Medicines & Healthcare products Regulatory Agency

Bladder anticholinergics: review of risk of dementia

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

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1. Plain Language Summary

Key messages:

Anticholinergic medicines work by blocking the action of a chemical, known as acetylcholine, which is found in the brain and body. In the last few years, many studies have been published looking at whether people who take anticholinergic medicines have a higher risk of dementia. Many of these studies have looked at the risk for anticholinergic medicines used to control bladder function (often referred to as bladder anticholinergics).

The Commission on Human Medicines (CHM) recommended that the Medicines and Healthcare products Regulatory Agency (MHRA) should undertake a review of the available data for bladder anticholinergic medicines. The review examined whether the data raise any new safety concerns or change current understanding about a possible link between the use of these medicines and the onset of dementia.

The overall findings of the review are that the available evidence is not sufficient to confirm that use of bladder anticholinergic medicines directly increases the risk of developing dementia; however, the limitations of these studies mean that a small increased risk cannot be ruled out completely.

Although the available data does not demonstrate that ‘bladder anticholinergics’ cause dementia, it is known that taking more than one anticholinergic medicine may increase your risk of experiencing side effects. Also, as we age, our body may not process medicines as well, so we may become more sensitive to them. For these reasons, it is advised that older adults limit the number of anticholinergic medicines they take and use the lowest dose to control their condition for the shortest length of time.

If you are a patient on a bladder anticholinergic medicine, please discuss any concerns you have with your healthcare professional. Patients should not stop taking their medicine without medical advice.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices, and blood components for transfusion in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines (CHM) advises government ministers and the MHRA on the safety, efficacy and quality of medicines.

In our public assessment reports, we discuss reviews based on the scientific evidence of safety issues linked with a particular medicine or group of medicines.

This report presents the review of safety data on the risk of dementia in association with the use of anticholinergic medicines used to control bladder function.

More information about bladder anticholinergics

Anticholinergic medicines work by blocking the action of acetylcholine, which is a chemical found in many parts of the body and in the brain. The effects of acetylcholine include helping you to stay alert, keeping a steady heart rate, and emptying your bladder. In the brain, acetylcholine is responsible for nerve communication, memory, and learning.

Anticholinergic medicines, can be prescribed for many medical conditions, including controlling bladder function. The medicines used to control bladder function are often called bladder anticholinergics but can also be called bladder antimuscarinics. They can be used for the management of the symptoms of overactive bladder. These include a sudden urgent need to pass urine (urinary urgency), having to pass urine more often than usual (urinary frequency), waking to go the toilet more than once at night (nocturia), and leaking of urine before you can get to the toilet (urge incontinence).

Bladder anticholinergics include products containing the following active drug substances:

- darifenacin hydrobromide (brand name Emselex)
- fesoterodine fumarate (brand name Toviaz, Teraleve)
- oxybutynin hydrochloride (brand names Ditropan, Kentera (skin patch))
- propiverine hydrochloride (brand name Detrunorm, Detrunorm XL)
- solifenacin succinate (brand name Giraxine, Vecit, Vesicare)
- tolterodine tartrate (brand name Detrusitol, Detrusitol XL, Inconex XL, Mariosea XL, Neditol XL, Tolterma XL, Tolthen XL)
- trospium chloride (brand name Regurin)

Flavoxate hydrochloride (brand name Urispas), is not usually classed as a bladder anticholinergic. It was included in this review, as it does have some anticholinergic effects. It was also included in some of the studies looked at in this review.

Reasons for the latest review and information considered

As with all medicines, anticholinergic medicines can cause side effects. Common side effects include short-term memory loss (forgetfulness) and confusion. Older people may be more likely to experience these side effects. Healthcare professionals already know to carefully consider the possible short-term impact on memory when prescribing anticholinergic medicines to older people. It is less certain if anticholinergic medicines, like bladder anticholinergics, have longer term effects on memory and thinking, including whether the use is linked to an increased risk of dementia.

In the last few years, many studies have been published looking at whether people who take anticholinergic medicines have a higher risk of dementia. Many of these studies have looked at the risk of dementia for bladder anticholinergics. The CHM recommended that the MHRA should undertake a review of the available data for these medicines. The review examined whether the data raise any new safety concerns or change current understanding about a possible link between the use of bladder anticholinergics and the onset of dementia.

How the CHM reached their conclusions

The CHM considered the available evidence on the risk of dementia associated with the use of bladder anticholinergics at its meeting in September 2025. This included information submitted by the companies who manufacture these medicines on possible mechanisms and studies examining the short-term effects of these medicines on thinking, attention and memory. Studies using healthcare records data to examine whether the use of bladder anticholinergics was associated with an increased risk of dementia were also evaluated. Along with adverse drug reaction reports submitted through the Yellow Card Scheme.

Another independent expert group, the Pharmacovigilance Expert Advisory Group was also consulted during this review; this Group’s findings were considered by CHM.

The MHRA presented the data and evidence to the CHM who was asked to advise on the strength of evidence for a link between the use of bladder anticholinergics and the risk of dementia.

Advice from CHM

The CHM carefully considered the available data examining the risk of dementia with the bladder anticholinergic medicines. This included how the design and conduct of studies may affect the results and confidence in the findings.

The CHM considered that, generally, the studies examining the risk of dementia produced findings in which we have low confidence.

There are a number of reasons for this, including that:

- the early symptoms of dementia may occur years before a diagnosis of dementia is made. So, it is possible that patients in these studies may have started to develop dementia prior to starting bladder anticholinergics. This would suggest a strong link but would not imply that the medicine caused the dementia.
- if taking bladder anticholinergics causes dementia, we would expect the studies to show that oxybutynin was associated the greatest risk. This is due to the way in which the bladder anticholinergic medicines work and are distributed in the body, including in the brain. However, this has not been seen in the studies included in this review.
- other health conditions or factors that could be linked with both dementia and the prescribing of bladder anticholinergics may not have been fully accounted for in the studies.

Considering the strengths and limitations of the available data, the CHM concluded that there is considerable uncertainty whether the use of bladder anticholinergics directly increases the risk of developing dementia. The data also do not allow us to conclude that there are true differences in risk of dementia with the different bladder anticholinergic medicines. Although the available data does not demonstrate that bladder anticholinergics cause dementia, the possibility of a small increased risk cannot be ruled out.

We know that taking more than one anticholinergic medicine may increase the risk of experiencing side effects. This includes effects on memory, attention and thinking. Older people may be more likely to experience these side effects. In line with clinical guidance, CHM recommended that healthcare professionals should aim to limit the number of anticholinergic medicines older people take. They should also use the lowest dose to control their condition for the shortest length of time.

Conclusions of the review

The data shows that use of oxybutynin can cause short-term memory loss (forgetfulness). It can also adversely affect attention and thinking. These possible side effects are included in oxybutynin Patient Information Leaflets and the product information for healthcare professionals. The data for other bladder anticholinergic medicines does not suggest similar adverse effects on memory, thinking or attention.

Overall, the available evidence is not sufficient to confirm that use of bladder anticholinergic medicines directly increases the risk of developing dementia; however, the limitations of these studies mean that a small increased risk cannot be ruled out completely.

If you are a patient on a bladder anticholinergic medicine, please discuss any concerns you have with your healthcare professional. Patients should not stop taking their medicine without medical advice

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulator of medicines, medical devices and blood components for transfusion in the UK. The MHRA is responsible for making sure these products meet acceptable standards for safety, quality and efficacy. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

This report presents the MHRA's review of safety data relating to the risk of dementia in association with the use of anticholinergic medicines (also known as antimuscarinic medicines) for the treatment of overactive bladder and stress urinary incontinence and expert advice on these data, as advised on by Commission on Human Medicines (CHM). The CHM advises the government about medicines safety. The CHM is independent – it is not part of the government or the pharmaceutical industry. Changes have been made to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the review in 2025. The MHRA and CHM will continue to monitor the safety of anticholinergic medicines closely, however the information in this report will not be actively updated with new data or studies.

3. Background

3.1 Anticholinergic medicines and effects on cognitive function

Anticholinergic medicines

Anticholinergic medicines, which are used to manage several medical conditions, block the action of the neurotransmitter, acetylcholine. Acetylcholine is found in the central nervous system (CNS) and also the peripheral nervous system. It plays an important role in many different body functions including slowing of the heart, dilating blood vessels and helping muscles contract, such as those in the bladder leading to bladder emptying. In the brain, amongst other actions, it helps learning, memory and attention.

To achieve its effects, acetylcholine binds to cholinergic receptors on cell membranes. There are two types of cholinergic receptors, these are the nicotinic receptors and the muscarinic receptors. Muscarinic receptors are the most common type of cholinergic receptors and there are five types (M1 – M5), which are all expressed in the brain to differing degrees. The urinary bladder smooth muscle contains both M2 and M3 receptors, but it is the M3 receptors, which are mainly responsible for bladder contraction (Chancellor and others, 2012).

Bladder anticholinergics

Anticholinergic medicines that are used for the management of urinary incontinence or overactive bladder work by blocking the effects of acetylcholine leading to reduced involuntary bladder contractions and increased bladder capacity. This leads to a decrease in the urgency and frequency of urination. They are also called bladder antimuscarinics because they exert their effects through muscarinic receptors. They will be referred to as bladder anticholinergics throughout this report.

The bladder anticholinergics include products containing the following active drug substances – darifenacin hydrobromide (brand name Emselex (prolonged release)), fesoterodine fumarate (brand name Toviaz and Teraleve), oxybutynin hydrochloride (brand names Ditropan and Kentera (skin patch)), propiverine hydrochloride (brand name Detrunorm, Detrunorm XL (modified release)), solifenacin succinate (brand name Giraxine, Vecit, and Vesicare), tolterodine tartrate (brand name Detrusitol, Detrusitol XL (modified release), Inconex XL (prolonged release), Mariosea XL (prolonged release), Neditol XL (prolonged release), Tolterma XL (prolonged release) and Tolthen XL (prolonged release)) and trospium chloride (brand name Regurin). They are authorised for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency, which may occur in patients with

overactive bladder syndrome. Additionally, some of these (oxybutynin, solifenacin) are also indicated for use in the treatment of detrusor overactivity due to idiopathic overactive bladder or neurogenic bladder disorders.

Flavoxate hydrochloride (brand name Urispas), is indicated for symptomatic relief of dysuria, urgency, nocturia, vesical supra- pubic pain, urinary frequency and urinary incontinence as may occur in conditions including cystitis, prostatitis and urethritis. It is not usually classed as a bladder anticholinergic, however, it does have some, albeit limited, anticholinergic activity and can be used for the treatment of urinary urgency. It was included in the class of bladder anticholinergics in some of the studies that have examined the risk of dementia in association with this class of medicines. Therefore, it was included in this review for completeness.

Association of anticholinergic medicines with adverse cognitive outcomes

The main properties of anticholinergic drugs are related to their action on central and/or peripheral cholinergic receptors. The peripheral adverse events associated with anticholinergics are well recognized and include dry mouth, nausea, flushing, palpitations, blurred vision and constipation. Many anticholinergics have also been associated with the potential for some adverse central nervous system (CNS) effects, including headache, dizziness, somnolence and cognitive effects.

Some medicines, like bladder anticholinergics, are used for their anticholinergic effects, while others have anticholinergic activity, but this is not related to their primary mode of action. The use of multiple anticholinergic medications leads to a cumulative effect, referred to as the anticholinergic burden.

Studies have shown that anticholinergic medicines can have short-term adverse CNS effects, such as confusion and memory loss in older people. It is recognised that anticholinergic drugs may cause confusion, amnesia, mood disturbances, insomnia and delirium and that older people may be more likely to experience the CNS adverse effects associated with their use. Some studies suggest that use in the elderly increases the risk of falls, cognitive impairment and mortality (Fox and others, 2011; Fox and others, 2014). Whilst anticholinergics medicines can cause cognitive impairment that may be reversible (Salahudeen and others, 2014), the longer-term effects, including whether long term use of anticholinergics is associated with an increased risk of dementia, are less certain.

3.2 Clinical Guidance

Management of Overactive bladder

Overactive bladder, which is a common condition occurring in both women and men, affects around 12-14% of the UK population (Irwin and others, 2008). Although overactive bladder syndrome can affect children and young adults, it is most common in patients over 40 years old and its occurrence increases with age. It is sometimes called irritable bladder or detrusor instability (detrusor is the medical name for the bladder muscle).

Symptoms include a sudden urgent need to pass urine (urinary urgency), having to pass urine more often than usual (urinary frequency), waking to go to the toilet more than once at night (nocturia), and leaking of urine before you can get to the toilet (urge incontinence). Overactive bladder syndrome can affect performance of daily activities and social functions such as work, travelling, physical exercise, sleep and sexual function.

Clinical guidelines (National Institute for Health and Care Excellence (NICE), European Association of Urology) generally recommend a stepwise approach in the management of overactive bladder symptoms based on individual symptom control, choices and tolerability to the treatment. Initial conservative management includes non-pharmacological treatments such as lifestyle interventions (including changes to diet and fluid intake), behavioural therapies, bladder training/timed voiding, pelvic floor muscle training, incontinence management strategies (e.g. pads, barrier creams).

For many people with overactive bladder, conservative management will be effective and will reduce their symptoms. In those who do not respond adequately to conservative management, then medication may be prescribed. NICE guidance recommends that if medication is required then bladder anticholinergics should be prescribed as a first line option. As there is little difference between the individual bladder anticholinergic drug substances in terms of how well they work, NICE guidance recommends that the lowest acquisition cost bladder anticholinergics are routinely offered first. Bladder anticholinergics are also a first-line pharmacological treatment option in other clinical guidance outside the UK, including guidelines by the European Association of Urology and the American Urological Association.

Use of a β3-adrenoreceptor agonist (i.e. mirabegron (brand name Betmiga) or vibegron (brand name Obgemsa) is recommended if bladder anticholinergic medicines are not suitable, do not work well enough or have unacceptable side effects. If these medicines are not successful in managing the symptoms, then

treatment with botulinum toxin A, nerve stimulation or surgery may be needed to treat overactive bladder syndrome.

Cognitive effects of anticholinergic medicines

NICE guidance [NG123] on the management of urinary incontinence and pelvic organ prolapse in women cautions about the uncertainty of long-term effects of anticholinergic medicines on cognitive function. It recommends that a discussion should take place with the patient before starting an anticholinergic medicine to emphasise that the long-term effects of these medicines on cognition are uncertain and also that the current use of other medicines that affect total anticholinergic burden should be taken into account when prescribing anticholinergic medicines to treat overactive bladder. It also states that in those with a diagnosis of dementia and for whom anticholinergic medicines are an option, that the recommendations on medicines that may cause cognitive impairment in the NICE guideline on dementia [NG97] should be followed.

NICE guidance [CG148] on the assessment and management of urinary incontinence in neurological disease recommends that when starting anticholinergic treatment it is important to take into account that anticholinergics that are known to cross the blood brain barrier (e.g. oxybutynin) have the potential to cause central nervous system-related side effects (such as confusion).

NICE guidance on dementia [NG97] highlights that some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment. It advocates that prescribers should consider minimising the use of medicines associated with increased anticholinergic burden and, if possible, look for alternatives:

- when assessing whether to refer a person suspected dementia for diagnosis
- during medication reviews for people living with dementia.

