National Institute for Health and Care Excellence

Draft for consultation

Urinary incontinence and pelvic organ prolapse in women: management

[C] Evidence review on the risks to cognitive function for women taking anticholinergic drugs for overactive bladder

NICE guideline tbc

Evidence reviews

October 2018

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

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Anticholinergic drugs for overactive bladder (OAB)

Review question

What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

Introduction

Anticholinergic drugs are the commonest treatment for OAB and there is increasing concern regarding longer term effects of anticholinergics on cognitive impairment, especially their impact on more vulnerable populations with multiple co-morbidities. The aim of this review is to determine if anticholinergic drugs negatively impact long-term cognitive function in women with OAB.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (aged 18 years of age and over) who are receiving anticholinergic drugs for the management of overactive bladder symptoms of any origin
Intervention	The following antimuscarinic agents for the treatment of OAB will be considered: • Oxybutynin • Tolterodine • Darifenacin • Solifenacin • Trospium chloride • Fesoterodine • Propiverine
Comparison	Each agent compared against: (i) each other, (ii) placebo, or (iii) Mirabegron
Outcomes	**Critical** • Long-term cognitive impairment measured using validated tools only, including: ○ Abbreviated metal test score (AMTS) ○ General practitioner assessment of cognition (GPCOG) ○ Mini-cog ○ Addenbrookes cognitive examination III (ACE_III) ○ Montreal cognitive assessment (MoCA) ○ Mini mental state examination (MMSE) ○ 6-item cognitive impairment test (6CIT) • Falls **Important** • Delirium • All-cause mortality

OAB: Overactive Bladder

For further details see the review protocol in appendix A. .

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A and for a full description of the methods see supplementary material C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Three studies were identified for inclusion in this review (Geller 2017, Gomes 2011, Jewart 2005). One of the included studies was an RCT which compared Trospium to placebo (Geller 2017). One study was a retrospective cohort which compared Tolterodine to oxybutynin (Gomes 2011), and the final study was a single-blind crossover trial which compared participants "on" or "off" Tolterodiene (Jewart 2005).

See the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E, and GRADE tables in appendix F.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention/ Comparison	Outcomes	Comments
Geller 2017 RCT USA N = 45	Trospium (n=21) *vs.* Placebo (n=24). Mean age 68 years; 78% white; 44% previously taken OAB medications 100% women included	Participants were randomised into either trospium chloride extended release 60 mg daily or placebo, and received a 4-week supply of blinded medication which they were to begin the following day	Cognitive function as assessed by: MMSE, Digit Span, the HVLT-R (higher values indicating better cognitive performance); Trails A & B, (higher scores indicating worse cognition),	44% of participants had previously taken anticholinergics. Study included women aged 50 years and older, and was not powered to draw conclusions about elderly adults

Study	Population	Intervention/ Comparison	Outcomes	Comments
			Measured at baseline, week 1 and week 4	
Gomes 2011 Retrospective cohort study Canada N = 40, 563	40,563 tolterodine users individually matched to a new user of oxybutynin Age: 66 years and older who commenced treatment with oxybutynin or tolterodine between	Mean daily dose of 8.6 mg (SD 6.6) for oxybutynin patients, and 3.6 (SD 2.2) for tolterodine patients (equivalent to a mean dose of 9 mg (SD 5.1) of oxybutynin.) Patients were followed mean of 88.3 days (SD 9.9) for tolterodine, and 88.1 days (SD 10.6) for oxybutynin	Falls (defined by ICD-10 codes W00 to W19) All-cause mortality	The authors had financial and/or other relationship with the funders of the study. The diagnosis and procedure codes used to identify falls were not externally validated. Only falls requiring emergency visits or hospitalization were recorded, therefore data on clinically important but less severe falls was not captured
Jewart 2005 Single-blind crossover USA N = 9	Participants with a diagnosis of Alzheimer's disease, MMSE score 10-26, requiring treatment for incontinence Male (n=2), Female (n=7); Mean age of 78.22 years (SD 9.80) Mean education level 11.71 years (SD 2.93); Mean disease duration 4.29 years (SD 2.06)	Interventions Patients were assessed both "on" and "off" medication. Patients already receiving UI medication were first tested "On" medication. Patients were given tolterodine. Outcomes were assessed after a 3 week wash-out period between "on" and "off" medication, with patients "on" medication were assessed after 3 week treatment with tolterodine, and patients "off" medication were assessed after a 3 week wash-out period of discontinuing medication.	Cognitive function as assessed by ADAS-Cog (total scores range from 0–70; higher score indicating greater cognitive impairment) and MMSE (range 0–30; lower scores indicate cognitive impairment).	Three participants (25%) were excluded because of technical difficulties with processing the serum assay

ADAS-COG: Alzheimer's Disease Assessment Scale; HVLT-R: Hopkins Verbal Learning Test-Revised; ICD: the International Classification of Diseases; MDS-COGS: Minimum Data Set cognitive scale; MMSE: Mini-Mental State Exam; OAB: Overactive Bladder; SD: Standard Deviation

See also clinical evidence tables in appendix D.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of critical and important outcomes. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question. See supplementary material D for further information.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to this review question.

Economic model

This topic was prioritised for de-novo economic modelling. The committee expressed their view that there may be important differences in the drug acquisitions costs and the population affected is large. Also, the committee explained that the only alternative to anticholinergic drugs is mirabegron which has high acquisition costs. However, the clinical evidence identified was insufficient to inform de-novo economic modelling in this area.

Clinical evidence statements

Trospium versus placebo

Cognitive function

- Low quality evidence from one RCT (n=45) showed there were no clinically-important differences in cognitive function as measured using HVLTR, in women aged ≥ 50 years who were treated with trospium chloride over a 4-week period compared to placebo, MD -3.4 (-8.97 to 2.17).
- Very low quality evidence from one RCT (n=45) showed there were no clinically-important differences in cognitive function as measured using MMSE, in women aged ≥ 50 years who were treated with trospium chloride over a 4-week period compared to placebo, MD -0.3 (-8.46 to 7.86).
- Low quality evidence from one RCT (n=45) showed there were no clinically-important differences in cognitive function as measured using Trials A, in women aged ≥ 50 years who were treated with trospium chloride over a 4-week period compared to placebo, MD -7.4 (-16.92 to 2.12).
- Moderate quality evidence from one RCT (n=45) showed there were no clinically-important differences in cognitive function as measured using Trials B, in women aged ≥ 50 years who were treated with trospium chloride over a 4-week period compared to placebo, MD -0.8 (-34.14 to 32.54).
- Very low quality evidence from one RCT (n=45) showed there were no clinically-important differences in cognitive function as measured using Digit Span, in women aged ≥ 50 years

who were treated with trospium chloride over a 4-week period compared to placebo, MD -0.2 (-0.86 to 0.46).

'On' Tolterodine versus 'off' Tolterodine

Cognitive function

- Very low quality evidence from one single-blind crossover study (n=9) showed no clinically-important difference on cognitive function of women aged ≥50 years with OAB who were 'off' tolterodine for a three-week period compared to those who were 'on' tolterodine, as assessed by ADAS-Cog: MD -1.00 (95% CI -16.71 to +14.71).
- Very low quality evidence from one single-blind crossover study (n=9) showed that there may be a clinically-important difference favouring being 'off' tolterodine over being 'on' tolterodine on cognitive function in women aged ≥50 years with OAB as assessed by MMSE, although there is some uncertainty: MD -1.00 (95% CI -8.39 to 6.39).

Tolterodine versus oxybutynin

Number of falls

- Very low quality evidence from a retrospective cohort study (n=40,563) showed no clinically-important difference between oxybutynin and tolterodine on falls in women aged ≥50 years with OAB, this was over a mean treatment period of 88 days: RR 0.97 (95% CI 0.89 to 1.06).

