang und Dranginkontinenz
Oxybutynin G04BD04 Dridase®	Zur symptomatischen Behandlung der Überaktivität des Detrusors (Harnblasenmuskels; idiopathische oder neurogene Detrusorüberaktivität), mit den Symptomen Pollakisurie, Nykturie, imperativem Harndrang und Drang-Inkontinenz.
Propiverin G04BD06 Propiver®	Zur symptomatischen Behandlung von Harninkontinenz und/oder erhöhter Miktionsfrequenz und Harndrang bei Patienten mit • idiopathischer Detrusorhyperaktivität (überaktiver Blase) oder • neurogener Detrusorhyperaktivität (Detrusorhyperreflexie) durch Rückenmarkschädigungen, z. B. Querschnittslähmung oder Meningomyelozele.
Tolterodin G04BD07 Detrusitol®	Symptomatische Behandlung von Dranginkontinenz und/oder Pollakisurie und imperativem Harndrang, wie sie bei Patienten mit dem Syndrom der überaktiven Blase vorkommen können.
Solifenacin G04BD08 Vesikur®	Symptomatische Therapie der Dranginkontinenz und/oder der Pollakisurie und des imperativen Harndrangs, wie sie bei Patienten mit dem Syndrom der überaktiven Blase auftreten können.
Trospium G04BD09 Spasmex®	Zur Behandlung der Detrusor-Instabilität oder der Detrusor-Hyperreflexie mit den Symptomen Pollakisurie, imperativer Harndrang und Dranginkontinenz.
Darifenacin G04BD10 Emselex®	Symptomatische Behandlung von Dranginkontinenz und/oder häufigem Wasserlassen und verstärktem Harndrang, wie es bei erwachsenen Patienten mit einem Syndrom der überaktiven Harnblase auftreten kann.

Fesoterodin G04BD11 Toviaz®	Symptomatische Behandlung von Dranginkontinenz und/oder häufigem Wasserlassen und verstärktem Harndrang, wie es bei erwachsenen Patienten mit einem Syndrom der überaktiven Harnblase auftreten kann.

Quellen: AMIS-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2012-A-016 (überaktive Blase)

Auftrag von: Abteilung Arzneimittel

bearbeitet von: Abteilung Fachberatung Medizin

Datum: 9.04.2013

Synoptische Evidenzübersicht zur Ermittlung der zweckmäßigen Vergleichstherapie:

Inhalt:

Indikation für die Recherche:

Überaktive Blase

Berücksichtigte Wirkstoffe/Therapien:

a) Nichtmedikamentöse (konservative) Therapien
b) medikamentöse Wirkstoffe: Flavoxat, Oxybutynin, Propiverin, Tolterodin, Solifenacin, Trospium, Darifenacin, Fesoterodin

Nicht betrachtete Therapieoptionen:

- Elektrostimulation nicht betrachtet, da erst die 3. Behandlungsstufe lt. AWMF-Leitlinie und lt. z.B. amerikanischer AUA-Leitlinie

- Chirurgische Interventionen nicht betrachtet, da erst die 6. Behandlungsstufe lt. AWMF-Leitlinie
- Botulinum-Toxin: off-label

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„überaktive Blase“*** durchgeführt (Recherche am ***19.03.2013*** abgeschlossen). Die Update-Recherche erfolgte ergänzend zur systematischen Recherche zum Wirkstoff MK-4618 (Stand August 2012, Suchzeitraum 2007-2012). Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Update Recherche ergab ***50*** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Davon wurden **5** Quellen eingeschlossen. Insgesamt ergab dies **15** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen:

BT bladder training
ER Extended-release
OAB over active bladder
PFMT pelvic floor muscle training
PTNS posterior tibial nerve stimulation
SUI Stress urinary incontinence
UI Urinary Incontinence
UUI Urgency urinary incontinence

Ausgewählte Auszüge

aus der in diesem Dokument vorliegenden gesamten Evidenzsynopse

I. EAU guidelines on urinary incontinence (Thuroff et al Eur Urol 2011)

aus dem Kapitel der Leitlinie "Comparison of antimuscarinic agents":

1. Studien und deren Methodik

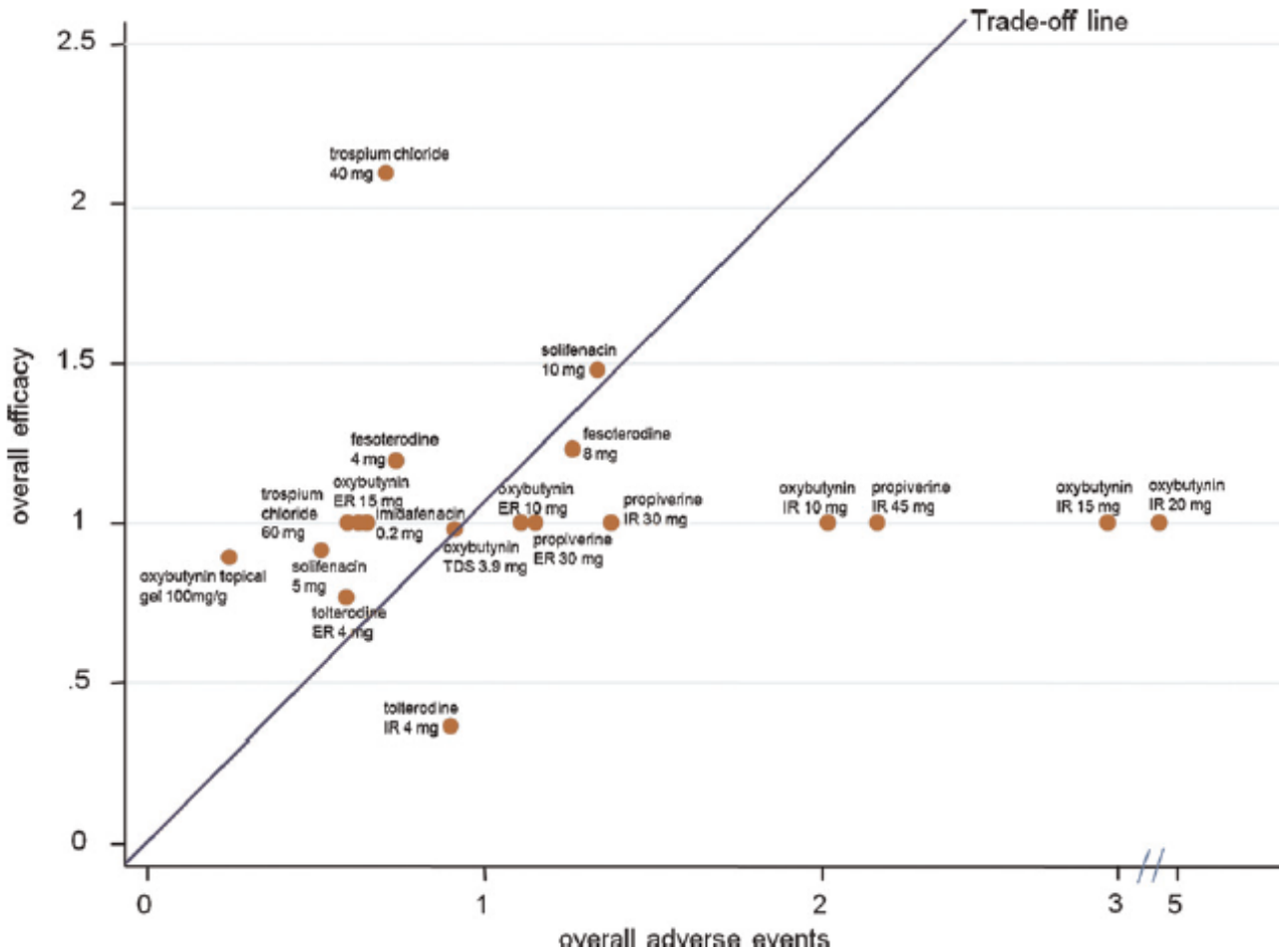
- There is a considerable body of evidence covering this question, comprising over 40 RCTs and five systematic reviews. Nearly all the primary studies have been funded and sponsored by the manufacturer of the newer drug under evaluation, which forms the experimental arm of the RCT. It was noted that upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm.
- In general, these studies have been designed for regulatory approval. They have a short treatment duration of typically 12 weeks and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. It is therefore difficult to use the results from these trials in daily clinical practice to select the best first-line drug or second-line alternative following the failure of initial treatment. A quality assessment carried out as part of the most recent systematic review found that all the trials were of low or moderate quality.

2. Evidence summary:

- There is no consistent evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI (Level of evidence: 1a)
- Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI. (Level of evidence: 1b)
- ER and once-daily formulations of antimuscarinic drugs are generally associated with lower rates of dry mouth than IR preparations, although discontinuation rates are similar. (Level of evidence: 1b)
- Oxybutynin IR or ER shows higher rates of dry mouth than the equivalent formulation of tolterodine. (Level of evidence: 1a)
- There is no evidence that any particular antimuscarinic agent is superior to another for improvement in QoL. (Level of evidence: 1a)

II. Trade-off Analyse zwischen Wirksamkeit und Nebenwirkungen

Aus: Buser N, Ivic S, et al. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. Eur Urol 2012; 62 (6): 1040-60.



(IR = immediate release, ER = extended release, TDS = transdermal)

Diese Analyse ergibt sich nicht aus direkten Vergleichen der Wirkstoffe, zur Methodik, siehe unter entsprechendem Systematischen Review

III. direkte Vergleiche der Wirkstoffe:

Oxybutynin, Tolterodin, Solifenacin, Trospium, Fesoterodin

(mit den meisten Angaben bzw. Vergleichen im Cochrane Review Madhuvrata, 2012)

Abkürzungen

k.A keine Angaben in Review
St Studien

Wirkstoffe
Feso Fesoterodin
Oxy Oxybutynin
Solif Solifenacin
Tolt Tolterodin
Trosp Trospium

Endpunkte
C Cure
I Improvement
QoL Lebensqualität
LE Leakage episodes

Nebenwirkungen
TM Trockener Mund
Abbr Studienabbrüche

↓ / ↑ / ↔ statistisch signifikante Verminderung / bzw. Erhöhung / nicht signifikant

Ergebnisse zu den vorhandenen direkten Vergleichen der 5 Wirkstoffe
(die Aussage zur Signifikanz gilt für den links in der Zeile gelisteten Wirkstoff jeweils im Vergleich zu dem in der Spalte genannten Wirkstoff)

	Feso	**Oxy**	**Solif**	**Tolt**	**Trosp**
Feso		k.A.	k.A.	3 Studien C or I ↑ LE ↑ QoL ↑ TM ↑ Abbr ↑	keine verwertbaren Daten aus Studien
Oxy			1 Studie keine Wirk-samkeitsdaten berichtet TM ↑ Abbr ↑	C or I (5 St) ↔ LE (7 St) ↔ QoL (2 St) ↔ TM (8 St) ↑ Abbr (10 St) ↑	C or I (2 St) ↔ LE (1 St) ↔ QoL (0 St) TM (4 St) ↑ Abbr (3 St) ↑
Solif				C or I (2 St) ↑ LE (3 St) ↑ QoL (4 St) ↑ TM (5 St) ↔ Abbr (4 St) ↓	k.A.
Tolt					keine verwertbaren Daten aus Studien
Trosp					

Gelb markierte Literatur wurde zusätzlich neu aufgenommen im Vergleich zur früheren Evidenzsynopse zu B-2012-042

Cochrane Reviews

Alhasso et al. Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Stand: 2009. Cochrane Database of Systematic Reviews.	**Authors' Conclusions** The use of anticholinergic drugs in the management of OAB is well established. The limited evidence available suggests that there will be more improvement of symptoms during treatment when (a) anticholinergics are used rather than bladder training, and (b) anticholinergics are combined with bladder training rather than using either modality on its own. There was not enough evidence with which to assess whether symptomatic improvement is sustained after stopping either treatment. This is important because the aim of bladder training is to achieve long-term improvement. Anticholinergic treatment has well recognised side-effects, such as dry mouth, and these are not uncommon. • The review was characterised by having few, and generally small, trials of moderate quality in each comparison. Some of the trials included patients with idiopathic OAB, with clear exclusion of those with neurological diseases, but others did not clearly report such exclusions. This in itself could result in interpretation difficulties, given that it is known that neuropathic bladders respond differently to anticholinergic drugs. • There is limited evidence to suggest that during treatment anticholinergic medication alone is better than bladder training (BT) alone. Data describing subjective cure were, however, only reported in two trials and did not show a consistent pattern. • There were too few data to draw any conclusions about various electrical stimulation modalities compared with drugs. • The combination of bladder training and biofeedback-assisted PFMT (see table 'Characteristics of included studies' for a detailed description of the technique) was compared with an anticholinergic drug alone in one trial by Burgio 1998. Although there was no apparent difference in cure rates, the data did suggest greater improvement in the combination group. Fragestellungen des Reviews: To compare the effects of various anticholinergic drugs with various non-pharmacologic therapies for idiopathic overactive bladder syndrome in adults. Einzelne Vergleiche des Reviews: 1. Anticholinergic drugs versus bladder training. 2. Anticholinergic drugs versus pelvic floor muscle training (PFMT) alone. 3. Anticholinergic drugs versus electrostimulation [nicht betrachtet, da Elektrostimultion erst die 3. Behandlungsstufe lt. AWMF und z.B. amerikanischer AUA-Leitlinie sind]. 4. Anticholinergic drugs versus surgery. [nicht betrachtet, da Chirurgische Interventionen erst die 6. Behandlungsstufe lt. AWMF-Leitlinie sind] 5. Anticholinergic drugs in combination with non-drug therapies versus non-drug therapies alone.

	6. Anticholinergic drugs in combination with non-drug therapies versus anticholinergic drugs alone. 7. Anticholinergic drugs versus combination non-drug therapies Methodik: • All randomised, controlled trials of treatment with anticholinergic drugs for overactive bladder syndrome or urge urinary incontinence in adults, in which at least one management arm involved a non-drug new therapy. Trials amongst patients with neuropathic bladder dysfunction were excluded. • Für alle Fragestellungen: 13 trials with 1770 participants; Treatment duration 3 to 12 weeks, one trial with a follow-up analysis at 24 weeks after starting treatment • primary measure of outcome was the number of participants whose symptoms were not 'cured' while on treatment • Weitere Endpunkte: **Participants' observations** (self-reported, subjective, Definitions based on criteria reported for each trial) **Quantification of symptoms** (e.g. Number of pad changes over 24 hours) **Clinician's observations** **Quality of life** **Adverse events** Die genannten Endpunkte werden im Folgenden nur berichtet, falls hierzu Daten im Review vorhanden waren. Ergebnisse zu den relevanten Fragestellungen (s.o.): **1. Anticholinergic drugs versus bladder training.** Six trials assessed various anticholinergics versus bladder training (oxybutynin, Collas 1994 (N=57); oxybutynin, Colombo 1995 (N=81, women); probantheline, Macaulay 1988 (N=50); oxybutynin, Milani 1987 (N=81, women); tolterodine, Park 2002 (N=74, women); and oxybutynin, Szonyi 1995 (N=60)). • Data describing **cure rates** during and after treatment were only available from two of the six trials (56 people). They tended to favour the anticholinergic groups but the differences were not statistically significant: not cured during treatment 7 out of 28 versus 14 out of 28 (RR 0.52; 95% 0.26 to 1.04; P = 0.07) (Colombo 1995; Macaulay 1988); not cured after treatment 9 out of 28 versus 16 out of 28 (RR 0.56, 95% CI 0.29 to 1.09, P = 0.09) (Colombo 1995; Macaulay 1988). In the latter comparison there was statistical heterogeneity- one trial suggested no difference whereas the other favoured anticholinergics. • Data describing **subjective improvement** during treatment were available for all six trials (288 participants). Fewer in the anticholinergic group did not improve during treatment (61 out of 142 versus 86 out of 146, RR 0.73, 95% CI 0.59 to 0.90, P = 0.004, Comparison 01.03). No data were available describing improvement after stopping treatment nor about nocturia, incontinence episodes or pad tests.