3.3 Dementia

The number of people living with dementia in the UK was estimated to be close to 1 million (982,000) in 2024 (Carnell Farrar, 2024) and by 2040 this figure is expected to rise to 1.4 million (Besley and others, 2023). Modifiable risk factors include smoking, high alcohol intake, hearing loss, hypertension, depression, diabetes and high cholesterol.

Dementia is a progressive condition and so the initial signs and symptoms may be mild, but they will get worse over time. Although dementia will affect everyone

differently, it is often thought of as progressing in stages. Alzheimer's disease is the most common form of dementia accounting for 60-80% of cases. Other forms of dementia include Lewy body dementia, frontotemporal lobe dementia, vascular dementia and mixed dementia. Each type has its own symptoms, patterns and progression.

The Alzheimer's disease process begins long before any obvious signs or symptoms are seen. This is often referred to as the preclinical or cognitively normal stage. At this stage, there will be no apparent signs of decline in memory, language, orientation or problem-solving skills. The individual will also be able to carry out day-to-day activities independently and engage in social interactions without any noticeable difficulty. There may, however, be changes in behaviour including apathy, mild irritability, a state of unease or dissatisfaction (dysphoria), and a reduced awareness of understanding of one's own health, behaviour or needs (impaired insight). Individuals may also reduce their normal activities, socialise less and exercise less. It can be very difficult for a healthcare professional to identify this stage of Alzheimer's disease and the changes in behaviour can often be attributed to normal ageing. During this stage, however, changes are occurring in the brain, which include the build-up of amyloid-beta peptide and tau protein, and these can start to occur 15-20 years before the onset of clinical Alzheimer's disease (Bateman and others, 2012; Fagan and others, 2014). This in turn leads to neurodegeneration, which will eventually lead to the more pronounced symptoms seen in the later stages of the disease.

The mild cognitive impairment stage of Alzheimer's disease (can also be referred to as the prodromal stage) is the stage where there are obvious signs of brain dysfunction. Individuals at this stage will show obvious short-term memory deficits, may misplace items more frequently and have more difficulty learning something new. Sometimes if these symptoms of cognitive impairment are recognised by the individual they may be put down to the forgetfulness of ageing or may be considered too minimal or embarrassing to raise with their doctor. So often a person at this stage of Alzheimer's disease only presents to their doctor an average of 3 to 4 years after the cognitive symptoms began (Leung and others, 2011). The duration of the stages of Alzheimer's disease, including the prodromal stage can vary, with age being found to have the biggest influence on the length of the different stages; the length of each stage decreasing with increasing age (Vermunt and others, 2019).

In the dementia stage of Alzheimer's disease, cognitive impairment is present to such a degree that a person who does not know the individual would usually be able to identify thinking problems after a short visit with them. Usually, they will not be able to recall the correct date, day of week and word finding difficultly for everyday

objects will be obvious. The individual would also be unable to carry out independently many activities of daily living that they used to perform well.

As the individual moves from the mild to moderate Alzheimer's disease dementia stage, neuropsychiatric disturbances become increasingly common. Loss or significant decline can occur in performance of activities of daily living (e.g., driving, shopping, cooking, using appliances, housekeeping, computer/tablet use, mobile phone use, and TV remote use). Then the ability to perform even basic activities of daily living (e.g., dressing, grooming, bathing, feeding, toileting, and continence) will gradually decline over time.

Overactive bladder and urinary incontinence are common in dementia. It has been estimated that around 53% of people with dementia have incontinence, whereas only 13% of those without dementia experience this problem (Price, 2011). For some people, urinary incontinence may develop because the messages between the brain and the bladder don't work properly, and they may not recognise that they have a full bladder. Other reasons in persons with dementia include memory loss leading to inability to recall bathroom locations, reduced ability to recognise urgency cues, mobility issues meaning they do not get to the toilet on time, and difficulty in communicating and being able to tell someone they need to go to the toilet.

3.4 Reasons for the Review

As with all medicines, the safety of anticholinergic medicines is kept under close review by the MHRA. Data on the risk of adverse effects on cognitive function and dementia in association with the use of anticholinergic drugs was last reviewed in 2017. It was considered that the studies available at that time had several important limitations, and many studies did not present information by medication class making it difficult to extrapolate the findings to specific products. Therefore, it was concluded that the available evidence did not justify taking regulatory action.

Since then, a growing number of studies have been published and some of the more recent ones have attempted to address key limitations that were previously identified. Many of these studies, particularly those that report data by medication class and/or individual drug substance, have examined the risk of dementia in association with bladder anticholinergics. It was considered important to conduct a further review to critically appraise the relevant studies and other relevant data, including studies that related to pathological mechanisms and risk factors. In particular, to focus on data on the risk of dementia with use of bladder anticholinergics to determine whether there may now be higher quality data to inform our understanding of the association.

4. Evidence

The Marketing Authorisation holders (MAHs) of the bladder anticholinergics were requested to provide a critical evaluation of the available data relating to the risk of dementia in association with the use of their products, including evidence on plausible mechanisms.

This report presents information on UK suspected adverse drug reaction (ADR) reports that have been submitted through the Yellow Card Scheme, information provided in the responses from the MAHs (including non-clinical and clinical studies), and a critical appraisal of the relevant observational studies published in the scientific literature since 2017.

4.1 Yellow Card/Adverse drug reaction data

The Yellow Card scheme run by the MHRA is the UK system for collecting and monitoring information on safety concerns such as suspected side effects involving medicines. Suspected side effects are reported by health professionals and the public, including patients, carers and parents.

All Yellow Card reports received are entered onto the MHRA's adverse drug reaction database so that they are available for signal detection. It is important to note that a reported reaction or case does not necessarily mean it has been caused by the drug or vaccine, only that the reporter had a suspicion it may have. Underlying or concurrent illnesses may be responsible and such events can also be coincidental. Additionally, it is also important to note that the number of reports received via the Yellow Card scheme does not directly equate to the number of people who suffer adverse reactions and therefore cannot be used to determine the incidence of a reaction. Adverse drug reaction reporting rates are influenced by the seriousness of these reports, their ease of recognition, the extent of use of a particular drug or vaccine and may be stimulated by promotion and publicity about a drug or vaccine.

A search was conducted of UK ADR reports within the mental impairment disorders HLGT (higher level group term) that have been submitted through the Yellow Card Scheme as of 1st August 2025 in association with the bladder anticholinergics included in this review.

Table 1 below includes the number of reports of mental impairment disorders that have been received in association with the individual bladder anticholinergic drug substances.

Table 1: Number of reports of mental impairment disorders received for bladder anticholinergics

	Dementia	Amnesia	Memory impairment	Disturbance in attention	Cognitive disorder	Mental impairment	Total no of cases
Darifenacin			1				1
Flavoxate				1			1
Fesoterodine	2			1	1		4
Oxybutynin	1	2	6	9	2		18
Propiverine			1				1
Solifenacin	6	11	10	3	3	1	33
Tolterodine	5	5	8	7	1	3	23
Trospium					1		1

Cases of dementia have been reported in association with solifenacin (n=6), tolterodine (n=5), fesoterodine (n=2) and oxybutynin (n=1). No cases of dementia have been reported through the Yellow Card Scheme in association with darifenacin, flavoxate, propiverine and trospium.

The highest number of reports of mental impairment disorders have been received in association with solifenacin (n=33), tolterodine (n=23) and oxybutynin (n=18) with very few reports received in association with the other bladder anticholinergics. However, the nature of spontaneous reporting data means that many factors may influence reporting and so a higher number of reports does not necessarily reflect a greater risk. Instead, it may in part reflect the greater use of these products as the exposure data provided by the MAHs suggests that these bladder anticholinergics are the ones with the highest usage.

In many of the reported cases of dementia and other mental impairment disorders, key information is missing such as time to onset, medical history and the action that has been taken with regards to the bladder anticholinergic treatment and/or the outcome of the reactions. Therefore, in most of the cases the available data does not really allow for possible causal association to be evaluated, and no real conclusions can be reached based on the spontaneous data.

4.2 Mechanistic data

The neurotransmitter acetylcholine is found in the CNS system and is fundamental to a wide array of cognitive functions within the human brain through its interaction with cerebral muscarinic receptors (M1, M2, M3, M4, M5). The five types of muscarinic receptors are all expressed in the brain to different degrees with some regions of the brain, such as the hippocampus, cortex and thalamus, having high densities of muscarinic receptors. These regions of the brain are responsible for memory, learning and other cognitive processes. The M1, M2 and M4 muscarinic receptors are more commonly expressed in the brain and are considered more likely to be related to any adverse cognitive effects of anticholinergic medicines. The M1 receptor (and to a lesser extent the M2 receptors) are involved in memory and learning processes.

Whilst the biological basis for the cognitive effects of anticholinergic medicines is not known, given the role of cholinergic system in cognition it is assumed that direct impairment of cholinergic neurons may underlie the effects. Administration of muscarinic receptor antagonists have been reported to decrease delayed recall in healthy volunteers, which is consistent with cholinergic transmission playing a key role in attention and memory tasks (Nakra and others, 1992; Pomara and others, 2010; Dumas and others, 2011).

Anticholinergic drugs may cause CNS effects such as confusion and effects on cognitive function due to their ability to cross the blood brain barrier and affinity for and ability to block muscarinic receptors in the brain, particularly the M1 subtype. Differences in ability to penetrate the CNS, and in affinity for the M1 receptor, may partially explain the differences in CNS effects observed among the bladder anticholinergics used in the treatment of overactive bladder.

Bladder anticholinergics such as oxybutynin, tolterodine, trospium and fesoterodine are non-selective as they have affinity for all muscarinic receptors. Whilst darifenacin and solifenacin are considered selective or weakly selective, respectively, due to their greater affinity for M2 and/or M3 receptors (that are more commonly expressed in the bladder smooth muscle) as compared to the M1 receptor.

Whether the individual bladder anticholinergics cross the blood brain barrier and are able to act centrally is governed by their physicochemical properties, including polarity, molecular size and lipophilicity. These properties mean that they can cross the blood brain barrier to differing extents, however, the levels that will accumulate in the brain are also important. The P-glycoprotein efflux transporter is an important mechanism at the blood brain barrier that actively pumps many foreign chemical substances, including some medicines, out of the brain. Therefore, whether a medicine is a substrate for P-glycoprotein will affect how likely it is that levels will accumulate in the brain.

Most of the bladder anticholinergics, with the exception of trospium, are lipophilic anticholinergics and so can potentially cross the blood brain barrier, however, their size and polarity will further influence this. Oxybutynin, which has low molecular weight and a neutral charge, will more easily cross the blood brain barrier and as it does not act as a substrate for P-glycoprotein oxybutynin can also accumulate in the CNS. Given their physicochemical properties, darifenacin, fesoterodine, solifenacin and tolterodine are likely to be able to cross the blood brain barrier, but not as readily as oxybutynin. As darifenacin and fesoterodine are P-glycoprotein substrates they can be actively removed by the P-glycoprotein efflux transporter and levels are unlikely to accumulate. This contrasts with solifenacin and tolterodine, which are not P-glycoprotein substrates, and removal will be dependent on passive diffusion and metabolism, potentially leading to accumulation in the brain, especially with chronic use.

Callegari and colleagues (2011) investigated the ability of bladder anticholinergics to penetrate the CNS to try and understand whether this may help explain their differential risks for CNS side effects. Using in vivo rat models and in vitro assays, they observed that oxybutynin showed extensive CNS penetration, while tolterodine and solifenacin had significant but restricted penetration. Darifenacin, 5-hydroxymethyl tolterodine and trospium exhibited low CNS penetration. In vitro, trospium had low permeability, while the other bladder anticholinergics demonstrated moderate to high permeability. However, 5-

hydroxymethyl tolterodine, darifenacin, and trospium were P-glycoprotein substrates with 5-hydroxymethyl tolterodine showing the highest efflux ratio followed by trospium and darifenacin. Therefore, this would limit the CNS access of these bladder anticholinergics, unlike oxybutynin, solifenacin, and tolterodine. The investigators consider that these findings align with clinical CNS side-effect profiles and highlight the role of P-glycoprotein and passive permeability in determining CNS penetration, guiding safer overactive bladder drug selection for older adults.

The permeability of the blood brain barrier also influences the penetration of medicines into the CNS. The integrity of the blood brain barrier is naturally reduced with older age but is also affected by certain conditions and illnesses like diabetes, stroke, multiple sclerosis and epilepsy, which can influence passive permeability and active transport mechanisms across the blood brain barrier. Therefore, in patients who are at greater risk of having compromised function of the blood brain barrier, bladder anticholinergics may be able to more readily cross the blood brain barrier than might be predicted.

Although the biological basis for the cognitive effects of anticholinergic medicines is not known, it is assumed that direct impairment of cholinergic neurons may underlie the effects with downregulation of cholinergic neurons, reduced neurotrophic support and increased oxidative stress and inflammatory cytokines, contributing to neurodegeneration. Atrophy of the cholinergic system in the basal forebrain has been observed in the early stages of Alzheimer's disease and a reduction in the quantity of cholinergic receptors and impaired acetylcholine binding within the hippocampus has been documented in Alzheimer's disease patients. Some animal studies have also suggested that anticholinergics may enhance the pathology of Alzheimer’s disease and lead to changes in brain structure (Seeger and others, 2004; Caccoma and others, 2006; Davis and others, 2010; Yoshiyama and others, 2012) but others have failed to show such effects (Klausner and others, 2008). However, this has not translated reliably to effects in humans (neuropathologic features and neuroimaging) where the data are less clear and the study findings are more mixed (Teipel and others, 2015; Risacher and others, 2016; Gray and others, 2018; Richardson and others, 2020; Kilimann and others, 2022; Mur and others, 2023; Li and others, 2024).

4.3 Clinical Studies on Cognitive Function

The data submitted by the Marketing Authorisation holders included information on short-term clinical studies that had examined the effect of the individual bladder anticholinergics on cognitive function. These are mostly studies published in the scientific literature but, some company conducted studies are mentioned. The information for each of the individual bladder anticholinergics is summarised below. No information has been provided for flavoxate and a search of the published literature has not identified any relevant clinical studies.

Darifenacin

Darifenacin, a selective M3 antagonist, has been shown to have little effect on the cognitive function of both older and younger adults in short-term studies (Kay and others, 2005; Lipton and others, 2005; Kay and others, 2006; Golding and others, 2018). In the study by Lipton and colleagues (2005), volunteers aged 65 years or older received darifenacin immediate release (3.75, 7.5 or 15 mg once daily) or placebo for 14 days. There was no statistically significant difference between darifenacin or placebo for the primary end points (memory scanning sensitivity, speed of choice reaction time and word recognition sensitivity) or for most of the secondary variables. In the study by Kay and colleagues (2006), healthy volunteers aged 60 years or older received darifenacin, oxybutynin extended release or placebo over a 3-week period. The primary endpoint was accuracy on the Name-Face Association test (NFAT) which showed no difference between darifenacin and placebo, but oxybutynin was associated with significantly lower scores than darifenacin or placebo. Similar results were seen for additional tests of delayed recall. No between-treatment differences were detected in self-rated memory suggesting subjects were unaware of the memory deterioration. The studies in younger adults (Kay and others, 2005; Golding and others, 2018) also reported that darifenacin did not affect cognitive function, including simple reaction time, speed of numeric and spatial working memory, and speed and sensitivity of picture recognition.