All-cause mortality

- Very low quality evidence from a retrospective cohort study (n=40,563) showed a clinically-important difference favouring tolterodine over oxybutynin on mortality in women aged ≥50 years with OAB, over a mean treatment period of 88 days: RR 0.84 (95% CI 0.75 to 0.94).

Economic evidence statements

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question. See supplementary material D for further information.

Recommendations

Medicines

C1.1 Before starting treatment with a medicine for OAB, explain to the woman:

- the likelihood of the medicine being successful
- the common adverse effects associated with the medicine
- that some adverse effects of anticholinergic medicines, such as dry mouth and constipation, may indicate that the medicine is starting to have an effect
- that she may not see the full benefits until she has been taking the medicine for 4 weeks
- that the long-term effects of anticholinergic medicines for OAB on cognitive function are uncertain. **[2019]**

C1.2 When offering anticholinergic medicines to treat OAB, take account of the woman's:

- coexisting conditions (such as poor bladder emptying, cognitive impairment or dementia)
- current use of other medicines that affect total anticholinergic load
- risk of adverse effects, including cognitive impairment. **[2019]**

C1.3 For women who have a diagnosis of dementia and for whom anticholinergic medicines are an option, follow the recommendations on medicines that may cause cognitive impairment in the NICE guideline on dementia. **[2019]**

Choosing medicine

C1.4 Offer the anticholinergic medicine with the lowest acquisition cost to treat OAB or mixed UI in women. **[2019]**

Reviewing medicine

C1.5 Offer a review in primary care to women who remain on long-term medicine for OAB or UI every 12 months, or every 6 months if they are aged over 75. **[2019]**

Research recommendations

What is the effectiveness and safety of anticholinergic medicines for overactive bladder in older women?

Rationale and impact

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that long-term cognitive impairment and falls should be considered critical outcomes as these were thought to have be the most important for the women's quality of life. The potential association between cognitive impairment and anticholinergic load has been increasingly documented, and the committee agreed this potential risk should be investigated specifically for women with OAB. Other outcomes considered important by the committee included delirium and all-cause mortality, as these will also be important to the woman.

The quality of the evidence

The studies were assessed for quality using the Cochrane risk of bias tool and the Cochrane ROBINS-I tool in the case of non-randomised studies. Pairwise outcomes were assessed for certainty using the GRADE tool. The evidence for outcomes was considered to be moderate, low or very low quality. Those of low or very low quality suggests there is limited confidence in the outcome data presented. The evidence was downgraded because it was indirect; studies included both men and women with OAB, were small and had short follow-up periods; therefore, they did not provide long-term evidence. In addition, observational data were included which did not control for all potential confounding factors.

Benefits and harms

The evidence included in this review was limited and the committee concluded that it did not allow them to answer the review question. This was despite the protocol including both men and women with OAB, which expanded the search beyond the population of interest of the

guideline. As a result of this and not having reviewed the effectiveness of medicines in this guideline update, the committee could not make major changes to the recommendations from the previous guideline. Nonetheless, they updated the advice and discussion that should take place with women before starting a medicine for OAB, with a view to emphasise that the long-term effects of anticholinergic medicines on cognitive function are uncertain; and also updated the recommendation on when offering anticholinergic medicines for OAB, underlining the importance of considering the woman's co-existing conditions. In addition, they agreed that recommendations made in the previous guideline (based on effectiveness data only) should remain.

The committee was of the opinion that this is a very important topic, as it is estimated that one in three women over 65 years has some degree of incontinence and large numbers of women are prescribed anticholinergic drugs. The committee also noted that there is an urgent need for high quality research into the long-term adverse effects of anticholinergic drugs on the cognitive function of women with OAB and therefore prioritised this area for future research.

The committee were aware that different anticholinergic drugs may have a different propensity to cause cognitive impairment. The committee also noted that the pathological changes in the brain start many years before a definitive diagnosis of cognitive impairment in conditions such as Alzheimer's disease. The evidence presented did not provide any long-term data. In view of this, the committee discussed at length the evidence in the wider literature, (which did not meet the inclusion criteria set out in the protocol for this evidence review), and decided that it should be considered as corroborative evidence. In a large prospective chart study, Gray et al 2015 investigated anticholinergic exposure (including tricyclic antidepressants, antihistamines, and urological medication) and the association with cognitive impairment. The study reported a 10 year cumulative dose response relationship with both dementia and Alzheimer's disease (test for trend, $p < 0.001$). A recent BMJ publication (Richardson 2018) found an association between some classes of anticholinergic drugs and the incidence of dementia. This was a large nested case-control study based on UK general practice data, and the results should not be ignored; however, the study included different classes of anticholinergic drugs, was based on retrospective data, where missing and confounding factors cannot always be accounted for, and specifically focused on dementia patients. The authors suggest that well conducted prospective cohorts exploring the long term effects of different anticholinergic drug classes in specific cohorts is needed. It should be noted however, that these studies are not without their limitations and their findings should be interpreted with caution, most notably that they demonstrate an association between anticholinergic drugs and increased risk of cognitive impairment and not a causation. As a result, the committee decided to highlight in the recommendations the uncertainty of the long term effect of anticholinergic medicines for OAB on cognitive function and that the woman's co-existing conditions should be considered when offering these medicines. They also decided that women who remain on long-term medicine for OAB or UI should be reviewed in primary care every 12 months, or every 6 months if they are aged over 75.

Despite the fact that no new evidence was found, the committee agreed that it was important to clarify the circumstances in which oxybutynin should not be offered, to ensure the woman receives as much information as possible about all treatment options, so she can make an informed choice about her treatment.

Due to the limited evidence, the committee made a research recommendation about the effectiveness and safety of anticholinergic medicines for overactive bladder in older women. This is important because longitudinal studies have shown that exposure to anticholinergic medications are associated with risk for developing mild cognitive impairment (MCI) and dementia. Most of the studies have been conducted among elderly people in primary prevention, whereas longer term studies assessing relationships between anticholinergics specifically for overactive bladder and development of MCI or dementia are scarce. The aim

would be to explore the potential risk for developing MCI/dementia and extent of this risk, looking at long term follow up for patients on bladder anticholinergics.

Cost effectiveness and resource use

There was no existing economic evidence on the cost-effectiveness of anticholinergic drugs for OAB with respect to cognitive function. The committee also acknowledged the lack of relevant clinical evidence and as a result, the recommendations in this area are largely unchanged. The committee explained that facilitating the discussion with women before starting and when offering anticholinergics for OAB may incur additional healthcare resources (that is, clinician's time required to facilitate such discussion). Nevertheless, the committee was of a view that the recommendations relate to the principles of care and factors that directly impact on the treatment outcomes for women with OAB. The committee expressed their view that the costs of this are going to be negligible if it identifies women at risk and alters the rate of cognitive impairment which may require expensive care further down the line.

The committee reviewed the unit costs associated with various anticholinergic drugs, and (based on the committee's knowledge that there is little difference between anticholinergic drugs in term of effectiveness), determined that anticholinergic drugs with the lowest unit cost should be used. The committee explained that by not recommending a specific anticholinergic drug there will be an incentive for more competitive pricing. The committee explained that the potential population affected is very large and only a small change in the drug acquisition cost may have a substantial impact on the NHS costs.

The committee also discussed that in women where anticholinergic drugs are contraindicated the only alternative is mirabegron which is very expensive and is associated with cardiac problems.

Other factors the committee took into account

The committee discussed the recent NICE guideline on Dementia, for women who have a diagnosis of dementia, and where anticholinergic drugs are being considered, referred to the dementia guideline.

The committee were also aware of the AUGS consensus statement (AUGS 2017) which states available evidence shows significant associations between anticholinergic medication use and increased risk of cognitive impairment. The statement advises healthcare providers to counsel people about the associated risks, prescribe the lowest effective dose, and consider alternative medications when the person is at risk.

