SUPPLEMENTAL APPENDICES

APPENDIX A SEARCH RESOURCES AND STRATEGIES

Table A.1: Information resources searched

Type of resource	Information Resource	Database platform
Prior research	YHEC scoping search	
	PRMA Consulting Library	
	YHEC proposal library	
Database	MEDLINE	OvidSP
	MEDLINE in Process	OvidSP
	EMBASE	OvidSP
	CINAHL	EBSCO
	Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library
	Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library
	Database of Abstracts of Reviews of Effects (DARE)	CRD website
	Health Technology Assessment Database (HTA)	CRD website
	NHS Economic Evaluation Database (NHS EED)	CRD website
Website	US Food and Drug Administration	
	European Medicines Agency	
	National Institute for Health and Care Excellence website	
	Canadian Agency for Drugs and Technologies in Health (CADTH)	
	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)	
Guidelines	American Urology Association	
	Society of Obstetricians and Gynaecologists of Canada	

A.1: Detailed search strategy for MEDLINE

Source: MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE

Interface / URL: OvidSP
Database coverage dates: 1946 to Present
Search date: 29/08/13
Retrieved records: 999
Search strategy:

1 Urinary Bladder, Overactive/ 2323
2 ((overactiv$ or over-activ$ or hyperactiv$ or hyper-activ$ or unstable or instability or incontinen$) adj3 bladder$).ti,ab. 5434
3 (OAB or OABS or lOAB or lOABS).ti,ab. 1458
4 (urge syndrome$ or urge frequenc$).ti,ab. 76
5 ((overactiv$ or over-activ$ or hyperactiv$ or hyper-activ$ or unstable or instability) adj3 detrusor$).ti,ab. 3115
6 Urination Disorders/ 10268
7 exp Urinary Incontinence/ 25807
8 Urinary Bladder Diseases/ 9090
9 (urge$ adj3 incontinen$).ti,ab. 3539
10 (urin$ adj3 (incontinen$ or leak$ or urgen$ or frequen$)).ti,ab. 23360
11 (urin$ adj3 (disorder$ or dysfunct$)).ti,ab. 3726
12 (detrusor$ adj3 (hyperreflexia$ or hyper-reflexia$ or hypertoni$ or hyper-toni$)).ti,ab. 585
13 (void$ adj3 (disorder$ or dysfunct$)).ti,ab. 2214
14 (micturition$ adj3 (disorder$ or dysfunct$)).ti,ab. 326
15 exp Enuresis/ 4228
16 Nocturia/ 384
17 (nocturia or nycturia or enuresis).ti,ab. 6090
18 or/1-17 62934
19 (mirabegron or betmiga$ or myrbetriq$ or betanis$ or YM-178 or YM178 or 223673-61-8 or "223673618" or MVR3JL3B2V).ti,ab,rn. 86
20 exp Electric Stimulation Therapy/ 57859
21 Electric Stimulation/ 108459
22 ((sacral or S3) adj3 (stimulat$ or modulat$)).ti,ab. 982
23 (neuromodulat$ or neuro-modulat$ or neural modulat$ or electromodulat$ or electro-modulat$ or neurostimulat$ or neuro-stimulat$ or neural stimulat$ or electrostimulat$ or electro-stimulat$).ti,ab. 15399
24 (InterStim or SNS).ti,ab. 2757
25 ((electric$ or nerve$1) adj3 (stimulat$ or modulat$)).ti,ab. 73668
26 (electric$ therap$ or electrotherap$ or electro-therap$).ti,ab. 1334
27 TENS.ti,ab.9341
28 exp Electrodes/ 97155
29 electrode$1.ti,ab.95507
30 ((implant$ or insert$) adj3 pulse generator$).ti,ab. 409

31 ((implant$ or insert$) adj3 (neuroprosthe$ or neuro-prosthe$ or neural prosthe$)).ti,ab. 168
32 PTNS.ti,ab.192
33 (SANS or Stoller Afferent or urosurg$).ti,ab. 2236
34 (evaluat$ adj3 peripheral nerve$).ti,ab. 312
35 exp Botulinum Toxins/ 12033
36 (botulinum$ or botox$ or onabotulinumtoxin$ or 1309378-01-5 or "1309378015").ti,ab,rn. 16224
37 or/19-36 357943
38 18 and 37 3322
39 randomized controlled trial.pt. 383304
40 controlled clinical trial.pt. 88946
41 random$.ti,ab. 721724
42 placebo.ti,ab. 164838
43 drug therapy.fs. 1741540
44 trial.ti,ab. 372172
45 groups.ab. 1347710
46 or/39-45 3527987
47 38 and 46 1281
48 animals/ not humans/ 3929809
49 47 not 48 1171
50 limit 49 to english language 999

Note: post-search identified a relevant search term which was not captured by the free text terms used above – 'urgency–frequency syndrome'.

On 30/08/13 re-ran the MEDLINE search, including following line, and compared final line results with original strategy:

(urgency frequenc$ adj (syndrome$ or disorder$ or dysfunction$)).ti,ab.

No additional studies retrieved.

A.2: Detailed search strategy for Embase

Source: Embase

Interface / URL: OvidSP
Database coverage dates: 1974 to 2013 August 28
Search date: 29/08/13
Retrieved records: 1228
Search strategy:

1 overactive bladder/ 7410
2 ((overactiv$ or over-activ$ or hyperactiv$ or hyper-activ$ or unstable or instability or incontinen$) adj3 bladder$).ti,ab. 7878
3 (OAB or OABS or IOAB or IOABS).ti,ab. 2695
4 (urge syndrome$ or urge frequenc$).ti,ab. 111
5 ((overactiv$ or over-activ$ or hyperactiv$ or hyper-activ$ or unstable or instability) adj3 detrusor$).ti,ab. 4500
6 micturition disorder/ 9693
7 exp urine incontinence/51095
8 bladder disease/ 7634
9 (urge$ adj3 incontinen$).ti,ab. 5332
10 (urin$ adj3 (incontinen$ or leak$ or urgen$ or frequen$)).ti,ab. 32536
11 (urin$ adj3 (disorder$ or dysfunct$)).ti,ab. 5099
12 detrusor dyssynergia/ 2622
13 (detrusor$ adj3 (hyperreflexia$ or hyper-reflexia$ or hypertoni$ or hyper-toni$)).ti,ab. 698
14 (void$ adj3 (disorder$ or dysfunct$)).ti,ab. 3253
15 (micturition$ adj3 (disorder$ or dysfunct$)).ti,ab. 487
16 nocturia/ 3848
17 (nocturia or nycturia or enuresis).ti,ab. 8302
18 or/1-17 86739
19 mirabegron/ 146
20 (mirabegron or betmiga$ or myrbetriq$ or betanis$ or YM-178 or YM178 or 223673-61-8 or "223673618" or MVR3JL3B2V).ti,ab,rn,tn. 199
21 exp electrostimulation therapy/ 166622
22 electrostimulation/ 73492
23 ((sacral or S3) adj3 (stimulat$ or modulat$)).ti,ab. 1430
24 neuromodulation/21457
25 (neuromodulat$ or neuro-modulat$ or neural modulat$ or electromodulat$ or electro-modulat$ or neurostimulat$ or neuro-stimulat$ or neural stimulat$ or electrostimulat$ or electro-stimulat$).ti,ab. 18967
26 (InterStim or SNS).ti,ab. 3551
27 ((electric$ or nerve$1) adj3 (stimulat$ or modulat$)).ti,ab. 86651
28 (electric$ therap$ or electrotherap$ or electro-therap$).ti,ab. 1954
29 TENS.ti,ab.9329
30 exp electrode/ 82565

31 electrode$1.ti,ab.109520
32 ((implant$ or insert$) adj3 pulse generator$).ti,ab. 602
33 ((implant$ or insert$) adj3 (neuroprosthe$ or neuro-prosthe$ or neural prosthe$)).ti,ab. 170
34 PTNS.ti,ab.279
35 (SANS or Stoller Afferent or urosurg$).ti,ab. 2742
36 (evaluat$ adj3 peripheral nerve$).ti,ab. 425
37 botulinum toxin/ 10950
38 botulinum toxin A/ 12641
39 (botulinum$ or botox$ or onabotulinumtoxin$ or 1309378-01-5 or "1309378015").ti,ab,rn,tn. 21298
40 or/19-39 435097
41 18 and 40 6129
42 randomized controlled trial/ 357371
43 "randomized controlled trial (topic)"/ 37890
44 crossover procedure/ 38246
45 double blind procedure/ 119779
46 single blind procedure/ 18156
47 random$.ti,ab. 852758
48 factorial$.ti,ab. 22133
49 (crossover$ or cross-over$).ti,ab. 69956
50 placebo$.ti,ab. 199768
51 doubl$ blind$.ti,ab. 146368
52 singl$ blind$.ti,ab. 14113
53 assign$.ti,ab. 234376
54 allocat$.ti,ab. 80677
55 volunteer$.ti,ab. 178584
56 trial.ti,ab. 454044
57 groups.ab. 1656177
58 or/42-57 2868208
59 41 and 58 1402
60 (animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ 3650936
61 59 not 60 1338
62 limit 61 to english language 1228

Note: post-search identified a relevant search term which was not captured by the free text terms used above – ‘urgency–frequency syndrome’.

On 30/08/13 re-ran the Embase search, including following line, and compared final line results with original strategy:

(urgency frequenc$ adj (syndrome$ or disorder$ or dysfunction$)).ti,ab.

No additional studies were retrieved.