Vasudeva and colleagues (2021) reported that in patients with a history of cerebrovascular accident, 3 months treatment with either darifenacin (7.5mg once daily, n=30) or mirabegron (25 mg once daily, n=30) was not associated with any detrimental effect on cognitive function examined, as measured using the Montreal Cognitive Assessment -Basic score (MoCA B). In the darifenacin group the MoCA-B score (median (IQR)) was 26.5 (23.25-27) at baseline and 26 (23-27) at 3 months.

Fesoterodine

A company conducted study evaluated the cognitive effect of fesoterodine 4 mg and 8 mg compared to placebo in 20 healthy elderly subjects (mean age 72.2 years). Based on primary and secondary endpoints of the Computer Based Objective Cognition Testing (CogState) and the Ray Auditory Verbal Learning Test (RAVLT), fesoterodine did not have a statistically significant effect on cognitive function compared with placebo. However, alprazolam (included as a positive control) demonstrated a statistically significant deterioration in cognitive function compared to placebo for all endpoints.

Another company conducted study was a 24-week study that involved 785 subjects (mean age in the fesoterodine treated group was 72.6 years). It comprised a 12-week, randomised, double-blind, placebo-controlled, parallel-group phase followed by a 12-week open-label phase. Mini-Mental State Examination (MMSE) was performed at baseline and week 12 and there were no clinically significant changes in MMSE score.

A further company conducted study was a 12-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre study that evaluated the efficacy and safety of fesoterodine (flexible dose regimen) in vulnerable elderly patients with overactive bladder (281 subject received fesoterodine, mean age 74.8 years). There was no deterioration of the mean MMSE scores from baseline in either treatment group and no significant difference between the placebo and fesoterodine groups at Week 12.

Wagg and colleagues (2013a) assessed the efficacy and safety of fesoterodine (flexible dose regimen) in elderly adults with overactive bladder. Participants were randomized to fesoterodine or placebo for 12 weeks, those receiving fesoterodine started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8 (sham escalation for placebo). MMSE was completed at baseline and week 12 and no meaningful change was observed in the fesoterodine (0.24 ± 1.76) or placebo (0.23 ± 1.82) group.

Rajabali and colleagues (2024) conducted a four-way randomised crossover study with 1-week treatment and washout periods to reach steady-state drug levels which included 27 older adults (aged 75+) with overactive bladder and mild cognitive impairment. It assessed the cognitive impact of fesoterodine (4 and 8 mg) and oxybutynin (5 mg twice daily) versus placebo. The primary outcome was the effect on Continuity of Attention at 1 and 4 hours post dose. At 1hr post-dose, there was no change in Continuity of Attention compared to placebo in any treatment group. At 4hr post-dose, a non-statistically significant trend toward improvement in Continuity of Attention compared to placebo was observed for fesoterodine 4 mg ($p = 0.0633$) while no differences were observed in the other treatment groups. For working memory, at 4hr post-dose, there was a statistically significant difference favouring improvement ($p = 0.0228$) between placebo and fesoterodine 4 mg not seen with 8 mg. There was no change in MMSE or MoCA score associated with any treatment.

Krebs and colleagues (2018) studied the use of fesoterodine, solifenacin, and darifenacin among cognitively intact patients with neurogenic bladder following spinal cord injuries in a prospective cohort study of 29 individuals (control group 19, anticholinergic group 10). There was no cognitive deterioration in the spinal cord injury patients with anticholinergic treatment based on neuropsychologic testing.

Oxybutynin

Katz and colleagues (1998) conducted a double-blind, placebo-controlled cross-over study in healthy volunteers. Baseline assessment was followed by randomised administration of placebo, oxybutynin (5 and 10mg) and diphenhydramine (5 and 10mg) in test sessions separated by 1 week. Oxybutynin caused significant cognitive decrements in 7 of the 15 cognitive measures and diphenhydramine in 5 of the 15 cognitive measures.

Kay and colleagues (2006) investigated the effects of darifenacin controlled-release and oxybutynin extended-release on cognitive function (NFAT (delayed recall)) in older subjects (≥ 60 years). There was no significant difference between darifenacin and placebo on delayed recall (mean difference, -0.06, p=0.908). In contrast, oxybutynin extended release resulted in memory impairment, with significantly lower scores than placebo and darifenacin (mean differences, -1.30, p=0.011 and -1.24, p=0.022, respectively) for delayed recall on the NFAT at week 3. Oxybutynin was included as a negative control and, unlike darifenacin, this was associated with negative effects on cognition.

The SENIOR study (Wagg and others, 2013b) was a randomized, double-blind, triple-crossover study that assessed the cognitive effects of solifenacin and oxybutynin compared to placebo in 26 elderly participants (≥75 years) with mild cognitive impairment (MCI). Each subject received solifenacin (5 mg once daily), oxybutynin (5 mg twice daily), and placebo over three 21-day treatment periods, with 21-day washouts between them. Cognitive function was evaluated using computerized tests. Neither drug produced significant changes in five composite cognitive outcomes (attention, working and episodic memory, and memory speed). However, secondary analysis revealed that oxybutynin led to reduced power and continuity of attention shortly after dosing.

Wesnes and colleagues (2009) conducted a single-centre, randomised, double-blind, placebo-controlled study in 12 healthy elderly volunteers, with three crossover periods separated by two 14-day washout periods. Each sequence consisted of a single dose of solifenacin 10 mg in one period, oxybutynin immediate release 10 mg in another and placebo in another. Aspects of attention, information processing, working memory, episodic memory and self-rated mood and alertness were tested using the validated Cognitive Drug Research computerised assessment system. Oxybutynin was associated with statistically significant impairment in several measures of cognitive function at a time point corresponding with its probable C(max).

Rajabali and colleagues (2024) showed that steady-state dosing of fesoterodine 4 mg and 8 mg or oxybutynin 5 mg twice daily was not associated with any detectable effect on cognitive function in older adults with mild cognitive impairment and overactive bladder.

Propiverine

A company conducted, randomised, double-blind, placebo-controlled safety study examined the effects of propiverine hydrochloride on psychomotor performance. A total of 32 subjects received either propiverine (15mg twice daily) or placebo for one week. No significant changes could be detected with propiverine on any of 16 psychometric tests, including tests on continuous attention, reaction time, and motor tasks, as compared with placebo. Oelke and colleagues examined the effects of extended release propiverine (30mg daily) on MMSE scores in elderly patients (mean age 75.8 years; range 70-93 years). After 12 weeks of treatment with propiverine no significant change in the MMSE score was observed, even in those who had mild to moderate cognitive impairment at baseline.

Solifenacin

Several short-term studies have examined the effects of solifenacin on cognitive function and these have generally showed minimal or no negative effects (Wesnes and others, 2009; Park and others, 2013; Wagg and others, 2013a; Hampel and others, 2017; Kosilov and others, 2018a and 2018b). The studies by Wesnes and colleagues and Wagg and colleagues included oxybutynin as a comparator and, unlike oxybutynin, solifenacin was not associated with any impairments in attention and memory. Wesnes and colleagues conducted a pilot study that examined the effects of a single dose of solifenacin (10 mg) or oxybutynin (10 mg) on attention and memory. Wagg and colleagues examined the effects of a 21-day course of either oxybutynin (immediate release 5 mg twice daily) or solifenacin (5 mg once daily) on cognition as measured by the Clinical Dementia Rating (CDR) system. Hampel and colleagues examined the effects of a 12-week course of flexible dosing of solifenacin on cognitive function as assessed by MMSE. Cognitive function was unchanged in this study that included older men (mean age 78 ± 6 years) as no change in MMSE scores was apparent at week 12.

Chen and colleagues (2022) examined the effects of mirabegron (50mg daily), solifenacin (5 mg daily) and combined solifenacin and mirabegron in patients with overactive bladder and CNS disorders (cerebrovascular accident, Parkinson’s disease and dementia). There was no significant change in cognitive function (MMSE) at 6 months in any of the treatment groups.

Tolterodine

Kay and colleagues (2006b) conducted a randomised, double-blind crossover study in healthy volunteers. They received tolterodine extended release (4mg daily) during weeks 1-3

(sham titration), followed by washout period and then 3 weeks of oxybutynin extended release (10mg daily week 1, 15mg daily week 2, and 20mg daily week 3). Computerised cognitive function tests were performed at baseline and 3 weeks. There was no significant change in delayed recall (Name-face association test (NFAT) or other outcome measures from baseline to week 3 of tolterodine treatment. With oxybutynin there was delayed recall (NFAT) at week 3 vs. baseline comparable to 20 years of ageing; the individuals had no awareness of changes in memory at any time point.

Diefenbach and colleagues (2008) examined data from two randomized, double-blind, placebo-controlled studies conducted in a cross-over design. Subjective quality of sleep and cognitive function were assessed. A single dose of 4 mg tolterodine or placebo was administered before sleep. Subjective sleep parameters did not show statistically significant changes after tolterodine. Cognitive skills were not affected as evaluated by reaction time (Zahlen-Verbindungs test) and attention (d2 test).

Nagels and colleagues (2004) conducted a randomised, double-blind crossover study in 14 patients with multiple sclerosis. They received oxybutynin immediate release (2.5 mg three times daily) for 8 weeks, followed by tolterodine immediate release (2mg twice daily) for a further 8 weeks. Cognitive function tests included paced auditory serial addition test (PASAT). Tolterodine was associated with a trend to better performance on PASAT than oxybutynin. Alzheimer's disease assessment scale, cognitive subscale (ADAS-Cog) and MMSE did not differ between the treatment periods.

Trospium

Diefenbach and colleagues (2003) conducted a randomised, double-blind, placebo-controlled, crossover study in young healthy volunteers without sleep related problems to determine whether oxybutynin, tolterodine or trospium affect sleep and psychometric test parameters. To evaluate cognitive impairment, the d2 attention test and the Zahlen-Verbindungs reaction time test (ZVT) were performed 1 hour after the administration of each study medication. The ZVT test was used as the primary parameter for cognitive testing and this did not show any significant differences between placebo and the three anticholinergic medicines included (oxybutynin 15mg, tolterodine 4mg, trospium chloride 45 mg). Similarly, the d2 test did not show any significant differences between the different groups. In a similar study, but this time in older healthy volunteers (aged ≥ 50 years), Diefenbach and colleagues (2005) reported that again that the cognitive skills (d2 test, ZVT) of the participants were not affected by the 3 anticholinergics tested (oxybutynin 15mg, tolterodine 4mg, and trospium 45mg) in the study.

Geller and colleagues (2017) conducted a randomised, double-blind, placebo-controlled trial in women aged ≥50 years of age seeking treatment for overactive bladder. Baseline cognitive function was assessed via Hopkins Verbal Learning Test-Revised (HVLT-R), Mini

Mental Status Exam, Mini Mental Status X, Digit Span, Trails A, Trails B, and Epworth Sleepiness Scale. Cognitive function was reassessed at week 1 and week 4. For the primary outcome, there was no difference in HVLT-R total score between trospium and placebo groups at week 4 (P = 0.29). There were also no differences based on the other cognitive tests.

Staskin and colleagues (2010) studied the effect of trospium chloride (60 mg once daily for 10 days) to determine if it is detectable in the CNS of older adults with overactive bladder and to assess whether deterioration of memory occurs (standardised memory tests – Hopkins Verbal Learning Test- Revised and Brief Visuospatial Memory Test-Revised). Trospium chloride was undetectable in cerebrospinal fluid samples and repeat memory testing revealed no significant effect on learning or recall.

Kosilov and colleagues (2018b) examined the effect of 8 weeks treatment with solifenacin plus trospium (high doses), solifenacin plus trospium (usual doses) or placebo on cognitive status. There was no difference in cognitive status between the groups at the beginning or end of the study, nor any significant changes within each group over the study period.

Isik and colleagues (2009) conducted a prospective cohort study in elderly patients with late onset Alzheimer's disease, and showed that use of trospium or galantamine monotherapy, or dual use of galantamine and trospium for 6 months did not have negative effects on cognition based on MMSE.

4.4 Observational Studies examining risk of dementia

Identification of relevant studies

To identify all relevant observational studies for inclusion in this review a literature search was conducted in the following databases (PubMed, Embase, Web of Science, PsycINFO and Scopus) using the following search strategy:

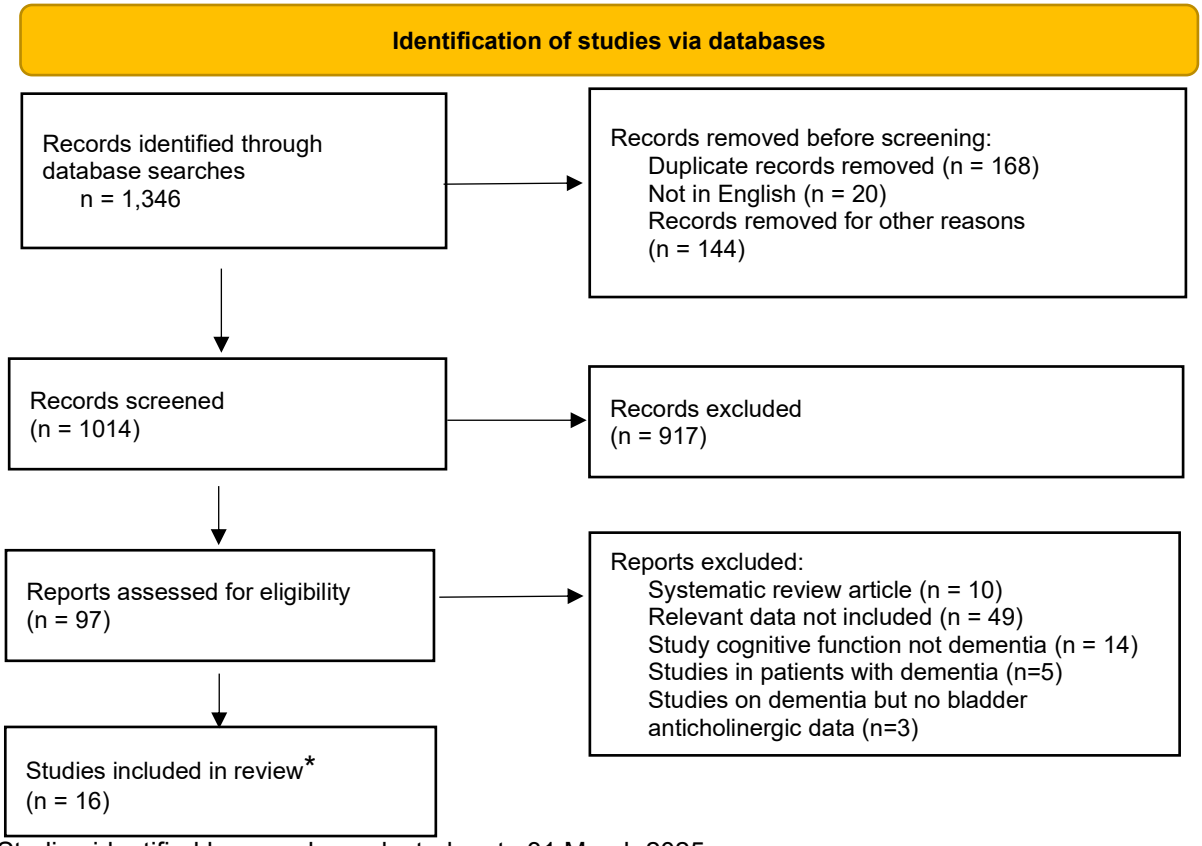
"bladder anticholinergic" OR "bladder cholinergic antagonist" OR "bladder anti-cholinergic" OR "bladder antimuscarinic" OR "bladder muscarinic antagonist" OR "bladder anti-muscarinic" OR darifenacin* OR fesoterodine* OR flavoxate* OR oxybutynin* OR propiverine* OR solifenacin* OR tolterodine* OR trospium*
AND
"cognitive disorder" OR "cognitive impairment" OR "cognitive deficit" OR "cognitive dysfunction" OR "mild cognitive impairment" OR "impaired cognition" OR dementia* OR alzheimer* OR "lewy bod*"

The search strategy covered studies published in English between 1 January 2017 (to capture studies published since the last review) and 31 March 2025.