- **Adverse events and withdrawal**
  All three trials (Colombo 1995;Milani 1987; Park 2002) reporting this outcome found more adverse events in the anticholinergic groups (overall 38 out of 100 versus 2 out of 100, RR 13.10, 95% CI 4.18 to 41.03, P < 0.001). Data on withdrawals from treatment were available for only one trial (Colombo 1995): four out of 42 in the anticholinergic group compared with 2 out of 39 in the bladder training group withdrew from treatment.

2. Anticholinergic drugs versus pelvic floor muscle training alone.
No eligible trials were identified.

5. Anticholinergic drugs in combination with non-drug therapies versus non-drug therapies alone.
Two trials assessed a combination of an anticholinergic drug with bladder training versus bladder training alone (tolterodine, Park 2002 (N=74, women); and oxybutynin, Szonyi 1995 (N=60)).

- In one small trial, the data were too few to assess differences in **cure rates** (Szonyi 1995).
- **subjective improvement**, the overall effect in the two small trials was in favour of a combination of an anticholinergic with bladder training compared with bladder training alone (RR 0.55, 95% CI 0.32 to 0.93).
- The percentage change from baseline in the **number of voids** per day for the anticholinergic plus bladder training and bladder training alone arms were 32.6% and 27.1% respectively, but statistical analysis was not possible (Park 2002).
- Similarly, the percentage change in the **sensation of urgency** from baseline for the same groups was reported as 63.2% and 48.4% respectively (Park 2002).
- **Adverse events and withdrawals**
  In one small trial (Park 2002) there were 7 out of 26 adverse events in the combination (anticholinergic plus bladder training) group compared to 0 out of 24 with bladder training alone. Adverse eventsweremainly drymouth, blurred vision, heartburn, constipation and dry skin.

6. Anticholinergic drugs in combination with non-drug therapies versus anticholinergic drugs alone.
(a) in combination with bladder training:
Two trials addressed this comparison (Park 2002(N=74, women); Mattiasson 2003 (N=501)): both trials compared tolterodine 4 mg daily in combination with bladder training with tolterodine alone.

- Although both trials favoured the combination, there was no statistically significant difference in **subjective improvement** between combination treatment (anticholinergic plus bladder training) versus the anticholinergic drug alone (RR 0.81, 95%CI 0.61 to 1.06, P = 0.13)
- In one trial (Mattiasson 2003), the percentage **change in incontinence episodes** per day from baseline was reported as 87% for the anticholinergic plus bladder training arm and 81% for the anticholinergic arm.
- **Adverse events and withdrawals**

	The proportion of people experiencing adverse events was similar in both groups (RR 0.94, 95% CI 0.83 to 1.07) (Mattiasson 2003; Park 2002). (b) in combination with pelvic floor muscle training (PFMT): One trial assessed tolterodine versus PFMT plus tolterodine (Millard 2004 (N=475)). • There was no statistically significant difference between the groups in terms of **subjective improvement** when PFMT was added to anticholinergic treatment • There were also no statistically significant differences in the **number of incontinence episodes** per day or **urinary frequency**, but there were fewer reports of the **sensation of urgency** with tolterodine alone (MD 0.6, 95% CI 0.10 to 1.10, Comparison 02.11) (Millard 2004) compared with the drug supplemented with PFMT. **7: Anticholinergic drugs versus combination non-drug therapies** One small trial (Burgio 1998 (N=197, women)) compared oxybutynin 7.5 mg daily with the combination of biofeedback-augmented pelvic floormuscle training and bladder training. • There was no statistically significant difference in **subjective cure** rates between combination therapy and anticholinergic drug alone. • However, for **subjective improvement**, the overall effect favoured the combination (bladder training plus PFMT) therapy (RR 2.42, 95%CI 1.00 to 5.85). • There were fewer **incontinence episodes** per day in the combination therapy group compared with the anticholinergic drug alone (MD 0.41, 95% CI 0.03, 0.79).
Herderschee et al.. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. Cochrane Database of Systematic Reviews 2011	Women of all ages with Stress UI, Urgency UI or Mixed UI included Nur zwei Studien für **Subgroup analysis nach Type of incontinence (urgency urinary incontinence,** UUI): Wang 2004 mit OAB), andere Studie neurogene Störung. **Wang 2004 (low risk of bisas RCT)** 1. PFMT (n=40 women). 2. PFMT + clinic biofeedback (BF) (n=38 women) Primary endpoint: 12 weeks. Ergebnisse: • Lebensqualität (King's Health Questionnaire, KHQ): alle 9 Domänen nicht signifikante Ergebnisse • Women's perception of change in incontinence - not cured or improved: 21/34 (PFMT + BF) vs. 24/34 (PFMT), RR = 0.88 [0.62, 1.23]
Madhuvrata et al.. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane	Dargestellte Fragestellung aus Review: 1. A particular anticholinergic drug versus another in the management of overactive bladder symptoms.

Database of Systematic Reviews 2012	Methodik: All randomised, controlled trials of of anticholinergic drugs for the treatment of overactive bladder symptoms or detrusor overactivity. adult men and women with a symptomatic diagnosis of overactive bladder syndrome. Although people with neurological disorders cannot, by definition, have overactive bladder syndrome, they often experience overactive bladder symptoms secondary to their neurologic disease and are offered anticholinergic drugs. Therefore, trials that recruited people with neurologic disorders complaining of overactive bladder symptoms or with a diagnosis of neurogenic detrusor overactivity, or both, were included. • primary measure of outcome: Condition-specific quality of life (e.g. Incontinence Impact Questionnaire) (Shumaker 1994), generic quality of life, and psychosocial measures. • Weitere Endpunkte: **Participants' observations** (e.g. symptom scores, perception of cure or improvement, satisfaction with outcome, subjective, Definitions based on criteria reported for each trial) **Quantification of symptoms** (e.g. number of leakage episodes, frequency, urgency and volume (urinary diary).) **Clinician's observations (**e.g. urodynamic measures (such as maximum cystometric capacity) and clinical findings**)** **Adverse events** Die genannten Endpunkte werden im Folgenden nur berichtet, falls hierzu Daten im Review vorhanden waren. • Included studies 86 trials, 70 parallel and 16 cross-over design, including a total of 31,249 adults, 22,996 women and 5426 men (note: some trials did not report by gender). Sample sizes ranged from 10 (Di Stasi 2001a) to 2417 (Kaplan 2010). Data were available for the quantitative synthesis from 158 reports of 68 studies. Cross-over studies did not present data in a way that could be included in the metaanalyses. Twenty-nine collected quality of life data (the primary outcome measure) using validated measures, but only 15 reported useable data. • Sensitivity analysis was performed by excluding studies comparing different preparations (extended release and immediate release) and different routes of administration of anticholinergics. Ergebnisse zur relevanten Fragestellung: **1. A particular anticholinergic drug versus another in the management of overactive bladder symptoms.** Treatment duration ranged from two weeks to three months in nearly all studies, with a median length of three months. The exceptions were one trial that investigated the effect of a single dose (Froehlich 1998), one trial that had a treatment period of one week (Chapple 2005c) and two studies that had treatment periods of one year or more (Hofner 2000; Salvatore 1995). Sixteen trials reported outcomes of interest but no useable data

	were provided (Bagger 1985; Burton 1994; But 2010; Chaliha 1998; Chapple 2002; Chapple 2007; Davila 2001a;Di Stasi 2001a;Di Stasi 2001b; Leung 2001;Massey 1986; Osca 1997; Salvatore 1995; Stohrer 2002;Wehnert 1992; Zeegers 1987). Due to deficiencies in data reporting (for example point estimates without measures of variation) many trials contributed little or no data to the review. The lack of similarity in measures limited the possibilities for combining data from individual trials. The primary outcome of interest in the review was quality of life (Qol). Validated incontinence specific quality of life measures were reported by 29 trials (Barkin 2004; But 2010; Chapple 2002; Chapple 2004b; Chapple 2004c; Chapple 2005b; Chapple 2007;Choo 2008;Davila 2001a;Dmochowski 2003; Fader 2007; Herschorn 2009; Herschorn 2010; Ho 2010; Homma 2002; Homma 2006; Homma 2008; Homma 2009; Junemann 2005; Junemann 2006; Kaplan 2010; Leung 2001; Minassian 2007; Nitti 2005; Nitti 2007; VanKerrebroeck 2001; Yamaguchi 2007; Yamanishi 2009; Zellner 2007) of which only 15 reported useable data. **<u>Oxybutynin versus:</u>** (a) <u>tolterodine</u> Thirteen parallel arm studies: Abrams 1998; Altan-Yaycioglu 2005; Appell 2001; Diokno 2003; Dmochowski 2003; Drutz 1999; Homma 2002; Lee 2001; Leung 2001; Malone-Lee 2001b; Qiu 2002; VanKerrebroeck 1997; Xia 2001a), • Oxybutynin versus Tolterodine: there were no statistically significant differences for quality of life, patient reported cure or improvement, leakage episodes or voids in 24 hours, • but **fewer withdrawals** due to adverse events with tolterodine (risk ratio (RR) 0.52, 95%confidence interval (CI) 0.40 to 0.66, data from eight trials) and less risk of dry mouth (RR 0.65, 95% CI 0.60 to 0.71, data from 10 trials). (b) <u>trospium</u> • Two trials reported data on **cure or improvement** (Hofner 2000; Zellner 2007). There was no statistically significant difference between the groups (RR 1.00, 95% CI 0.90 to 1.11). • **Quantification of symptoms:** Zellner et al. (Zellner 2007) reported on change from baseline in leakage episodes in 24 hours and micturition in 24 hours at end of treatment. None of the results were statistically significant at 12 weeks. • **Clinician measures:** Three trials reported maximum cystometric capacity (Froehlich 1998; Madersbacher 1995; Osca 1997) and two trials reported residual volume at the end of treatment (Froehlich 1998; Madersbacher 1995). There was no statistically significant difference between the groups for either comparison. The confidence intervals for both outcomes were wide. • **Adverse events:** Three trials reported on withdrawals due to adverse events (Hofner 2000;Madersbacher 1995; Zellner 2007) with significantly fewer withdrawals in the trospium group (RR 0.66, 95% CI 0.48 to 0.91). The result reflected the higher weighting given for the larger Zellner trial. Four trials reported data on dry mouth (Hofner 2000; Madersbacher 1995; Osca 1997; Zellner 2007); the meta analyses showed a statistically

	significant result favouring trospium (RR 0.64, 95% CI 0. 52 to 0.77). (c) propantheline (Gajewski 1986; Thuroff 1991), → in D nicht zugelassen (d) propiverine (Madersbacher 1999; Stohrer 2002), • **Quantification of symptoms:** One trial (Stohrer 2002) reported data on change from baseline leakage episodes and micturitions in 24 hours, with no significant difference between the groups at three weeks • **Clinician measures:** The combined data from two trials did not show any statistically significant difference in maximum cystometric capacity post-treatment (WMD -6.42, 95% CI -33.94 to 21.10) or residual volume at the end of treatment (WMD 1.65, 95% CI -2.73 to 6.03) • **Adverse events:** The combined data showed no statistically significant difference (RR 1.78, 95% CI 0.91 to 3.50) between the groups for withdrawals due to adverse events at three to four weeks. Meta-analysis of data from two trials found statistically significantly fewer reports of drymouth in those taking propiverine at three to four weeks (RR 0.77, 95% CI 0.65 to 0.90) *(e)* solifenacin (Herschorn 2010). • Keine Wirksamkeitsdaten berichtet. • The withdrawals due to adverse events and dry mouthwere statistically significantly lower in the solifenacin group. **Tolterodine versus:** (a) oxybutynin (see above). (b) solifenacin (Chapple 2002; Chapple 2004b; Chapple 2005b; Choo 2008; Ho 2010), all favouring solifenacin: • there were statistically significant differences for **quality of life** (standardised mean difference (SMD) -0.12, 95% CI -0.23 to -0.01, data from three trials), • patient reported cure or improvement (RR 1.25, 95% CI 1.13 to 1.39, data from two trials), • leakage episodes in 24 hours (weighted mean difference (WMD) -0.30, 95% CI -0.53 to -0.08, data from four studies) urgency episodes in 24 hours (WMD -0.43, 95% CI -0.74 to -0.13, data from four trials) • There was no difference in withdrawals due to adverse events and dry mouth but after sensitivity analysis dry mouth rates (RR 0.69, 95% CI 0.51 to 0.94) were statistically significantly lower with solifenacin when compared to immediate release (IR) tolterodine. (c) propiverine (Junemann 2005): • Qol was comparable between the groups • no statistically significant difference in the change from baseline in leakage episodes per 24 hours, incontinence per 24 hours and urgency episodes per 24 hours between the groups