APPENDIX B STUDY SELECTION PROCESS

Table B.1: List of studies excluded, and reason for exclusion, following full text review

Full Reference	Reason for Exclusion
Abrams, P., *et al.* (2013). "Combination treatment with mirabegron and solifenacin in patients with overactive bladder (OAB)-efficacy and safety results from a randomised phase II study (symphony)." Neurourology and Urodynamics **32 (6)**: 930-931. Abrams, P., *et al.* (2013). "Combination treatment with mirabegron and solifenacin in patients with overactive bladder (OAB)-efficacy results from a phase 2 study (symphony)." Journal of Urology **1)**: e803.	Outcomes reported for combined therapy with mirabegron and solifenacin
Dowson, C., *et al.* (2011) The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: a randomised double-blind placebo-controlled trial. International Journal of Clinical Practice 65, 698-704 Dowson, C., *et al.* (2010). "Intra-detrusor injections of botulinum toxin-a do not appear to alter the gene expression of neurotrophic factors in the urothelium of patients with idiopathic detrusor overactivity." Journal of Endourology 24: A3.	Population described as having bladder oversensitivity (not OAB). Following discussion with Allergan, it was agreed that studies of patients described in this way should be excluded to avoid introducing further heterogeneity
Eltink, C., *et al.* (2012) Single dose pharmacokinetics and absolute bioavailability of mirabegron, a ??-adrenoceptor agonist for treatment of overactive bladder. International journal of clinical pharmacology and therapeutics **50**, 838-850	Healthy population not OAB; comparing sites of admin
Flynn MK, Amundsen CL, Perevich M, Liu F, Webster GD. Outcome of a Randomized, Double-Blind, Placebo Controlled Trial of Botulinum A Toxin for Refractory Overactive Bladder. Journal of Urology. 2009;181(6):2608-15. Flynn, M., *et al.* (2008) Short-term outcomes of a randomized, double-blind placebo controlled trial of botulinum A toxin for the management of severe idiopathic detrusor overactivity incontinence (Abstract number 33, poster). Neurourology and Urodynamics 151-152 Flynn, M., *et al.* (2007) Short-term outcomes of a randomized, double-blind placebo controlled tiral of botulinum A toxin for the management of severe idiopathic detrusor overactivity incontinence (Abstract number 3 Oral). Journal of Pelvic Medicine & Surgery 225-226	Comparison of BOTOX® 200U and 300U
Hampel, C., *et al.* (2012). "Comparison of two different Botulinumtoxin A products (Xeomin, Botox) used for detrusor injection in patients with bladder overactivity (BO) - A prospective randomized double-blind study." European Urology, Supplements 11 (1): e463-e463a.	Comparison of two types of BOTOX. Results not reported seperately for the non-neurogenic OAB subgroup
Jabs, C. and E. Carleton (2013). "Efficacy of Botulinum Toxin A Intradetrusor Injections for Non-neurogenic Urinary Urge Incontinence: A Randomized Double-Blind Controlled Trial." Journal of Obstetrics & Gynaecology Canada: 35(1): 53-60. Jabs, C. and E. Carleton (2010) Efficacy of botulinum toxin A intradetrusor injections for non-neurogenic urinary urge incontinence - a randomized double-blind control trial (Abstract number 296). Neurourology and Urodynamics 1228-1229	No outcomes of interest: Only data for maximum bladder capacity and quality of life were reported
Krauwinkel, W., *et al.* (2012) Pharmacokinetic properties of mirabegron, a 3-adrenoceptor agonist: results from two phase I, randomized,	Healthy population not OAB; comparing sites of

Full Reference	Reason for Exclusion
multiple-dose studies in healthy young and elderly men and women. Clinical Therapeutics **34**, 2144-216	administration.
Kuo, H. (2011). "Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics." Neurourology & Urodynamics 30(7): 1242-1248.	Evaluates different injection sites
Kuo, H. C. (2007) Comparative study of the therapeutic effects of different intravesical injections of botulinum toxin A on overactive bladder (Poster abstract number 1190). Journal of Urology	Evaluates different injection sites
Kuo, H. C., *et al.* (2010). "Adverse events of intravesical botulinum toxin a injections for idiopathic detrusor overactivity: risk factors and influence on treatment outcome." European Urology 58(6): 919-926.	Cohort study
Malik, M., *et al.* (2012) Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study. Clinical pharmacology and therapeutics **92**, 696-706	Healthy population not OAB
Truzzi, J. C., *et al.* (2004) What is the best dose for intravesical botulinum-A toxin injection in overactive bladder treatment? A prospective randomized preliminary study (Abstract). Proceedings of the Joint Meeting of the International Continence Society (ICS and the International UroGynecological Association (IUGA), 2004 Aug 23-27, Paris, France Abstract number 520 (abstract)	No outcomes of interest. Not relevant population.

APPENDIX C COMPARABILITY ASSESSMENT

Table C.1: Study similarity assessment tool (adapted from PBAC[20])

PBAC Element	Information required
Quality of study methods	• Adequate concealment of randomization; • Reported blinding; • Duration of study (pre-treatment; treatment; post-treatment); • Loss to follow-up (across study arms).
Confounding factors: Participant populations	• Age; • Sex; • Intensity of surveillance; • Severity of pathology; • Duration of disease; • Prior therapy for overactive bladder; • Co-existing disease; • Background or concomitant treatment.
Confounding factors: Circumstances	• Health system; • Geography (countries; total sites); • Setting; • Date of trials.
Similarity of common treatment arms	• Dose and administration; • Treatment duration; • Timing.
Similarity of outcome assessment	• Definition; • Rating instrument; • Frequency of measurement; • Data availability (time point).

Table C.2: Summary of criteria addressing concepts of bias

Author / Trial	Concealment of randomization	Blinding of treatment	Loss to follow-up (across study arms)	Outcome assessment
OnabotulinumtoxinA studies				
Al Taweel 2011[26]	Unclear	Not reported	0%	Patient-reported (voiding diary)
Chapple 2013[23]	Not reported	Double-blind	9.7%-11.8%	Patient-reported (3-day bladder diary)
Cohen 2009[28]	Unclear	Not reported	Not reported	Patient-reported (3-day voiding diary)
Denys 2012[29]	Unclear	Double-blind	4.3 - 10.0%	Patient-reported (3-day micturition diary)
Dmochowski 2010[30]	Not reported	Double-blind	10.7%-18.4%	Patient-reported (7-day bladder diary)
King 2007[31]	Unclear	Double-blind	Not reported	Patient-reported (bladder diary)
Nitti 2013[24]	Unclear	Double-blind	4.6%-7.6%	Patient-reported (3-day bladder diary)
Brubaker 2008[27]	Not reported	Double-blind	Not reported	Patient-reported (3-day urinary diary)
Sahai 2007[32]	Yes	Double-blind	0-11.1 %	Patient-reported (3-day voiding diary)
Tincello 2012[33]	Yes	Double-blind	4.9-5.9%	Patient-reported (3-day voiding diary)
Visco 2012[34]	Yes	Double-blind	7.1-7.4%	Patient-reported (3-day periods in monthly bladder diary)
Mirabegron studies				
ARIES[35]	Not reported	Double-blind	12.2%-15.2%	Patient-reported (3-day diary)
Astellas 178-CL-045[36]	Yes	Double-blind	5.2-7.4%	Patient-reported (3-day diary)
BLOSSOM[37]	Unclear	Double-blind	Not reported	Patient-reported (3-day micturition diary)
CAPRICORN[38]	Not reported	Double-blind	10.6%-15.2%	Patient-reported (3-day diary)
DRAGON[39]	Unclear	Double-blind	4.7-9.6%	Patient-reported (3-day micturition diary)
SCORPIO[40]	Yes	Double-blind	8.8%-11.5%	Patient-reported (3-day micturition diary)
TAURUS[41]	Unclear	Double-blind	21.7-23.6%	Patient-reported (3-day micturition diary)
Yamaguchi 2012[42]	Yes	Double-blind	6.1-8.2%	Patient-reported (3-day diary)

Table C.3: Similarity assessment of quality and methods of the randomized trials

Author / Trial	**Adequate concealment of randomization**	**Reported blinding**	**Duration of study** a) Pre-treatment b) Treatment c) Post-treatment	**Loss to follow-up** (across study arms)
ONABOTULINUMTOXINA				
Al Taweel 2011[26]	Unclear	NR	a) – b) 9 months c) -	0%
Chapple 2013[23]	NR	Double-blind treatment	a) 3-day screening period b) 12 weeks placebo-controlled c) 12 weeks (non placebo-controlled; retreatment allowed)	9.7%-11.8%
Cohen 2009[28]	Unclear	NR	a) – b) 24 weeks? c) -	NR
Denys 2012[29]	Unclear	Double-blind treatment	a) Baseline data collection (-15 days) b) 6 months c) -	4.3 - 10.0%
Dmochowski 2010[30]	NR	Double-blind treatment	a) 7-day screening period b) 36 weeks c) -	10.7%-18.4%
King 2007[31]	Unclear	Double-blind treatment	a) Baseline data collection (2 weeks) b) 6 weeks c) Unclear	NR
Nitti 2013[24]	Unclear	Double-blind treatment	a) ≤ 3-week screening period b) 12 weeks placebo-controlled c) 12 weeks (non placebo-controlled; retreatment allowed)	4.6%-7.6%
Brubaker 2008[27]	NR	Double-blind treatment	a) Screening visit (-14 days) b) 12 months c) ≤1 month	NR

Author / Trial	**Adequate concealment of randomization**	**Reported blinding**	**Duration of study** a) Pre-treatment b) Treatment c) Post-treatment	**Loss to follow-up** (across study arms)
Sahai 2007[32]	Yes	Double-blind treatment	a) – b) 12 weeks c) 12-week open label extension in BTX-A arm only	0- 11.1 %
Tincello 2012[33]	Yes	Double-blind treatment	a) Screening/unspecified 'washout' period b) 6 months c) Extension study	4.9-5.9%
Visco 2012[34]	Yes	Double-blind treatment	a) Screening period 3-week washout for those receiving anticholinergic at baseline b) 6 months double-blind treatment c) 6-month off-treatment follow-up	7.1-7.4%
MIRABEGRON				
ARIES[35]	NR	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 weeks c) 30 days	12.2%-15.2%
Astellas 178-CL-045[36]	Yes	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 weeks c) -	5.2-7.4%
BLOSSOM[37]	Unclear	Single-blind run-in Double-blind treatment Single-blind follow-up	a) 2-week placebo run-in b) 4 weeks c) 2-week placebo follow-up	NR
CAPRICORN[38]	NR	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 weeks c) 2 weeks	10.6%-15.2%
DRAGON[39]	Unclear	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 weeks c) -	4.7-9.6%
SCORPIO[40]	Yes	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 weeks c) 30 days	8.8%-11.5%

Author / Trial	**Adequate concealment of randomization**	**Reported blinding**	**Duration of study** a) Pre-treatment b) Treatment c) Post-treatment	**Loss to follow-up** (across study arms)
TAURUS[41]	Unclear	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 months c) -	21.7-23.6%
Yamaguchi 2012[42]	Yes	Single-blind run-in Double-blind treatment	a) 2-week placebo run-in b) 12 weeks c) 2 weeks	6.1-8.2%
Summary of similarity	Several trials did not report sufficient detail to assess this.	Where reported, all were double blind for the treatment period. Cohen and Al Taweel do not report information on blinding.	Duration of treatment period ranged from 4weeks (BLOSSOM) to 12 months (Brubaker 2008) with the majority of studies reporting a treatment period of 12 weeks. Follow up ranged from 2 weeks to 6 months.	Proportion of patients lost to follow up ranged from 4.3-23.6% across treatment groups.