The PICO-framework (i.e. Participants, Interventions, Comparison, Outcome) was used to determine inclusion and exclusion criteria for this review. Observational studies with the following criteria were included:

> Population: studies in adults aged >=18 years prescribed drugs to treat overactive bladder were included.
>
> Intervention: studies included if they evaluated bladder anticholinergics (darifenacin, fesoterodine, flavoxate, oxybutynin, propiverine, solifenacin, tolteridone, trospium) either as a whole class or individually.
>
> Comparison: studies included if there was a comparator group, which was defined as β-3 agonists (e.g. mirabegron, vibegron) or patients unexposed to any type of overactive bladder drug.
>
> Outcome: outcome of interest was dementia (any type or stage), and studies had to describe how dementia patients were identified in the data source, e.g. through the presence of a dementia diagnosis code and/or prescriptions for drugs used to specifically treat dementia (e.g. acetylcholinesterase inhibitors, memantine hydrochloride).

A total of 1,346 articles were identified by this literature search, 332 were removed before screening and a further 998 were excluded as they did not investigate dementia or they did not meet criteria for inclusion in the review. This left 16 observational studies that are considered to provide information on risk of dementia in association with bladder anticholinergics.



* Studies identified by search conducted up to 31 March 2025.

The MAHs also searched the published literature to identify relevant studies. Their searches either did not identify any additional studies or identified studies that had been considered not to be suitable for inclusion in this review.

Since the literature search was completed (31/03/2025), a further study had been published that met the criteria for inclusion in this review.

Therefore, a total of 17 studies were identified as being suitable for inclusion in this review. There was a roughly equal mix of cohort and case-control studies and these have been conducted across a number of countries including the UK (Richardson and others, 2018; Coupland and others, 2019; Iyen and others, 2024), France (Malcher and others, 2022), Denmark (Pourhadi and others, 2025), US (Barthold and others, 2020; Sheyn and others, 2025), Canada (Welk and others, 2020; Matta and others, 2022; Li and others, 2025), Japan (Okita and others 2023 and 2025), Taiwan (Yang and others, 2017; Wang and others, 2019; Harnod and others, 2021), and Korea (Joung and others, 2019; Park and others, 2024).

Generally, these studies examine the risk in older people (>50 years of age) receiving bladder anticholinergics, however, data for younger age groups are available in some studies (Park and others, 2024; Li and others, 2025; Sheyn and others, 2025).

Assessment of risk of bias in relevant studies – ROBINS-I assessment

Methods

For the studies which fulfilled the PICO criteria, the quality of these studies was independently evaluated by two assessors using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool[1]. The ROBINS-I approach is based on the evaluation of bias in relation to a target trial, which is designed to allow an unbiased unconfounded study of the association without concern over feasibility or ethical considerations.

The aim of the review was to ascertain the effect of assignment to intervention (akin to an intent-to-treat approach) rather than adherence to an intervention, which was assumed as a prescription issued or dispensed as the primary exposure.

The data were synthesised by carrying out a descriptive evaluation of the studies and by summarising the ROBINS-I assessment using tables stratified by study design. No meta-analyses were conducted.

ROBINS-I assessment

Each study was assessed across seven bias domains as presented below (adapted from Sterne and others, 2016). Any adaptations to the tool are also summarised below.

Domain 1 (D1) considers bias arising from confounding, including selection bias, allocation bias and channeling bias. This is explained as ‘baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline. ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline.’

Specific consideration was given to the following confounders as these were considered major potential confounders: i) confounding by anticholinergic burden/exposure to other drugs with anticholinergic effects, ii) unmeasured confounding, iii) channeling bias, and iv) covariate adjustment during the intervention period.

Domain 2 (D2) considers bias arising from intervention classification, including misclassification bias, information bias, recall bias and observer bias. This is explained as bias ‘introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when

[1] https://www.riskofbias.info/welcome/robins-i-v2

misclassification of intervention status is related to the outcome or the risk of the outcome and is likely to lead to bias.'

Protopathic bias arises when a drug is associated with subclinical disease stages, or an early manifestation of the still undiagnosed condition under study which gives rise to the prescription of the treatment. The ROBINS-I tool does not consider protopathic bias in any of the domains, but this was considered one of the major sources of bias in this review. Therefore, modifications to the tool were made with respect to the risk of protopathic bias.

It was considered that in the studies included in this review, protopathic bias can be mitigated at the study design stage by:

1. A requirement of a minimum period of follow-up in cohort studies/exclusion of selected period of follow-up following initial exposure.
2. Excluding a specific period of time prior to the date of diagnosis of the disease outcome (usually termed a lag-time) from the etiologic window in case-control studies.
3. Restricting the comparator group to a population with the same indication (β-3 agonists in this review).

Whilst it was difficult to determine the optimum lag and minimum exposure periods to completely mitigate the risk of protopathic bias, the reviewers agreed pre-specified categories with corresponding ranges from low to serious risk of bias as follows.

- Low risk of bias: lag period or follow-up ≥ 1 year or use of an active comparator.
- Moderate risk of bias: lag period or follow-up > 6 months and < 1 year.
- Serious risk of bias: lag period or follow-up ≤ 6 months or no lag period.

If a study was considered at low risk of protopathic bias, the overall risk of bias for this domain was upgraded to moderate due to the effect of exposure misclassification which was deemed to affect all the studies. If protopathic bias was considered as serious, then the overall risk of bias for this domain was classified as serious.

Domain 3 (D3) considers bias arising from participant selection, including selection bias, inception bias and immortal time bias. This is explained as 'when exclusion of some eligible participants, or the initial follow up time of some participants, or some outcome events, is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical. This form of selection bias is distinct from confounding.'

Domain 4 (D4) considers bias arising from deviation from intended interventions, including performance bias. This bias is explained as arising 'when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s). Depends on the type of effect of interest (assignment to intervention or adherence to intervention).'

Domain 5 (D5) considers bias arising from missing data, including attrition bias and selection bias. This is explained as bias arising 'when later follow-up is missing for individuals initially included and followed (for example differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.'

Domain 6 (D6) considers bias arising from measurement of outcomes, including detection bias, recall bias, information bias, misclassification bias, observer bias, and measurement bias. This bias is explained as 'introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.'

Modifications were made to the ROBINS-I tool for this domain to specifically consider the following sources of potential bias: i) outcome misclassification – prevalent dementia, ii) outcome misclassification – dementia diagnosis, iii) outcome misclassification – undiagnosed dementia, and iv) detection bias using proxy measures of healthcare utilisation.

Domain 7 (D7) considers bias arising from selection of the reported result, including outcome reporting bias and analysis reporting bias. This is explained as 'selective reporting of results in a way that depends on the findings.'

The judgement on the risk of bias was recorded as low, moderate, serious or critical for each of the bias domains:

1) **Low risk of bias**: the study is comparable to a well-performed randomised trial.
2) **Moderate risk of bias**: the study is sound for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.
3) **Serious risk of bias**: the study has important problems.
4) **Critical risk of bias**: the study is too problematic to provide any useful evidence on the effects of intervention.

The overall risk of bias was determined by combining the outcomes from seven domains with priority given to the most serious risk of bias. The final decision on the risk of bias was reached through discussion between the reviewers, with discrepancies in judgement being resolved by consensus.

Results

As can be seen in Tables 2 and 3 below, almost all the observational studies included in this review have been found to be at ‘Serious risk of bias’ meaning that the study has some important limitations and these give rise to a serious risk of bias in the results, which should be interpreted with caution. The exception is the study by Sheyn and colleagues (2025) that is considered to be at ‘Critical risk of bias’, meaning that the study has significant limitations which give rise to a critical risk of bias, such that the result should generally be excluded from the evidence syntheses.

For all the studies the risk of bias in the management of outcomes (D6) is categorised as serious, as it is considered that it is possible that some patients may have been misclassified as non-dementia due to under recording or due to dementia being underdiagnosed. Whilst this is likely to be a non-differential measurement error and so would bias towards the null (i.e. underestimating an effect), it is still sufficient to categorise this domain as serious, which in turn leads to the studies being considered at ‘Serious risk of bias’.

In most studies, with exception of Richardson and colleagues (2018), Welk and colleagues (2020), Okita and colleagues (2025) and Li and colleagues (2025), there are additional domains where the risk of bias has been considered to be serious, these are bias due to confounding (D1), bias in classification of interventions (D2), and bias in selection of participants in the study (D3). The important components that contribute to the categorisation for the separate domains include unmeasured confounding by anticholinergic burden (D1), unmeasured/residual confounding (D1), channeling bias (D1), protopathic bias (D2), exposure misclassification, immortal time bias (D2/3) and prevalent user bias (D3).

Table 2: ROBINS-I V2 – Risk of bias assessment: Cohort studies

Cohort studies	Bias due to confounding	Bias in classification of interventions	Bias due to selection of participants	Bias due to deviations from intended interventions	Bias due to missing data	Bias in management of outcomes	Bias in selection of the reported results	Overall risk of bias
	D1	D2	D3	D4	D5	D6	D7	
Barthold and others 2020	X	X	-	+	+	X	-	X
Joung and others 2019	X	-	+	+	+	X	-	X
Li and others 2025	-	-	+	+	-	X	-	X
Okita and others 2025	-	-	+	+	+	X	-	X
Park and others 2024	X	-	+	+	+	X	-	X
Sheyn and others 2025	X	X	X	+	+	X	-	!
Wang and others 2019	X	-	-	+	+	X	-	X
Welk and others 2020	-	-	+	+	+	X	-	X
Yang and others 2017	X	X	+	+	+	X	-	X

!	Critical
X	Serious
-	Moderate
+	Low

Table 3 ROBINS-I V2 – Risk of bias assessment: Case-control studies

Case-control studies	Bias due to confounding	Bias in classification of interventions	Bias due to selection of participants	Bias due to deviations from intended interventions	Bias due to missing data	Bias in management of outcomes	Bias in selection of the reported results	Overall risk of bias
	D1	D2	D3	D4	D5	D6	D7	
Coupland and others 2019	X	-	-	+	+	X	-	X
Harnod and others 2021	X	-	-	+	+	X	-	X
Iyen and others 2025	X	-	-	+	-	X	-	X
Malcher and others 2022	X	-	-	+	+	X	-	X
Matta and others 2022	X	X	-	+	+	X	-	X
Okita and others 2023	-	X	+	+	+	X	-	X
Pourhadi and others 2025	X	-	+	+	+	X	-	X
Richardson and others 2018	-	-	+	+	+	X	-	X

!	Critical
X	Serious
-	Moderate
+	Low

Further information on the main biases that are considered most likely to affect the studies are provided below.

Confounding

Unmeasured anticholinergic burden

Bladder anticholinergics is only one of the classes of drugs that include anticholinergic medicines. If there is a causal link between use of anticholinergic medicines and the risk of dementia, an individual's anticholinergic burden would influence their risk of dementia and hence it is important that this is adjusted for in analyses. Most of these studies either adjusted for anticholinergic burden (Richardson and others, 2018; Matta and others, 2022; Iyen and others, 2025; Sheyn and others, 2025) or examined use of other classes of medicines that would include anticholinergics, such as antidepressants and antipsychotics (Coupland and others, 2019; Welk and others, 2020; Harnod and others,2021; Malcher and others, 2022; Li and others, 2025; Okita and others, 2023 and 2025). However, in some of the studies (Yang and others, 2017; Wang and others, 2019; Barthold and others, 2020; Pourhadi and others, 2025; Park and others, 2024, and possibly Joung and others, 2019) no attempt has been made to adjust for anticholinergic burden.

Unmeasured or residual confounding

If people who receive a medicine are also more likely to have a particular risk factor, then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This is known as confounding and can affect the results of epidemiological studies. Unmeasured or residual confounding occurs when a risk factor has not been adjusted for or adequately adjusted for in the statistical analysis. The consequence is that the estimated association is not the same as the true effect.

Whilst some risk factors, such as age, sex and genes, cannot be changed, there are behaviours or conditions that individuals can change to influence their risk of developing dementia (modifiable risk factors). The most recent Lancet Commission on Dementia (Livingston and others, 2024) evaluates the available data to look for risk factors with high-quality, consistent, dose respondent, validly measured evidence, which precedes dementia and remain when measured a decade or more before onset. It considers that the following are amongst the most important modifiable risk factors: early life – education (less education associated with increased risk); mid-life hearing loss, hypercholesterolaemia, depression, traumatic brain injury, physical inactivity, diabetes, smoking, hypertension, obesity, excessive alcohol; late life social isolation, air pollution and visual loss. The Lancet Commission highlights that some medical conditions, including stroke (including those

caused by atrial fibrillation) and Parkinson's disease, are causes of dementia rather than risk factors.

For studies where bladder anticholinergic use is compared with non-users, it is important to either limit the possible differences between the groups with regards to risk factors or causes of dementia, including underlying medical conditions and use of medicines, or to adjust for these in the analyses.

In all studies, groups were either matched on age or sex, or these were included as covariates and adjusted for in the analyses. With regards to modifiable risk factors, most of the important risk factors were adjusted for in the analyses. However, there are some risk factors or causes of dementia that have not been adjusted for in all studies, such as stroke (Yang and others, 2017; Okita and others, 2023; Sheyn and others, 2025) and hyperlipidaemia (Okita and others, 2023 and 2025; Park and others, 2024; Sheyn and others, 2025), though other vascular risk factors have been adjusted for in these studies. Additionally, less than half of the studies adjusted for traumatic brain injury.

Only eight of the studies collected information related to lifestyle factors, including body mass index (BMI), smoking status, alcohol consumption. In half of these, the information relied on prescriptions for smoking cessation aids or comorbidities such as alcohol abuse and so may not have been fully captured. Physical activity is not usually captured in electronic healthcare databases and so this was not adjusted for in the analyses for any of the studies. Hearing loss and vision loss were also not included as covariates in any of the studies, but diabetes that may increase the risk of vision loss has been included in almost all studies.

Additionally, only two studies (Coupland and others, 2019; Harnod and others, 2021) included pre-existing cognitive impairment or cognitive decline as a covariate that was adjusted for in the analyses.

Given the moderate increases in effect estimates that have been observed in these studies it cannot be excluded that residual confounding may contribute to the findings that have been reported.