References

AUGS 2017

American Urogynecologic Society Guidelines Committee, Thomas, T. N., Walters M.D., AUGS Consensus Statement: Association of Anticholinergic Medicatin Use and Cognition in Women With Overactive Bladder, Female Pelvic Medicine & Reconstructive Surgery, 23, 177-178, 2017

Geller 2017

Geller, E. J., Dumond, J. B., Bowling, J. M., Khandelwal, C. M., Wu, J. M., Busby-Whitehead, J., Kaufer, D. I., Effect of Trospium Chloride on Cognitive Function in Women Aged 50 and Older: A Randomized Trial, Female Pelvic Medicine & Reconstructive Surgery Female pelvic med, 23, 118-123, 2017

Gomes 2011

Gomes, T., Juurlink, D. N., Ho, J. M., Schneeweiss, S., Mamdani, M. M., Risk of serious falls associated with oxybutynin and tolterodine: a population based study, Journal of Urology, 186, 1340-4, 2011

Jewart 2005

Jewart,R.D., Green,J., Lu,C.J., Cellar,J., Tune,L.E., Cognitive, behavioral, and physiological changes in Alzheimer disease patients as a function of incontinence medications, American Journal of Geriatric Psychiatry, 13, 324-328, 2005

Appendices

Appendix A – Review protocols

Review protocol for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Review question	What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?
Type of review question	Intervention
Objective of the review	The aim of this review is to determine if anticholinergic drugs negatively impact cognitive function in women with OAB. Anticholinergic drugs are the main way of treating OAB and there is increasing concern regarding longer term effects of anticholinergics and cognitive impairment, as well as their impact on more vulnerable populations. The GC are aware of the limited evidence referring to adult women with overactive bladder only. Therefore, this systematic review will assess the evidence for all patients who have been prescribed anticholinergic drugs for overactive bladder (OAB), and the GC will be extrapolate from this evidence when making their recommendations.
Eligibility criteria – population/disease/condition/issue/domain	Adults (aged 18 years of age and over) who are receiving anticholinergic drugs for the management of OAB symptoms of any origin.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	The following antimuscarinic agents for the treatment of OAB will be considered: • Oxybutynin • Tolterodine • Darifenacin • Solifenacin • Trospium chloride • Fesoterodine • Propiverine

Field (based on PRISMA-P)	Content
Eligibility criteria – comparator(s)/control or reference (gold) standard	Each agent compared against: (i) each other, (ii) placebo, or (iii) Mirabegron
Outcomes and prioritisation	**Critical** • Long-term cognitive impairment measured using validated tools only, including: ○ Abbreviated metal test score (AMTS) ○ General practitioner assessment of cognition (GPCOG) ○ Mini-cog ○ Addenbrookes cognitive examination III (ACE_III) ○ Montreal cognitive assessment (MoCA), ○ Mini mental state examination (MMSE) ○ 6-item cognitive impairment test (6CIT), • Falls Justification: increasing anxiety about the risk of developing irreversible long-term cognitive impairment from prolonged use of anticholinergic drugs. Falls are a major problem that may result from the use of these drugs, and in the older population have a great impact on morbidity and mortality. **Important** • Delirium • All-cause mortality
Eligibility criteria – study design	• Systematic reviews of RCT • RCT • Observational studies Conference abstracts of RCTs (Only if RCTs unavailable and the quality assessment of abstracts will conducted based on the available information and if necessary the authors of abstracts will be contacted)
Other inclusion exclusion criteria	No restriction on number of participants No date restriction

Field (based on PRISMA-P)	Content
Proposed sensitivity/sub-group analysis, or meta-regression	Groups that will be reviewed and analysed separately, if possible: • Pre- and post-menopausal women • Older people • Studies that include people on propantheline Subgroup analyses (in the presence of substantial heterogeneity): • Drug presentation (including route of administration)
Selection process – duplicate screening/selection/analysis	Duplicate screening will be performed using STAR - minimum sample size is 10% of the total for <1000 titles and abstracts, and 5% of the total for ≥1000 titles and abstracts. All discrepancies are discussed and resolved between 2 screeners. Any disputes will be resolved in discussion with the Senior Systematic Reviewer. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for: • bibliographies/citations, text mining, and study sifting • data extraction and quality assessment/critical appraisal
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates from 1995. Studies published post 1995 will be considered for this review question as the GC believed that this was an appropriate threshold for studies representing current practice See appendix B for full strategies.
Identify if an update	New area of the guideline.
Author contacts	Developer: NGA

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014 Appraisal of methodological quality will be conducted using the appropriate tool: • ROBIS (systematic reviews and meta-analyses), • Cochrane risk of bias tool (RCTs). • Cochrane risk of bias tool (Non-randomised studies) The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ .
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – Current management	For details please see the introduction to the evidence review.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Dr Fergus Macbeth in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered with PROSPERO

1

Appendix B – Literature search strategies

Literature search strategies for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

Database: Medline & Embase (Multifile)
Last searched on Embase Classic+Embase 1947 to 2018 January 12, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present,

Date of last search: 15th January 2018.

#	Searches
1	Urinary Incontinence/ use ppez
2	urine incontinence/ use emczd
3	Urinary Incontinence, Urge/ use ppez
4	urge incontinence/ use emczd
5	mixed incontinence/ use emczd
6	Urinary Bladder, Overactive/ use ppez
7	overactive bladder/ use emczd
8	bladder instability/ use emczd
9	Nocturia/ use ppez
10	nocturia/ use emczd
11	exp Enuresis/ use ppez
12	exp enuresis/ use emczd
13	((mix$ or urg$ or urin$) adj5 incontinen$).tw.
14	(bladder$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$ or incontinen$)).tw.
15	(detrusor$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$)).tw.
16	OAB.tw.
17	((urgency adj2 frequency) or (frequency adj2 urgency)).tw.
18	((urin$ or bladder$) adj2 (urg$ or frequen$)).tw.
19	(nocturia$ or enuresis$).tw.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Mandelic Acids/ use ppez
22	exp Muscarinic Antagonists/ use ppez
23	exp Cholinergic Antagonists/ use ppez
24	exp mandelic acid derivative/ use emczd
25	muscarinic receptor blocking agent/ use emczd
26	cholinergic receptor blocking agent/ use emczd
27	(antimuscarinic$ or (anti adj muscarinic$)).tw.
28	(anticholinergic$ or (anti adj cholinergic$)).tw.
29	((muscarinic$ or cholinergic$) adj5 (antagonist$ or block$)).tw.
30	oxybutynin/ use emczd
31	(oxybutynin$ or Ditropan$).tw.
32	Tolterodine Tartrate/ use ppez
33	tolterodine/ use emczd
34	(tolterodin$ or Detrol$).tw.
35	darifenacin/ use emczd
36	(darifenacin$ or Enablex$).tw.
37	Solifenacin Succinate/ use ppez
38	solifenacin/ use emczd
39	(solifenacin$ or VESIcare$).tw.
40	trospium chloride/ use emczd
41	(trospium$ or Sanctura$).tw.
42	propiverine/ use emczd
43	(propiverin$ or Detrunorm$).tw.
44	fesoterodine/ use emczd
45	(fesoterodin$ or Toviaz$).tw.
46	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47	exp Cognition/ use ppez
48	Cognition Disorders/ use ppez
49	Cognitive Dysfunction/ use ppez
50	exp cognition/ use emczd