NR = not reported

Table C.4: Similarity assessment of circumstances

Author / Trial	Health systems	Geography a) Countries b) Total sites	Setting	Date of trials
ONABOTULINUMTOXINA				
Al Taweel 2011[26]	Single country	a) Saudi Arabia b) 1 centre (from author details)	Tertiary care hospital	2008-2009
Chapple 2013[23]	Complex (multinational)	a) Europe, USA b) NR	NR	2009-2011
Cohen 2009[28]	Single country	a) USA b) 1 centre (from author details)	University school of medicine (from author details)	2002-2007
Denys 2012[29]	Single country	a) France b) 11 centres	NR	2005-2009
Dmochowski 2010[30]	Complex (multinational)	a) Europe, USA, Canada b) 40 sites	NR	2005-2008
King 2007[31]	Single country	a) Australia b) 1centre (from author details)	Hospital (from author details)	NR
Nitti 2013[24]	Complex (multinational)	a) USA, Canada b) 72 sites	NR	2009-2011
Brubaker 2008[27]	Single country	a) USA b) 7 centres	University clinical centres	NR
Sahai 2007[32]	Single country	a) UK b) 1 site (from author details)	Hospital outpatient clinic	2004-2006
Tincello 2012[33]	Single country	a) UK b) 8 centres	Hospital (urogynaecology centres)	2006-2009

Author / Trial	Health systems	Geography a) Countries b) Total sites	Setting	Date of trials
Visco 2012[34]	Single country	a) USA b) 10 centres (from author / investigator details)	Universities, clinics (from author / investigator details)	2010-2012
MIRABEGRON				
ARIES[35]	Complex (multinational)	a) USA, Canada b) 132 sites	NR	2008-2009
Astellas 178-CL-045[36]	Single country	a) Japan b) 60 sites	NR	2007-2008
BLOSSOM[37]	Complex (multinational)	a) International b) Multicentre	NR	NR
CAPRICORN[38]	Complex (multinational)	a) Europe, N. America b) 151 sites	NR	NR
DRAGON[39]	Complex (multinational)	a) International (14 countries) b) 97 centres	NR	NR
SCORPIO[40]	Complex (multinational)	a) Europe, Australia b) 189 sites	NR	NR
TAURUS[41]	Complex (multinational)	a) Europe, USA, Canada, South Africa, Australia, New Zealand b) 306 sites	NR	2008-2010
Yamaguchi 2012[42]	Single country	a) Japan b) 93 centres	Universities (from author details)	2009-2010
Assessment of similarity	A mix of complex (multinational) and single country studies	Studies ranged from single centre studies to international studies across 189 sites	Range of University, hospital and clinic settings. Unlikely to impact on efficacy data	All trials conducted post 2000

NR = not reported

Table C.5: Similarity assessment of participant populations

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
	a) Eligible population b) Mean age (overall or across study arms)	% Female (overall or across study arms)	a) Individual b) Study assessments	a) Grade of urgency b) Daily UIE c) Daily urge UIE d) Inadequately managed by anticholinergics			a) Detrusor over activity b) Type of OAB / incontinence c) Mean BMI d) Depression e) Menopausal symptoms f) Smoking status	a) Treatment-related b) OAB drugs c) Other
ONABOTULINUMTOXIN A								
Al Taweel 2011[26]	NR	NR	a) Patient diary b) Typically 3-monthly intervals	a) NR b) NR c) 3.8-4.2 (daily?) d) Yes	NR	NR	NR	a) Anaesthesia; post injection antibiotics b) NR c) NR
Chapple 2013[23]	a) NR b) 59.2 - 59.5 years	84.5 - 88.1%	a) 3-day patient diary b) Non-regular intervals	a) NR b) 5.5-5.7 c) NR d) Yes	5.5 years	OAB drugs:: on average, 2.4 drugs over 2 years	a, b, d-f) NR c) 28.7 - 29.5 kg/m2	a) Anaesthesia / sedation b) Not permitted during study c) NR
Cohen 2009[28]	NR	NR	a) 3-day patient diary. b) Non-regular intervals	a) NR b) NR c) 19.6-26.2 (OAB-Dry); 9.3-9.8 (OAB-Wet) d) Yes	NR	NR	NR	a) Anaesthesia; post injection antibiotics b) NR c) NR

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
Denys 2012[29]	a) >18 years b) 61.6 years (data for 99/ 107 randomized)	Protocol adherents (data for 99/107 randomized): 87.9%	a) 3-day patient diary. b) Non-regular intervals	a) NR b) NR c) 5.0 (data for 99/107 randomized) d) Yes	NR	NR	a) Detrusor over activity (no specific details) b-f) NR	a) Anaesthesia; pre-injection antibiotics b) 8 patients restarted anticholinergics c) NR
Dmochowski 2010[30]	a) 18 -85 years b) 58.8 years	92.0%	a) Patient diary preceding visit b) Typically 6-weekly intervals	a) NR b) NR c) Weekly urge UIE: 25-32.9 (DO present) and 20.4-31.8 (no DO) d) Yes	Median: >5 years	NR	a) Detrusor over activity: 76.0% b-f) NR	a) Anaesthesia/sedation b) Not permitted during study c) NR
King 2007[31]	a) 18-85 years b) 60.7 - 64.3 years	100.0%	a) Patient diary b) 6-weekly intervals	a) NR b) NR c) NR d) Minimal response	NR	NR	a) Detrusor over activity (no specific details) b-f) NR	a) Anaesthesia b) NR c) NR
Nitti 2013[24]	a) ≥18 years b) 61.0 - 61.7 years	88.4 - 90.0%	a) 3-day patient diary b) Typically 6-weekly intervals	a) NR b) 5.1-5.5 c) NR d) Yes	6.7 years	OAB drugs: on average, 2.5 drugs over 2.4 years	NR	a) Anaesthesia/sedation b) Not permitted during study c) NR
Brubaker 2008[27]	a) ≥21 years b) 64.7 - 69.2 years	100.0%	a) 3-day patient diary b) Monthly intervals	a) NR b) Total UIE on 3-day bladder diary: 19.0-21.4 (data for 38/ 43 randomized) d) Yes	NR	Drug treatments: 2.8 - 2.9 Non medication treatments: 1.5 - 1.7	a) Detrusor over activity (no specific details) b-f) NR	a) Anaesthesia; pre-and post-injection antibiotics b,c) Patients receiving new treatments for OAB symptoms were withdrawn from

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
								study
Sahai 2007[32]	a) 18-80 years b) 49.8-50.8 years (data for 34 of 36 randomized)	Treatment completers (data for 34 of 36 randomized patients): 55.9%	a) 3-day patient diary. b) Non-regular intervals	a) NR b) NR c) 3.9-5.0 (data for 34/ 36 randomized) d) Unclear (see details under diagnostic work up)	NR	Unclear	a) Detrusor over activity (no specific details) b-f) NR	a) Anaesthesia; post injection antibiotics b) The 17 patients taking anticholinergics were asked to continue use (data for 34 of 36 randomized). c) NR
Tincello 2012[33]	a) NR b) Median: 58.2-60.7 years	100.0%	a) 3-day patient diary b) Non-regular intervals	a) NR b) median 6.2 (both groups) c) NR d) Yes	NR	Continence surgery: 36.1-39%	b, d, e) NR a) Detrusor over activity (no specific details) c) BMI >30 kg/m2: 40.2-43.5% f) Smokers: 20.5-24.6%	a) NR b) Anticholinergic use at 6 months: 14-32% (226 of 240 randomized)
Visco 2012[34]	a) ≥21 years b) 56.7-59.3 years (247 of 249 randomized)	100.0%	a) 3-day patient diary b) Monthly intervals	a) NR b) NR c) 5.0 (data for 247 of 249 randomized) d) Unclear	NR	OAB drugs: 59% (data for 247 of 249 randomized)	a, b, d, e) NR c) 32.1-32.9 kg/m2 f) Current: 10-12% Previous: 32% Never: 55-59%	a) Antibiotics for patients that were catheterizing b,c) Patients asked to agree not to begin any off protocol treatment for urge UI (including

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
								medication management, behavioural therapy, or neuromodulation)
MIRABEGRON								
ARIES[35]	a) ≥18 years b) 60.1 years	74.3%	a) 3-day patient diary b) Typically 4-weekly intervals	a) Grade 3/4 (PPIUS) b) 2.8 (data for 933 / 1329 randomized) c) NR d) NR	NR	OAB drugs: 56-60% (data for 1270 of 1329 randomized)	a, d-f) NR b) Urgency incontinence: 29.7%. Frequency: 32.0%. Mixed: 38.3%. (data for 1270/ 1329 randomized): c) 30.2 kg/m2	NR
Astellas 178-CL-045[36]	a) 20-80 years b) 54.9-56.9 years (data for 835/842 randomized)	80.1-85.1% (data for 835/ 842 randomized)	a) 3-day patient diary b) Typically 4-weekly intervals	a) NR b) 1.7-2.2 c) 1.6-2.0 (data for 835/ 842 randomized) d) NR	80.9-89.3 months (data for 835/ 842 randomized)	NR	a, d-f) NR b) Urge: 55.3-61.4% Mixed: 31.3-37.0% Absent: 6.8-9.0% c) 22.6-22.9 kg/m2 72.2-73.9% of patients had complications (unspecified)	Allowed/prohibited medications were listed
BLOSSOM[37]	a) ≥18 years b) NR	NR	a) 3-day patient diary b) Typically 2-weekly intervals	a) Grade 3/4 b) 2.4-3.6 c) 2.1-3.5 (subset of 160 patients) d) NR	NR	NR	NR	NR