Channeling bias

It is important to consider whether the studies may be subject to channeling bias. This is a form of selection bias where a clinician may be more or less likely to prescribe a treatment based on the patient's characteristics or severity of their illness. Given the concerns that exist about the short-term cognitive effects of bladder anticholinergics and the uncertainty over whether in the longer term they may increase the risk of dementia, it is possible that β-3

agonists, which may be considered less likely to have detrimental effects on cognition, are more likely to be prescribed to patients who are considered at greater cognitive risk. If channeling were to occur in these studies, it may lead to the group prescribed β-3 agonists to include a higher proportion of patients at greater risk of developing dementia compared to the group prescribed bladder anticholinergics. The β-3 agonist group may then end up reporting more dementia outcomes compared to the bladder anticholinergic group, which may be attributed erroneously to drug characteristics rather than underlying patient characteristics causing potential bias in the estimates of treatment effect.

Channeling bias is a possible issue in some of the studies (Matta and others, 2022; Park and others, 2024; Li and others, 2025; Okita and others, 2025; Pourhadi and others,2025). Two of these studies (Park and others, 2024, and Okita and others, 2025) generally report an increased risk of dementia for bladder anticholinergic users compared with β-3 agonist users, whilst the others either do not report any difference in risk between the treatment groups (Matta and others, 2022, and Li and others, 2025) or suggest a lower risk with bladder anticholinergics (Pourhadi and other, 2025).

The results of analyses from the new user cohort in the study by Pourhadi and colleagues (2025) suggest that channeling bias is likely in this study. These analyses reported that the risk of dementia for the bladder anticholinergic class and for some individual bladder anticholinergics (tolterodine and solifenacin but not fesoterodine or trospium) was statistically significantly reduced when compared to mirabegron. Whilst the long-term cognitive safety of mirabegron remains unclear it has not previously been linked to detrimental effects on cognition and hence these results are highly suggestive of the possibility of channeling bias. Li and colleagues (2025) conducted a post-hoc analysis that excluded bladder anticholinergic users who filled their prescription during the 2-year period at the start study (2012-2014). This was conducted to address the potential effect of differential follow-up time and prescribing practices with the inclusion of bladder anticholinergic users prior to introduction of mirabegron; it showed similar results to the main analyses.

Channeling bias may also be an issue in the studies by Welk and colleagues (2020) and Sheyn and colleagues (2025). In the study by Welk and colleagues, the impact of channeling bias is of particular concern for the analyses that compare bladder anticholinergic users to β-3 agonist users. However, this may not be such a concern for the exploratory analyses that examine the risk with individual bladder anticholinergics as these examine whether there is any difference between the risk of dementia in association with oxybutynin (the reference) and other bladder anticholinergics. Sheyn and colleagues compared the risk of dementia in bladder anticholinergic users to that of nonuser controls, they included a β-3 agonist (mirabegron) user group and found that mirabegron also appears to be associated with an increased risk of dementia compared to nonuser controls. Trospium, which due to its physicochemical properties may be considered a low-risk bladder anticholinergic, was

associated with some of the highest risks observed in this study. Hence these finding needs to be interpreted with caution.

Protopathic bias (reverse causation)

Lower urinary tract symptoms have been linked to future dementia incidence. It has been suggested that overactive bladder and incontinence may be a symptom of early neurodegeneration (Sakakibara and others 2014) and that urinary symptoms increase the risk of future dementia by 63%, with divergence of the Kaplan Meier curves over 12 years (Chiang and others, 2015). Protopathic bias (also referred to as reverse causation) can affect epidemiological studies when a medicine is prescribed for symptoms that are an early sign of the onset of the specific illness or condition that is being studied. This creates an artefactual excess of cases in the group with prior use of the medicine and a tendency to overestimate the association between the medicine and the risk of the illness or condition. Therefore, it is important to consider what steps have been taken in these studies to account for protopathic bias, which could result in an overestimation of the association between the use of bladder anticholinergics and the development of dementia. This is particularly important in studies where bladder anticholinergic use is compared to non-use.

Including a requirement for a lag time or a minimum period of follow-up is a way to reduce the risk of protopathic bias; this approach has been taken in the majority of studies in this review. The duration of this lag period in the primary analysis varies across the studies from 3 months (Park and others, 2024) to 5 years (Pourhadi and others, 2025). A 1 to 2-year lag period for the primary analysis is the time period that is most commonly employed (Coupland and others, 2019; Joung and others, 2019; Wang and others, 2019; Barthold and others, 2020; Malcher and others, 2022). There are some studies that employ a longer lag period in the primary analysis (4 years - Richardson and others, 2018; 3 years - Iyen and others, 2025; 5 years - Pourhadi and others, 2025) and/or explore the effect of a longer lag period through supplementary or sensitivity analyses (Wang and others, 2019 - additional analyses looking at 2, 3 and 4 year lag period; Coupland and others, 2019 - additional analysis of 3 and 5 years; Richardson and others, 2018 - additional analysis with lag period of 15-20 years).

The rationale for the lag period that was chosen was not described in many of the studies but where it was discussed the reasons for the chosen period included that it was consistent with that used in previous research or the average time between time between onset of symptoms and dementia diagnosis (1 to 5 years – Coupland and others, 2019).

In the study by Coupland and colleagues, the results of the primary analysis, which employed a 1-year lag period were very similar to the sensitivity analyses that employed 3- and 5-year lag period. In the sensitivity analyses, conducted for anticholinergics as a whole and bladder anticholinergics, the adjusted odds ratios were slightly lower but they still

showed a statistically significant increased risk of dementia that increased with increasing dose. The secondary analyses in the study by Richardson and colleagues examined the longest lag period of up to 15-20 years. For the bladder anticholinergic class, they reported that an increased risk of dementia was observed with exposure that occurred 4-10 years, 10-15 years and 15-20 years before the dementia diagnosis. Similarly, they reported a significantly increased risk of dementia in association with use of anticholinergic antidepressants and antiparkinson drugs, which remained increased even with exposures 15-20 years before dementia diagnosis. However, this was not true for all anticholinergic drug classes included in the review.

Richardson and colleagues have highlighted that to account for their findings urinary incontinence would need to be a substantial risk factor for dementia diagnosed 15-20 years later. Dementia is known to have a long prodromal period, which can begin many years and possibly decades before dementia diagnosis. Therefore, even in this study where additional analyses were conducted that explored the effect of increasing the lag period of up to 15-20 years, the risk of protopathic bias cannot be completely excluded.

Prevalent user bias

For the studies where bladder anticholinergic use is compared with an active comparator, such as β-3 agonists, it is particularly important to understand how confident we can be that those in the active comparator group have not been previously exposed to bladder anticholinergics.

Of the studies included in this review, there are 9 that include new users. These studies generally support an increased risk of dementia in association with use of bladder anticholinergics as a class (Richardson and others, 2018; Joung and others, 2019; Okita and others, 2023; Pourhadi and others, 2025) or individual bladder anticholinergics (Yang and others, 2017; Pourhadi and others, 2025) when compared with non-users. However, when the risk is compared with active comparators the findings are more mixed (Welk and others, 2020; Park and others, 2024; Li and others, 2025; Okita and others, 2025; Pourhadi and others, 2025).

Park and colleagues (2024) excluded patients with prior use of a bladder anticholinergic, and Okita and colleagues (2025) excluded patients if they were insured for less than 6 months before being prescribed a bladder anticholinergic or a β-3 agonist and if they were not diagnosed with overactive bladder before being prescribed a bladder anticholinergic or β-3 agonist. Therefore, for both studies it is assumed that the cohort will comprise new users. Both studies reported an increased risk of dementia in association with the bladder anticholinergic class and also in association with some individual bladder anticholinergics

(fesoterodine, propiverine, and solifenacin). Neither of these studies observed an increased risk with oxybutynin and the authors speculate that this may reflect that it is more often prescribed to patients who are not considered to be at high risk for dementia and so these patients may not be so closely monitored compared with patients who use other bladder anticholinergics, which cannot be adjusted for in the analyses.

Welk and colleagues (2020) excluded patients who used a bladder anticholinergic or β-3 agonist in the 6 months prior to the index date. They observed an increased risk of dementia for the bladder anticholinergic class compared with β-3 agonists, however, there was no difference in risk between individual bladder anticholinergics, but it is of note that oxybutynin was the active comparator in these post-hoc exploratory analyses.

In the study by Li and colleagues (2025), the index date was the date of the first eligible prescription during the study period. Although it is not clear if a washout period was used to identify new users, given the whole population of Ontario has access to a single universal healthcare system is it unlikely the index date was misclassified. In the primary analysis, there was no significant difference in the association between new onset of dementia and the class of overactive bladder medication used and similar results were seen in the post-hoc analyses.

The study by Pourhadi and colleagues (2025) included two cohorts. The primary cohort included the general population and examined the risk of dementia in association with bladder anticholinergics (class and individual drugs) compared with that of non-users. The secondary cohort was a population of new users of overactive bladder drugs and examined the risk of dementia with bladder anticholinergics (class and individual drugs) with that of users of mirabegron. They observed an increased risk for the bladder anticholinergic class and for individual bladder anticholinergics when compared to non-users. However, in the new user cohort the risk of dementia for the bladder anticholinergic class and most of the individual bladder anticholinergics was significantly lower than that for the mirabegron group.

Bias in the management of outcomes

Outcome misclassification – undiagnosed dementia

Undiagnosed dementia was considered a serious source of bias across all studies. It is widely acknowledged that the prevalence of dementia in electronic healthcare record data is under-recorded due to undiagnosed and unrecorded cases of dementia. This bias is likely to be non-differential and would tend to bias effect estimates towards the null. Methods to investigate this type of bias include the use of quantitative bias analysis (QBA) as sensitivity analyses to evaluate the effect on risk estimates, but none of the studies used such methods and were thus considered at serious risk of bias.

Detection bias

Detection bias occurs when differences in how outcomes are identified or recorded may affect results, potentially leading to misleading conclusions. This may occur in studies where use of bladder anticholinergics in patients with overactive bladder is compared to non-use; because receiving a medicine may increase the likelihood of individuals going to see the doctor and increasing the likelihood of dementia being identified and bias the effect estimates away from the null. This bias may also be an issue in the studies which include an active comparator (β-3 agonist), particularly if healthcare professionals and prescribers are aware of the emerging evidence of an association between anticholinergics (including bladder anticholinergics) and risk of dementia. This in turn may result in them monitoring patients more closely for this outcome, subsequently increasing the likelihood of diagnosing dementia in patients prescribed bladder anticholinergics and would bias the effect estimates away from the null. Whilst this is often not well captured in studies, some of the studies (Richardson and others, 2018; Wang and others, 2019; Barthold and others, 2020; Welk and others 2020; Matta and others, 2022; Okita and others, 2023 and 2025) have included number of physician visits or outpatient visits as one of the covariates. which have been adjusted for in the analyses. This approach is unlikely to fully mitigate this risk, and it is unclear if these covariates are a good enough proxy for potential detection bias, which may still be an issue particularly given the accumulating evidence over time suggesting that an increased risk of dementia may be associated with use of anticholinergic medicines. However, it is possible these studies may not be at such a high risk of this bias compared to the others.

Outcome misclassification (dementia diagnosis)

This is a type of measurement error that can bias epidemiologic studies of healthcare outcomes. It can occur if outcomes are missed, which suggests the approach to identifying cases of the outcome may not be sensitive enough. It can also occur if outcomes are incorrectly diagnosed, which suggests the approach may not be specific enough to correctly identify cases.

The different approaches to identifying dementia cases that have been used in the studies may increase the likelihood of cases either being missed or incorrectly diagnosed.

Some studies relied only on International Classification of Diseases codes (ICD codes) to identify dementia cases and did not include the prescription claims for anti-dementia drugs as an additional criterion, which could be used to identify cases of dementia (Yang and others, 2017; Wang and others, 2019; Barthold and others, 2020; Harnod and others, 2021; Okita and others, 2023 and 2025). This may have led to some cases being missed; however, this is likely to be non-differential between the groups and so would likely bias the risk estimates towards the null.

Of the remaining studies, Joung and colleagues (2019) took the approach of identifying a dementia diagnosis based on ICD codes plus the prescription of dementia drugs, which may increase the specificity of the diagnosis. The other studies identified dementia cases using ICD codes and/or prescription of dementia drugs. Diagnosing dementia on ICD codes or dementia drug prescriptions should increase the sensitivity to detect potential cases of dementia and reduce the likelihood of missing cases. Whilst requiring both ICD codes and prescriptions for dementia drugs may increase the likelihood of those cases that are identified as dementia cases being true cases of dementia. However, this is based on several assumptions and a way to understand how likely an approach is to identify true cases is to use one that has previously been validated for use within the database in which the study is being conducted. The three Canadian studies (Welk and others, 2020; Matta and others, 2022; Li and others, 2025) appear to have used the same validated algorithm to detect dementia (Jaakkimainen and others, 2016). This is based on hospital admission ICD-10 codes, ≥2 physician billing claims for dementia, or a new prescription of a cholinesterase medication or two or more visits within 6 months to community health care with ICD-10 code for dementia. It is stated that this definition has a sensitivity of 79%, specificity of 99%, positive predictive value of 80%, and negative predictive value of 99% compared to medical chart diagnoses of dementia.

Of note, Sheyn and colleagues (2025) conducted their study in TriNetX and a publication that looked at the applications, advantages and pitfalls of this database state that ‘One of the most significant limitations is the accuracy and completeness of its data, as not all participating organizations employ standardized methods of data collection and entry’ (Hackl and others, 2024). Therefore, validity of dementia diagnosis could be an issue in this study.

Inclusion of prevalent dementia

Including patients with pre-existing dementia is a concern in the study by Park and colleagues (2024) as patients were excluded if dementia was diagnosed 90 days prior to the bladder anticholinergic initiation. This may not be sufficiently long enough to exclude all patients with pre-existing dementia and so there may be a risk of prevalent dementia patients included in the cohort. This would bias the effect estimates towards the null.

Key findings of relevant studies

Findings for bladder anticholinergics as a class

Of the 17 studies that met the criteria for inclusion in this review, 15 provide information on the risk of dementia in association with use of bladder anticholinergics as a class (Richardson and others, 2018; Coupland and others, 2019; Joung and others, 2019; Wang and others, 2019; Barthold and others, 2020; Welk and others, 2020; Harnod and others, 2021; Malcher and others, 2022; Matta and others, 2022; Okita and others, 2023 and 2025; Iyen and others, 2024; Park and others, 2024; Li and others, 2025; Pourhadi and others, 2025). Nine of these studies compare the risk of dementia in association with bladder anticholinergics to that of non-users and 7 studies compare the risk of dementia to that of users of an active comparator. The study by Pourhadi and colleagues compared use of bladder anticholinergics with non-users in a primary cohort, and use of bladder anticholinergics with an active comparator, mirabegron, in a secondary cohort, hence is included in both the study counts stated above.

Studies with non-user controls

The nine studies that evaluated the risk of dementia in association with bladder anticholinergics as a class included three studies conducted in the UK. These studies used UK data from the Clinical Practice Research Datalink (Richardson and others 2018; Iyen and others, 2024) and the Q Research database (Coupland and others, 2019). These UK studies broadly report consistent findings and suggest that compared with non-users, patients who received bladder anticholinergics had an approximately 1.2-1.6-fold statistically significantly increased risk of developing dementia and that this is a dose-dependent risk.