#	Searches
51	cognitive defect/ use emczd
52	(cogniti$ adj5 (effect$ or impair$ or function$ or dysfunction$ or decline$ or burden$ or change$ or deficit$ or imbalance$ or deteriorat$ or safety or test$ or scale$ or performance or impact$ or outcome$ or event$ or adverse$)).tw.
53	exp Memory/ use ppez
54	exp Memory Disorders/ use ppez
55	exp memory/ use emczd
56	exp memory disorder/ use emczd
57	memory$.tw.
58	exp Dementia/ use ppez
59	exp Confusion/ use ppez
60	exp dementia/ use emczd
61	exp delirium/ use emczd
62	exp confusion/ use emczd
63	intellectual impairment/ use emczd
64	(dementia$ or confusion$ or deliriu$).tw.
65	Accidental Falls/ use ppez
66	falling/ use emczd
67	falls.tw.
68	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69	20 and 46 and 68
70	(bladder$ adj3 (antimuscarinic$ or anti-muscarinic$ or anticholinergic$ or anti-cholinergic$)).tw.
71	69 or 70
72	remove duplicates from 71
73	limit 72 to english language
74	letter/
75	editorial/
76	news/
77	exp historical article/
78	Anecdotes as Topic/
79	comment/
80	case report/
81	(letter or comment*).ti.
82	74 or 75 or 76 or 77 or 78 or 79 or 80 or 81
83	randomized controlled trial/ or random*.ti,ab.
84	82 not 83
85	animals/ not humans/
86	exp Animals, Laboratory/
87	exp Animal Experimentation/
88	exp Models, Animal/
89	exp Rodentia/
90	(rat or rats or mouse or mice).ti.
91	84 or 85 or 86 or 87 or 88 or 89 or 90
92	letter.pt. or letter/
93	note.pt.
94	editorial.pt.
95	case report/ or case study/
96	(letter or comment*).ti.
97	92 or 93 or 94 or 95 or 96
98	randomized controlled trial/ or random*.ti,ab.
99	97 not 98
100	animal/ not human/
101	nonhuman/
102	exp Animal Experiment/
103	exp Experimental Animal/
104	animal model/
105	exp Rodent/
106	(rat or rats or mouse or mice).ti.
107	99 or 100 or 101 or 102 or 103 or 104 or 105 or 106
108	91 use ppez
109	107 use emczd
110	108 or 109
111	73 and 110
112	73 not 111
113	*Aged/ use ppez
114	*aged/ use emczd
115	((old$ or elderly) adj3 (population or people or adult$)).tw.
116	113 or 114 or 115

#	Searches
117	46 and 68 and 116
118	remove duplicates from 117
119	limit 118 to english language
120	110 and 119
121	119 not 120
122	112 or 121

Database: Cochrane Library via Wiley Online

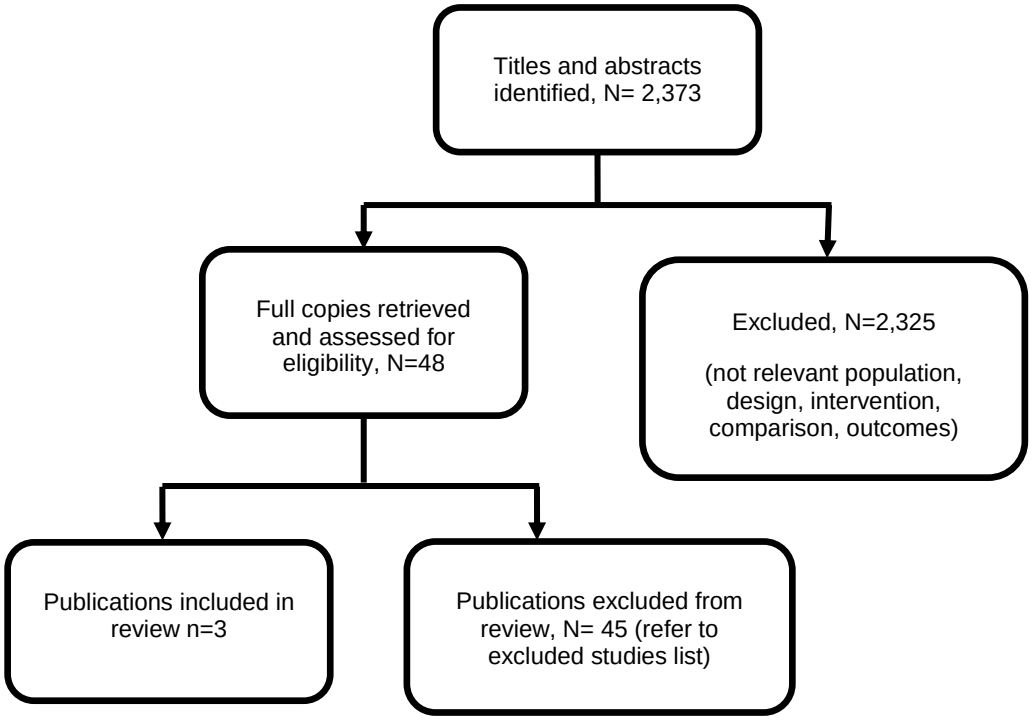
Date of last search: 15th January 2018.

#	Searches
#1	MeSH descriptor: [Mandelic Acids] explode all trees
#2	MeSH descriptor: [Muscarinic Antagonists] explode all trees
#3	MeSH descriptor: [Cholinergic Antagonists] explode all trees
#4	(antimuscarinic* or (anti next muscarinic*)):ti,ab,kw (Word variations have been searched)
#5	(anticholinergic* or (anti next cholinergic*)):ti,ab,kw (Word variations have been searched)
#6	((muscarinic* or cholinergic*) near/5 (antagonist* or block*)):ti,ab,kw (Word variations have been searched)
#7	(oxybutynin* or Ditropan*):ti,ab,kw (Word variations have been searched)
#8	MeSH descriptor: [Tolterodine Tartrate] this term only
#9	(tolterodin* or Detrol*):ti,ab,kw (Word variations have been searched)
#10	(darifenacin* or Enablex*):ti,ab,kw (Word variations have been searched)
#11	MeSH descriptor: [Solifenacin Succinate] this term only
#12	(solifenacin* or VESIcare*):ti,ab,kw (Word variations have been searched)
#13	(trospium* or Sanctura*):ti,ab,kw (Word variations have been searched)
#14	(propiverin* or Detrunorm*):ti,ab,kw (Word variations have been searched)
#15	(fesoterodin* or Toviaz*):ti,ab,kw (Word variations have been searched)
#16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17	MeSH descriptor: [Urinary Incontinence] this term only
#18	MeSH descriptor: [Urinary Incontinence, Urge] this term only
#19	MeSH descriptor: [Urinary Bladder, Overactive] this term only
#20	MeSH descriptor: [Nocturia] this term only
#21	MeSH descriptor: [Enuresis] explode all trees
#22	((mix* or urg* or urin*) near/5 incontinen*):ti,ab,kw (Word variations have been searched)
#23	(bladder* near/5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex* or incontinen*)):ti,ab,kw (Word variations have been searched)
#24	OAB:ti,ab,kw (Word variations have been searched)
#25	((urgency near/2 frequency) or (frequency near/2 urgency)):ti,ab,kw (Word variations have been searched)
#26	((urin* or bladder*) near/2 (urg* or frequen*)):ti,ab,kw (Word variations have been searched)
#27	(detrusor* near/5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex*)):ti,ab,kw (Word variations have been searched)
#28	(nocturia* or enuresis*):ti,ab,kw (Word variations have been searched)
#29	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30	MeSH descriptor: [Cognition] explode all trees
#31	MeSH descriptor: [Cognition Disorders] this term only
#32	MeSH descriptor: [Cognitive Dysfunction] this term only
#33	(cogniti* near/5 (effect* or impair* or function* or dysfunction* or decline* or burden* or change* or deficit* or imbalance* or deteriorat* or safety or test* or scale* or performance or impact* or outcome* or event* or adverse*)):ti,ab,kw (Word variations have been searched)
#34	MeSH descriptor: [Memory] explode all trees
#35	MeSH descriptor: [Memory Disorders] explode all trees
#36	memory*:ti,ab,kw (Word variations have been searched)
#37	MeSH descriptor: [Dementia] explode all trees
#38	MeSH descriptor: [Confusion] explode all trees
#39	(dementia* or confusion* or deliriu*):ti,ab,kw (Word variations have been searched)
#40	MeSH descriptor: [Accidental Falls] this term only
#41	falls:ti,ab,kw (Word variations have been searched)
#42	#30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
#43	(bladder* near/3 (antimuscarinic* or anti-muscarinic* or anticholinergic* or anti-cholinergic*)):ti,ab,kw (Word variations have been searched)
#44	#16 and #29 and #42
#45	MeSH descriptor: [Aged] explode all trees
#46	((old* or elderly) near/3 (population or people or adult*)):ti,ab,kw (Word variations have been searched)
#47	#45 or #46
#48	#16 and #42 and #47
#49	#43 or #44 or #48

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder?