	(d) fesoterodine (Chapple 2007; Herschorn 2009; Kaplan 2010): • statistically significantly **better QoI** with 8mg of fesoterodine compared to ER tolterodine (SMD -0.20, 95% CI -0.27 to -0.14) • statistically significantly **higher patient reported cure** or improvement with fesoterodine 8 mg (RR 1.11, 95% CI 1.06 to 1.16) • statistically significantly lower end of treatment leakage episodes per 24 hours (WMD -0.19, 95% CI -0.30 to -0.09) (Analysis 1.4), micturition per 24 hours (WMD -0.27, 95% CI -0.47 to -0.06) (Analysis 1.5) and urgency per 24 hours (WMD -0.44, 95% CI -0.72 to -0.16) (Analysis 1.6) favouring fesoterodine 8mg. There was statistically significant heterogeneity in the analysis of end of treatment urgency per 24 hours. This appeared to be due to the Chapple trial and the reason for heterogeneity could not be explained. • significantly higher withdrawals due to **adverse events** (RR 1.45, 95% CI 1.07 to 1.98) and dry mouth (RR 1.80, 95% CI 1.58 to 2.05) with fesoterodine 8 mg. (e) trospium (Junemann 2000): Abstract only, No useable data were published. (f) darifenacin (Romanzi 2005): Abstract only, No useable data were published. **Propiverine versus:** (a) solifenacin (Yamaguchi 2007): • **QoL:** No data were reported but the article stated that there was no statistically significant difference between the groups except for severity domain, where there was a significantly greater reduction with solifenacin 10 mg than with propiverine 20 mg. • no difference in patient reported **cure or improvement**. • no statistically significant difference between the groups but wide confidence intervals for the change in number of **leakage episodes,** change in number of **micturitions** per 24 hours and change in **urgency** per 24 hours. • no significant difference in the number of withdrawals due to **adverse events**. Dry mouth rates were significantly lower in the solifenacin group (b) imedafenacin (Homma 2009): → in D nicht zugelassen **Solifenacin versus:** (a) oxybutynin (see above), (b) tolterodine (see above), (c) propiverine (see above), and (d) darifenacin (But 2010): Abstract only, No useable data were published.
Nabi et al.. Anticholinergic drugs	Methodik: Sixty-one trials, 42 with parallel-group designs and 19 crossover

versus placebo for overactive bladder syndrome in adults. Cochrane Database of Systematic Reviews 2006	trials were included (11,956 adults). Most trials were described as double-blind but were variable in other aspects of quality. The crossover trials did not present data in a way that allowed inclusion in the meta-analysis. All randomised, controlled trials were placebo controlled. Nine medications were tested: darifenacin; emepronium bromide or carrageenate; oxybutynin; propiverine; propantheline; tolterodine; trospium chloride; and solifenacin. Trials compared the following active treatments with placebo: • tolterodine (14 trials, Abrams 1996; Abrams 1998; Abrams 2001; Drutz 1999; Freeman 2003; Jacquetin 2001; Jonas 1997; Junemann 2000; Landis 2004; Malone-Lee 2001; Millard 1999; Rentzhog 1998; VanKerrebroeck 1998; VanKerrebroeck 2001); • oxybutynin (eight trials, Abrams 1998; Burgio 1998; Drutz 1999; Goode 2002; Madersbacher 1999; Szonyi 1995; Thuroff 1991; Wein 1978); • trospium (eight trials, Alloussi 1998; Cardozo 2000; Chaliha 1998; Junemann 1999; Junemann 2000; Stohrer 1991; Ulshofer 2001; Zinner 2004), propiverine (five trials, Dorschner 2000; Halaska 1994; Madersbacher 1999; Stohrer 1999; Tago 1990); • propiverine (five trials, Dorschner 2000; Halaska 1994; Madersbacher 1999; Stohrer 1999; Tago 1990); • solifenacin (three trials, Chapple 2004a; Chapple 2004b; Cardozo 2004); • propantheline (two trials → in D nicht zugelassen); Zusammengefasste Ergebnisse: • At the end of the treatment period, **cure or improvement** (relative risk (RR) 1.39, 95%CI 1.28 to 1.51), **difference in leakage episodes** in 24 hours (weighted mean difference (WMD) -0.54; 95% CI -0.67 to -0.41) and **difference in number of voids** in 24 hours (WMD - 0.69; 95%CI -0.84 to -0.54) were statistically significant favouring medication. • Statistically significant but modest sized improvements in **quality of life** scores were reported in recently completed trials. • Adverse Events: There was three times the rate of **dry mouth** in the medication group (RR 3.00 95% CI 2.70 to 3.34) but no statistically significant difference in withdrawal (RR 1.11, 95% CI 0.91 to 1.36). • Sensitivity analysis, while limited by small numbers of trials, showed little likelihood that the effects were modified by age, sex, diagnosis, or choice of drug. **A. Patient observations, for example symptom scores, perception of cure or improvement, satisfaction with outcome** **Patients' perception of change in symptoms**: **Parallel-arm trials** (eight trials) • Relative risk (RR) for cure or improvement 1.39 (95% CI 1.28 to 1.51) → medication were more likely to report cure or improvement in their symptoms than those taking placebo (873 out of 1570, 56% cured or improved in medication group; and 481 out of 1172, 41% cured or improved in placebo group); There was no

	statistically significant heterogeneity. **Crossover trials** (eight trials), reporting all in a different way. • In all trials the patient preference was in favour of anticholinergic drugs. **Quantification of symptoms** (e.g. number of leakage episodes, frequency, urgency and volume (urinary diary)) • leakage episodes less per 24 hours (three trials): Those in the anticholinergic drug groups had approximately 0.38 leakage episodes less per 24 hours than those taking placebo medication (WMD for leakage episodes in 24 hours -0.38, 95%CI -0.63 to -0.13, P = 0.003 • number of leakage episodes at the end of treatment, measured over a 24 hour period (10 trials): All except oneshowed greater reduction in leakage episodes in the anticholinergic group (WMD -0.58; 95% CI - 0.76 to 0.40, P < 0.00001) • **Quality of life** When data from all three trials were combined all separate domains apart from general health perception showed statistically significant difference favouring anticholinergic treatment (for example WMD for incontinence impact score -6.95; 99% CI -10.36 to -3.53; P < 0.0000). Due to the fact that multiple domains in quality of life are reported we have chosen to report 99% confidence intervals. **Adverse events** • Twenty parallel-group trials reported the number of people withdrawing due to adverse events There was no statistically significant difference in the number of withdrawals due to adverse events betweenmedication and placebo groups (RR for withdrawal 1.11, 95% CI 0.91 to 1.36) • Dry mouth was the most frequently reported side effect and data were available from 27 parallel-group trials. The risk of dry mouth was three times greater in the medication group (1907/6165, 31%, with dry mouth in the medication group versus 350/3567, 9.8%, in the placebo group); the RR for dry mouth was 3.0, (95% CI 2.70 to 3.34, outcome Metaview 01.11). Statistically significant heterogeneity was observed in this comparison (P<0.00001). It was difficult to determine the possible causes of heterogeneity; the possible influence of the type of medication was explored. Fourteen trials compared tolterodine with placebo (Abrams 1996; Abrams 1998; Drutz 1999; Freeman 2003; Jacquetin 2001; Jonas 1997; Junemann 2000; Khullar 2004; Malone-Lee 2001; Millard 1999; Rentzhog 1998; VanKerrebroeck 2001; VanKerrebroeck 1998; Zinner 2002). The risk of dry mouth was three times higher in the tolterodine group (1184/3951, 29%, in tolterodine group versus 178/2091, 8.5%, in the placebo group); RR for dry mouth 3.37 (95% CI 2.90 to 3.90). • • Seven trials made comparisons of oxybutynin and placebo (Abrams 1998; Burgio 1998; Drutz 1999; Homma 2003; Madersbacher 1999; Szonyi 1995; Thuroff 1991). The risk of dry

	mouth was more than twice as great in the oxybutynin group (RR for dry mouth 2.41, 95% CI 2.02 to 2.87). However, statistically significant heterogeneity was observed amongst the oxybutynin trials (P < 0.00001). Two trials in the elderly had very high rates of dry mouth in the placebo arm (Burgio 1998; Szonyi 1995), perhaps as a consequence of polypharmacy. When these two trials were excluded from the pooled analysis the risk of dry mouth was three times greater in the oxybutynin groups (266/434, 61% in oxybutynin group versus 48/284, 17%, in placebo group); RR for dry mouth 3.23 (95% CI 2.48 to 4.20) and the test for heterogeneity was no longer significant (P = 0.43). • Three trials (Chapple 2004a; Chapple 2004b; Cardozo 2004) compared solifenancin and placebo (RR for dry mouth 3.62, 95%CI 2.29 to 5.74). • Four trials compared trospium and placebo (Cardozo 2000; Junemann 2000; Ulshofer 2001; Zinner 2004). The risk of dry mouth was twice as great in the trospium group (RR for dry mouth 2.66, 95% CI 1.98 to 3.55) but statistically significant heterogeneity was observed in this comparison (P = 0.0065). Both Cardozo et al. (Cardozo 2000) and Junemann et al. (Junemann 2000) found significantly higher rates of dry mouth in the trospium groups but Ulshofer et al. (Ulshofer 2001) found similar rates (approximately 50%) in both medication and placebo groups. The drug dose in the two former trials was 20 mg trospium twice daily, while the latter used 15 mg three times a day; otherwise the trials were very similar with regard to method and study population. Ulshofer et al. (2001) also stated that trial participants were asked specific questions about side effects, including dry mouth, and it is possible this yielded high positive rates of reporting. • Propiverine was compared with placebo in two trials (Madersbacher 1999; Stohrer 1999) and propantheline with placebo in a single trial (Thuroff 1991). All three trials found significantly higher rates of dry mouth in the medication groups.
Roxburgh et al.. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. Cochrane Database of Systematic Reviews 2007 *Kommentar: wegen in D nicht zugelassenen Substanzen nur Vergleiche von flavoxate mit*	Flavoxat ist die einzige in D zugelassene Substanz, die in diesem Review mit Anticholinergika verglichen wurde. Fazit: • Nine trials compared flavoxate with anticholinergics. • There was no evidence of a difference in cure rates between anticholinergics and flavoxate. • Adverse effects were more frequent in anticholinergic groups versus flavoxate groups (RR 2.28 95% CI 1.45 to 3.56). **Hypothese des Reviews:** **Anticholinergic drugs are better than flavoxate** Nine eligible trials were identified, six crossover trials (Cardozo 1979; Meyhoff 1981; **Milani 1993; Riva 1989**; Stanton 1973; **Wehnert 1989)** and three parallel group trials (Gaudenz 1978; Herbst 1970; Takayasu 1990). Two trials compared **flavoxate** with **oxybutynin** (Milani 1993; Riva 1989), three with propantheline (Gaudenz 1978; Herbst 1970; Takayasu 1990), three with

oxybutynin (Milani 1993; Riva 1989), und mit propiverine (Wehnert 1989) relevant!	emepronium (Cardozo 1979; Gaudenz 1978; Stanton 1973) and one with **propiverine** (Wehnert 1989). For meta analysis, the comparison between flavoxate and propantheline was abstracted from the Gaudenz trial. Whilst nine trials assessed oral medications only, one trial compared the parenteral administration of flavoxate with emepronium (Cardozo 1979). No evidence of a difference was found in the subjective cure rates after treatment in two trials included in the meta-analysis (Gaudenz 1978; Takayasu 1990) (RR 0.97; 95% CI 0.90 to 1.05 comparison 05.02); or in the subjective improvement rate (RR 1.01; 95%CI 0.46 to 2.22 comparison 05.04).There was evidence of heterogeniety between trials for the latter comparison. The participants in these two studies differed: one study (Gaudenz 1978) had exclusively female participants in a European population and the other study (Takayasu 1990) included both male and female participants drawn from a Japanese population. Based upon one small trial (Gaudenz 1978) there was no evidence of a difference in the number with nocturia after treatment (RR 0.96; 95% CI 0.66 to 1.39 comparison 05.06). Two trials reported results of symptomatic assessment favouring the use of flavoxate (Herbst 1970; Stanton 1973). It is worth noting that these trials favouring flavoxate were published in the early 1970s. Four trials (Gaudenz 1978; Meyhoff 1981; Riva 1989; Wehnert 1989) reported that there were no statistically significant differences between flavoxate and anticholinergic drugs. Gaudenz 1978 found more patients preferred flavoxate although objective assessment with urodynamics was equivocal. **Milani 1993 et al. found flavoxate was the preferred drug.** Two crossover trials (Cardozo 1979; Milani 1993) reported favourable results for anticholinergics. Based on three studies (Gaudenz 1978; Herbst 1970; Takayasu 1990) included in the meta-analysis adverse effects were generally worse in the anticholinergic groups (RR 2.28 95% CI 1.45 to 3.56 comparison 5.14). Reported adverse events included dryness of mouth, dizziness, nausea, blurred vision, swelling of lips, diarrhoea and constipation. Four crossover trials (Cardozo 1979; **Milani 1993; Riva 1989**; Stanton 1973) stated in the reports of the trials that there were significant differences between flavoxate and the anticholinergic drug with more adverse effects reported in the anticholinergic group. A further crossover trial (Meyhoff 1981) stated that there was an increase in adverse effects in the anticholinergic group; the differences between flavoxate and anticholinergics, no comment was made on statistical significance. The combined results of two trials showed no evidence of a difference in the number of patients withdrawing between anticholinergics and flavoxate (RR 0.93 95% CI 0.49 to 1.77 comparison 5.15) (Gaudenz 1978; Takayasu 1990). No dropouts were reported in four trials (Herbst 1970; Meyhoff 1981; Riva 1989; Stanton 1973). **Wehnert 1989 et al. did not provide figures for adverse effects or dropouts**.
Wallace et al.. Bladder training for urinary incontinence in adults. Stand: 2009.	Review nur sehr eingeschränkt passend für Fragestellung, da mit der nachfolgenden Auswertung nur zusammenfassende Analysen über 3 Arten der Inkontinenz (Drang-, Stress- und weitere Inkontinenz) gemacht wurden.

Cochrane Database of Systematic Reviews 2004	• Wenn Subgruppen-Analysen vorhanden für Dranginkontinenz, dann sind diese Ergebnisse nachfolgend gelistet (Definition urge incontinence: either urge urinary incontinence based upon a symptom classification or detrusor overactivity incontinence based on a urodynamic diagnosis) • Endpunkte werden im Folgenden nur berichtet, falls hierzu Daten im Review vorhanden waren. **1. Bladder training compared with no bladder training for the management of urinary incontinence** Urge urinary incontinence (however diagnosed): two trials (Fantl 1991; Lagro-Janssen 1992) included women with urodynamically diagnosed urge incontinence. One trial (Lagro-Janssen 1992) included only 18 participants and therefore the confidence intervals are very wide. The other trial (Fantl 1991) provided data for one outcome, for the 14 participants who had detrusor overactivity incontinence alone: number of incontinent episodes per week. Results for primary outcomes are summarised below: • (a) participant's perception of cure of urinary incontinence (Lagro-Janssen 1992) at two months, 1/9 vs 0/9; RR 3.00; 95% CI 0.14 to 65.16; • (b) participant's perception of improvement of urinary incontinence (Lagro-Janssen 1992) at two months, 8/9 vs 0/9; RR 17.00; 95 % CI 1.13 to 256.56; • (c) number of incontinent episodes (Fantl 1991) per week, at the end of the treatment phase, seven in each group; mean (SD), bladder training = 5 (6), control group = 18 (14) **2. Bladder training compared with anticholinergic drugs** Urge urinary incontinence (however diagnosed) One trial Colombo (Colombo 1995): primary outcomes: • (a) participant's perception of cure of urinary incontinence - at the end of the treatment phase 27/37 vs. 28/38; RR 0.99; 95% CI 0.75 to 1.30, and six months after the treatment ended 26/27 vs. 16/28; RR 1.69; 95% CI 1.21 to 2.34; (b) participant's perception of improvement of urinary incontinence - at the end of the treatment phase 34/37 vs. 31/38; RR 1.13; 95% CI 0.94 to 1.35; • adverse events a statistically significant difference was demonstrated favouring bladder training (0/37 vs. 18/38; RR 0.03; 95% CI 0.00 to 0.44). Adverse events included dry mouth, constipation, nausea; and one participant developed tachycardia. The dosage of the drug was halved in those reporting adverse events.
Rai BP, Cody JD, Alhasso A, Stewart L. Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults.	Neuerer Review der derselben Autorengruppe (s.o., Alhasso et al.: Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adult, 2009) → vergleichbare Fragestellung und Methodik des Reviews • Fragestellungen: To compare the effects of anticholinergic drugs with various non-pharmacologic therapies for non-neurogenic overactive bladder syndrome in adults:

2012; (12): CD003193.	1. Anticholinergic drugs versus bladder training (BT) alone. 2. Anticholinergic drugs versus pelvic floor muscle training (PFMT) alone. 3. Anticholinergic drugs versus external electrostimulation (endocavitary, percutaneous or sacral nerve modulation). 4. Anticholinergic drugs versus surgery. 5. Anticholinergic drugs in combination with non-drug therapies versus non-drug therapies alone. 6. Anticholinergic drugs in combination with non-drug therapies versus anticholinergic drugs alone. 7. Anticholinergic drugs versus combination non-drug therapies. • Methodik o Aktualität der Recherche (Suchzeitraum bis 4 September 2012) o Vergleiche/Komparatoren, s. Fragestellung o Endpunkt primary outcome: number of participants whose symptoms were not 'cured' while on treatment o Weitere Endpunkte: - Participants' observations (self-reported, subjective, Definitions based on criteria reported for each trial) - Quantification of symptoms (e.g. Number of pad changes over 24 hours) - Clinician's observations - Quality of life - Adverse events o # der eingeschlossenen Studien (insgesamt): 23, davon 19 in der Meta-analyse o # der eingeschlossenen Patienten (insgesamt): 3685 • Ergebnisdarstellung <u>The trials were generally small and of poor methodological quality</u> o duration of follow up varied from two to 52 weeks <u>Ergebnisse mit Anzahl der jeweiligen Studien:</u> o Comparison 1: anticholinergic drugs versus bladder training (BT): Seven trials addressed this comparison, N=346 participants (Collas 1994; Colombo, 1995; Macaulay 1988; Milani 1987; Park 2002; Song 2006; Szonyi 1995): <u>signifikanter Vorteil für Anticholinergika</u>: symptomatic improvement was more common amongst those participants on anticholinergic drugs compared with bladder training in seven small trials (73/174, 42% versus 98/172, 57% not improved: risk ratio 0.74, 95% confidence interval 0.61 to 0.91). o Comparison 2: anticholinergic drugs versus pelvic floor muscle training (PFMT) alone: No eligible trials were identified.

	o Comparison 3: anticholinergic drugs versus external electrostimulation: seven small trials comparing an anticholinergic to various types of electrical stimulation modalities such as Intravaginal Electrical Stimulation (IES), transcutaneous electrical nerve stimulation (TENS), the Stoller AfferentNerve Stimulation System(SANS) neuromodulation and percutaneous posterior tibial nerve stimulation (PTNS) were identified. (Ozdedeli 2010; Peters 2009; Smith 1996; Soomro 2001, Svihra 2002; Wang 2006; Wise 1993; but the Wise trial did not report usable data). Signifikanter Vorteil für Anticholinergika (jedoch hohe Ergebnisunsicherheit): Subjective improvement rates tended to favour the electrical stimulation group in three small trials (54% not improved with the anticholinergic versus 28/86, 33% with electrical stimulation: risk ratio 0.64, 95% confidence interval 1.15 to 2.34). However, this was statistically significant only for one type of stimulation, percutaneous posterior tibial nerve stimulation (risk ratio 2.21, 95% confidence interval 1.13 to 4.33), and was not supported by significant differences in improvement, urinary frequency, urgency, nocturia, incontinence episodes or quality of life. o Comparison 4: anticholinergic drugs versus surgery: No eligible trials were identified. o Comparison 5: anticholinergic drugs in combination with non-drug therapies versus non-drug therapies alone: Three trials addressed this comparison (Park 2002; Song 2006; Szonyi 1995): signifikanter Vorteil für Augmentation of bladder training with anticholinergics: improvement at the end of treatment, the overall effect in the three small trials was in favour of a combination of an anticholinergic with bladder training compared with bladder training alone (RR 0.57, 95% CI 0.38 to 0.88; (23/85, 27% versus 37/79, 47% not improved) o Comparison 6: anticholinergic drugs in combination with non-drug therapies versus anticholinergic drugs alone: Nine trials compared anticholinergic drugs plus a non-drug treatment versus the anticholinergic on its own (bladder training (Mattiasson 2003; Mattiasson 2009; Park 2002; Song 2006); • behavioural modification therapy (Burgio 2008; Burgio 2010; Chancellor 2008); • PFMT (Millard 2004); • interferential therapy plus PFMT plus bladder training (Kaya 2011). However, the nondrug treatments were considered too different to combine in metaanalysis: Nicht-signifikante bzw. Unklare Ergebnisse: It was less clear whether an anticholinergic combined with bladder training was better than the anticholinergic alone. In three trials (for example 74/296, 25% versus 95/306, 31% not improved: risk ratio 0.80, 95%confidence interval 0.62 to 1.04). The other information on whether combining behavioural modification strategies with an anticholinergic was better than the anticholinergic alone was scanty and

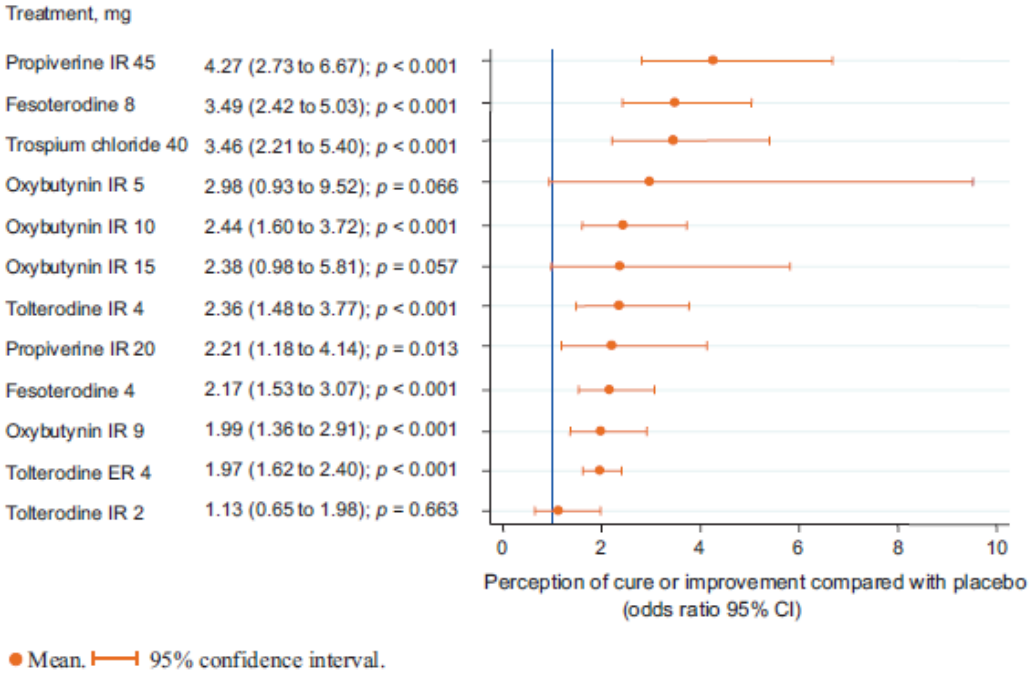
	inconclusive. Similarly, it was unclear whether these complex strategies alone were better than anticholinergics alone. o Comparison 7: anticholinergic drugs versus combination non-drug therapies (3 trials): One small trial (Burgio 1998) compared oxybutynin 7.5 mg daily with behavioural treatment: no statistically significant difference in subjective cure rates between the two groups. Signifikanter Vorteil for subjective improvement: the result favoured the behavioural treatment therapy (RR 2.42, 95%CI 1.00 to 5.85). One small trial compared trospiumchloride with a combination of inferential current therapy plus pelvic floor exercises plus bladder training (Kaya 2011): No statistically significant difference between scores for nocturia. Signifikanter Vorteil bei quality of life: Score in the combination group was higher (better) in the non-drug group in one small trial (13.70, 95% CI 0.94 to 26.46). Another trial (Burgio 2011) compared oxybutynin (5 to 30 mg) with behavioural treatment for men who continued to have overactive bladder symptoms with alpha-blocker therapy. Nicht-signifikanter bzw. Unklares Ergebnis für Number of micturitions per day: No statistically significant difference between the two groups in either of the two trials (Burgio 2008 und 2011). The combined result of three trials (Burgio 1998; Burgio 2011; Kaya 2011) for incontinence episodes per day showed fewer incontinence episodes in the combination therapy group compared with the anticholinergic drug alone (MD 0.41, 95% CI 0.11 to 0.70). However there was heterogeneity in the result, and when a random-effects model was used the result was no longer statistically significant. • Schlussfolgerungen der Autoren: During initial treatment of overactive bladder syndrome there was more symptomatic improvement when (a) anticholinergics were compared with bladder training alone, and (b) anticholinergics combined with bladder training were compared with bladder training alone. Limited evidence from small trials might suggest electrical stimulation is a better option in patients who are refractory to anticholinergic therapy, but more evidence comparing individual types of electrostimulation to the most effective types of anticholinergics is required to establish this. These results should be viewed with caution in view of the different classes and varying doses of individual anticholinergics used in this review. Anticholinergics had well recognised side effects, such as dry mouth.

Systematische Reviews

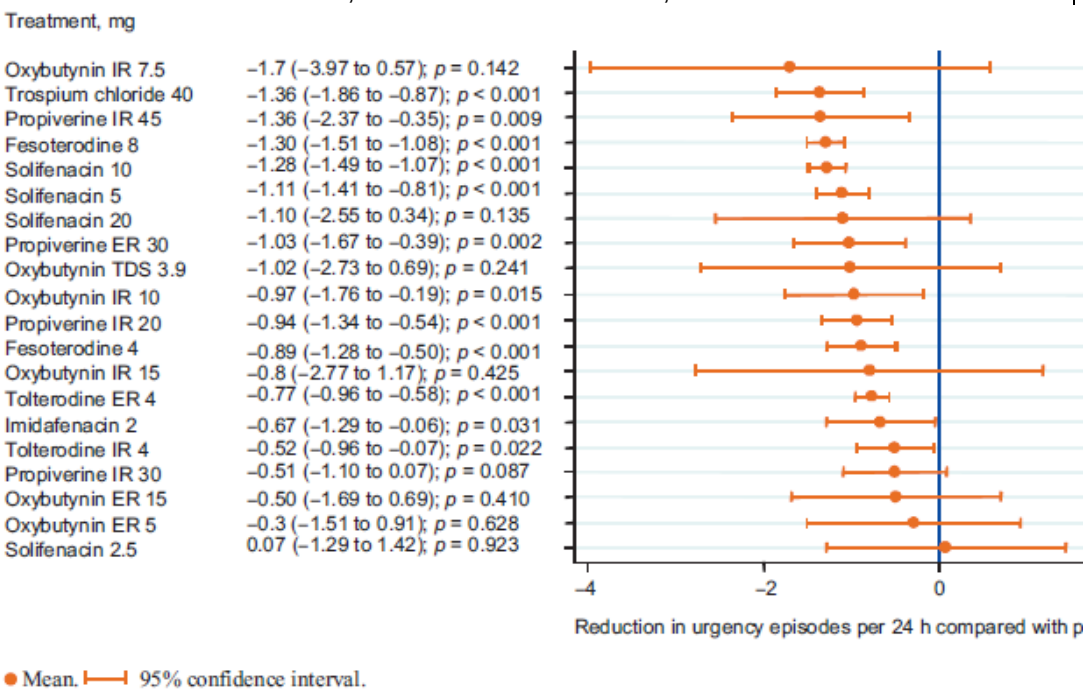
Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. Eur Urol 2012; 62 (6): 1040-60.	• Fragestellung: Analyse der Wirksamkeit und des Nebenwirkungen von verfügbaren Anti-muscarinika • Methodik o Aktualität der Recherche: Suchzeitraum 6/2005-4/2012 o Untersuchte Wirkstoffe (zumeist pro Wirkstoff in unterschiedlichen Dosierungen bzw. Darreichungsformen): Darifenacin (nur Nebenwirkungen) Fesoterodin, Oxybutynin, Propiverin, Solifenacin, Tolterodin und Trospium o Vergleich gegen Placebo o Endpunkte (primär/sekundär) 1. perception of cure or improvement, 2. urgency episodes per 24 h, 3. leakage episodes per 24 h, 4. urgency incontinence episodes per 24 h, 5. micturitions per 24 h, 6. nocturia episodes per 24 h o # der eingeschlossenen Studien: 76 für Wirksamkeitsanalyse 90 für Schadensanalyse (keine 90 zusätzlichen Studien, zum Teil gleiche Studien wie zur Wirksamkeit) o # der eingeschlossenen Patienten (insgesamt): 38662 für Wirksamkeitsanalyse 39919 für Schadensanalyse Trotz Einschluss von sowohl placebo-vergleichenden (überwiegender Anteil) als auch Head-to-head Studien wurden die Effekte der Wirkstoffe nur im Vergleich gegen Placebo analysiert. Unübliche Methodik der Netzwerk-Analyse, da diese zum einen auf individuellen Patientendaten basiert, die zur Schätzung der Effekte verwendet wurden und nicht wie meist üblich in Netzwerk-Metaanalysen auf Basis von aggregierten Daten der einzelnen Behandlungsarme. Zum anderen mußten diese individuellen Patientendaten, da in Einzelstudien nicht angebeben, wiederum erst aus den aggregierten Daten der Behandlungsarme mittels verschiedener (plausibler) Verfahren geschätzt werden. Berechnung der Nebenwirkungen, s. Ergebnisse. • Ergebnisdarstellung Effekte jeweils im Vergleich zu Placebo (nur graphische Darstellung vorhanden), gelistetes Ranking ergibt sich aus den ermittelten Effektgrößen gegen Placebo und nicht wie oftmals in Netzwerken mittels Bayes'schen Analysen als Ranking im jeweils (indirekten) Vergleich gegeneinander o # der eingeschlossenen Studien (für Fragestellung bzw. Patientenpopulation) o # der eingeschlossenen Patienten (für Fragestellung bzw. Patientenpopulation) o (Einheitliches) Wording zu Beginn eines Ergebnisberichts für einen Endpunkt (z.B. „signifikanter Vorteil" / „nicht-signifikanter Unterschied") o Angabe der Effektschätzer (inkl. Konfidenzintervall; zwingend nur bei stat. signifikantem Ergebnis)

Wirksamkeit

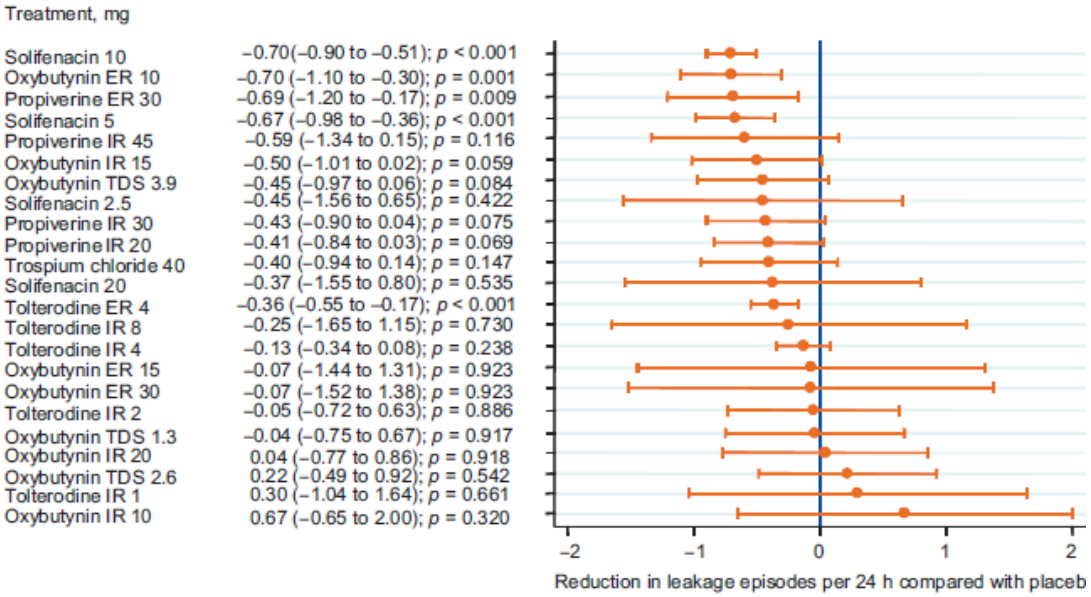
1. <u>perception of cure or improvement</u>, 5245 Patienten,
   IR = immediate release, ER = extended release, TDS = transdermal