Similar findings were seen with the other studies which explored data from Taiwan (Wang and others, 2019; Harnod and others, 2021), Korea (Joung and others, 2019; Okita and others, 2023), France (Malcher and others, 2022) and Denmark (Pourhadi and others, 2025). The reported magnitudes of effect were broadly consistent with those seen in the UK studies. Where dose effect was studied (Wang and others, 2019; Harnod and others, 2021; Malcher and others, 2022; Okita and others, 2023; Pourhadi and others, 2025), the findings were generally supportive of a dose-dependent risk.

It is notable that the effect estimates reported in the study by Harnod and colleagues (2021), which examined the risk of dementia in patients aged ≥ 55 years of age who were exposed to bladder anticholinergics for 1 year or more, were considerably greater than those observed in other studies. They observed that the risk of dementia was increased 2.46-fold in those who had used bladder anticholinergics for 1 year or more and that the risk proportionally increased with increasing dosage in patients taking bladder anticholinergics for less than 4 years (adjusted odds ratios increasing from 2.23 for ≤207 total standardised daily doses to 12.8 for >3271 total standardised daily doses) but longer duration of exposure

did not appear to show a dose-dependent risk. What is striking in this study is that in the analyses conducted it is often observed that compared with the crude odds ratio the adjusted odds ratio moved away from the null (overall bladder anticholinergic use crude odds ratio 1.17 (95% CI 1.08-1.26), adjusted odds ratio 2.46 (95% CI 2.22-2.73)); this direction of confounding is not observed in other studies and the reason for this difference is unclear.

The most pertinent results from these studies are presented in Table 4 below (adjusted analyses presented where possible) and further details of the findings of these studies are provided in Annex 1

Table 4: Key results from studies examining risk with bladder anticholinergic class versus non-use control

Study	Results	Additional Analyses
Richardson and others 2018 Case-control (UK)	**1.23** (95% CI 1.18-1.28) Exposure period (years before index date) 4-10 years **1.23** (95% CI 1.18-1.29) 10- 15 years **1.22** (95% CI 1.13-1.32) 15-20 years **1.27** (95% CI 1.09-1.48)	New user analysis **1.22** (95% CI 1.16-1.28)
Coupland and others 2019 Case-control (UK)	Exposure period 1 to 11 years before index date 1-90 TSDDs **1.19** (95% CI 1.13-1.26) 91-365 TSDDs **1.35** (95% CI 1.27-1.45) 366-1095 TSDDs **1.65** (95% CI 1.53-1.78) >1095 TSDDs **1.65** (95% CI 1.56-1.75)	Exposure period 3- to 13 years 1-90 TSDDs **1.18** (95% CI 1.11-1.26) 91-365 TSDDs **1.33** (95% CI 1.22-1.44) 366-1095 TSDDs **1.55** (95% CI 1.41-1.70) >1095 TSDDs **1.57** (95% CI 1.46-1.69) Exposure period 5- to 20 years 1-90 TSDDs 1.06 (95% CI 0.91-1.23) 91-365 TSDDs **1.35** (95% CI 1.12-1.63) 366-1095 TSDDs **1.48** (95% CI 1.20-1.83) >1095 TSDDs **1.55** (95% CI 1.29-1.86)
Joung and others 2019 Cohort (Korea)	0-2 doses/year 1.0 (reference) ≥3 doses/year **1.31** (95% CI 1.24-1.38)	
Wang and others 2019 Cohort (Taiwan)	Excluding diagnosis within 1 year <28 cDDD 1.0 (reference) 28-34 cDDD 0.88 (95% CI 0.73-1.06) 85-336 cDDD 1.15 (95% CI 0.97-1.37) ≥337 cDDD **1.40** (95% CI 1.12-1.75)	Sensitivity analyses excluding diagnosis within 2 years 28-34 cDDD 1.00 (95% CI 0.82-1.22) 85-336 cDDD **1.30** (95% CI 1.07-1.59) ≥337 cDDD **1.69** (95% CI 1.33-2.15) 3 years 28-34 cDDD 1.06 (95% CI 0.86-1.31) 85-336 cDDD **1.33** (95% CI 1.07-1.65) ≥337 cDDD **1.77** (95% CI 1.39-2.26) 4 years 28-34 cDDD 1.15 (95% CI 0.92-1.43) 85-336 cDDD **1.36** (95% CI 1.08-1.71) ≥337 cDDD **1.88** (95% CI 1.44-2.46)

Harnod and others 2021 Case-control (China)	Any exposure **2.46** (95% CI 2.22-2.73) Exposure 1 to <4 years before index date ≤207 TSDDs **2.23** (95% CI 1.12-4.44) 207-3271 TSDDs 2.35 (95% CI 0.87-6.32) >3271 TSDDS **12.8** (95% CI 5.15-32.1)	Exposure 4 to 7 years before index date ≤207 TSDDs **2.82** (95% CI 1.68-4.75) 207-3271 TSDDs **2.23** (95% CI 1.10-4.53) >3271 TSDDS 1.90 (95% CI 0.94-3.81 Exposure > 7 years before index date ≤207 TSDDs 1.07 (95% CI 0.89-1.29) 207-3271 TSDDs **1.19** (95% CI 1.00-1.41) >3271 TSDDS 1.03 (95% CI 0.87-1.23)
Malcher and others 2022 Case-control (France)	Any use **1.23** (95% CI 1.10-1.37) 1-90 cDDD 1.07 (95% CI 0.91-1.25) 91-365 cDDD **1.29** (95% CI 1.05-1.58) >365 cDDD **1.48** (95% CI 1.22-1.80)	
Okita and others 2023 Case-control (Japan)	1-30 **1.29** (95% CI 1.21-1.38) >30 **1.47** (95% CI 1.40-1.55)	
Pourhadi and others 2025 Case-control (Denmark)	5 year lag period Ever use **1.44** (95% CI 1.40-1.48) 1-90 DDDs **1.31** (95% CI 1.27-1.36) 91-365 DDDs **1.53** (95% CI 1.44-1.61) >365 DDDs **1.68** (95% CI 1.59-1.76) User status Current user **2.18** (95% CI 2.11-2.25) Recent user **1.57** (95% CI 1.51-1.63) Past user **1.24** (95% CI 1.20-1.28)	No lag period Ever use **1.61** (95% CI 1.58-1.65) 1-90 DDDs **1.37** (95% CI 1.33-1.41) 91-365 DDDs **1.66** (95% CI 1.60-1.73) >365 DDDs **1.99** (95% CI 1.92-2.06)
Iyen and others 2024 Case-control (UK)	**1.18** (95% CI 1.16 to 1.20)	

Key: Effect estimates that are emboldened are those found to be statistically significantly different.
TSDDs – total standardised daily doses, DDDs – daily defined doses, cDDDs – cumulative daily defined doses,

Studies including active comparator

Of the studies that evaluated bladder anticholinergics as a class, about one half (7 out of 15) examined the risk of dementia in patients exposed to bladder anticholinergics compared with those who used an active comparator. The active comparator in the studies was a β-3 agonist, mainly mirabegron but there was one study (Okita and others, 2025) that examined the risk compared with use of mirabegron or vibegron. Another study (Barthold and others, 2020), compared the risk of dementia between users of different types of bladder anticholinergics: M3-selective (darifenacin, solifenacin) versus non-selective (fesoterodine, flavoxate, oxybutynin, tolterodine, trospium) bladder anticholinergics.

In these 7 studies the findings are more mixed. Three of the studies (Welk and others, 2020; Park and others, 2024; Okita and others, 2025) suggest an approximately 1.2-fold increased risk of dementia in bladder anticholinergic users compared with use of β-3 agonists. Other studies, either do not support an increased risk of dementia in association with the use of bladder anticholinergics compared with the use of a β-3 agonist, mirabegron (Li and others, 2025; Pourhadi and others, 2025) or do not suggest a differential risk of dementia between M-3 selective and non-selective bladder anticholinergics (Barthold and others, 2020). Of note, one of the studies (Matta and others, 2022) did not observe an increased risk of dementia in association with the bladder anticholinergic class in the primary analysis (overactive bladder drug dispensed in the 180 day period prior to the index date) but an increased risk of around 1.3-fold was reported in a sensitivity analysis (overactive drug exposure in the 181-365 day period prior to the index date).

The most pertinent results from these studies are presented in Table 5 below (adjusted analyses presented where possible) and further details of the findings of these studies are presented at Annex 2.

Table 5: Key results from studies examining risk with bladder anticholinergic class versus active-comparator control

Study	Results	Comparator
Welk and others 2020 Cohort (Canada)	**1.23** (95% CI 1.12-1.35) primary analysis **1.20** (95% CI 1.06-1.35) secondary analysis (≥3 months continuous use)	β-3 agonist (mirabegron)
Barthold and others 2020 Cohort (US)	Primary analysis 1-364 TSDDs 0.97 (95% CI 0.89-1.04) 365-729 TSDDs 0.94 (95% CI 0.83-1.06) 730-1094 TSDDs 1.00 (95% CI 0.87-1.16) >1094 TSDDs 1.03 (95% CI 0.88-1.20) Sensitivity analyses - patients who used only NSL or M3S 1-364 TSDDs 0.96 (95% CI 0.91-1.02) 365-729 TSDDs 0.97 (95% CI 0.89-1.06) 730-1094 TSDDs 1.02 (95% CI 0.91-1.14) >1094 TSDDs 1.04 (95% CI 0.92-1.17)	Non-selective bladder anticholinergics (NSL) (fesoterodine, flavoxate, oxybutynin, tolterodine, trospium) compared with M-3 selective bladder anticholinergics (M3S) (darifenacin, solifenacin)
Matta and others 2022 Case-control (Canada)	1.12 (95% CI 0.98-1.27)	β-3 agonist (mirabegron)
Park and others 2024 Cohort (Korea)	Buffer period 3 months Bladder anticholinergics alone **1.213** (95% CI 1.195-1.232) Bladder anticholinergics combination **1.345** (95% CI 1.323-1.366) Buffer period 1 year Bladder anticholinergics alone **1.186** (95% CI 1.164-1.209) Bladder anticholinergics combination **1.346** (95% CI 1.320-1.372)	β-3 agonist (mirabegron)
Okita and others 2025 Cohort (Japan)	Adjusted model **1.22** (95% CI 1.15-1.30 (all) **1.20** (95% CI 1.11-1.29) (excludes those with <6 months follow-up) **1.09** (95% CI 1.03-115) (ITT analysis) IPTW model* Sensitivity analysis – excludes those with <6 months follow-up **1.19** (95% CI 1.11-1.28) (all) **1.21** (95% CI 1.12-1.30) (excludes those with <6 months follow-up) **1.09** (95% CI 1.03-1.15) (ITT analysis)	β-3 agonists (mirabegron and vibegron)

Pourhadi and others 2025 Case-control (Denmark)	No lag period Ever use **0.82** (95% CI 0.74-0.91) Cumulative use 1-90 DDDs **0.72** (95% CI 0.62-0.82) 91-365 DDDs **0.84** (95% CI 0.72-0.78) >365 DDDs 1.00 (95% CI 0.85-1.18) 2 year lag period Ever use 0.85 (95% CI 0.74-0.98) Cumulative use 1-90 DDDs **0.82** (95% CI 0.69-0.98) 91-365 DDDs **0.74** (95% CI 0.59-0.92) >365 DDDs 1.10 (95% CI 0.88-1.38)	β-3 agonist (mirabegron)
Li and others 2025 Cohort (Canada)	0.99 (95% CI 0.86-1.15) primary analysis post-hoc analysis 1 – cohort restricted to oldest 50th percentile of age 1.08 (95% CI 0.93-1.25) post-hoc analysis 2 – excluded overactive bladder users from 2012 to 2014 0.87 (95% CI 0.73-1.04)	β-3 agonist (mirabegron)

Key: Effect estimates that are emboldened are those found to be statistically significantly different.
* Cox proportional hazards model in the propensity-weighted sample
Abbreviations: TSDDs – total standardised daily doses, DDDs- daily defined doses, IPTW – Inverse Probability of Treatment Weighting, ITT – Intention to Treat

Findings for individual Bladder Anticholinergics

As well as providing information on the risk of dementia associated with use of the class of bladder anticholinergics, nine of the studies also provide information on the risk of dementia associated with individual bladder anticholinergics. For the individual bladder anticholinergics, data are most commonly available for solifenacin (9 studies), tolterodine (8 studies), oxybutynin (8 studies), fesoterodine (7 studies) and trospium (7 studies). Whilst fewer studies (3 studies each) provide data for darifenacin, flavoxate and propiverine.

The studies include those that compare the risk for bladder anticholinergic users with non-users (Yang and others, 2017; Malcher and others, 2022; Pourhadi and others, 2025) and those that that compare the risk with an active comparator (Welk and others, 2020 (limited data); Matta and others, 2022; Park and others, 2024; Okita and others, 2025; Pourhadi and others, 2025). In two studies (Iyen and others, 2024; Sheyn and others, 2025) the comparator was non-use, however, these also included mirabegron as a separate group (i.e. not as a comparator group).

The most pertinent results are presented in Tables 6 and 7 in Annex 3 (adjusted analyses have been presented where possible).

Solifenacin is the most studied individual bladder anticholinergic (9 studies). Generally, the available data report an increased risk of dementia of approximately 1.3-fold in association with its use compared with either no use or use of a β3 agonist and there are some data to suggest a dose-response relationship. The exceptions are the studies by Welk and colleagues (2020) and Pourhadi and colleagues (2025 - new user cohort). Oxybutynin was used as the reference by Welk and colleagues and therefore this study does not exclude the possibility of an increased risk in association with solifenacin but rather that there is no differential risk between the bladder anticholinergics studied (oxybutynin, solifenacin and tolterodine). In the study by Pourhadi and colleagues, there was an increased risk of dementia when solifenacin use was compared to no use. However, the risk of dementia with solifenacin was statistically significantly lower than that for the β3 agonist, mirabegron. Given that mirabegron use is not known to be associated with adverse effects on cognition following short-term use and is often considered more cognitively safe than bladder anticholinergics, it appears likely that study is subject to channeling bias. If patients considered at greater risk for dementia have been preferentially prescribed mirabegron, the statistically significantly lower risk of dementia observed with solifenacin, and also tolterodine, needs to be interpreted with caution.

Whilst the effect estimates generally support an approximately 1.3-fold increased risk of dementia in association with the use of solifenacin, the studies by Yang and colleagues (2017) and Sheyn and colleagues (2025) report higher effect estimates of 2.2-fold and 1.7-fold. The increased effect estimates seen in these studies seem to apply to most of the

bladder anticholinergics included and not just solifenacin. Both studies appear to be at substantial risk of protopathic bias, which would lead to an overestimation of risk. Given the competing biases that exist in these studies, it is unclear that this would necessarily explain the higher effect estimates observed. In both studies, but particularly the study by Yang and colleagues, only limited covariates were adjusted for in the analyses, and it is possible that these findings are heavily confounded. It is also of note that in the study by Sheyn and colleagues the confidence intervals were wider suggesting less precision in the effect estimates, which may reflect that the analyses conducted for the individual bladder anticholinergics had low numbers in the subgroups.