Figure 1: PRISMA flow chart for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder?



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

Table 4: Clinical evidence studies and reasons for their exclusion

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Geller, E. J., Dumond, J. B., Bowling, J. M., Khandelwal, C. M., Wu, J. M., Busby-Whitehead, J., Kaufer, D. I., Effect of Trospium Chloride on Cognitive Function in Women Aged 50 and Older: A Randomized Trial, Female Pelvic Medicine & Reconstructive Surgery Female pelvic med, 23, 118-123, 2017 Ref Id 764436 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study	Sample size n = 59 women randomized (28 trospium vs. 31 placebo) n = 45 women completed assessment (21 trospium vs. 24 placebo) Characteristics Mean age 68 years 78% white 44% previously taken OAB medications Inclusion criteria Women aged ≥ 50 years with a diagnosis of OAB (as defined by International Continence Society) recruited from University of North Carolina Female Pelvic Medicine and Reconstructive Surgery clinics English literacy	Interventions Participants were randomised into either trospium chloride extended release 60mg daily or placebo, and received a 4-week supply of blinded medication which they were to begin the following day	Details Outcomes: Cognitive function (assessed by the Hopkins Verbal Learning Test-Revised (HVLT-R), Mini Mental Status Exam (MMSE), Digit Span, and Trails A & B, . Measured at baseline, week 1 and week 4.	Results Outcome: Cognitive function as assessed by HVLT-R (mean (SD) at week 4) Tropsium (n=21): 50.7 (8.1) Placebo (n=24): 54.1 (10.9) Outcome: Cognitive function as assessed by MMSE (mean (SD) at week 4) Tropsium (n=21): 28.1 (1.9)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk. Randomisation performed with computer-generated number blocks of 6. Allocation concealment: Low risk. Group assignment numbers placed in sequential, opaque envelopes. Performance bias Blinding of participants and personnel: Low risk. Group assignments were opened after screening and enrolment were completed. Participants received a 4-week supply of blinded medication. Detection bias Blinding of outcome assessment: Low risk. Research teams and physicians were blinded. Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine the effect of trospium chloride on the cognitive function in postmenopausal women treated for overactive bladder (OAB) Study dates April 2013 to April 2015 Source of funding Supported by the American Urogynecologic Society Research Foundation Award	Ability to swallow oral medication Cognitive ability to give consent Participants who were taking an anticholinergic at the time of enrolment, had a washout period of 2 weeks where they discontinued their current medication Exclusion criteria Active diagnoses of dementia (MMSE score ≤ 26) Depression (Geriatric Depression Scale ≥ 20) Delirium Urinary retention Gastric retention, severe decreased gastrointestinal motility conditions Anticholinergic use Current cholinesterase use And a diagnosis of renal impairment (creatinine clearance ≤ 30 mL/min) based on medical review and subject interview at the time of enrolment			Placebo (n=24): 28.4 (1.8) Outcome: Cognitive function as assessed by Trails A (mean (SD) at week 4) Tropsium (n=21): 31.6 (12.9) Placebo (n=24): 39.0 (19.4) Outcome: Cognitive function as assessed by Trails B (mean (SD) at week 4) Tropsium (n=21): 92.2 (42.0) Placebo (n=24): 93.0 (70.2) Outcome: Cognitive function as	Incomplete outcome data: High risk. Dropout rates (>20%) due to lack of efficacy (n=3), lost to follow-up (n=9), constipation (n=1), felling weepy (n=1). Reporting bias Selective reporting: Low risk. All outcomes reported Other bias Other sources of bias: Unclear risk. 44% of participants had previously taken anticholinergic. Study included women aged 50 years and older, and not powered to draw conclusions about elderly adults. No long term follow-up of outcomes. Other information Findings suggest tropsium chloride does not cause cognitive changes when used in women aged ≥ 50 years

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				assessed by Digit Span (mean (SD) at week 4) Tropsium (n=21): 6.5 (1.3) Placebo (n=24): 6.7 (0.9)	
Full citation Gomes, T., Juurlink, D. N., Ho, J. M., Schneeweiss, S., Mamdani, M. M., Risk of serious falls associated with oxybutynin and tolterodine: a population based study, Journal of Urology, 186, 1340-4, 2011 Ref Id 764473 Country/ies where the study was carried out Canada Study type Retrospective cohort study Aim of the study	Sample size n=111,522 new users of urinary incontinence drugs (Tolterodine n=48,947 vs. Oxybutynin n =62,575) 40,563 tolterodine users individually matched to a new user of oxybutynin. Characteristics Not stated Inclusion criteria Ontarians 66 years and older who commenced treatment with oxybutynin or tolterodine between April 1, 2002 and December 31, 2008. Identified using the Ontario Public Drug Benefit Program database	Interventions Mean daily dose of 8.6 mg (SD 6.6) for oxybutynin patients, and 3.6 (SD 2.2, oxybutynin equivalent mean dose of 9.1 mg [SD 5.1, standardised difference 0.08]) for tolterodine patients. Patients were followed mean of 88.3 days (SD 9.9) for tolterodine, and 88.1 days (SD 10.6) for oxybutynin.	Details Outcome: Falls (defined by ICD-10 codes W00 to W19); All-cause mortality.	Results Outcome: Number of falls (%) Tolterodine exposure group = 998 (2.5) Oybutynin exposure group = 1,027 (2.5) Outcome: Number of all-cause mortality events (%) Tolterodine exposure group = 567 (1.4)	Limitations Confounding bias: low risk of bias – confounding was adjusted for Selection of participant's bias: moderate risk of bias – very few inclusion/exclusion details given, of those given criteria are reasonable Classification of interventions bias: low risk of bias – intervention groups clearly predefined Deviations from intended interventions bias: low risk of bias – data was censored at 90 days if study drugs were changed Missing data bias: moderate risk of bias – missing data was accounted for as a separate group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the short-term risks of falls among recipients of oxybutynin or tolterodine to treat urinary incontinence Study dates April 2002 to December 2008 Source of funding Supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and the Institute for Clinical Evaluative Sciences (ICES)	Exclusion criteria Not stated			Oybutynin exposure group = 675 (1.7)	Measurement of outcomes bias: low risk of bias – all outcomes were assessed using the same methods / definitions Selection of the reported results bias: low risk of bias – all data covered, statistical adjustments are reasonable Other information No difference in falls between oxybutynin and tolterodine users. Slight significant increase in mortality (p=0.0006) with the use of oxybutynin than tolterodine.
Full citation Jewart,R.D., Green,J., Lu,C.J., Cellar,J., Tune,L.E., Cognitive, behavioral, and physiological changes in Alzheimer disease patients as a function of incontinence medications, American Journal of Geriatric Psychiatry, 13, 324-328, 2005 Ref Id 100266	Sample size n = 12 enrolled n = 9 assessed Characteristics Participants recruited from the Emory Alzheimer's Disease Centre and the Geriatric Medicine Incontinence Clinic at the Wesley Woods Centre at Emory University.	Interventions Patients were assessed both "on" and "off" medication. Patients already receiving UI medication were first tested "On" medication. Patients were given tolterodine. Outcomes were assessed after a 3 week wash-out period between "on" and "off" medication, with patients "on" medication were assessed after 3 week treatment with tolterodine, and patients "off" medication were assessed after a 3 week wash-	Details Outcomes: Cognitive function as assessed by the Alzheimer's Disease Assessment Scale (ADAS-Cog) and the Mini-Mental State Exam (MMSE)	Results Outcome: ADAS-Cog On medication: 28.00 (16.89) Off medication: 29.00 (17.12) Outcome: MMSE	Limitations Confounding bias: high risk of bias – depending on presentation (i.e. already on medication) treatment protocols were assigned Selection of participant's bias: low risk of bias – detailed and reasonable inclusion/exclusion given Classification of interventions bias: not applicable – participants took part in both being on and off medication