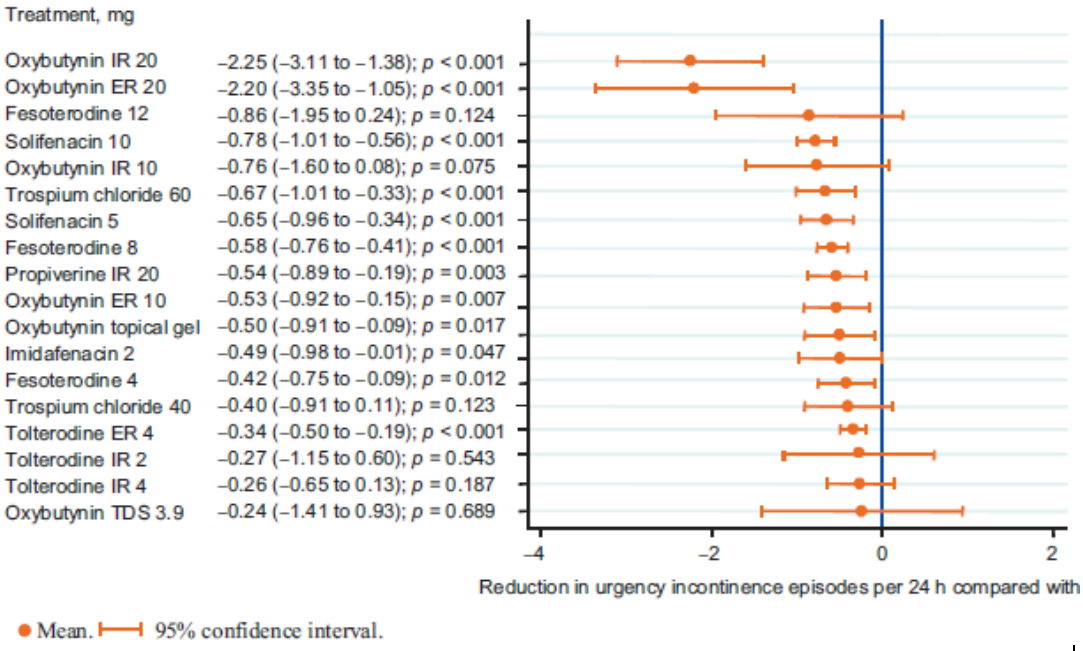
2. <u>urgency episodes per 24 h</u>, 19479 Patienten,
   IR = immediate release, ER = extended release, TDS = transdermal



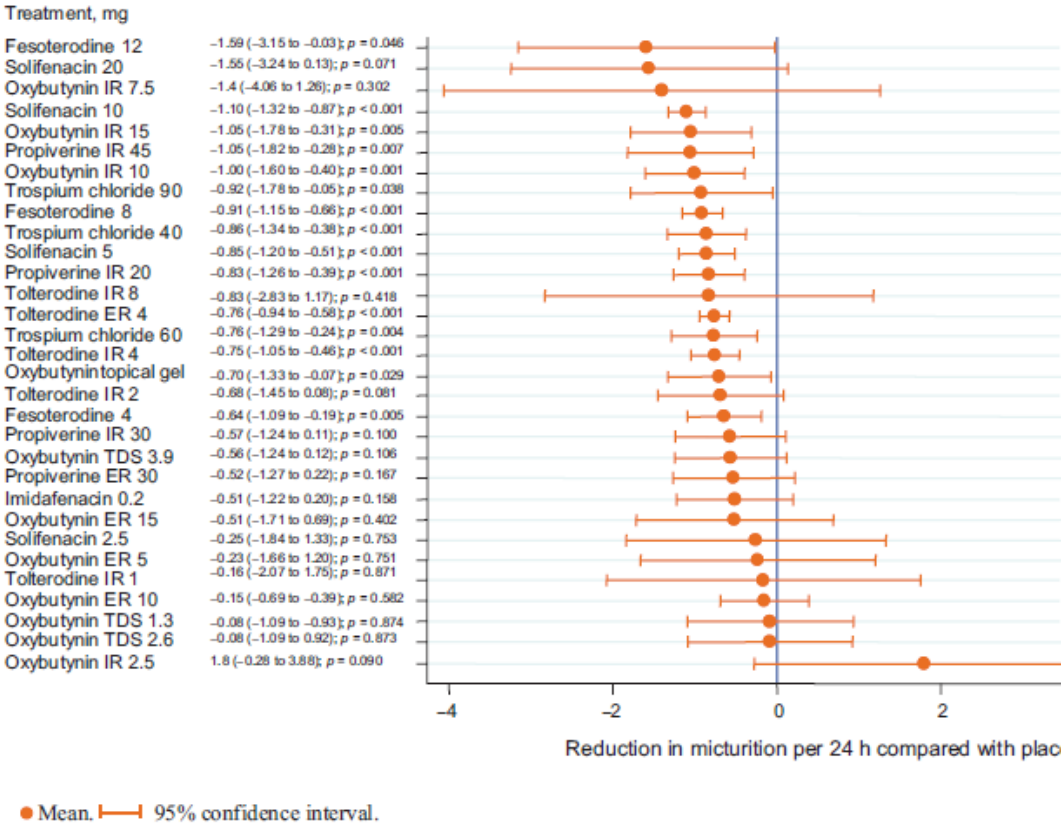
3. <u>leakage episodes per 24 h</u>, 14807 Patienten,
IR = immediate release, ER = extended release, TDS = transdermal



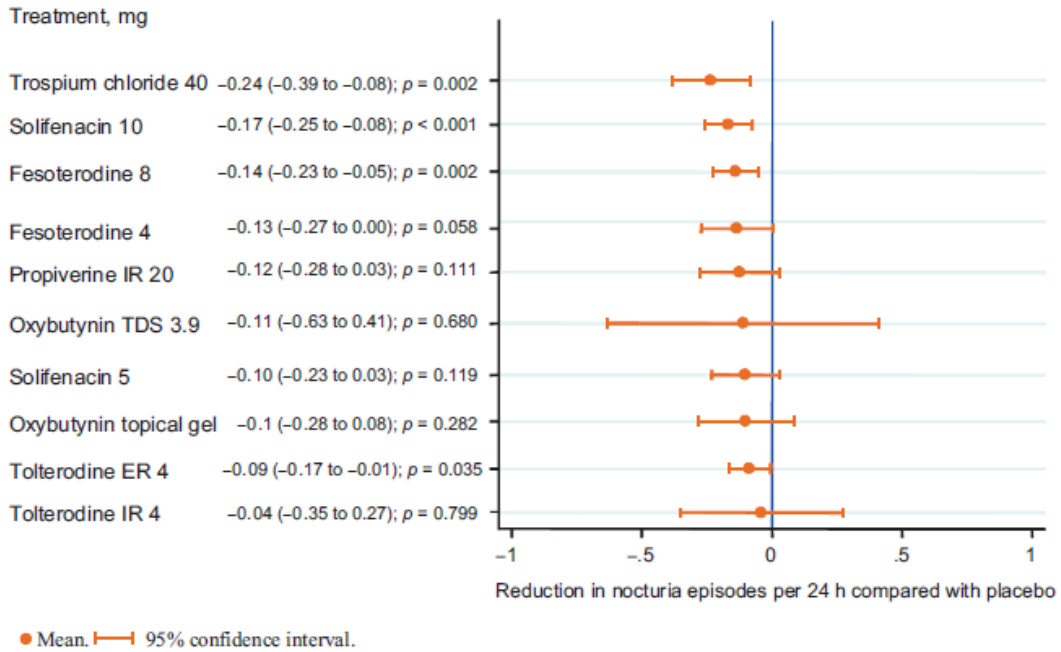
4. <u>urgency incontinence episodes per 24 h</u>, 17251 Patienten,
IR = immediate release, ER = extended release, TDS = transdermal



5. micturitions per 24 h, 32020 Patienten,
IR = immediate release, ER = extended release, TDS = transdermal

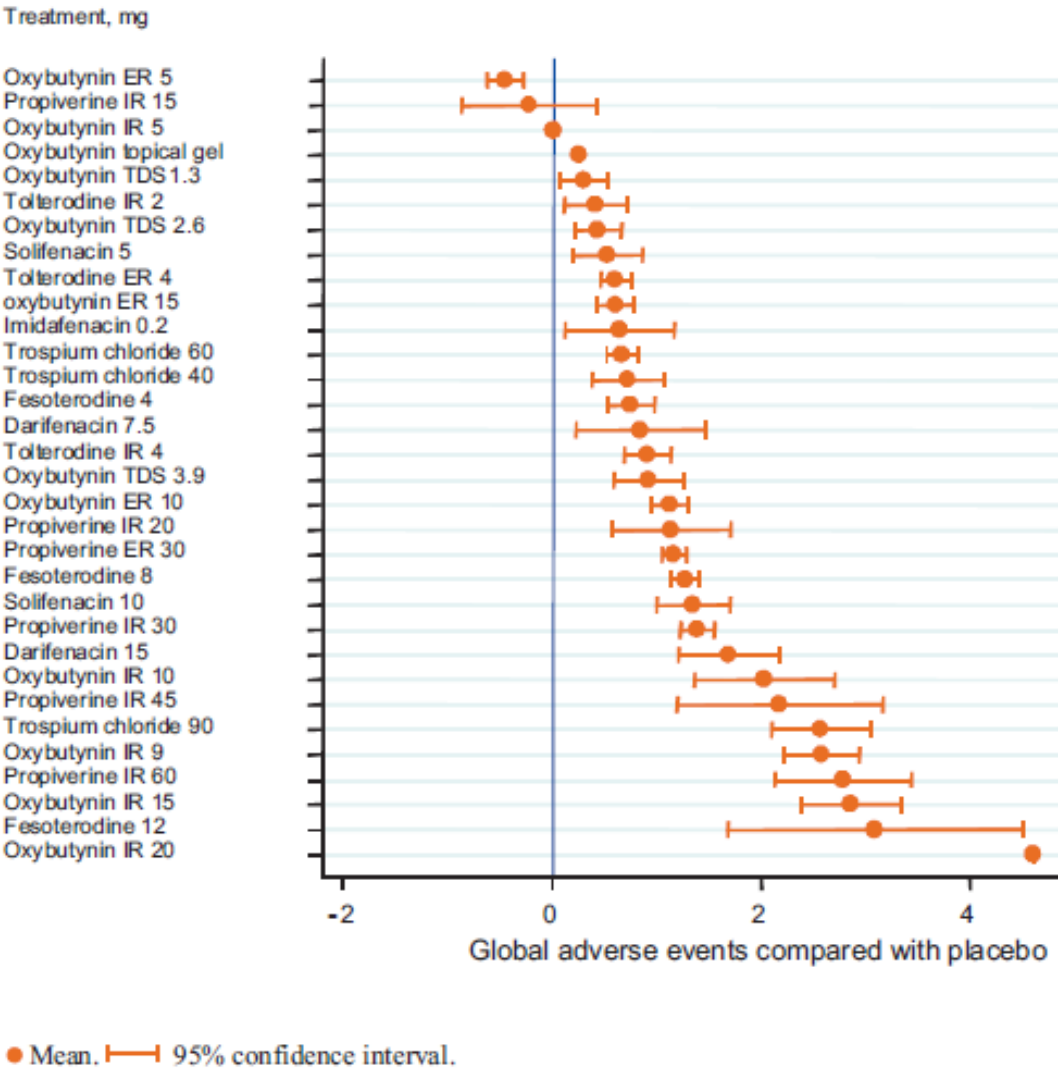


6. nocturia episodes per 24 h, 13247 Patienten,
IR = immediate release, ER = extended release, TDS = transdermal



Nebenwirkungen

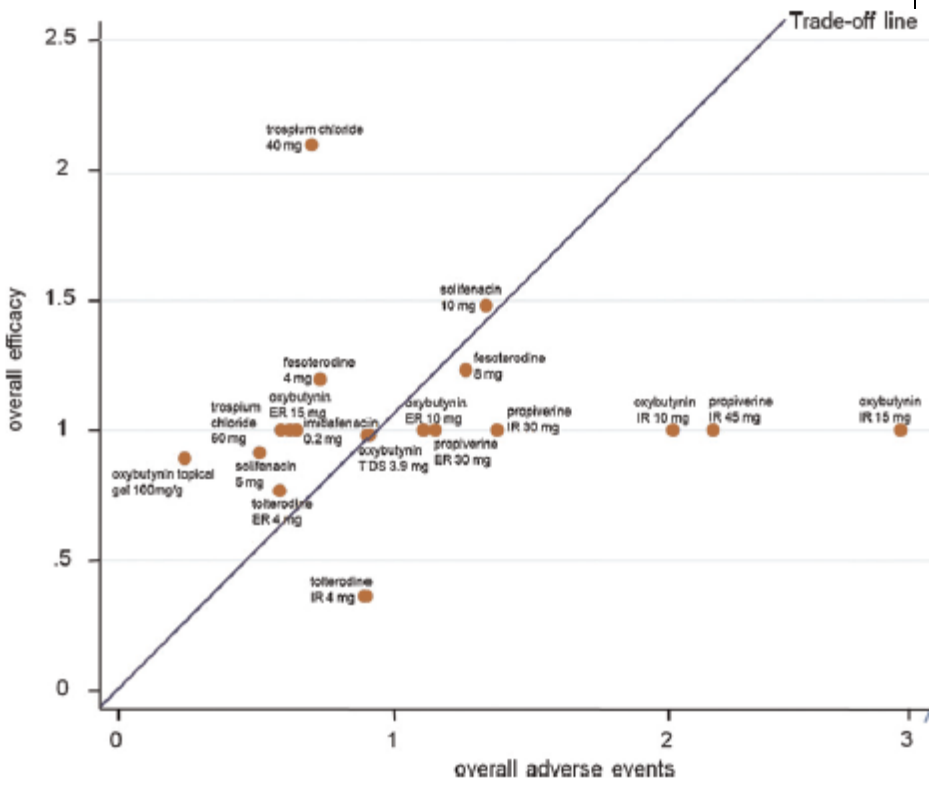
Aus den 90 Studien, wurde ein Nebenwirkungs-Score gebildet (aus 7 Nebenwirkungskategorien [gastrointestinal, Augen/Visus, Harnwege, neurologisch, kardial, Atemwege, Haut]). Anhand einer Befragung von 5 klinischen Experten wurden diese Nebenwirkungen gewichtet. Vom Prinzip her wurde der Score berechent, indem die Anzahl der (gewichteten) Nebenwirkungen pro Studienarm addiert und durch die jeweilige Anzahl der Patienten pro Studienarm dividiert wurde.