Eight of the studies provide information on the risk of dementia with tolterodine or oxybutynin. These data support an increased risk of dementia in association with their use compared with non-users and some data suggest a dose-response relationship. However, when tolterodine or oxybutynin use is compared with an active comparator, most of the studies do not suggest an increased risk of dementia in association with their use (Matta and others, 2022; Okita and others, 2025; Pourhadi and others, 2025). The exception is the study by Park and colleagues (2024) that reports an increased risk of approximately 1.2-fold in association with tolterodine monotherapy use compared with β3 agonist use but no increased risk was observed with oxybutynin monotherapy. The authors state that this might be due to the well-known harmful effects of oxybutynin on cognition, which may have led to this being less likely to be prescribed to patients at risk of dementia. Where the risk of dementia in association with tolterodine is compared with that of oxybutynin (Welk and others, 2020 - exploratory post-hoc analysis), the data do not support a differential risk. It is of note that in some of the studies where no increased risk of dementia was seen in association with oxybutynin or tolterodine the number of exposures for these bladder anticholinergics was amongst the lowest and this may reflect limited power to detect differences. This cannot be said of the study by Matta and colleagues (2022) where numbers in both the oxybutynin and tolterodine groups were greater than for solifenacin. The primary analysis (in patients prescribed a bladder anticholinergic in the 180 days prior to diagnosis), reported an increased risk for solifenacin and darifenacin but not for the other bladder anticholinergics. In this study, however, a further sensitivity analysis was conducted where drug exposure was adjusted to include the 181-365 day prior to the index date. This introduction of a lag period resulted in a stronger association than for the primary analyses and reported a statistically significant increased risk of dementia with darifenacin, fesoterodine, solifenacin and tolterodine but the observed increased risk with oxybutynin just failed to reach statistical significance. This is an unexpected result and the reason for this is unclear, but it is of note that exposure period in this study is very short (6 months) and it questionable whether it is likely that dementia would develop following such short-term exposure.

The findings were more mixed for fesoterodine (7 studies). Most of the studies do not report an increased risk of dementia with fesoterodine, however, in many of the studies where no

increased risk was seen, the fesoterodine groups were amongst those with the smaller number of exposures. Hence the findings of these studies may reflect the more limited power to examine the risk with fesoterodine. An increased risk of dementia in association with fesoterodine use was reported in one out of four studies that compared fesoterodine use with non-use (Pourhadi and others, 2025) but in this study when the risk with fesoterodine was compared with a β3 agonist there was no statistically significant difference in the risk of dementia between the groups. Both Park and colleagues (2024) and Okita and colleagues (2025) reported statistically significant increased risk of dementia for fesoterodine compared with a β3 agonist. Neither of these studies reported an increased risk of dementia in association with oxybutynin, which Okita and colleagues (2025) consider may reflect that Japanese clinical guidelines recommend caution when using oxybutynin due to its high risk of cognitive impairment. Hence for both studies there is a concern that patients with cognitive impairment are possibly being channelled to other bladder anticholinergics or a β-3 agonist and the findings should be interpreted with caution. Overall, the available studies do not consistently support an increased risk of dementia in association with fesoterodine.

Data are available from 7 studies with regards to use of trospium. Mixed findings were reported from the four studies where non-use was the comparator. Malcher and colleagues (2022) did not observe an increased risk, however, an increased risk was observed by Pourhadi and colleagues (2025) and in some but not all dose categories or age groups in the other studies (Iyen and others, 2024; Sheyn and others, 2025, respectively). The three studies that compared the use of trospium with a β3 agonist do not suggest an increased risk of dementia in association with the use of trospium. However, in two of the studies (Matta and others, 2022; Pourhadi and others, 2025) there were very few dementia cases in the trospium group (50-60) and where the trospium cohort size was larger (Park and others, 2024, n=10,695) it was still among the smaller cohort sizes and the increased effect estimate just failed to reach statistical significance, suggesting that these results might reflect more limited power to evaluate the effects of trospium in these studies. Additionally, there is a risk of channeling bias in some studies (Park and others, 2024; Sheyn and others, 2025). Overall, the available studies do not suggest an increased risk of dementia in association with trospium.

The information that is available for darifenacin, flavoxate and propiverine is more limited and only available from three studies. For flavoxate, only the study by Iyen and colleagues (2024) reported an increased risk in association with flavoxate use compared with non-use and that was only observed in the highest dose category (>1095 total standardised daily doses); the other studies compared risk with non-use and showed no increased risk of dementia (Malcher and others, 2022) or compared risk with a β3 agonist and showed a reduced risk of dementia (Park and others, 2024). Neither propiverine or darifenacin were associated with an increased risk of dementia at any dose group in the study by Iyen and colleagues (2024) but numbers of exposures for both bladder anticholinergics were amongst the lowest. Also, the study did not incorporate a washout period prior to first prescription of a

bladder anticholinergic, so it is likely to include prevalent users. In the other studies, propiverine was associated with an increased risk of dementia when compared to a β3 agonist (Park and others, 2024; Okita and others, 2025) and darifenacin was associated with an increased risk compared with non-use (Sheyn and others, 2025; certain age groups) or a β3 agonist (Matta and others, 2022).

Factors that may affect the risk

Bladder Anticholinergic Dose

The possibility of a dose-response relationship was explored in 10 of the studies (Richardson and others, 2018; Coupland and others, 2019; Wang and others, 2019; Barthold and others, 2020; Harnod and others, 2021; Malcher and others, 2022; Okita and others, 2023; Iyen and others, 2024; Park and others, 2024; Pourhadi and others, 2025).

Generally, the available studies support a dose-dependent risk of dementia in association with the use of the class of bladder anticholinergics. Where information is provided on the dose effects for the individual bladder anticholinergics, the studies suggest that use of solifenacin and oxybutynin and possibly tolterodine may be associated with a dose-dependent risk of dementia but such an effect is not seen for the other bladder anticholinergics. However, the lack of dose-effect for some individual bladder anticholinergics may simply reflect the lack of power due to the lower number of individuals included in the dose groups, especially at the higher doses, or the biases that may be at play in these studies.

Analyses from some studies (Richardson and others, 2018; Coupland and others, 2019; Pourhadi and others, 2025), which compare the risk of dementia in association with bladder anticholinergics to that of non-users, suggest that the dose-dependent increased risk of dementia in association with any anticholinergic or the class of bladder anticholinergics starts to become apparent even after low dose/shorter term use (up to 90 total standardised daily doses) and increases with increasing dose and duration. Similarly, Iyen and colleagues (2024) reported that for some individual bladder anticholinergics (oxybutynin, solifenacin and tolterodine) even low dose/short-term use (up to 90 total standardised daily doses) is associated with an increased risk of dementia compared with use of a β-3 agonist. In other studies (Wang and others, 2019; Harnod and others, 2021), the increased risk is only observed in the higher dose/longer duration categories. It seems that the inclusion of prevalent users is likely in the studies by Coupland and colleagues (2019) and Iyen and colleagues (2024). So, in the low dose category group in these studies there is the possibility that there is a longer exposure to bladder anticholinergics that is not captured in the patients' current primary care record, and this may in part explain the results observed. Richardson

and colleagues (2018) have also commented that this may be an issue in their study, but the methodology used in this study of including a 1-year washout period prior to the drug exposure period, suggests that this would be less of an issue than for the other studies.

Patient age

Most of the studies have examined the risk in older subjects: ≥50 years of age (Wang and others, 2019), ≥ 55 years of age (Coupland and others, 2019; Harnod and others, 2021; Iyen and others, 2024), ≥ 60 years of age (Joung and others, 2019; Malcher and others, 2022; Pourhadi and others, 2025), ≥ 65 years of age (Richardson and others, 2018; Barthold and others, 2020; Matta and others, 2022; Okita and others, 2025). For a couple of studies, the inclusion criteria for age were unclear (Yang and others, 2017: mean age 62 years after matching; Welk and others, 2020: median age around 73). However, some of the more recent studies have included younger age groups. Park and colleagues (2024) conducted a large cohort study using Korean National Health Insurance Service data and the information presented suggests that 31% of the study cohort are under the age of 50. While the study by Sheyn and colleagues (2025) included adults of all ages (≥18 years) and the study by Li and colleagues (2025) included patients aged ≥18 and <65 years of age.

The subgroup analyses conducted in many of these studies examined the risk in the <80 years and ≥80 years of age. Generally, the studies support an interaction with age and report a greater risk of dementia in the younger versus the older age groups studied. A possible explanation is that this is due to selective survival of the most resistant subjects at an advanced age and these “survivors” could be more resistant to the effect of a risk factor. Another explanation is that physicians are more likely to search for contraindications to these treatments in older patients, such as the presence of a preexisting cognitive disorder or risk factors for acute confusional syndrome. Therefore, those with a higher risk of dementia would be less frequently prescribed a bladder anticholinergic, thus reducing the association in this subgroup compared to younger subjects. Other explanations include that medications with adverse effects on cognitive functions may have a greater impact on the expression of Alzheimer’s disease phenotypes in young-old subjects, as they may be less affected than old-old subjects by age itself and underlying diseases. In a study of longitudinal rates of change as a function of baseline age for Alzheimer’s Disease individuals (Vermunt and others, 2019), the rate of decline in Alzheimer’s Disease decreased with age. The possibility of a shorter prodromal period and fewer potential comorbidities and medications in the younger age groups may in part explain the results observed and may support a causal association.

Matta and colleagues (2022) were the only ones to observe an increased risk of dementia in the older age group (>80 years of age) and not in the other age group (≤80 years) but this was only observed for some bladder anticholinergics (solifenacin, fesoterodine, oxybutynin and tolterodine) and not others; the differences did not appear to be statistically significant.

The investigators considered that this may be due to the increased sensitivity of the cognitive effects of bladder anticholinergics in this age group due to metabolic and biological factors. They also comment that it may be due to competing effects, with the cognitive effects of less selective bladder anticholinergics (oxybutynin) versus the prescribers' preference for more selective agents in cognitively susceptible individuals.

Patient Sex

Some studies have suggested that the risk factors for progression from mild cognitive impairment to dementia are different between men and women, and that anticholinergic medications may have differential effects on visual memory, executive function and verbal retrieval (Artero and others 2008, Carriere and others, 2009). Therefore, it is important to understand whether the data suggest differences between the sexes with regards to the association between bladder anticholinergic use and the risk of dementia.

Subgroup analyses that stratified on sex have been conducted in many of these studies (Yang and others, 2017; Coupland and others, 2019; Wang and others, 2019; Barthold and others, 2020; Welk and others, 2020; Malcher and others, 2022; Matta and others, 2022; Iyen and others, 2024; Okita and others, 2025; Sheyn and others, 2025). They do not suggest differences between the sexes in the risk of developing dementia following exposure to bladder anticholinergics, or where differences were reported there was no consistent pattern.

Dementia type

Dementia type has only been examined by Coupland and colleagues (2019) and their analyses suggest that there may be a stronger association with use of bladder anticholinergics and vascular dementia than Alzheimer disease for cumulative use of anticholinergic medicines and for some individual drug classes, including bladder anticholinergics. The investigators comment that this raises questions about whether the potential mechanisms may include vascular and inflammatory changes as well as the more obvious mechanism of chronic cholinergic depletion. However, this is only one study, and it would be important to replicate these findings in other studies.

Individual Bladder Anticholinergic Drug Substances

Differences in ability to cross the blood brain barrier and penetrate the CNS, along with their affinity for the muscarinic receptors expressed in the brain, may partially explain the differences in effects on cognitive function observed amongst bladder anticholinergics. If interference with the normal functioning of the cholinergic system is the only mechanism by which bladder anticholinergics are considered to possibly increase the risk of dementia this would support non-selective bladder anticholinergics, which readily cross the blood brain barrier and have the potential to accumulate in the brain, such as oxybutynin, to be expected

to be associated with the greatest risk. However, this does not appear to be born out in the results of the available studies, which show that solifenacin is the one where the data most consistently support an increased risk of dementia in association with its use compared with either non-use or use of an active comparator. For oxybutynin and tolterodine, whilst the data showed an increased risk of dementia in association with their use compared with no use, the findings are more mixed when the use of oxybutynin or tolterodine are compared with an active comparator. The findings for the other bladder anticholinergics are more mixed and do not consistently support an increased risk (fesoterodine and trospium) or there are more limited data (darifenacin, flavoxate and propiverine).

Whilst the pharmacokinetic and pharmacodynamic properties of oxybutynin suggest that this might be expected to be associated with the highest risk of dementia, both tolterodine and solifenacin are able to cross the blood brain barrier and as they are not substrates for the p-glycoprotein efflux transporter they may accumulate in the brain. As solifenacin is a M-3 selective bladder anticholinergic it may be expected to be less likely to be associated with an increased risk of dementia than non-selective bladder anticholinergics like oxybutynin or tolterodine. However, radioligand receptor binding assays (Ohtake and others, 2007) suggest that although solifenacin is considered to be a M3 selective bladder anticholinergic (along with darifenacin) its relative affinity for the M3 receptor compared with other receptor subtypes is not as great as that of darifenacin. The study also suggests that were solifenacin to cross the blood brain and accumulate in the brain it would exert effects at the M1, M2 and M4 receptor subtypes, which are the receptors that are more commonly expressed in the brain and are considered more likely to be related to any adverse cognitive effects of anticholinergic medicines

When comparing the differences in effects observed in the studies it is important to consider whether the findings reflect true differences in risk or may reflect differences in design and conduct of the studies and or power to detect increases in risk. The studies by Matta and colleagues (2022), Park and colleagues (2024), and Okita and colleagues (2025) do not report an increased risk of dementia in association with oxybutynin but do report increased risk with other bladder anticholinergic substances, however, it is possible this may reflect channeling bias rather than genuine differences in risk between bladder anticholinergic substances. For the bladder anticholinergics where the findings are more mixed (fesoterodine and trospium) in the studies where no increased risk was observed the numbers of exposures in these groups were relatively low, and so there may be insufficient power in these groups to detect differences in risk. For other bladder anticholinergics (darifenacin, flavoxate and propiverine), they are only included in a very small number of studies and sometimes with only low number of exposures. Therefore, the data do not allow us to confidently conclude that there is a differential risk between the individual bladder anticholinergics. Furthermore, where studies have directly compared the risk between bladder anticholinergics (Bartold and others, 2020; Welk and others, 2020) the findings do not report differential risks. Welk and colleagues (2020) conducted post-hoc exploratory

analyses, which did not report any difference in the risk of dementia when use of solifenacin or tolterodine was compared with that of oxybutynin. Barthold and colleagues (2020) also did not observe any difference in the risk of dementia in association with the use of non-selective bladder anticholinergics compared with M-3 selective bladder anticholinergics, but in this study some patients may have used both non-selective bladder anticholinergics and M-3 selective bladder anticholinergics, which may obscure any differences.

5. Discussion and Conclusions

The risk of cognitive impairment during bladder anticholinergic therapy for overactive bladder is an important concern, particularly for vulnerable populations such as the elderly (a substantial proportion of the overactive bladder population) and those with comorbid conditions that may impair CNS function (frequently associated with overactive bladder).