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
CAPRICORN[38]	a) ≥18 years b) 59.0 years	68.7%	a) 3-day patient diary b) Typically 4-weekly intervals	a) Grade 3/4 (PPIUS) b) 2.4-2.6 (data for 773/1306 randomized) c) NR d) NR	94 months (data for 1251/ 1306 randomized)	OAB drugs: 48-53% (data for 1251/ 1306 randomized)	a, d-f) NR b) Urgency incontinence: 28.2-38.5% Mixed stress/urgency incontinence: 30.2-33.0% Frequency: 26.8-38.8% c) 29.5 kg/m2	NR
DRAGON[39]	a) ≥18 years b) 57.2 years	89.3%	a) 3-day patient diary 4b) 4-weekly intervals	a) Grade 3/4 (PPIUS) b) NR c) NR d) NR	40.6-54.2 months	Prior OAB therapy comparable in each group	a, d-f) NR b) Urgency incontinence: 38.0-47.3%; Mixed stress/urgency incontinence: 24.6-38.0%. No incontinence: 24.1-31.7% c) 26.9-27.8 kg/m2	NR
SCORPIO[40]	a) ≥18 years b) 59.0 - 59.2 years	71.6 - 72.9%	a) 3-day patient diary b) 4-weekly intervals	a) NR b) 2.6-2.9 (data for 1165 of 1987 randomized) c) NR d) NR	77 - 85 months (data for 1906 of 1987 randomized)	OAB drugs: 49-51% OAB surgery: 4-7% (data for 1906 of 1097 randomized)	a, d-f) NR b) Urgency incontinence: 37.4 - 41.9%. Frequency: 36.6 - 39.2%. Mixed: 21.3 - 24.3% (data for 1906 of 1987 randomized) c) 27.5 - 28.0 kg/m2	NR
TAURUS[41]	a) ≥18 years	73.9-	a) 3-day	a) Grade 3/4 (PPIUS)	83.8-87.9	OAB drugs:	a, c, f) NR	a) NR

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
	b) 59.2-60.1 years (data for 2440 of 2452 randomized)	74.1% (data for 2440 of 2452 randomized)	patient diary b) Typically 3-monthly intervals	b) 2.4-2.7 (data for 2444 of 2452 randomized) c) NR d) NR	months (data for 2444 of 2452 randomized)	51.1-55.0% (data for 2444 of 2452 randomized). 21-24% and 14.1% had received mirabegron or tolterodine, respectively, in previous phase 3 studies	b) Urgency incontinence: 36.5-39.0% Mixed stress/urgency incontinence:25.9-28.6% Frequency: 35.0-35.1% d) Depression: 12.3-16.0%. e) Menopausal symptoms: 18.9-20.6%	b) Unclear c) Unclear; antihypertensives were allowed
Yamaguchi 2012[42]	a) ≥20 years b) NR	NR	a) 3-day patient diary b) 4-weekly intervals	a) NR b) NR c) NR d) NR	NR	NR	NR	Allowed/prohibited medications were listed
Similarity assessment of studies	Similar mean/median and range of ages.	Where reported, the majority of patients were female.	Patient diaries were analysed at intervals ranging from fortnightly to 3 monthly.	Where reported, patients experienced grade 3/4 urgency episodes and average number of daily UIE ranged from 2-3 in mirabegron studies and 5-6 in BOTOX® studies.	Where reported, disease duration across studies ranged from 40.6 months to 94 months.	Where reported, between 48-60% of patient samples were treated with OAB drugs and 4-39% of patients had undergone continence surgery. No restrictions were placed on prior therapy in the	Several studies reported that patients also experienced urgency, frequency and mixed incontinence to various extents across the studies. Detrusor over activity was also reported in several trials. Unclear how important these variations could be to permitting indirect comparisons.	In the majority of studies patients received local anaesthesia and/or antibiotics in association with their treatment and were not permitted to take non-treatment OAB drugs during the trial. In Sahai 2007, patients taking anticholinergics were asked to

Author / Trial	Age	Sex	Intensity of surveillance	Severity of pathology	Duration of disease (mean)	Prior therapy for OAB	Co-existing disease	Background therapy or concomitant treatments / advances in standard of care
						eligibility of studies		continue taking them. compromises the similarity of this study to other studies where patients discontinued other OAB treatments

BMI = body mass index; DO = detrusor overactivity; NR = not reported; OAB = overactive bladder; UIE = urinary incontinence episodes

Table C.6: Similarity assessment of common treatment arms: OnabotulinumtoxinA

Author / Trial	Dose and administration	Treatment duration	Timing
	ONABOTULINUMTOXINA 100 U	**Not applicable**	
Al Taweel 2011[26]	Single injection procedure of intradetrusor BOTOX® 100 u (in 10 ml saline) at 1 ml/site	-	Single treatment
Chapple 2013[23]	OnabotulinumtoxinA 100 U Single injection procedure of 20 intradetrusor injections of 0.5 ml, evenly spaced but avoiding the trigone muscle	-	Single treatment however, patients had the option of re-treatment at 12 weeks)
Cohen 2009[28]	BOTOX® 100 U Single injection procedure of 10 intradetrusor injections (1 ml per site) into the supra-trigonal detrusor muscle	-	Single treatment
Denys 2012[29]	BOTOX® 100 U Single-injection procedure of 15 injections (in 15 ml normal saline) into the detrusor muscle avoiding the trigone.	-	Single treatment
Dmochowski 2010[30]	OnabotulinumtoxinA 100 U (intradetrusor injection) Single injection procedure of 20 injections of 0.5 ml per site evenly distributed into the detrusor muscle, avoiding the trigone muscle and dome	-	Single treatment
Nitti 2013[24]	OnabotulinumtoxinA 100 U Single injection procedure of 20 intradetrusor injections of 0.5 mL (in 10 ml normal saline)	-	Single treatment
Visco 2012[34]	OnabotulinumtoxinA 100 U Single-injection procedure of BOTOX® 100 U (in 10 ml saline) into 15-20 different intradetrusor muscle sites.	-	Single treatment
Comparability	Differences noted in the administration of BOTOX® injections across the studies in terms of the number of injections, dose per site and saline dilution. Following discussion with Allergan it was anticipated that these differences are not a cause for concern. This was confirmed by Allergan's clinical team	Not applicable	OnabotulinumtoxinA was administered in a single procedure in all the studies however, in Chapple 2013, retreatment was allowed after 12 weeks.
	ONABOTULINUMTOXINA 150 U	**Not applicable**	

Author / Trial	Dose and administration	Treatment duration	Timing
Cohen 2009[28]	BOTOX® 150 U 15 injections (1 ml per site) into the supra-trigonal detrusor muscle.	-	Single treatment
Denys 2012[29]	BOTOX® 150 U 15 injections of BTX-150 U (in 15 ml normal saline) into the detrusor muscle.	-	Single treatment
Similarity assessment	Both gave multiple injections into the detrusor muscle. However, the number of injections and dose per site varied across studies. Following discussion with Allergan it was anticipated that these differences are not a cause for concern.	Not applicable	Yes - All were single treatments

Table C.7: Similarity assessment of common treatment arms: Mirabegron

Author / Trial	Dose and administration	Treatment duration	Timing
	MIRABEGRON 25 mg		
Astellas 178-CL-045[36]	Mirabegron 25 mg (oral). One mirabegron 25-mg tablet and one placebo tablet were taken orally, after breakfast each day	12 weeks	Once daily
DRAGON[39]	Mirabegron 25 mg. A total of 3 tablets, corresponding to a dose of 25 mg mirabegron and one placebo capsule were taken orally after breakfast each day	12 weeks	Once daily
CAPRICORN[38]	Mirabegron 25 mg (oral)	12 weeks	Once daily
Similarity assessment	Yes - All doses were comparable	Yes - all studies were 12 weeks	Yes - all doses taken once daily
	MIRABEGRON 50 mg		
ARIES[35]	Mirabegron 50 mg (oral)	12 weeks	Once daily
Astellas 178-CL-045[36]	Mirabegron 50 mg (oral). One mirabegron 50-mg tablet and one placebo tablet were taken orally, after breakfast	12 weeks	Once daily
CAPRICORN[38]	Mirabegron 50 mg (oral)	12 weeks	Once daily
DRAGON[39]	Mirabegron 50 mg. A total of 3 tablets one placebo capsule were taken orally after breakfast each	12 weeks	Once daily
SCORPIO[40]	Mirabegron 50 mg (oral)	12 weeks	Once daily
TAURUS[41]	Mirabegron 50 mg (oral)	12 months (results presented at 3 months)	Once daily
Yamaguchi 2012[42]	Mirabegron 50 mg (oral). One mirabegron 50-mg tablet and one placebo capsule were taken orally, once daily after breakfast	12 weeks	Once daily
Similarity assessment	Yes - All doses were comparable	All studies were 12 weeks duration except TAURUS, where results were presented at 3 months	Yes - All treatments administered once daily
	MIRABEGRON 100 mg		

SCORPIO[40]	Mirabegron 100 mg	12 weeks	Once daily
TAURUS[41]	Mirabegron 100 mg (oral)	12 months	Once daily
Similarity assessment	Yes - All doses were comparable	All studies were 12 weeks duration except TAURUS, where results were presented at 3 months	Yes - All treatments administered once daily

C.1: Key differences between the included studies

Some notable differences were identified that could impact on potential inclusion in an indirect treatment comparison.

The impact of differences in treatment period was assessed for each outcome in turn when finalising the networks. Variations in the study settings (single-centre to international studies across 306 sites) were not considered to compromise the analyses.