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type Single-blind crossover design Aim of the study To evaluate the effects of anticholinergic incontinence medication on the cognitive, behavioural and physiological changes in patients with Alzheimer's disease. Study dates Not stated Source of funding Funded by Emory University, Nell Hodgson Woodruff School of Nursing.	Male (n=2), Female (n=7) Mean age of 78.22 years (SD 9.80) Mean education level 11.71 years (SD 2.93) Mean disease duration 4.29 years (SD 2.06) Inclusion criteria Diagnosis of Alzheimer disease (AD) MMSE score 10-26, required treatment for incontinence with either oxybutynin chloride or tolterodine for a minimum of 4 weeks English comprehension Caregiver present to accompany participants Exclusion criteria Regular use of antipsychotics, narcotic analgesics, or sedatives Use of antihypertensive agents with frequent CNS side effects (e.g. clonidine, propranolol) within 4 weeks before baseline Use of systemic corticosteroids within 3 months before baseline	out period of discontinuing medication. A psychometrician blinded to treatment condition blinded to treatment condition administered the cognitive assessments.		On medication: 16.44 (7.83) Off medication: 17.44 (8.16)	Deviations from intended interventions bias: moderate risk of bias – not reported whether deviations occured from being on or off medication, but given the design of the study is presumed unlikely Missing data bias: moderate risk of bias – participants were excluded from the analysis entirely if their data was not complete (25% of total study population) Measurement of outcomes bias: low risk of bias – all outcomes were assessed using the same methods study Selection of the reported results bias: high risk of bias – some insignificant findings were not reported Other information MMSE scores were significantly higher when subjects were off incontinence medication when subjects were on incontinence medication (p=0.017). The ADAS-Cog score did not vary whether subjects were on or off medication (p=0.1555)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Initiation of an acetylcholinesterase inhibitor within the previous 2 months History of stroke, alcohol abuse or other diagnosed neurological disorders, such as multiple sclerosis, amyotrophic lateral sclerosis, or Parkinson's disease				

Appendix E – Forest plots

Forest plots for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

No studies were identified which were applicable to this review question.

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Appendix F – GRADE tables

GRADE tables for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

Table 5: Clinical evidence profile for Trospium versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trospium	Placebo	Relative (95% CI)	Absolute		
Cognitive function (follow-up mean 4 weeks; measured with: HVLTR; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21	24	-	MD 3.4 lower (8.97 lower to 2.17 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (follow-up mean 4 weeks; measured with: MMSE; range of scores: 0-30; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21	24	-	MD 0.3 lower (8.46 lower to 7.86 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (follow-up mean 4 weeks; measured with: Trials A; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	21	24	-	MD 7.4 lower (16.92 lower to 2.12 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (follow-up mean 4 weeks; measured with: Trials B; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	24	-	MD 0.8 lower (34.14 lower to 32.54 higher)	⊕⊕⊕O MODERATE	CRITICAL
Cognitive function (follow-up mean 4 weeks; measured with: Digit Span; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	21	24	-	MD 0.2 lower (0.86 lower to 0.46 higher)	⊕OOO VERY LOW	CRITICAL

[1] Evidence downgraded by 1 due to serious risk of bias; risk of attrition bias as dropout rates were greater than 20%.
[2] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross one of the default MID for continuous outcomes, calculated as 0.5+/- SD of placebo at baseline (+/-5.45).
[3] Evidence downgraded by 2 due to very serious imprecision; 95% confidence intervals cross both of the default MID for continuous outcomes, calculated as 0.5+/- SD of placebo at baseline (+/-0.9).
[4] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross one of the default MID for continuous outcomes, calculated as 0.5+/- SD of placebo at baseline (+/-9.7).
[5] Evidence downgraded by 2 due to very serious imprecision; 95% confidence intervals cross both of the default MID for continuous outcomes, calculated as 0.5+/- SD of placebo at baseline (+/-0.45).

Table 6: Clinical evidence profile for 'on' Tolterodine versus 'off' Tolterodine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**"on" Tolterodine**	**"of" Tolterodine**	**Relative (95% CI)**	**Absolute**		
Cognitive function - ADAS-Cog (follow-up mean 3 weeks; range of scores: 0-70; Better indicated by lower values)												
1	Cross over study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	9	9	-	MD 1 lower (16.71 lower to 14.71 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function - MMSE (follow-up mean 3 weeks; range of scores: 0-30; Better indicated by higher values)												
1	Cross over study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	9	9	-	MD 1 lower (8.39 lower to 6.39 higher)	⊕OOO VERY LOW	CRITICAL

[1] Evidence downgraded by 2 due to very serious risk of bias; risk of bias due to reporting bias, insignificant findings were not presented. Moderate risk of intervention bias, unclear deviations occurred form being on or off medication. High risk of confounding bias as some participants already on medication.
[2] Participants had Alzheimer's disease.
[3] evidence downgraded by 2 due to very serious imprecision; 95% confidence intervals cross both of the default MID for continuous outcomes, calculated as 0.5+/- SD of being "off" medication at baseline (+/-8.6).

Table 7: Clinical evidence profile for Tolterodine versus oxybutynin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tolterodine	Oxybutynin	Relative (95% CI)	Absolute		
Falls - number of falls (follow-up mean 88 days)												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	998/40563 (2.5%)	1027/40563 (2.5%)	RR 0.97 (0.89 to 1.06)	1 fewer per 1000 (from 3 fewer to 2 more)	⊕OOO VERY LOW	IMPORTANT
Mortality - mortality												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	567/40563 (1.4%)	675/40563 (1.7%)	RR 0.84 (0.75 to 0.94)	3 fewer per 1000 (from 1 fewer to 4 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] Evidence downgraded by 1 due to serious risk of bias; moderate risk of selection bias as little information provided in methods regarding inclusion and exclusion criteria. Moderate risk of missing data bias, missing data was accounted for in a separate group.
[2] Evidence downgraded for indirectness, both men and women were included in the study; however, the review relates to OAB in women only.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

One global search was conducted for this review question. See supplementary material D for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

No economic studies were identified which were applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

No economic studies were identified which were applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

Clinical studies

Table 8: Excluded studies and reasons for their exclusion

Excluded studies – What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?	
Study	**Reason for Exclusion**
Aalto, U. L., Roitto, H. M., Finne-Soveri, H., Kautiainen, H., Pitkala, K., Use of Anticholinergic Drugs and its Relationship With Psychological Well-Being and Mortality in Long-Term Care Facilities in Helsinki, Journal of the American Medical Directors Association, 26, 26, 2017	Population do not meet the inclusion criteria - No adults with OAB, includes all older people living in nursing homes and assisted living facilities
Aaron, L. E., Morris, T. J., Jahshan, P., Reiz, J. L., An evaluation of patient and physician satisfaction with controlled-release oxybutynin 15mg as a one-step daily dose in elderly and non-elderly patients with overactive bladder: results of the STOP study, Current Medical Research & OpinionCurr Med Res Opin, 28, 1369-79, 2012	Outcome data not reported in full - unable to extract the MMSE results as no means or standard deviations are reported
Abrams, P., Malone-Lee, J., Jacquetin, B., Wyndaele, J. J., Tammela, T., Jonas, U., Wein, A., Twelve-month treatment of overactive bladder: efficacy and tolerability of tolterodine, Drugs & AgingDrugs Aging, 18, 551-60, 2001	No relevant outcomes presented in the article
Alexander, L., Shakespeare, K., Barradell, V., Orme, S., Management of urinary incontinence in frail elderly women, Obstetrics, Gynaecology and Reproductive Medicine, 25, 75-82, 2015	Narrative literature review
Ancelin, M. L., Artero, S., Portet, F., Dupuy, A. M., Touchon, J., Ritchie, K., Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study, BMJBmj, 332, 455-9, 2006	Population do not meet the inclusion criteria - no adults with OAB
Appell,R.A., Abrams,P., Drutz,H.P., van Kerrebroeck,P.E., Millard,R., Wein,A., Treatment of overactive bladder: long-term tolerability and efficacy of tolterodine, World Journal of UrologyWorld J.Urol., 19, 141-147, 2001	No relevant outcomes reported in the article
Burgio, K. L., Locher, J. L., Goode, P. S., Hardin, J. M., McDowell, B. J., Dombrowski, M., Candib, D., Behavioral vs drug treatment for urge urinary	Intervention not relevant to protocol - a behavioural treatment study