Trade-off Analyse zwischen Wirksamkeit und Nebenwirkungen

Graphischer Abgleich eines Wirksamkeits-Score gegen einen Nebenwirkungs-Score für die jeweilige Wirkstoffformulierung
Berechnung des Nebenwirkungs-Score: s.o. unter Nebenwirkungen.
Berechnung des Wirksamkeits-Score: die 6 Wirksamkeits-Zielgrößen wurden anhand einer Befragung von 5 klinischen Experten nach klinischer Relevanz geordnet und gewichtet (1. Zielgröße Gewicht = 1, 2. Zielgröße Gewicht = 0,5, etc):

1. urgency episodes per 24 h,
2. urgency incontinence episodes per 24 h,
3. leakage episodes per 24 h,
4. micturitions per 24 h,
5. perception of cure or improvement,
6. nocturia episodes per 24 h



(IR = immediate release, ER = extended release, TDS = transdermal)

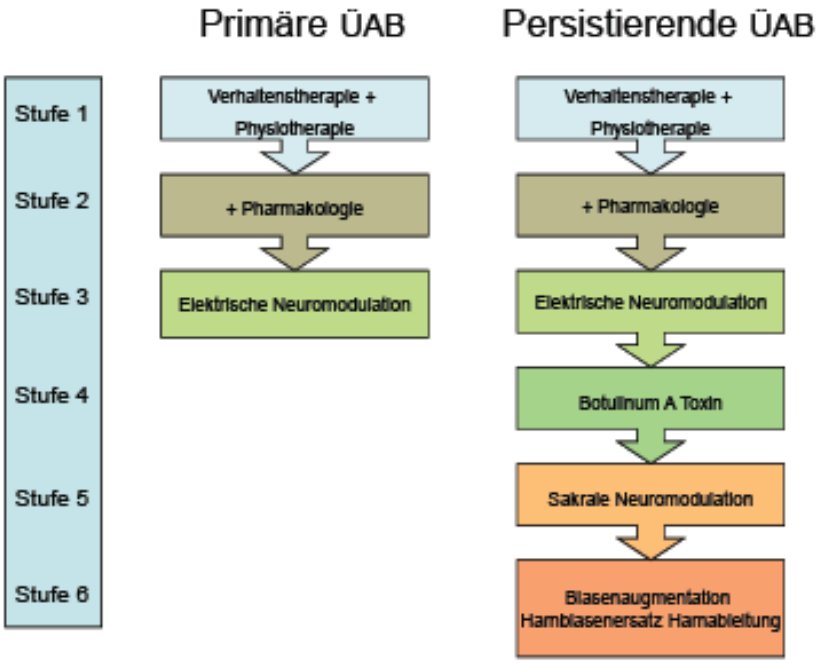
- Schlussfolgerungen der Autoren:
  Differences among the various antimuscarinics call for careful, patient-centered management in which regimen changes should be considered.

Xu C, Jiang XZ, Zhang NZ, Zhao HF, Xu ZS. [Safety of solifenacin and tolterodine in the treatment of overactive bladder: a meta-analysis]. Zhonghua Yi Xue Za Zhi 2012; 92 (48): 3398-402.	3 Studien eingeschlossen, wovon 2 (Chapple und Choo) auch im o.g. Cochrane Review von Madhuvrata et al. (2012) enthalten sind, allerdings schließt dieser Cochrane Review insgesamt 5 Studien zu diesem Vergleich ein Originalarbeit nur in chinesisch vorhanden, lediglich Abstrakt auf Englisch (eingeschlossene Studien: Chapple CR et al, in: BJU Int 2004, Choo MS et al, in: Int J Clin Pract 2008 und eine Chinesische Studie aus 2009): COBJECTIVE: To evaluate the safety of solifenacin and tolterodine in the treatment of overactive bladder (OAB). METHODS: Studies on the solifenacin, tolterodine and OAB were searched and those fulfilling the inclusion criteria were selected. Three studies were included with an overall sample size of 1013 cases. The experimental group of solifenacin contained 517 cases while the control group had 496 cases. RESULTS: The incidence rates of overall adverse event, dry mouth, constipation and blurred vision of the experimental group (solifenacin 5 mg once per day) was 26.69% (138/517), 10.64% (55/517), 5.42% (28/517) and 6.55% (26/397) while those of the control group (tolterodine 2 mg twice per day) 33.27% (165/496), 16.73% (83/496), 2.22% (11/496) and 4.20% (16/381) respectively. There was no statistically significant difference in overall adverse event (RR = 0.76, 95%CI: 0.52 - 1.12, P = 0.170) and blurred vision (RR = 1.59, 95%CI: 0.88 - 2.90, P = 0.130) between two groups. However, the incidence rate of key antimuscarinic adverse events such as dry mouth (RR = 0.63, 95%CI: 0.46 - 0.87, P = 0.005) and constipation (RR = 2.38, 95%CI: 1.21 - 4.66, P = 0.010) showed statistically significant difference. CONCLUSIONS: Dry mouth is the most common adverse event of solifenacin (5 mg once per day) and tolterodine (2 mg twice per day). Solifenacin has a lower incidence rate of dry mouth and a higher rate of constipation than tolterodine. A clinical physician should consider the incidence of adverse events during treating OAB, especially for those patients prone to constipation

Leitlinien

American Urological Association (AUA). Diagnosis and training of overactive bladder (Non-Neurogenic) in adults: AUA/SUFU GUIDELINE. Stand: May 2012.	**First-Line Treatments:** 1. Clinicians should offer **behavioral therapies** (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. Standard (Evidence Strength Grade B) 2. Behavioral therapies may be **combined with anti-muscarinic therapies**. Recommendation (Evidence Strength Grade C) **Second-Line Treatments:** 1. Clinicians should offer oral anti-muscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium (listed in alphabetical order; no hierarchy is implied) as second-line therapy. Standard (Evidence Strength Grade B) 2. If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. Standard (Evidence Strength Grade B) 3. Transdermal (TDS) oxybutynin (patch or gel) may be offered. Recommendation (Evidence Strength Grade C) 4. If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried. Clinical Principle 5. Clinicians should not use anti-muscarinics in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. Clinical Principle 6. Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. Clinical Principle 7. Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. Expert Opinion 8. Clinicians should use caution in prescribing anti-muscarinics in the frail OAB patient. Clinical Principle 9. Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. Expert Opinion **Third-line Treatments:** **FDA-Approved:** 1. Clinicians may offer sacral neuromodulation (SNS) as third line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candi-dates for second-line therapy and are willing to undergo a surgical procedure. Recommendation (Evidence Strength – Grade C) 2. Clinicians may offer peripheral tibial nerve stimulation (PTNS) as third-line treatment in a carefully selected patient population. Option (Evidence Strength Grade C) **Non-FDA-Approved:** Clinicians may offer intradetrusor onabotulinumtoxinA as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and

	willing to perform self-catheterization if necessary. Option (Evidence Strength Grade C) **Additional Treatments:** 1. Indwelling catheters (including transurethral, suprapubic, etc.) are not recommended as a management strategy for OAB because of the adverse risk/benefit balance except as a last resort in selected patients. Expert Opinion 2. In rare cases, augmentation cystoplasty or urinary diversion for severe, refractory, complicated OAB patients may be considered. Expert Opinion
Bettez M, Tu IM, Carlson K, Corcos J, Gajewski J, Jolivet M, Bailly G. 2012 update: guidelines for adult urinary incontinence collaborative consensus document for the canadian urological association. Can Urol Assoc J 2012; 6 (5): 354-63.	Aktualität der Recherche (Suchzeitraum: Januar 2005 bis November 2011) Focus auf systematischen Rreviews, Meta-analysen and evidence-based Empfehlungen, soweit vorhanden **Grade: Nature of recommendations** A: Clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial Based on level 1 evidence (recommended) B: Well-conducted clinical studies, but without randomised clinical trials Consistent level 2 or 3 evidence (recommended) C: Made despite the absence of directly applicable clinical studies of good quality Level 4 studies or majority evidence (optional) **Ergebnisdarstellung: Treatment of UUI** Conservative therapy should be considered prior to the initiation of medical or surgical treatment of UUI. These include behavioural modifications such as scheduled voiding, fluid restriction when appropriate **(grade B)**, smoking cessation **(grade C)**, avoidance of caffeine and bladder training **(grade A)**.2,26 Pelvic floor muscle training (PFMT) has been shown to be effective in improving UUI. In fact, it has been suggested to be better than oxybutinin as first-line therapy **(grade B)**.20 Medikamentöse Therapie: Antimuscarinics are appropriate as first- or secondline treatment for UUI **(grade B)**. The available pharmacological treatment includes oxybutinin immediate release (IR), extended release (ER) or transdermal, tolterodine (IR or ER), solifenacin, darifenacin, trospium chloride and fesoterodine. There is **Level 1A evidence** for each of these drugs showing superior efficacy versus placebo. Choice of agent may depend on physician experience and preference, formulary coverage, and/or patient preference and insurance coverage. A trial of 4 to 12 weeks is recommended to assess efficacy.2 Another antimuscarinic agent can be considered in cases of failure or intolerability. Possible adverse effects are dry mouth, blurred vision, pruritus, tachycardia, somnolence, impaired cognition, headache and constipation. Antimuscarinics are contraindicated in patients with urinary retention, gastric retention and uncontrolled narrow-angle glaucoma.27 OnabotuliniumtoxinA (BoNT-A) (off-label), neuromodulation and surgical interventions, such as augmentation cystoplasty, are all acceptable options for a small percentage of patients who do not respond to conservative and drug therapies depending on availability of resources.
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe	S2k Leitlinientyp (Formaler Expertenkonsens aufgrund nominalem Gruppenprozess) A = starke Empfehlung, B = Empfehlung, 0 = Empfehlung offen Die Leitlinie ist auf das weibliche Geschlecht bezogen und definiert den Nutzen für die Betroffenen über die Verbesserung der Lebensqualität,

(DGGG). Die überaktive Blase (ÜAB). Stand: Juni 2010. AWMF Leitlinien Register Nr. 015/007	welche durch Qualityof- Life-Scores erfasst wird. Entsprechend den Ergebnissen der Diagnostik ist eine Stufentherapie indiziert (s. Flowchart Stufentherapie).  **Konservative Therapie** **Verhaltenstherapie** • Erstellen und Führen eines Miktionstagebuches. • Miktionstraining: Verlängerung von zu kurzen Miktionsintervallen auf Basis des Miktionstagebuchs. Dies geschieht durch Anspannen des Beckenbodens bei Auftreten von Harndrang (sog. Bladder Drill). • Toilettentraining: Anpassung des Entleerungsrhythmus an die individuelle Blasenkapazität auf Basis des Miktionstagebuches, um dem unwillkürlichen Harnverlust zuvorzukommen. **Physiotherapie** Beckenbodentraining in der Inkontinenztherapie wird entweder konservativ in Gruppen-/Einzelsitzungen oder intensiviert durch Elektrostimulations- und Biofeedbackgeräte angeboten. **Statement** Beckenbodentraining und Biofeedback sind sinnvoll bei der Behandlung der ÜAB, jedoch ist die Kombination aus Beckenbodentraining und Elektrostimulation die wirkungsvollste Therapieoption. (B) **Pharmakotherapie** Muskarin-Rezeptorantagonisten (Anticholinergika/Antimuskarinika). In Deutschland zugelassene Substanzen (alphabetische Reihenfolge): Darifenacin, Fesoterodin, Oxybutinin, Propiverin, Solifenacin, Tolterodin, Trospiumchlorid (4-6, 13, 14, 20, 30, 33, 36, 37, 42, 49). Anticholinergika sind Mittel der 1. Wahl in der medikamentösen Therapie der ÜAB. Die Therapie wird als Mono- oder Kombinationsbehandlung mit oben genannten Alternativen durchgeführt (Östrogenisierung, Blasentraining, Physiotherapie [Biofeedback, Elektrostimulation]). Kombinationstherapien sind effektiver als die Monotherapie

	Statement Zur medikamentösen Therapie der ÜAB sind Anticholinergika mit geringem Nebenwirkungsprofil unter Beachtung der Kontraindikationen zu empfehlen. (B) **Operative Therapie (bisher alles Off-Label-Use)** **Statement** Empfehlungen zur operativen Therapie der ÜAB können nur als Expertenmeinung mit einem Evidenzlevel 4 gegeben werden. (Empfehlung offen)
European Association of Urology (EAU). Guidelines on Conservative Treatment of Non-neurogenic Male LUTS [lower urinary tract symptoms]. Stand: 2010.	The new Guidelines are intended to give advice on the pathophysiology and definitions, assessment, treatment, and follow-up of the various forms of non-neurogenic LUTS [lower urinary tract symptoms] in men aged 40 years or older. These guidelines cover mainly BPH-LUTS, OAB, and nocturnal polyuria. The latest knowledge and developments suggest that not all bladder symptoms of elderly men are necessarily linked to the prostate (BPH-LUTS), but instead might be caused by the bladder (detrusor overactivity-overactive bladder syndrome (OAB), detrusor underactivity) or kidney (nocturnal polyuria) **Conservative Treatment** **Evidence summary:** • Men with LUTS should be offered lifestyle advice prior to or concurrent with treatment. (Level of evidence: 1b, Grade of Recommendation A) **Drug Treatment** **Evidence summary:** • Muscarinic receptor antagonists might be considered in men with moderate to severe LUTS who have predominantly bladder storage symptoms [OAB]. (Level of evidence: 1a, Grade of Recommendation B) The efficacy of the anticholinergic drug tolterodine, and lately also fesoterodine, was tested as a single agent in adult men with bladder storage symptoms (OAB symptoms) but without bladder outlet obstruction. Maximum trial duration was 25 weeks, but most of the trials lasted for only 12 weeks. In open-label trials with tolterodine, daytime frequency, nocturia, urgency incontinence, and IPSS [international prostate symptom score] were all significantly reduced compared to baseline values after 12-25 weeks (8, 9). In an open-label study with α–blocker non-responders, each answer of the IPSS questionnaire was improved during tolterodine treatment irrespective of storage or voiding symptoms (8). Randomized, placebo-controlled trials demonstrated that tolterodine can significantly reduce urgency incontinence and daytime or 24-hour frequency compared to placebo. It was also demonstrated that urgency related voiding is significantly reduced by tolterodine (10-12). Although nocturia, urgency, or IPSS were reduced in the majority of patients these parameters did not reach statistical significance in most of the trials. **Tolerability and safety** Muscarinic receptor antagonists are generally well tolerated and associated with approx. 3-10% study withdrawals which were not significantly different compared to placebo in most of the studies. Compared to placebo, drug-related adverse events appear with higher frequencies for dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%)

	nasopharyngitis (up to 3%), and dizziness (up to 5%).
Geoffrion	Methodik: 1. Suchzeitraum nicht angegeben 2. Quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care. [82] (I: Evidence obtained from at least one properly randomized controlled trial, III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees) 3. Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[82] (A. There is good evidence to recommend the clinical preventive action, B. There is fair evidence to recommend the clinical preventive action) **Ergebnisdarstellung: Treatment for Overactive Bladder** 1. Behavioural management protocols and functional electrical stimulation should be offered in the spectrum of effective primary treatments for overactive bladder syndrome. (I-A) 2. Overactive bladder syndrome patients should be offered a choice between bladder training, functional electric stimulation, and anticholinergic therapy, as there is no difference in cure rates. Combination therapy does not have a clear advantage over one therapy alone. (I-A) Since the most recent Cochrane update of this review, an additional randomized controlled trial was published comparing darifenacin with darifenacin and a behavioural modification program consisting of patient education given in a primary physician's office (timed voiding, dietary modifications, Kegel exercises). There were no significant differences between treatment groups in efficacy or health-related quality of life variables.[60] 3. Oral oxybutynin, immediate and extended release, as well as transdermal oxybutynin, may be offered as treatment for overactive bladder syndrome, as they are associated with significant objective clinical improvement at 12 weeks. (I-A) Oxybutynin immediate release has superior cost-effectiveness but more side effects than other anticholinergics. (I-A) Adverse events associated with transdermal oxybutynin are fewer than with oral oxybutynin. (I-A) 4. Tolterodine, immediate and extended release, may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks. (I-A) 5. Trospium, immediate and extended release, may be offered as treatment for overactive bladder syndrome as it is associated with significant clinical improvement at 12 weeks. (I-A) Trospium is an adequate anticholinergic choice for overactive bladder syndrome patients with pre-existing cognitive impairment (II-B) and for overactive bladder syndrome patients taking concurrent CYP450 inhibitors. (III-B) 6. Solifenacin may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks. (I-A) Solifenacin may be an adequate anticholinergic choice for elderly overactive bladder syndrome patients or patients with pre-existing cognitive dysfunction. (I-B) 7. Darifenacin may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks. (I-A) Darifenacin is an adequate