Patients in the onabotulinumtoxinA and mirabegron trials showed systematic differences in the severity of their urinary incontinence (UI) and urgency symptoms: at baseline, onabotulinumtoxinA patients reported a higher number of both UI episodes and urgency episodes (5−6 and 7−9 per day, respectively) than mirabegron patients (1−3 and 4−6 per day, respectively). Multiple linear regression models, with terms included for baseline episodes, treatment and their interaction, explored these differences further using onabotulinumtoxinA study individual patient data (IPD) and found treatment effect for change from baseline in UI episodes and urgency to be influenced by baseline severity of symptoms, i.e. patients with a greater number of episodes at baseline have greater potential for improvement.

There were no restrictions on prior therapy in determining the eligibility of studies for the network meta-analysis. However, one study (Sahai 2007) was excluded because patients continued to take anticholinergics alongside their assigned study treatments, rather than discontinuing overactive bladder (OAB) treatment prior to the study.

Differences in the administration of onabotulinumtoxinA in terms of the number of injections, dose per site and saline dilution were considered not to compromise the similarity of studies and no studies were excluded on this basis. However, the ‘placebo’ used in onabotulinumtoxinA studies (saline injection) and mirabegron studies (oral tablet) represented an important difference between these trials and an assumption was made that the mode of administration does not impact the treatment effect, recognising that this may impact the analyses and introduce heterogeneity.

APPENDIX D STATISTICAL METHODOLOGY

For each outcome network meta-analysis based on Bayesian methodology was used to estimate the relative efficacy of the treatments. Network meta-regression (NMR) was also applied where differences in the baseline value of the outcome between studies considered important.

Network meta-analysis

Standard Bayesian methodology for random effects network meta-analysis was applied.[1] For both binomial and continuous models, baseline and treatment effect parameters were given vague prior distributions as required: Normal $(0,100^2)$. For continuous models, the between-study variance was also given a vague prior distribution: $1/\varphi^2 \sim$ Gamma (0.001,0.001).

For binomial models standard informative priors for the between-study variance are available (no such standard priors are available for continuous models). As the data are sparse, these informative priors were used to reduce the uncertainty in the between-study variance.

The informative priors come from Turner *et al.*[2] which evaluated the between-study variances from 14,886 published meta-analyses of binary outcomes. The meta-analyses evaluated different types of outcomes, compared different types of interventions and came from diverse areas of medicine. The outcomes were categorised as all-cause mortality, semi-objective outcomes and subjective outcomes. The meta-analyses were divided into those that compared pairs of pharmacological treatments, those that compared pharmacological treatments to placebo and those that included any non-pharmacological intervention. The results of the analysis showed that between-study variances were influenced by the type of outcome and the type of intervention comparison but not the medical specialty.

Turner *et al.*[2] developed nine informative priors for the between-study variance according to the outcome type and the intervention comparison type. Under the definitions used by Turner *et al.*[2] the binary OAB outcomes were considered to be subjective outcomes (general physical health). Most of the comparisons in the networks compare pharmacological treatments to placebo. For comparisons of subjective outcomes between pharmacological treatments and placebo, Turner *et al.*[2] developed the following prior for the between-study variance: $\varphi^2 \sim$ Log-normal (-2.13, 1.58^2), where the parameters are, respectively, the mean and standard deviation on the log scale. This prior distribution is used for the between-study variance in the binomial models.

Network meta-regression

A fundamental assumption of NMA is that the included studies do not differ in any patient or study characteristics that may be predictors of the treatment effect. This assumption was not appropriate for two of the outcomes studied: change in the number of UI episodes per day (UIE) and change in the number of urgency episodes per day ('urgency'). For these outcomes, patients in the onabotulinumtoxinA studies had higher baseline severity than those in the mirabegron studies, and baseline severity was thought to be a modifier of the treatment effect.

Network meta-regression was used to account for differences between studies in their baseline severity. For UIE and urgency, based on the aggregate data (AD) alone, there was limited

information to inform a meta-regression. All of the mirabegron studies have low baseline severity and of all the onabotulinumtoxinA studies have high baseline severity. Hence, it was not possible for an AD meta-regression to determine accurately whether any effect was due to a difference between the treatments or the difference in baseline severity. However, IPD are available for the Allergan onabotulinumtoxinA trials. The IPD can help to estimate the effect due to baseline severity. A meta-regression including both IPD from the Allergan onabotulinumtoxinA trials and AD from the other trials can be used to account for the differences in baseline severity and provided an unbiased estimate of the treatment effect.

Methodology for combining both AD and IPD within an NMR has been developed by Jansen[3] and Saramago *et al.*[4] Their methodology was designed for a binary outcome and binary covariate. Pairwise meta-regression (but not network meta-regression) using both AD and IPD for continuous outcomes and covariates has been proposed by Riley *et al.*[5] Here, the NMR methodology for AD and IPD is adapted for a continuous outcome and continuous covariate.

The network meta-regressions incorporated all studies with either AD or IPD on both baseline severity and change from baseline. The meta-regression model assumed that the onabotulinumtoxinA studies and mirabegron studies both have the same relationship between baseline severity and change from baseline, relative to placebo, however, the two treatments will have a different underlying effectiveness We also assumed that the relationship between baseline severity and change from baseline was the same for both IPD and AD More complex meta-regression models, with fewer assumptions, are generally possible; however these would require more data (ideally more than two onabotulinumtoxinA studies and IPD from mirabegron studies).

The overall meta-regression model was composed of separate models for the IPD and AD. Studies with IPD contributed only to the IPD model (IPD studies are not included in AD model). These separate models shared key parameters that were used to estimate the difference between treatments. With the exception of variance parameters, parameters were given vague normal prior distributions: Normal (0, 1000^2). Variance parameters were given vague Gamma distributions: Gamma (0.001, 0.001).

Implementation

Analysis was undertaken using WinBUGS version 1.4.3[6] and R version 3.0.1.[7] The package 'R2WinBUGS' was used to run WinBUGS from within R.[8] The results of each model were assessed for convergence by viewing the trace plots and reviewing the Brooks-Gelman-Rubin diagnostic.[9] For each outcome, a burn-in of 20,000, followed by another 60,000 iterations, was found to be sufficient for convergence.

Table D.1: Summary of outcome analyses conducted

Outcome	**Network analysis** **(method; model; prior distribution for between-study precision)**
Urinary Incontinence	
100% reduction from baseline in number of UI episodes/day	Standard NMA; random-effects; informative prior
50% reduction from baseline in number of UI episodes/day	Standard NMA; random-effects; informative prior
Change from baseline in number of UI episodes/day	Standard NMA; random-effects; Gamma prior
	NMR; random-effects; Gamma prior
Urgency	
100% reduction from baseline	Standard NMA; random-effects; informative prior
Change from baseline in number of urgency episodes/day	Standard NMA; random-effects; Gamma prior
	NMR; random-effects; Gamma prior
Micturition	
Change from baseline in number of episodes/day	Standard NMA; random-effects; Gamma prior
Nocturia	
Change from baseline in number of nocturia episodes/night	Standard NMA; random-effects; Gamma prior

NMA = network meta-analysis; NMR = network meta-regression

APPENDIX E STUDIES INCLUDED IN THE NETWORK

Table E.1: Summary of studies contributing to the network meta-analysis

Outcome	Studies contributing to network meta-analysis	
100% reduction in number of daily UI episodes	7 RCTs	Chapple 2013[23] Nitti 2013[24] Cohen 2009[28] Denys 2012[29] CAPRICORN[38] DRAGON[39] SCORPIO[40]
50% reduction in number of daily UI episodes	4 RCTs	Chapple 2013[23] Nitti 2013[24] CAPRICORN[38] SCORPIO[40]
Change in number of daily UI episodes	8 RCTs	Chapple 2013[23] Nitti 2013[24] ARIES[35] Astellas 178-CL-045[36] CAPRICORN[38] DRAGON[39] SCORPIO[40] Yamaguchi 2012[42]
100% reduction in daily urgency episodes	3 RCTs	Chapple 2013[23] Nitti 2013[24] DRAGON[39]
Change in number of daily urgency episodes	9 RCTs	Chapple 2013[23] Nitti 2013[24] Denys 2012[29] ARIES[35] Astellas 178-CL-045[36] CAPRICORN[38] DRAGON[39] SCORPIO[40] Yamaguchi 2012[42]
Change in frequency of daily micturition	8 RCTs	Chapple 2013[23] Nitti 2013[24] ARIES[35] Astellas 178-CL-045[36] CAPRICORN[38] DRAGON[39] SCORPIO[40] Yamaguchi 2012[42]
Change in number of nightly episodes of nocturia	6 RCTS	Chapple 2013[23] Nitti 2013[24] ARIES[35] Astellas 178-CL-045[36] DRAGON[39] Yamaguchi 2012[42]

Table E.2: Summary of patient numbers in trials contributing to network analyses

Study	Treatment arm	Number of patients
Chapple 2013[23]	Placebo	271
	BTX 100 U	277
Cohen 2009[28]	BTX 100 U	12
	BTX 150 U	12
Denys 2012[29]	Placebo	28
	BTX 100 U	20
	BTX 150 U	26
Nitti 2013[24]	Placebo	277
	BTX 100 U	280
ARIES[35]	Placebo	325
	MBG 50 mg	312
Astellas 178-CL-045[36]	Placebo	140
	MBG 25 mg	134
	MBG 50 mg	144
CAPRICORN[38]	Placebo	262
	MBG 25 mg	254
	MBG 50 mg	257
DRAGON[39]	Placebo	106
	MBG 25 mg	99
	MBG 50 mg	108
SCORPIO[40]	Placebo	291
	MBG 50 mg	293
Yamaguchi 2012[42]	Placebo	380
	MBG 50 mg	381

BTX = onabotulinumtoxinA; MBG = mirabegron

APPENDIX F COMPARISON OF FIXED-EFFECT AND RANDOM-EFFECTS RESULTS FOR NMA AND NMR[#]