Excluded studies – What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?	
incontinence in older women: a randomized controlled trial, Jama, 280, 1995-2000, 1998	
Campbell, N. L., Boustani, M. A., Lane, K. A., Gao, S., Hendrie, H., Khan, B. A., Murrell, J. R., Unverzagt, F. W., Hake, A., Smith-Gamble, V., Hall, K., Use of anticholinergics and the risk of cognitive impairment in an African American population, Neurology, 75, 152-9, 2010	Population do not meet the inclusion criteria - no adults with OAB
Campbell, N., Boustani, M., Limbil, T., Ott, C., Fox, C., Maidment, I., Schubert, C. C., Munger, S., Fick, D., Miller, D., Gulati, R., The cognitive impact of anticholinergics: a clinical review, Clinical interventions in aging, 4, 225-33, 2009	Population do not meet the inclusion criteria - no adults with OAB
Campbell, N., Perkins, A., Hui, S., Khan, B., Boustani, M., Association of anticholinergic medications with incident delirium: A cohort study, Journal of the American Geriatrics Society, 1), S128-S129, 2011	Population do not meet the inclusion criteria - no adults with OAB
Cardozo, L., Hall, T., Ryan, J., Ebel Bitoun, C., Darekar, A., Wagg, A., Does fesoterodine provide efficacy, tolerability, and treatment satisfaction? A study of British patients with the overactive bladder syndrome, International Urogynecology Journal and Pelvic Floor Dysfunction, 22, S776-S777, 2011	Conference abstract
Carriere,I., Fourrier-Reglat,A., Dartigues,J.F., Rouaud,O., Pasquier,F., Ritchie,K., Ancelin,M.L., Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: The 3-city study, Archives of Internal Medicine, 169, 1317-1324, 2009	Population do not meet the inclusion criteria - no adults with OAB
Cetinel, B., Onal, B., Rationale for the use of anticholinergic agents in overactive bladder with regard to central nervous system and cardiovascular system side effects, Korean Journal of Urology, 54, 806-15, 2013	No relevant outcomes presented in the article
Chapple, C. R., Khullar, V., Gabriel, Z., Muston, D., Bitoun, C. E., Weinstein, D., The Effects of Antimuscarinic Treatments in Overactive Bladder: An Update of a Systematic Review and Meta-Analysis, European Urology, 54, 543-562, 2008	Systematic review - references checked for inclusion. Review itself excluded as pooled data does not distinguish which studies have been included in the analysis
Chapple, C., Khullar, V., Gabriel, Z., Dooley, J. A., The effects of antimuscarinic treatments in overactive bladder: A systematic review and meta-analysis, European Urology, 48, 5-26, 2005	Systematic review - references checked for inclusion
Diokno, A. C., Appell, R. A., Sand, P. K., Dmochowski, R. R., Gburek, B. M., Klimberg, I. W., Kell, S. H., Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin	No relevant outcomes presented in the article

Excluded studies – What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?	
and tolterodine for overactive bladder: Results of the OPERA trial, Mayo Clinic Proceedings, 78, 687-695, 2003	
Diokno,A., Sand,P., Labasky,R., Sieber,P., Antoci,J., Leach,G., Atkinson,L., Albrecht,D., Long-term safety of extended-release oxybutynin chloride in a community-dwelling population of participants with overactive bladder: a one-year study, International Urology and NephrologyInt.Urol.Nephrol., 34, 43-49, 2002	No relevant outcomes presented in the article
Dmochowski,R., Chapple,C., Nitti,V.W., Chancellor,M., Everaert,K., Thompson,C., Daniell,G., Zhou,J., Haag-Molkenteller,C., Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial, Journal of Urology, 184, 2416-2422, 2010	Intervention not relevant to the protocol - Onabotulinumtoxin
Fox, C., Richardson, K., Maidment, I. D., Savva, G. M., Matthews, F. E., Smithard, D., Coulton, S., Katona, C., Boustani, M. A., Brayne, C., Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study, Journal of the American Geriatrics Society, 59, 1477-83, 2011	Population do not meet the inclusion criteria - no adults with OAB
Gallego Galisteo, M., Nunez Ortiz, C., Marmesat Rodas, B., Villanueva Jimenez, P., Anticholinergic drugs and false diagnosis of demential syndrome in the elderly, International Journal of Clinical Pharmacy, 38 (6), 592-593, 2016	Conference abstract
Geller,E.J., Crane,A.K., Wells,E.C., Robinson,B.L., Jannelli,M.L., Khandelwal,C.M., Connolly,A., Parnell,B.A., Matthews,C.A., Dumond,J.B., Busby-Whitehead,J., Effect of anticholinergic use for the treatment of overactive bladder on cognitive function in postmenopausal women, Clinical Drug Investigation, 32, 697-705, 2012	Study design does not meet the inclusion criteria - no relevant comparator group
Grant, R. L., Drennan, V. M., Rait, G., Petersen, I., Iliffe, S., First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database, PLoS Medicine / Public Library of Science PLoS Med, 10, e1001505, 2013	No relevant outcomes presented in the article
Gray, S. L., Anderson, M. L., Dublin, S., Hanlon, J. T., Hubbard, R., Walker, R., Yu, O., Crane, P. K., Larson, E. B., Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study, JAMA Internal Medicine, 175, 401-7, 2015	Population do not meet the inclusion criteria - no adults with OAB

Excluded studies – What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?	
Gray, S. L., Hanlon, J. T., Anticholinergic medication use and dementia: latest evidence and clinical implications, Therapeutic Advances in Drug Safety, 7, 217-224, 2016	Population do not meet the inclusion criteria - no adults with OAB
Lechevallier-Michel, N., Molimard, M., Dartigues, J. F., Fabrigoule, C., Fourrier-Reglat, A., Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study, British Journal of Clinical Pharmacology, 59, 143-51, 2005	Population do not meet the inclusion criteria - no adults with OAB
Lenherr, S. M., Cox, L., Cognitive Effects of Anticholinergics in the Geriatric Patient Population: Safety and Treatment Considerations, Current Bladder Dysfunction Reports, 12, 104-111, 2017	Narrative literature review
Rai, Bhavan Prasad, Cody, June D, Alhasso, Ammar, Stewart, Laurence, Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults, Cochrane Database of Systematic Reviews, 2012	Systematic review - references checked for inclusion
Richardson, K., Bennett, K., Maidment, I. D., Fox, C., Smithard, D., Kenny, R. A., Use of Medications with Anticholinergic Activity and Self-Reported Injurious Falls in Older Community-Dwelling Adults, Journal of the American Geriatrics Society, 63, 1561-9, 2015	Population do not meet the inclusion criteria - no adults with OAB
Risacher, S. L., McDonald, B. C., Tallman, E. F., West, J. D., Farlow, M. R., Unverzagt, F. W., Gao, S., Boustani, M., Crane, P. K., Petersen, R. C., Jack, C. R., Jr., Jagust, W. J., Aisen, P. S., Weiner, M. W., Saykin, A. J., Alzheimer's Disease Neuroimaging, Initiative, Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults, JAMA Neurology, 73, 721-32, 2016	Population do not meet the inclusion criteria - no adults with OAB
Robinson, D., Kelleher, C., Staskin, D., Mueller, E. R., Falconer, C., Wang, J., Ridder, A., Stoelzel, M., Paireddy, A., van Maanen, R., Hakimi, Z., Herschorn, S., Patient-reported outcomes from SYNERGY, a randomized, double-blind, multicenter study evaluating combinations of mirabegron and solifenacin compared with monotherapy and placebo in OAB patients, Neurourology and Urodynamics., 2017	No relevant outcomes presented in the article
Roe, C. M., Anderson, M. J., Spivack, B., Use of anticholinergic medications by older adults with dementia, Journal of the American Geriatrics Society, 50, 836-42, 2002	Population do not meet the inclusion criteria - no adults with OAB