<table>
<tr><td></td><td>anticholinergic choice for overactive bladder syndrome patients with pre-existing cardiac concerns or cognitive dysfunction. (I-B)
8. The choice of anticholinergic therapy should be guided by individual patient comorbidities, as objective efficacy of anticholinergic drugs is similar. (I-A)
Several other comparative randomized controlled trials comparing anticholinergics have been published since the most recent Cochrane Review update. One trial compared solifenacin 5 mg and 10 mg daily with tolterodine extended release 4 mg daily.62 Subjective cure was significantly more common in the solifenacin group (59% vs. 49%, P = 0.006). Objective measures of improvement and withdrawals because of side effects were not significantly different between the groups. Another trial comparing darifenacin 15 mg and 30 mg daily with oxybutynin 5 mg 3 times daily showed comparable efficacy and improved tolerability of darifenacin.63 The other trials compared fesoterodine 4 mg and 8 mg daily with tolterodine extended release 4 mg daily.64,65 Fesoterodine was superior to tolterodine on several objective measures of improvement such as urge incontinence episodes, severe urgency with incontinence, mean voided volume, and number of continent days per week. Diary dry rates were significantly better in the fesoterodine group than in the tolterodine group (64% vs. 57%; P = 0.015).[64,65]
Dose escalation does not improve objective parameters and causes more anticholinergic adverse effects. It is, however, associated with improved subjective outcomes. (I-A) To decrease side effects, switching to a lower dose or using an extended release formulation or a transdermal delivery mechanism should be considered. (I-A)

9. Oral or transdermal estrogen supplementation should not be recommended for treatment of overactive bladder syndrome as its effects are comparable to placebo. (I-E)
Vaginal estrogen can be suggested for subjective improvements in overactive bladder syndrome symptoms. (III-B)</td></tr>
<tr><td>Thuroff et al
EAU guidelines on urinary incontinence. Eur Urol 2011</td><td>Leitlinie adressiert hauptsächlich das Management der Urininkontinenz als ein Syndrom und schlüsselt die Evidenz und Empfehlungen nicht systematisch getrennt nach UUI, SUI oder MUI auf.

Im folgenden werden die Empfehlungen gelistet, die explizit – soweit vereinzelt vorhanden – die Dranginkontinenz (UUI) betreffen:

<table>
<tr><th>Type of evidence</th><th>LE</th></tr>
<tr><td>Evidence obtained from meta-analysis of randomised trials.</td><td>1a</td></tr>
<tr><td>Evidence obtained from at least one randomised trial.</td><td>1b</td></tr>
<tr><td>Evidence obtained from one well-designed controlled study without randomisation.</td><td>2a</td></tr>
<tr><td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td><td>2b</td></tr>
<tr><td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td><td>3</td></tr>
<tr><td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td><td>4</td></tr>
</table>

Konservative Therapie
• supervised bladder training: There is limited evidence that supervised bladder training is better than no treatment in women with UUI and mixed urinary incontinence (Level of evidence LE: 1b). BT does not improve an individual’s capacity to discontinue drug therapy and maintain improvement of UUI (12). However, the addition of BT to antimuscarinic drugs may increase patient satisfaction with pharmacological treatment (15), including in patients previously dissatisfied with the antimuscarinic treatment (16).
Evidence summary:</td></tr>
</table>

- **PFMT:** There is no consistent difference between PFMT and bladder training for women with UUI or MUI. (Level of evidence: 2)
- PFMT is better tolerated than oxybutynin for UUI. (Level of evidence: 2)

- **What remains unproven about PFMT**
  (keine Unterscheidung zwischen Art der Inkontinenz)
  - There is a lack of evidence about what is the most effective regimen for PFMT. (Level of evidence: 4)
  - The long-term durability of PFMT, augmented or not by other therapies, remains uncertain in all clinical situations. (Level of evidence: 4)
  - There is insufficient evidence that adding electrical stimulation or vaginal cones to PFMT alters the efficacy of PFMT alone. (Level of evidence: 4)

Electrical stimulation (surface electrodes):

Most evidence on electrical stimulation refers to women. The studies were considered to be of generally low quality, with small sample size and a variety of stimulation parameters, treatment regimes and outcome parameters. In addition, most of the studies lacked detail of the statistical methods used, e.g. power calculation. Due to the lack of consistency in the parameters used for electrical stimulation and in the outcome measures, it has not been possible to compare or pool data from most of these studies. The role of electrical stimulation is complicated by a lack of knowledge of how it might work in UI. Physiotherapists have used electrical stimulation to help women identify and contract pelvic floor muscles during PFMT. It has been suggested that electrical stimulation probably targets the pelvic floor directly in SUI, and the detrusor muscle or pelvic floor muscle or afferent innervation in UUI.

- **Evidence summary:** The evidence is inconsistent for whether electrical stimulation alone can improve UI. (Level of evidence: 2)

- **Magnetic stimulation** (Extracorporeal)
  Three RCTs induced magnetic stimulation in women with UI, using a coil placed over the sacral foramina. Two were poor-quality RCTs, with a short follow-up and an inconclusive effect in SUI and UUI or OAB (1,2). The third better-quality RCT observed no improvement in UUI or OAB after a longer 12-week follow-up and did not recommend treatment with magnetic stimulation (3). A further poor-quality RCT using the NeoControl chair also found no benefit in women with UUI or OAB (9).
  - **Evidence summary:** The negative or inconclusive effects obtained from the reviewed literature were considered to be consistent and generally applicable to adult women with SUI or UUI. There was a lack of evidence in men with UI.
- **PTNS = posterior tibial nerve stimulation**.
  The reviewed studies included 2 RCTs of PTNS against sham treatment (1,2) and one comparing PTNS to tolterodine in patients with UUI (3). The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results allow the conclusion that PTNS has a benefit in women with UUI who have had no benefit from antimuscarinic therapy or who are not able to tolerate these drugs. However, there is no evidence that PTNS cures UUI in women. In men there is insufficient data to make a conclusion about efficacy.

Evidence summary

	– There are not enough data to make a conclusion about the effectiveness of PTNS in men(Level of evidence: 4) – PTNS is effective for improvement of UUI, but not curing UUI in some women who have had no benefit from antimuscarinic medication. (Level of evidence: 1b) – PTNS is no more effective than tolterodine for improvement of UUI in women. (Level of evidence: 2b) – No serious adverse events have been reported for PTNS in UUI. (Level of evidence: 3) **Drug Treatment** **Antimuscarinic drugs** are currently the mainstay of treatment for UUI. Antimuscarinic agents differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action, in their pharmacokinetic properties, e.g. lipid solubility and half-life, and in their formulation, e.g. immediate release (IR) or extended release (ER) and transdermal. The evaluation of cure/improvement of UI using oxybutynin and tolterodine IR formulations is made harder by the lack of a standard definition of improvement. Outcome measures vary and are not standardised, and never use 'cure' as a primary outcome. Meta-analysis of the published evidence is therefore not always possible. **Evidence summary:** • Oxybutynin IR and transdermal, tolterodine IR, and propiverine IR provide a significantly better rate of cure/improvement compared to placebo. (Level of evidence: 1a) • Trospium IR provides significantly better reduction in incontinence episodes than placebo. (Level of evidence: 1a) **Extended-release (ER) and longer-acting antimuscarinic agents** Most studies included patients with OAB, with a mean age of 55-60 years. Because most patients were women, the results can be generalised to women, but not to men. The reported rates for improvement or cure of UUI were only short term (up to 12 weeks). The evidence reviewed was consistent, indicating that ER formulations of antimuscarinics offer clinically significant short-term cure rates and improvement rates for UUI. • <u>Darifenacin</u> Two RCTs compared darifenacin to placebo, involving 838 patients (681 women). One study included only patients older than 65 years. The second study by Hill et al. found that darifenacin was superior to placebo for cure of UUI. No new data comparing darifenacin with placebo have been published since the AHRQ and Oregon Health and Science University systematic reviews, published in 2009 (1,2). • <u>Fesoterodine</u> Two randomised trials have been reported since the AHRQ review (4,5). Both trials compared fesoterodine, 8 mg/day, versus tolterodine ER, 4 mg/day, versus placebo. The first study reported higher cure rates with fesoterodine than with placebo, but also higher rates of dry mouth. In the second study, the cure rates were also higher than with placebo, but again with higher rates of dry mouth. These trials are consistent with previous reports showing the effectiveness of fesoterodine compared to no treatment (placebo). • <u>Oxybutynin</u>

None of the identified studies that compared oxybutynin ER with placebo included incontinence as a measured outcome. One study reported that oxybutynin ER produced less cognitive disturbance than placebo (6).

- Tolterodine

A study of mostly women (n=361) compared tolterodine ER, transcutaneous oxybutynin, and placebo (7). Tolterodine ER resulted in a significantly higher chance of cure than placebo. Another study (8) in 337 incontinent men and women calculated the daytime incontinence outcomes in a secondary analysis of data from a previous study of tolterodine ER in OAB with nocturia. The analysis found higher cure rates of UUI using tolterodine ER. These data are consistent with the studies summarised in the AHRQ and Oregon systematic reviews (1,2) showing that tolterodine was effective for improvement of UUI compared to placebo.

- Propiverine

We found three RCTs comparing propiverine ER with placebo, all with improvement of UUI as an outcome (9-11). All trials showed propiverine ER had a significant benefit over placebo in terms of improvement (11) and cure (9,10). Adverse effects reported included dry mouth and a prolonged QTc interval (9,10).

- Solifenacin

Karram et al. reported a study in 707 patients comparing solifenacin and placebo, although their primary outcome measure was urgency rather than incontinence (12). Cure rates for urgency were 58% for solifenacin and 42% for placebo. Concerning an improvement in UUI, there have been no high-quality studies published since the AHRQ and Oregon systematic reviews (1,2), which already contained useful data on improvement in UI with solifenacin.

- Trospium

Several authors (13-15) have done a secondary analysis of two previously published studies of trospium ER versus placebo (16,17). Cure rates for UUI were reported as 21% with trospium ER and 11% with placebo (14).

Evidence summary:

- ER formulations of antimuscarinic agents are effective for improvement and cure of UUI. (Level of evidence: 1b)
- ER formulations of antimuscarinic agents result in higher rates of dry mouth compared to placebo. (Level of evidence: 1b)
- The clinical significance of prolonged QT for propiverine is uncertain. (Level of evidence: 3)

Comparison of antimuscarinic agents

There is a considerable body of evidence covering this question, comprising over 40 RCTs and five systematic reviews. Nearly all the primary studies have been funded and sponsored by the manufacturer of the newer drug under evaluation, which forms the experimental arm of the RCT. It was noted that upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm (Table).

Comparison of agents	No. of trials
Experimental IR agent vs. standard IR drug	11
Experimental ER agents vs. standard IR drug	19
Experimental ER agents vs. standard ER drug	12
Transcutaneous oxybutynin vs. standard IR oral drug	1
Transcutaneous oxybutynin vs. standard oral ER drug	1

In general, these studies have been designed for regulatory approval. They have a short treatment duration of typically 12 weeks and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. It is therefore difficult to use the results from these trials in daily clinical practice to select the best first-line drug or second-line alternative following the failure of initial treatment. A quality assessment carried out as part of the most recent systematic review found that all the trials were of low or moderate quality.

- For **cure of UI**, there was weak evidence that oxybutynin ER was more effective than tolterodine ER (1,7). Three recent studies found some evidence that fesoterodine, 8 mg daily, was better than tolterodine ER, 4 mg daily, for cure of UI (6,8,9).
- For **improvement in UI**, there was weak evidence that both oxybutynin ER and tolterodine ER were superior to tolterodine IR (2,3), and that oxybutynin ER was superior to tolterodine ER (3,7). Evidence from two trials where improvement in UI was the primary outcome suggests greater benefit is obtained with fesoterodine, 8 mg daily, compared with tolterodine ER, 4 mg daily (6,10). All other comparisons showed no difference in efficacy for improvement of UI.
- There was no evidence that any one antimuscarinic agent improved **QoL** more than another agent.
- **Dry mouth** is the most prevalent and most studied adverse effect of antimuscarinic agents. Good evidence indicates that, in general, ER formulations of both short-acting drugs and longer-acting drugs are associated with lower rates of dry mouth than IR preparations (1,3). Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin, 15 mg daily (1,3). Overall, oxybutynin ER had higher rates of dry mouth than tolterodine ER, but generally oxybutynin did not have higher rates for moderate or severe dry mouth.

- **Conclusion**:
  there is no consistent evidence for the superiority of one antimuscarinic agent over another for the cure or improvement of UI. Recent trials with incontinence as the primary outcome suggest that fesoterodine, 8 mg daily, is superior to tolterodine ER, 4 mg daily, but meta-analysis is required to determine the size of effect. There is good evidence that ER, once-daily, and transdermal preparations, are associated with lower rates of dry mouth than ER preparations, although discontinuation rates are similar.