Outcome	Total number of studies	Max. studies within 1 pairwise comparison	OnabotulinumtoxinA 100 U vs Mirabegron 25 mg		OnabotulinumtoxinA 100 U vs Mirabegron 50 mg	
			Estimate of odds ratio (95% CrI)		Estimate of odds ratio (95% CrI)	
			FE	RE(1)	FE	RE(1)
Binary outcomes						
100% reduction from baseline in UI episodes/day	6	3	3.44 (2.20, 5.43)	3.54 (1.93, 6.81)	3.39 (2.25, 5.18)	3.49 (1.97, 6.55)
50% reduction from baseline in UI episodes/day	4	2	1.83 (1.18, 2.80)	1.83 (0.80, 4.25)	2.06 (1.46, 2.94)	2.07 (0.98, 4.49)
100% reduction from baseline in urgency episodes/day	3	2	6.10 (2.57, 15.31)	6.16 (1.43, 28.58)	6.97 (2.88, 17.71)	7.01 (1.62, 32.60)
Continuous outcomes						
[#]Change in number of UI episodes/day	6	4	-0.64 (-1.15, -0.14)	-0.62 (-1.20, -0.02)	-0.72 (-1.19, -0.25)	-0.70 (-1.23, -0.16)
[#]Change in number of urgency episodes/day	7	4	-1.48 (-2.09, -0.86)	-1.49 (-2.16, -0.80)	-1.30 (-1.90, -0.71)	-1.32 (-2.00, -0.67)
Change in frequency of daily micturition	8	6	-0.89 (-1.30, -0.49)	-0.89 (-1.35, -0.45)	-0.81 (-1.19, -0.44)	-0.81 (-1.24, -0.40)
Change in number of nocturia episodes/night	6	4	-0.06 (-0.25, 0.13)	-0.06 (-0.31, 0.19)	-0.11 (-0.28, 0.06)	-0.10 (-0.32, 0.12)

Results presented are those from the network meta-analysis, unless otherwise indicated: [#] indicates results of the network meta-regression.

FE indicates the fixed-effect model.

RE(1) indicates the random-effects model is based on the primary prior distribution for the between-study variance; for binary outcomes this is the informative prior, for continuous outcomes this is the Gamma prior.

APPENDIX G FOREST PLOTS FOR INDIVIDUAL OUTCOMES

Figure G.1: 100% reduction in daily UI episodes (random-effects model, informative prior distribution for between-study variance)

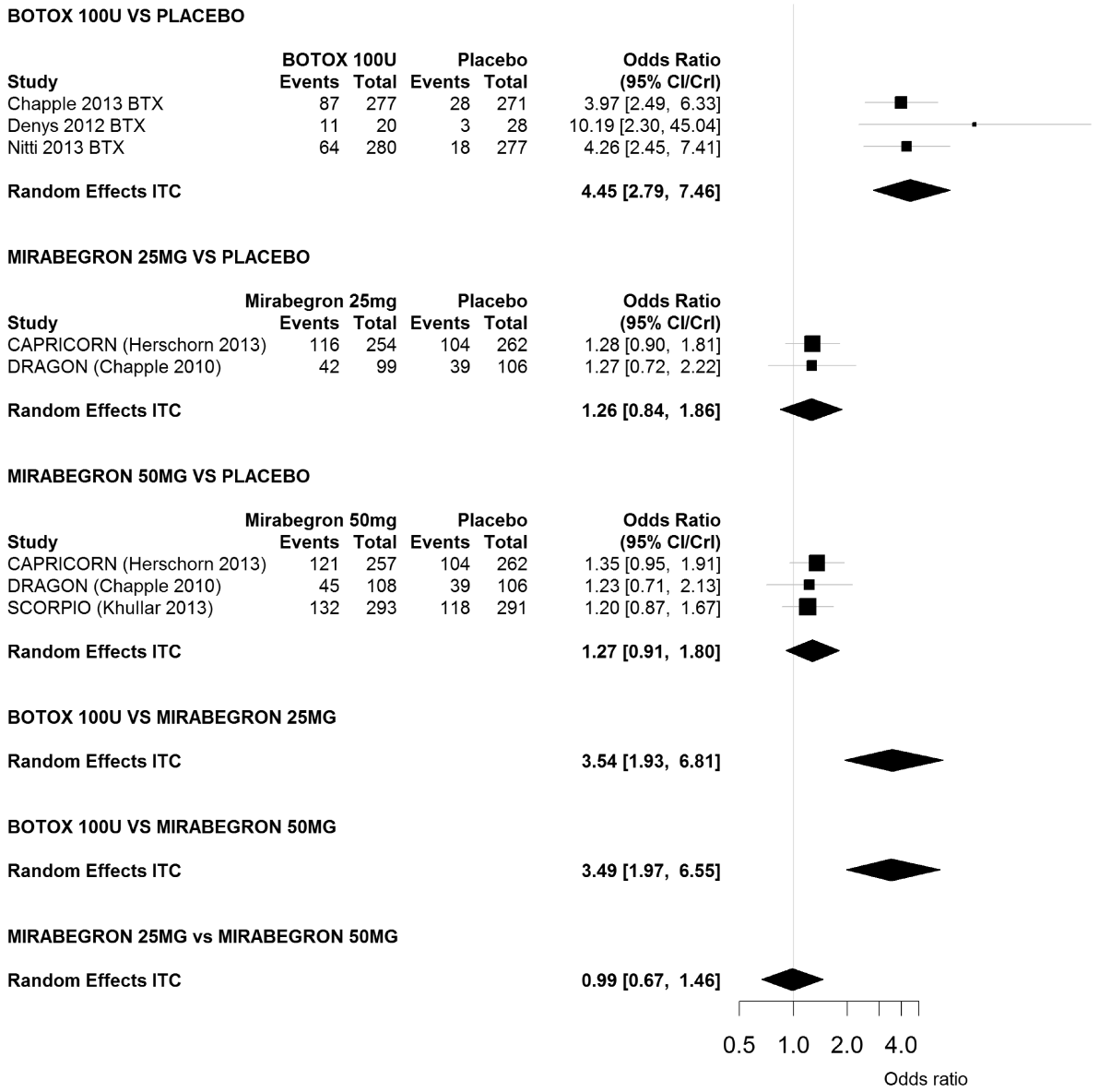


Figure G.2: 50% reduction in daily UI episodes (random-effects model, informative prior distribution for between-study variance)

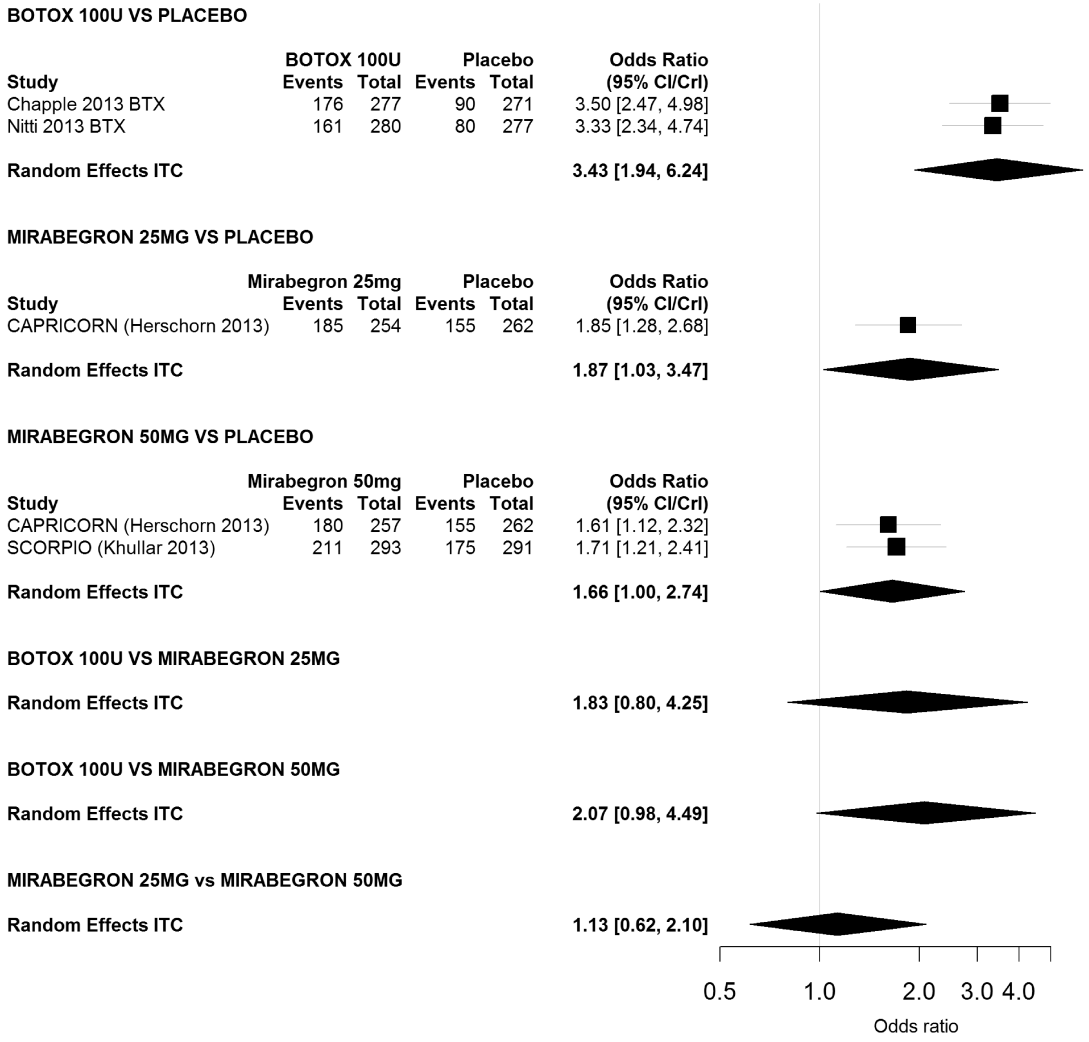
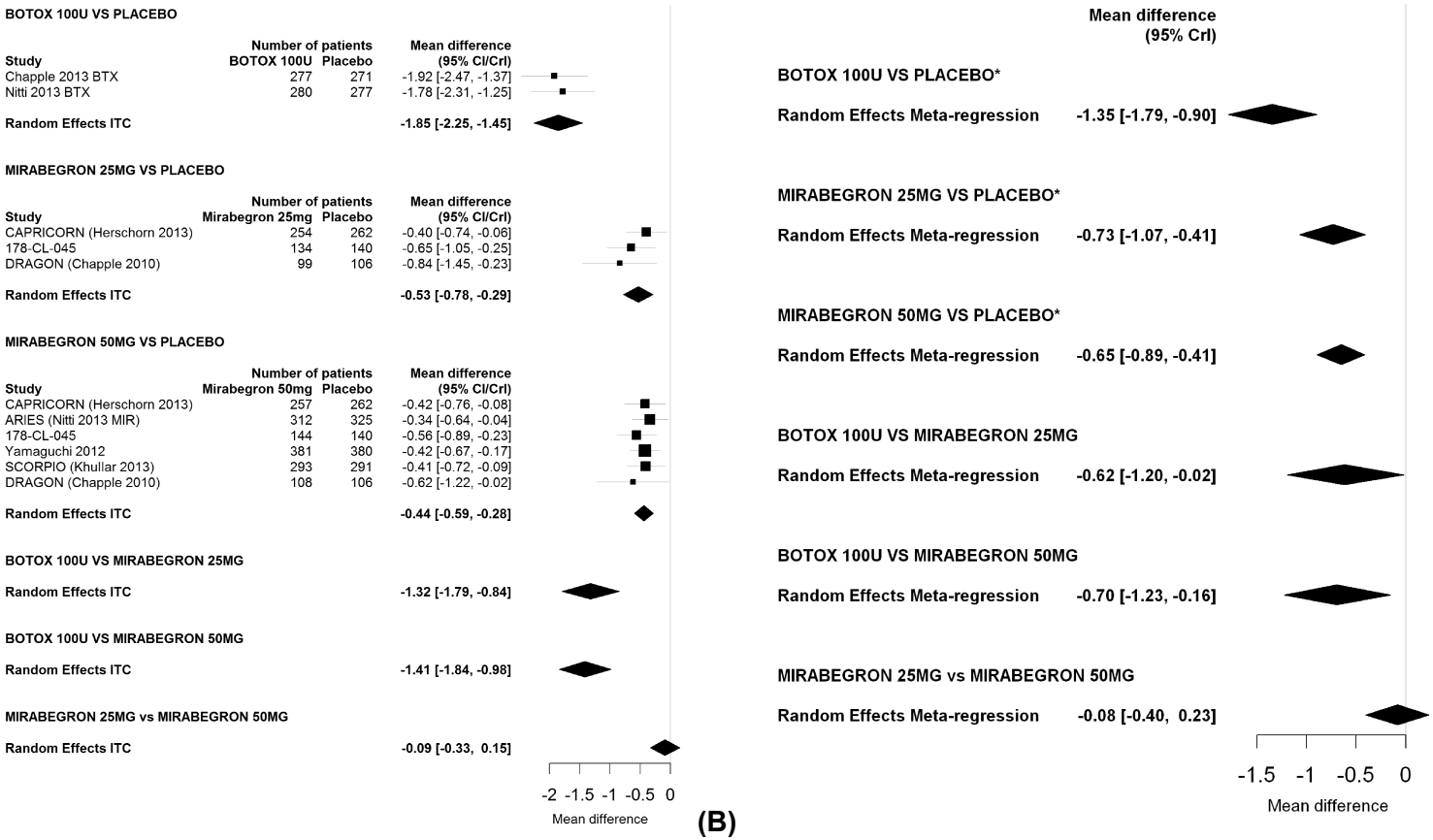