Excluded studies – What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?	
Ruxton, K., Woodman, R. J., Mangoni, A. A., Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis.[Erratum appears in Br J Clin Pharmacol. 2015 Oct;80(4):921-6], British Journal of Clinical Pharmacology, 80, 209-20, 2015	Population do not meet the inclusion criteria - no adults with OAB
Salahudeen, M. S., Chyou, T. Y., Nishtala, P. S., Serum Anticholinergic Activity and Cognitive and Functional Adverse Outcomes in Older People: A Systematic Review and Meta-Analysis of the Literature, 11, e0151084, 2016	Population do not meet the inclusion criteria - no adults with OAB
Salahudeen, M. S., Duffull, S. B., Nishtala, P. S., Impact of anticholinergic discontinuation on cognitive outcomes in older people: a systematic review, Drugs & AgingDrugs Aging, 31, 185-92, 2014	Population do not meet the inclusion criteria - no adults with OAB
Sand,P., Zinner,N., Newman,D., Lucente,V., Dmochowski,R., Kelleher,C., Dahl,N.V., Oxybutynin transdermal system improves the quality of life in adults with overactive bladder: a multicentre, community-based, randomized study, BJU International, 99, 836-844, 2007	No relevant outcomes presented in article
Sexton,C.C., Notte,S.M., Maroulis,C., Dmochowski,R.R., Cardozo,L., Subramanian,D., Coyne,K.S., Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature, International Journal of Clinical Practice, 65, 567-585, 2011	No relevant outcomes presented in the article
Sink, K. M., Thomas, J., 3rd, Xu, H., Craig, B., Kritchevsky, S., Sands, L. P., Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes, Journal of the American Geriatrics Society, 56, 847-53, 2008	Data cannot be used in analysis. The study provides change in function on the MDS-COGS scale for intact, moderate and severe impairment, but no mean or SD values are provided
Sittironnarit, G., Ames, D., Bush, A. I., Faux, N., Flicker, L., Foster, J., Hilmer, S., Lautenschlager, N. T., Maruff, P., Masters, C. L., Martins, R. N., Rowe, C., Szoeke, C., Ellis, K. A., Aibl research group, Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study, Dementia & Geriatric Cognitive DisordersDement Geriatr Cogn Disord, 31, 173-8, 2011	Population do not meet the inclusion criteria - no adults with OAB
Sura, S. D., Carnahan, R. M., Chen, H., Aparasu, R. R., Anticholinergic drugs and health-related quality of life in older adults with dementia, Journal of the American Pharmacists Association: JAPhAJ Am Pharm Assoc (2003), 55, 282-7, 2015	Population do not meet the inclusion criteria - no adults with OAB

Excluded studies – What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?	
Sura, S. D., Carnahan, R. M., Chen, H., Aparasu, R. R., Prevalence and determinants of anticholinergic medication use in elderly dementia patients, Drugs & AgingDrugs Aging, 30, 837-44, 2013	Population do not meet the inclusion criteria - no adults with OAB
Uusvaara, J., Pitkala, K. H., Kautiainen, H., Tilvis, R. S., Strandberg, T. E., Association of anticholinergic drugs with hospitalization and mortality among older cardiovascular patients: A prospective study, Drugs & AgingDrugs Aging, 28, 131-8, 2011	Population do not meet the inclusion criteria - no adults with OAB
Uusvaara, J., Pitkala, K. H., Kautiainen, H., Tilvis, R. S., Strandberg, T. E., Detailed cognitive function and use of drugs with anticholinergic properties in older people: a community-based cross-sectional study, Drugs & AgingDrugs Aging, 30, 177-82, 2013	Population do not meet the inclusion criteria - no adults with OAB
Wagg, A., Dale, M., Tretter, R., Stow, B., Compion, G., Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study, European Urology, 64, 74-81, 2013	No relevant outcome data is provided and unclear if if adults with OAB are included
Wein, A. J., Re: Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: The SENIOR study, Journal of Urology, 191, 739-740, 2014	Editorial paper
Wein, A. J., Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence, Journal of Urology, 184, 2030-2031, 2010	Editorial paper

Economic studies

No economic evidence was identified for this review question. See supplementary document D for further information.

Appendix L – Research recommendations

Research recommendations for review question: What are the risks to cognitive function for women taking anticholinergic drugs for overactive bladder (OAB)?

What is the effectiveness and safety of anticholinergic medicines for overactive bladder in older women?

Why is it important?

Longitudinal studies have also shown that exposure to anticholinergic medications are associated with risk for developing mild cognitive impairment (MCI) and dementia. Most of the studies have been conducted among elderly people in primary prevention, whereas longer term studies assessing relationships between anticholinergics for overactive bladder and development of MCI or dementia are scarce. The aim would be to explore the potential risk for developing MCI/dementia and extent of this risk, looking at long term follow up for patients on bladder anticholinergics.

Table 9: Research recommendation rationale

Research question	What is the effectiveness and safety of anticholinergic drugs for OAB in older women?
Importance to 'patients' or the population	Anticholinergic drugs are commonly prescribed for women with OAB and it is not known whether they cause a deterioration in cognitive function or dementia Women currently do not have enough information about the longer term risks of these drugs before starting them. Cognitive impairment and dementia are associated with significant morbidity and mortality. They affect the individual's ability to self-care and this impacts on them, their family and society as a whole.
Relevance to NICE guidance	Anticholinergics are currently the first line medications recommended for OAB. It is important to consider the long-term effects of these medications on cognition. There is insufficient evidence on whether bladder anticholinergics are associated with cognitive decline. There is insufficient evidence to make recommendations on the use of bladder anticholinergics in women who already have cognitive impairment and OAB. It is difficult to counsel women regarding unknown risk association.
Relevance to the NHS	Cognitive impairment and dementia impact significantly on NHS and social care resources.
National priorities	Cognitive decline and dementia are national priorities.
Current evidence base	There are no longitudinal studies looking at long term effects of bladder anti-cholinergic drugs on cognition in women or older women. Evidence available for anticholinergic medications in general shows a possible association between long term use and cognitive impairment/dementia.
Equality	None known

Table 10: Research recommendation modified PICO table

Criterion	Explanation
Population	Women at or over 65 years commencing anticholinergic drug therapy for OAB
Intervention	Anticholinergic drugs indicated for OAB

Criterion	Explanation
Comparator	Women who do not receive anticholinergic treatment for OAB (could include women who are only trailing mirabegron)
Outcome	Cognitive function (as measured by validated cognitive screening tools) at 3 years (primary outcome), cognitive function (as measured by validated screening tools) at 5 years (secondary outcome), development of incident dementia, at 3 and 5 years, quality of life, QoL specific to urinary incontinence.
Study design	Prospective case controlled cohort, propensity matched for exposure to anticholinergic OAB treatment or not. Ideally trials would be done using different bladder anticholinergics as if all are grouped together the data may produce results which cannot be interpreted on an individual basis.
Timeframe	5 years
Additional information	Anticipated drop out with cohort follow up will be high (up to 60% within 1 year