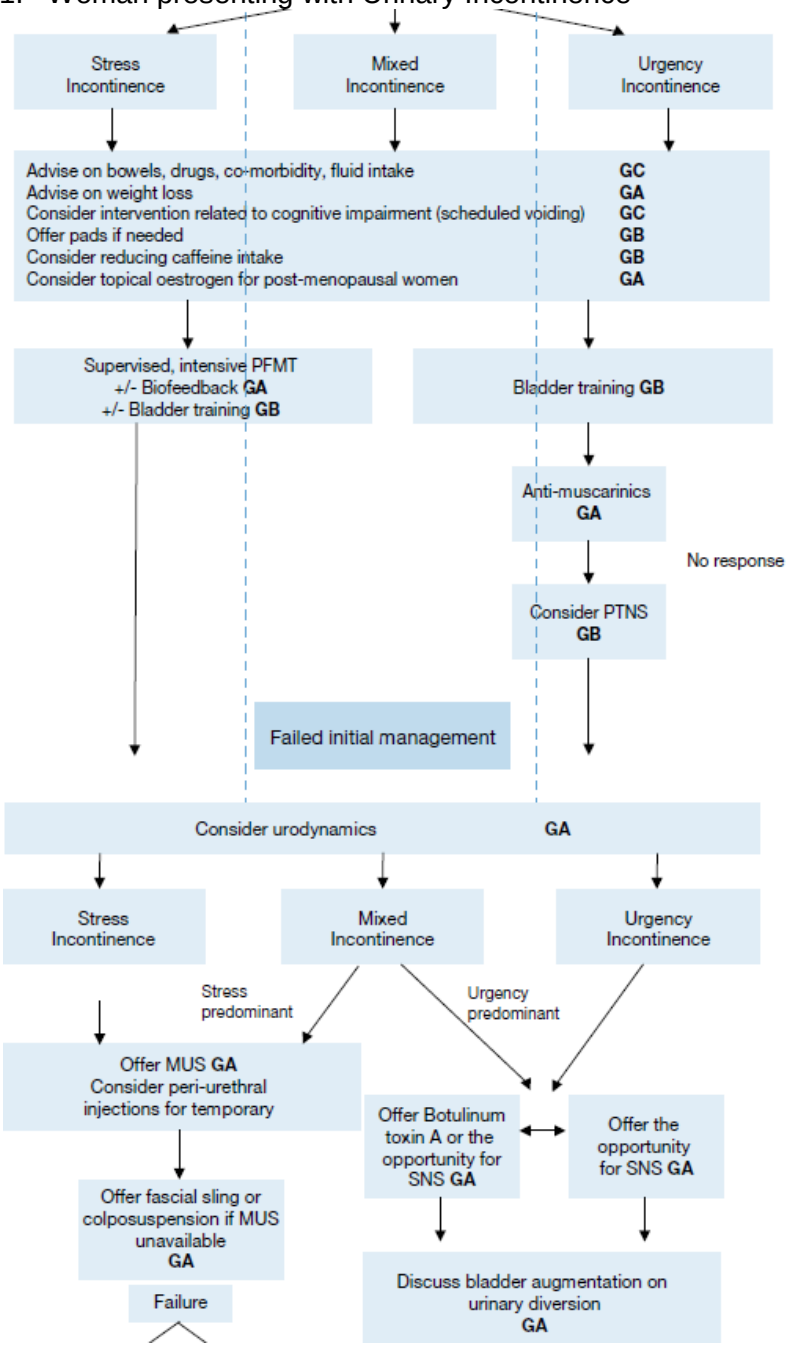
Evidence summary:

- There is no consistent evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI (Level of evidence: 1a)
- The ER formulation of oxybutynin is superior to the ER and IR

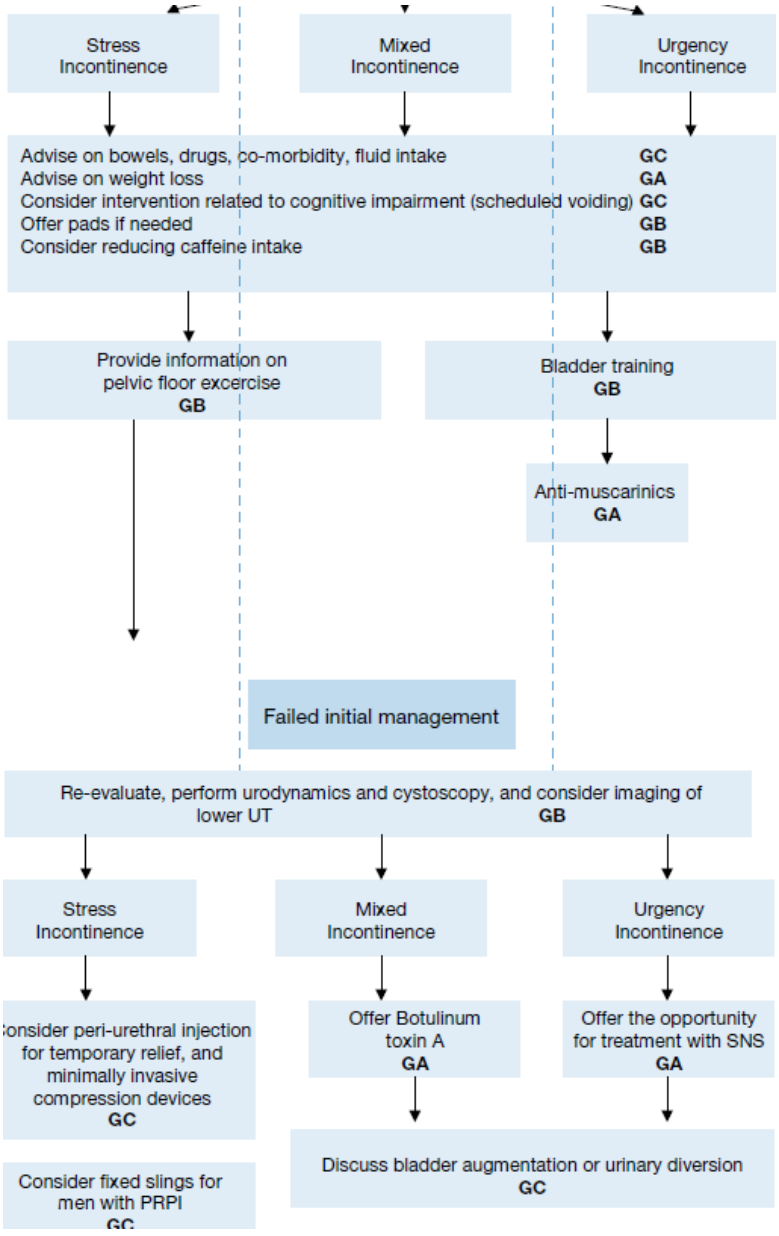
	formulations of tolterodine for improvement of UUI. (Level of evidence: 1b) – Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI. (Level of evidence: 1b) – ER and once-daily formulations of antimuscarinic drugs are generally associated with lower rates of dry mouth than IR preparations, although discontinuation rates are similar. (Level of evidence: 1b) – Oxybutynin IR or ER shows higher rates of dry mouth than the equivalent formulation of tolterodine. (Level of evidence: 1a) – There is no evidence that any particular antimuscarinic agent is superior to another for improvement in QoL. (Level of evidence: 1a) In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI and/or greater improvement in QoL, and/or lesser likelihood of adverse effects compared to an alternative non-drug treatment? **<u>Antimuscarinic drugs vs. non-drug treatment in adults with UUI?</u>** The US Health Technology Appraisal found that trials were of low- or moderate-quality with none categorized as high quality. The main focus of the review was to compare the different drugs used to treat UUI. Non-drug treatments were mentioned only in the evidence tables for the treatment of UUI. The behavioural approaches included bladder training, multicomponent behavioural approaches and electrical stimulation. Only one of these studies showed superiority for behavioural therapy. In one study, multicomponent behavioural modification produced significantly greater reductions in incontinence episodes compared to oxybutynin, and higher patient satisfaction for behavioural versus drug treatment. In summary, although medication may enhance the effect of behavioural therapy, there is no evidence that behavioural therapy enhances the effect of drugs. In conclusion, there is no consistent evidence for the superiority of antimuscarinic drugs over non-drug treatments, especially behavioural treatment. More side effects have been reported for drug therapy compared to non-drug treatment. Electrical stimulation appears to be inferior to other treatment alternatives. Several trials have suggested that a combination of drug and behavioural therapy produce the best results, including in longterm follow-up. **Evidence summary:** – There is no consistent evidence to show superiority of drug therapy or behavioural therapy. (Level of evidence: 1b) – Behavioural treatment results in increased patient satisfaction versus drug treatment alone. (Level of evidence: 1b)

Behandlungsalgorithmus
GA = Grade of Recommendation A,
GB = Grade of Recommendation B

1. Woman presenting with Urinary Incontinence



2. Man presenting with Urinary Incontinence



Detaillierte Darstellung der Recherchestrategie zu 2012-10-A-016 (Wirkstoff Mirabegron):

Cochrane Library am 19.03.2013

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor Urinary Incontinence, Urge explode all trees	60
#2	MeSH descriptor Urinary Bladder, Overactive explode all trees	233
#3	(overactiv* AND bladder):ti,ab,kw or (overactiv* AND detrusor):ti,ab,kw or (urge AND incontinen*):ti,ab,kw	1076
#4	(#1 OR #2 OR #3) : 2012 to 2013	15

Cochrane Reviews [5] | Other Reviews [1] | Technology Assessments [1]

MEDLINE (PubMed) am 19.03.2013

Suchschritt	Suchfrage	Treffer
#1	Search "Urinary Bladder, Overactive"[Mesh]	1943
#2	Search overactiv*[Title/Abstract] AND bladder[Title/Abstract]	4057
#3	Search overactiv*[Title/Abstract] AND detrusor[Title/Abstract]	2019
#4	Search "urinary incontinence, urge"[Mesh]	451
#5	Search urge[Title/Abstract] AND incontinen*[Title/Abstract]	2913
#6	Search ((((#1) OR #2) OR #3) OR #4) OR #5	7123
#7	Search guideline*[Title]	45039
#8	Search (#6) AND #7	24
#9	Search ((((#1) OR #2) OR #3) OR #4) OR #5 Filters: Practice Guideline	23
#10	Search ((((#1) OR #2) OR #3) OR #4) OR #5 Filters: Practice Guideline; Guideline	23
#11	Search (#8) OR #10	32
#12	Search (#8) OR #10 Filters: Publication date from 2012/08/01 to 2013/12/31	4
#13	Search ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))	144007
#14	Search (#6) AND #13	185
#15	Search ((((#1) OR #2) OR #3) OR #4) OR #5 Filters: Systematic	291

	Reviews	
#16	Search ((((#1) OR #2) OR #3) OR #4) OR #5 Filters: Systematic Reviews; Meta-Analysis	291
#17	Search ((((#1) OR #2) OR #3) OR #4) OR #5 Filters: Systematic Reviews; Meta-Analysis; Technical Report	291
#18	Search (#14) OR #17	340
#19	Search (#14) OR #17 Filters: Publication date from 2012/08/01 to 2013/12/31	32
#20	Search (#19) NOT #12	31

#12 und #20 importiert
Darüber hinaus wurde in den HTA- und Leitliniendatenbanken AWMF, GIN, NGC, Trip, ÄZQ, DAHTA, sowie auf den Internetseiten des GBA, IQWiG, NICE und HSC-NHSC per Handsuche nach aktuellen Publikationen mit den Begriffen „urinary incontinence“, „overactive bladder“ in verschiedenen Variationen gesucht.
Die Recherche ergab insgesamt **50** Quellen.

Detaillierte Darstellung der Recherchestrategie zu 2012-B-042 (Wirkstoff MK4618):

Cochrane Library am 28.08.2012

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor Urinary Incontinence, Urge explode all trees	58
#2	MeSH descriptor Urinary Bladder, Overactive explode all trees	226
#3	(overactiv* AND bladder):ti,ab,kw or (overactiv* AND detrusor):ti,ab,kw or (urge AND incontinen*):ti,ab,kw	1061
#4	(#1 OR #2 OR #3)	1061
#5	(#4), from 2007 to 2012	446

Cochrane Reviews [18] | Other Reviews [16] | Clinical Trials [391] | Methods Studies [3] | Technology Assessments [4] | Economic Evaluations [14] | Cochrane Groups [0]
15 Cochrane Reviews, 3 Other Reviews, 1 Technology Assessments in Datenbank aufgenommen

MEDLINE (PubMed) am 28.08.2012

Suchschritt	Suchfrage	Treffer
#1	Search "Urinary Bladder, Overactive"[Mesh]	1770
#2	Search overactiv*[Title/Abstract] AND bladder[Title/Abstract]	3915
#4	Search overactiv*[Title/Abstract] AND detrusor[Title/Abstract]	1955
#5	Search "urinary incontinence, urge"[Mesh]	415
#6	Search urge[Title/Abstract] AND incontinen*[Title/Abstract]	2947
#7	Search ((((#1) OR #2) OR #4) OR #5) OR #6	6764
#8	Search ((((((HTA[Title/Abstract]) OR (technology assessment*[Title/Abstract])) OR (technology report*[Title/Abstract])) OR (systematic [Title/Abstract] AND review*[Title/Abstract])) OR (meta-analysis[Title/Abstract]) OR (meta-analyt*[Title/Abstract]) OR (meta[Title/Abstract] AND analysis[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))	85640
#9	Search (#8) AND #7	127

Suchschritt	Suchfrage	Treffer
#10	Search ((((#1) OR #2) OR #4) OR #5) OR #6 Filters: Meta-Analysis; Systematic Reviews; Technical Report	269
#11	Search (#9) OR #10	285
#12	Search (#10) OR #9 Filters: Publication date from 2007/01/01 to 2012/12/31	178

#12 101 Treffer in Datenbank aufgenommen

MEDLINE (PubMed) nach Leitlinien am 27.08.2012

Suchschritt	Suchfrage	Treffer
#1	Search "Urinary Bladder, Overactive"[Mesh]	1770
#2	Search overactiv*[Title/Abstract] AND bladder[Title/Abstract]	3915
#4	Search overactiv*[Title/Abstract] AND detrusor[Title/Abstract]	1955
#5	Search "urinary incontinence, urge"[Mesh]	415
#6	Search urge[Title/Abstract] AND incontinen*[Title/Abstract]	2947
#7	Search ((((#1) OR #2) OR #4) OR #5) OR #6	6771
#8	Search guideline*[Title]	43173
#9	Search (#8) AND #7	20
#10	Search ((((#1) OR #2) OR #4) OR #5) OR #6 Filters: Practice Guideline; Guideline	22
#11	Search (#10) OR #9	28
#12	Search (#10) OR #9 Filters: Publication date from 2007/01/01 to 2012/12/31	26

#12 10 Treffer in Datenbank aufgenommen

Darüber hinaus wurde in den HTA- und Leitliniendatenbanken AWMF, GIN, NGC und Trip sowie auf den Internetseiten des NICE und NHSC per Handsuche nach aktuellen Publikationen mit den Suchbegriffen urinary incontinence, overactive bladder in verschiedenen Variationen gesucht.
Nach Dublettenkontrolle ergab die Recherche insgesamt **145** Quellen.

Literatur:

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Xu C, Jiang XZ, Zhang NZ, Zhao HF, Xu ZS. [Safety of solifenacin and tolterodine in the treatment of overactive bladder: a meta-analysis]. Zhonghua Yi Xue Za Zhi 2012; 92 (48): 3398-402.