Figure G.3: Mean difference in change from baseline for the number of UI episodes per day

(A) Unadjusted (standard NMA, random effects model, Gamma prior distribution for between-study precision)

(B) Adjusted (NMR random-effects model, Gamma prior distribution for between-study precision)



* For comparisons between placebo and active treatment, the mean difference is estimated for patients with an average baseline value (i.e. 3.48 episodes per day). For comparisons between active treatments, the mean difference does not depend on the baseline value.

Figure G.4: 100% reduction in daily urgency episodes (random-effects model, informative prior distribution for between-study variance)

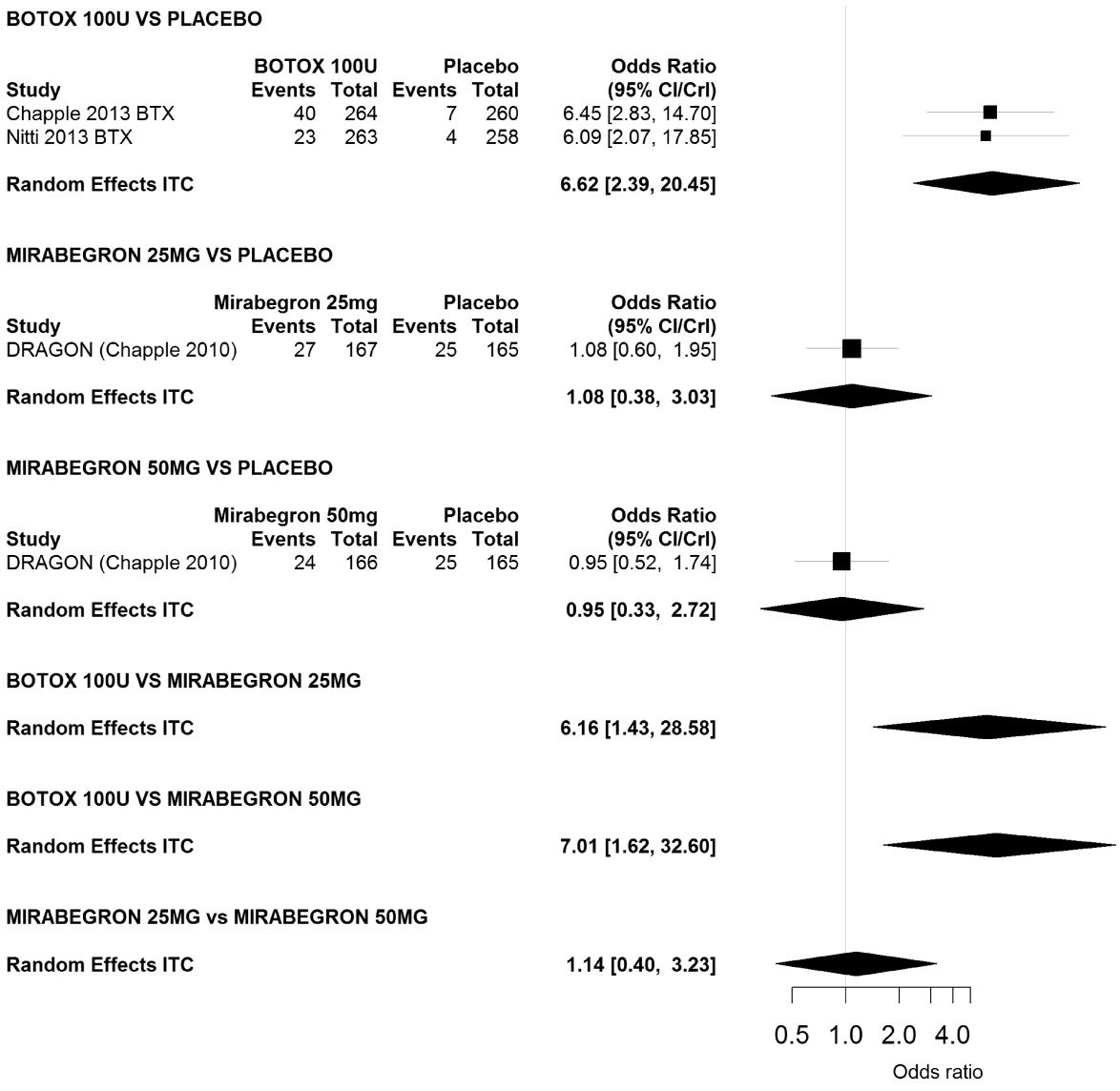
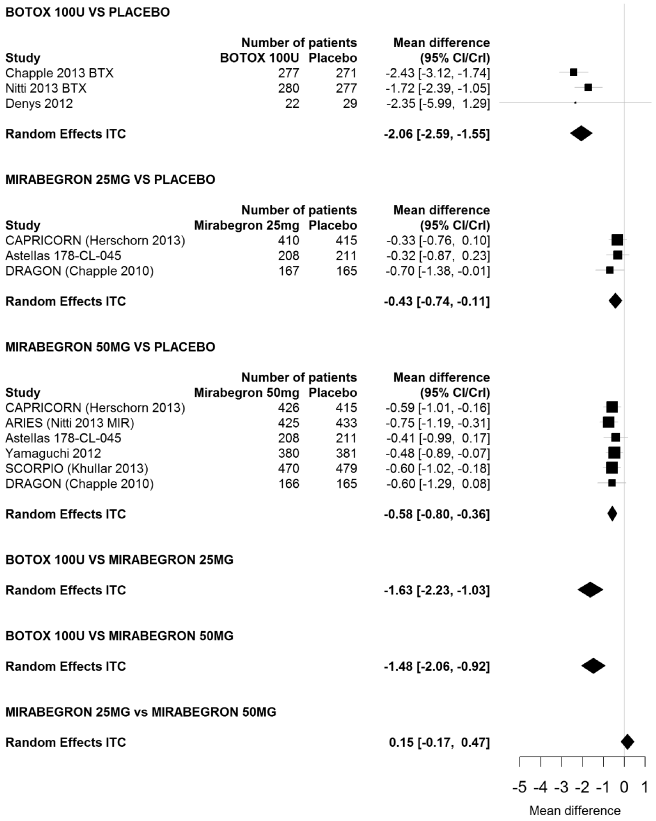


Figure G.5: Mean difference in change from baseline for the number of urgency episodes per day.

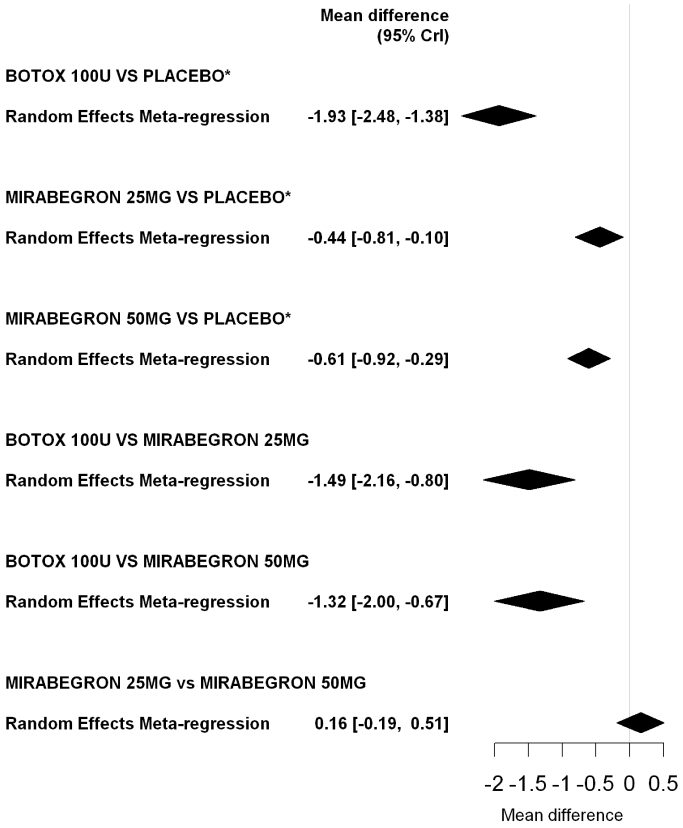
(A) Unadjusted (standard NMA, random effects model, Gamma prior distribution for between-study precision)

(B) Adjusted ((NMR random-effects model, Gamma prior distribution for between-study precision)

(A)



(B)



* For comparisons between placebo and active treatment, the mean difference is estimated for patients with an average baseline value (i.e. 6.32 episodes per day). For comparisons between active treatments, the mean difference does not depend on the baseline value.

Figure G.6: Mean difference in change from baseline in daily micturition (random-effects model, Gamma prior distribution for between-study precision)

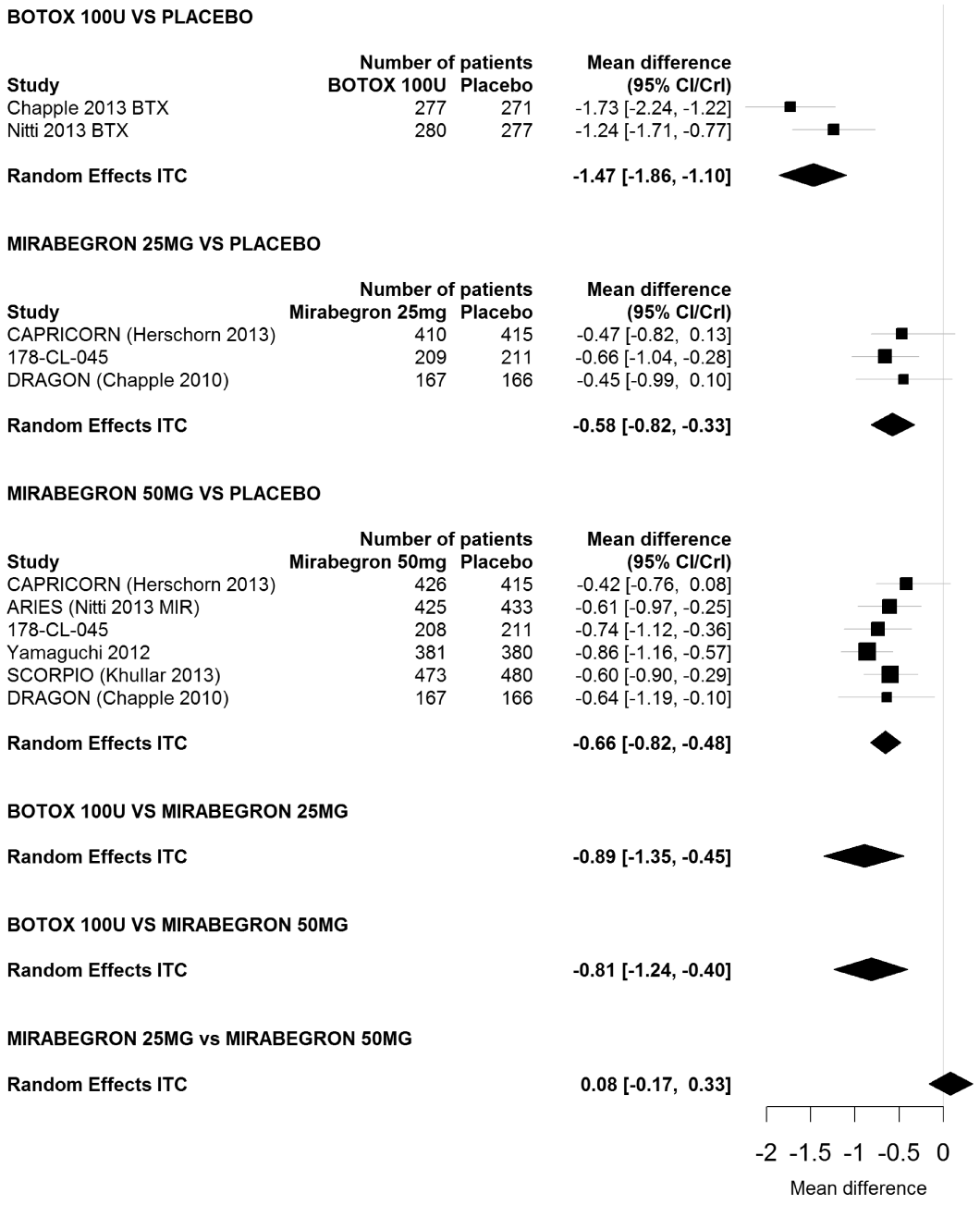
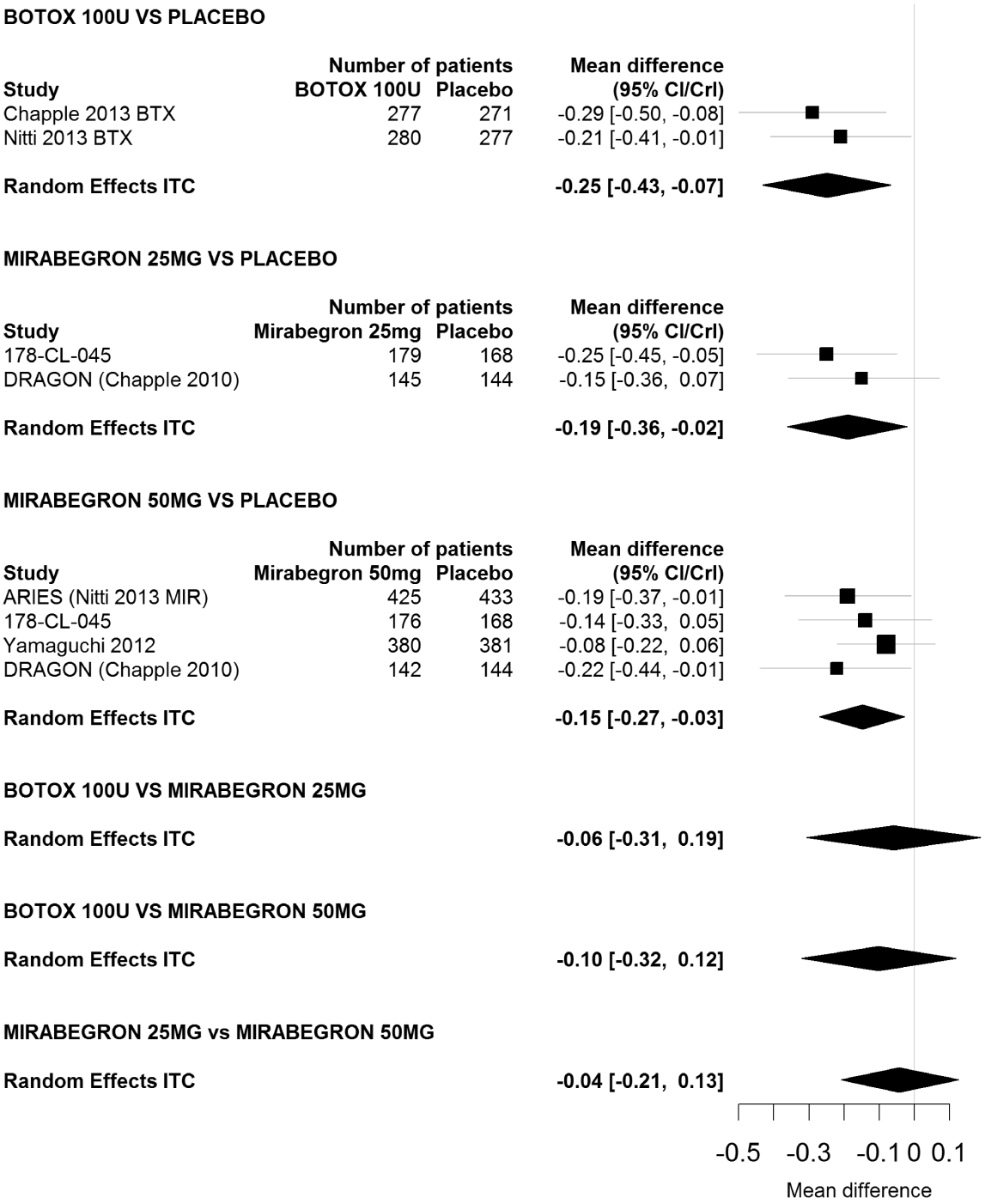


Figure G.7: Mean difference in change from baseline in episodes of nocturia (random-effects model, Gamma prior distribution for between-study precision)



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