Differences in physicochemical properties of the bladder anticholinergics may contribute to the likelihood of them having effects on cognition. In particular, differing abilities to penetrate the blood–brain barrier and accumulate in the brain, and affinities for the muscarinic receptors in the brain. Amongst the anticholinergic agents, oxybutynin, which is a non-selective bladder anticholinergic, that readily crosses the blood brain barrier and has the potential to accumulate in the brain, may be expected to be associated with the greatest risk of cognitive impairment.

Studies that examine the effects of short-term treatment with bladder anticholinergics (generally not exceeding 3 months) provide consistent and convincing evidence of cognitive impairment in association with oxybutynin and this is reflected in the product information for prescribers and patients. Where data are available for the other bladder anticholinergics it suggests that for most short-term treatment has no or minimal effect on cognitive function. For some bladder anticholinergics, namely solifenacin and trospium there are studies that have evaluated slightly longer-term treatment (up to 6 months) and again these do not suggest any detrimental effects on cognition.

Whilst the biological basis for the cognitive effects of anticholinergic medicines is not known, it is assumed that direct impairment of cholinergic neurons may underlie the effects with downregulation of cholinergic neurons, reduced neurotrophic support and increased oxidative stress and inflammatory cytokines, contributing to neurodegeneration. Atrophy of the cholinergic system in the basal forebrain has been observed in the early stages of Alzheimer's disease and a reduction in the quantity of cholinergic receptors and impaired acetylcholine binding within the hippocampus has been documented in Alzheimer's disease patients. Animal studies have also suggested that anticholinergics may enhance the pathology of Alzheimer’s disease and lead to changes in brain structure. However, this has not translated reliably to effects in humans (neuropathologic features and neuroimaging) where the data are less clear.

Although there may be some biological plausibility supporting the potential for bladder anticholinergics to lead to detrimental effects on cognitive function, it remains unclear whether they are associated with long-term detrimental effects on cognitive function or an increased risk of dementia. Using the ROBINS-I tool, the quality of the 17 observational studies, which met the criteria for inclusion in the review, was critically and independently evaluated by two epidemiological assessors. This has concluded that all of these studies are

either at serious or critical risk of bias, which means that the results should be interpreted with caution (serious risk) or the results should generally be excluded from the further evaluation (critical risk, study by Sheyn and others, 2025).

For some studies they are only categorised as being at serious risk of bias due to one domain (domain 6 - bias in management of outcomes; Richardson and others, 2018; Welk and others, 2020; Li and others, 2025; Okita and others, 2025). The concerns related to bias in the management of outcomes in these studies are two fold. The first relates to detection bias as prescribers may be aware that some anticholinergics may increase the risk of dementia and due to this may more closely monitor or screen patients receiving bladder anticholinergics compared with patients receiving other overactive bladder drugs or non-users. To address this two of these studies (Richardson and others, 2018; Okita and others, 2025) included number of physician visits or outpatient visits as one of the covariates that were adjusted for in the analyses; this will reduce but not fully mitigate this bias, as it is unclear how well these variables address this bias. The second is misclassification of the outcome (undiagnosed or misdiagnosed dementia) and here the use of a validated dementia algorithm in two of the studies will have helped to reduce the risk of bias related to misdiagnosed dementia (Welk and others, 2020; Li and others, 2025). However, undiagnosed dementia is considered a serious source of bias across all studies. It is widely acknowledged that the prevalence of dementia in electronic healthcare record data is under-recorded due to undiagnosed and unrecorded cases of dementia. This would likely underestimate the effect estimates.

In most of the studies with only one domain classified as serious, use of bladder anticholinergics as a class was associated with a statistically significant increased risk of dementia of about 1.2-fold compared with non-use (Richardson and others, 2018) or compared with β-3 agonists (Welk and others, 2020; Okita and others, 2025). The exception is the study by Li and colleagues (2025) which did not report an increased risk for the bladder anticholinergic class compared with mirabegron. In these studies, where risk for individual bladder anticholinergics is reported the findings are either not consistent with that seen in other studies (Okita and others, 2025 – increased risk for fesoterodine, propiverine and solifenacin but not oxybutynin or tolterodine) or do not suggest any differential risk between bladder anticholinergics (Welk and others, 2020 – oxybutynin vs solifenacin or tolterodine). Although bias in the management of outcomes is the domain that has been categorised as serious for these studies it is considered that most of these studies (Welk and others, 2020; Li and others, 2025; Okita and others, 2025) may also be at risk of channeling bias that may have influenced the results. Therefore, even though these studies suffer from potentially fewer limitations compared with the others included in the review, they still have important limitations that need to be factored into the interpretation of the findings. Of note, for all the studies in this review and the associated biases identified in the ROBINS-I, it is important to consider the direction of biases i.e. whether a particular bias will overestimate or

underestimate an association with risk of dementia, when interpreting the results of the studies.

Although all the studies included in this review are, based on the ROBINS-I tool, considered to be at serious or critical risk of bias, it is unclear that if additional studies were to be conducted that their methodology and statistical analyses would necessarily be able to address the concerns and limitations of previous studies to the extent that this would allow their risk of bias to be considered to be lower. The nature of dementia means that conducting prospective studies where cognitive function (and other variables) is assessed at baseline and patients are actively followed up for development of dementia is highly unlikely, especially given the prolonged duration of follow-up that would be needed. Therefore, any further studies that would be conducted would rely on electronic healthcare records and suffer from many of the limitations that have been seen with the existing studies. Hence the data that are currently available may be the best data that we will have to inform the need for regulatory action and therefore the findings need to be carefully considered.

Considering the findings from all the observational studies included in this review, the available data suggest that compared with non-users patients who receive bladder anticholinergics (either at class level or at individual substance level) are at an approximately 1.2-1.3-fold increased risk of developing dementia and this risk may be dose-dependent. For studies including non-user controls it is important to understand the extent to which the risk of protopathic bias has been mitigated. Many of the studies have attempted reduce the risk of protopathic bias by including a lag period (i.e. exclusion of exposure for a defined period prior to diagnosis) or a minimum duration of follow-up, but mostly this lag period (either in the primary analysis or additional sensitivity analyses) does not go beyond 5 years. Ordinarily this would be considered a long lag period, however, the prodromal symptoms of dementia can start many years and possibly a decade or more prior to the diagnosis of dementia. The only study that included lag periods beyond 5 years was the study by Richardson and colleagues (2018) in which the primary analysis included a lag period of 4 years and sensitivity analyses included lag periods of up to 15-20 years. In this study the primary analysis showed a statistically significant increased risk of dementia with bladder anticholinergics, which was dose-dependent. Similar findings were reported in the sensitivity analyses. They also examined the risk of dementia in association with other anticholinergic drug classes. If anticholinergic medicines increase the risk of dementia by direct impairment of cholinergic neurons, then one would expect an increased risk to be observed for all classes, but this was not the case. Richardson and colleagues (2018) reported an increased risk of dementia in association with anticholinergic antidepressants, antiparkinson medicines and bladder anticholinergics but not with other classes included (antihistamines, antipsychotics and antispasmodics). Similar findings were observed by Coupland and colleagues (2019) who reported a dose-dependent risk of dementia in association with some classes (antidepressants, antiparkinson, antipsychotics, bladder anticholinergics) but not others (antiarrhythmics, antihistamines, antimuscarinic bronchodilators, gastrointestinal

antispasmodics, and skeletal muscle relaxants). The observed increased risks for only certain anticholinergic classes (antidepressants, antiparkinson and bladder anticholinergics) raises questions over whether protopathic bias may still be contributing to the findings observed in these studies.

Including a control group that is receiving another overactive bladder medicine is another way to try to reduce the risk of protopathic bias and to limit the likelihood of major differences in characteristics between the groups. The β-3 agonist, mirabegron, is most often used as the active comparator in these studies as, based on shorter term studies (up to 6 months) that do not suggest it has adverse effects on cognitive function, it may be considered to have low cognitive risk. The studies that compare bladder anticholinergic use to an active comparator (either at class level or at individual substance level) report more mixed findings (Barthold and others, 2020; Welk and others, 2020; Matta and others, 2022; Park and others, 2024; Li and others, 2025; Okita and others, 2025; Pourhadi and others, 2025). Of these, four studies support an increased risk of dementia in association of bladder anticholinergics (either class or individual bladder anticholinergics) of around 1.2-fold and the remaining studies show either no difference in risk of dementia between bladder anticholinergics and the active comparator or suggest a lower risk for bladder anticholinergics (Pourhadi and others, 2025). However, almost all these studies are at possible risk of channeling bias, which may influence the findings. The exception is the study by Barthold and others (2020), which did not suggest an increased risk of dementia in association with bladder anticholinergics, however, this was considered at possible risk of prevalent user bias. Therefore, the findings of these studies need to be interpreted with caution and whilst they may not provide convincing data to suggest an increased risk of dementia for bladder anticholinergics compared with other overactive bladder medicines, equally they do not exclude the possibility of an increased risk of dementia for bladder anticholinergics.

Across all the studies there are important risk factors that may either not have been included or not been fully accounted for in the statistical analyses and the possibility of residual confounding may also, in part, explain the results observed. None of the studies have been able to adjust for anticholinergic burden that may result from use of over-the-counter products. Other covariates such as lifestyle factors (BMI, alcohol consumption and smoking status) are often poorly recorded in databases and so may not have been fully adjusted for. Cognitive impairment was not adjusted for in the analyses in most of the studies as only two studies included it as a covariate. Therefore, residual confounding may still be an issue in these studies.

Based on the physicochemical properties of bladder anticholinergics it might be expected that the available studies would suggest that oxybutynin is associated with the greatest risk of dementia followed by tolterodine and solifenacin. However, this is not born out in the findings from the studies where solifenacin is the bladder anticholinergic for which the data

most consistently support an increased risk of dementia. If there are other mechanism(s) that contribute to the risk of dementia in association with bladder anticholinergics this might explain this finding, however the alternative mechanisms that have been suggested do not provide a clear explanation for solifenacin to be associated with the greatest risk. The findings may also reflect differences in the design and methodology of the studies and possible bias and confounding that they are subject to. Given the concerns that exist about the cognitive effects of oxybutynin it is possible that patients who are considered at greater baseline risk of developing dementia are being preferentially prescribed other bladder anticholinergics or other overactive bladder medicines. Channeling bias, rather than true differences in risk between individual bladder anticholinergics, appears likely to be influencing the findings in the studies by Matta and colleagues (2022), Park and colleagues (2024), and Okita and colleagues (2025), where other bladder anticholinergics but not oxybutynin are associated with an increased risk of dementia. The differences in observed risks between individual bladder anticholinergics may also reflect the small number of exposures in some of the individual bladder anticholinergic groups resulting in insufficient power to detect differences. Therefore, the available studies do not allow us to conclude with any confidence that there are clear differences in the risk between individual bladder anticholinergics. Especially as the studies that do compare risk within the bladder anticholinergic class (Barthold and others, 2020; Welk and others, 2020) do not suggest differences between individual bladder anticholinergics (oxybutynin vs solifenacin or tolterodine) or between M-3 selective bladder anticholinergics (darifenacin, solifenacin) or non-selective bladder anticholinergics (fesoterodine, flavoxate, oxybutynin, tolterodine, and trospium).

Overall, the available studies support an association between use of bladder anticholinergics and dementia but given the limitations of the available studies and risk of bias (especially protopathic bias, channeling bias and undiagnosed/unrecorded dementia), the available data do not allow us to conclude with any certainty that the association is a causal one or that there are clear differences in risk for the individual bladder anticholinergics. Furthermore, the small effect sizes reported in these studies (mainly 1.2-1.3-fold increased risk) suggest that if the studies are subject to residual confounding this may, in part, also explain the observed increased risk of dementia with bladder anticholinergics.

6. CHM advice

The CHM considered a review of the available data examining the risk of dementia in association with anticholinergic medicines used to treat overactive bladder at its meeting on the 28th November 2025. The review evaluated the available data, including information on possible mechanisms, clinical studies examining the short-term effects of these medicines on cognitive function, adverse drug reaction reports submitted through the Yellow Card Scheme and observational studies that have examined whether use of these medicines was associated with an increased risk of dementia.

The CHM heard feedback from discussions of this topic at the Pharmacovigilance Expert Advisory Group (PEAG) from the chair of this group.

The CHM noted that in recent years a growing number of observational studies had been published, which provided further evidence on the risk of dementia in association with bladder anticholinergics (either as a class or for individual bladder anticholinergics). A total of 17 studies were identified for inclusion in the review. The studies comparing non-users to those who used bladder anticholinergics suggest an approximately 1.3-fold increased risk of developing dementia in association with bladder anticholinergics, which may be dose-dependent. Whilst studies that compare patients receiving bladder anticholinergics to those receiving another treatment for overactive bladder report more mixed findings, with some reporting an increased risk of dementia and others showing no difference in risk or suggesting a lower risk for bladder anticholinergics.

The CHM noted that the quality of the observational studies was evaluated using an adapted ROBINS-I framework, which is commonly used in the systematic reviews of non-randomised or observational studies. Using this approach, all 17 observational studies were found to be at serious or critical risk of bias and consequently their results should be interpreted with caution. The CHM agreed that there were important sources of bias in these studies, including protopathic bias, channeling bias and bias in the management of outcomes (undiagnosed or misdiagnosed dementia), which may have influenced the results and in part explain the differences observed. Furthermore, the possibility of residual confounding exists, particularly since no or very few studies have adjusted for over-the-counter use of other anticholinergics, lifestyle factors (such as BMI, smoking and alcohol consumption) and baseline cognitive impairment.

The CHM considered that any future studies, which will probably rely on electronic healthcare record data, are likely to suffer from similar limitations to those identified in the review. It was commented that a better understanding of the potential mechanisms and the identification of valid biomarkers, such as peripheral blood biomarkers, may help inform the link between anticholinergic medicines, including bladder anticholinergics, and the risk of dementia. However, it was recognised that any such studies would need to be large, longer-

term studies and be expensive to conduct. Consequently, it was important to consider the strengths and limitations of the currently available data and whether this supports a causal association. It was discussed that it is biologically plausible that anticholinergics, including bladder anticholinergics, may lead to detrimental effects on cognition due to impairment of cholinergic neurons. However, where other classes of anticholinergics were included in the studies these are not consistently associated with an increased risk of dementia, and the increased risks tend to be observed with the anticholinergic classes that are more likely to be used to treat some prodromal symptoms of dementia. Furthermore, the findings for the review with regards to the risk of dementia in association with individual bladder anticholinergic drug substances are not in line with that which would be expected based on their physicochemical properties. Therefore, either other mechanisms are involved and/or the methodology, biases and confounding of the studies may explain the differences observed.

Overall, the CHM concluded that whilst the studies suggest an association between use of bladder anticholinergics and a risk of dementia, due the complexities of the data and the limitations of these studies including the risk of bias and confounding that exist, there remained considerable uncertainty as to whether there is a causal link. Nor do the data allow us to conclude that there are clear differences in risk of dementia for the individual bladder anticholinergic drug substances. Nevertheless, given the known risk associated with use of anticholinergics medicines, it was highlighted that it remains important that prescribers aim to reduce patients' anticholinergic burden wherever possible.

The CHM considered that regulatory action to update the marketing authorisations for the bladder anticholinergics was not warranted at this time. They did, however, recommend that the findings and conclusions of this review are communicated through a public assessment report and that there should be engagement with patient groups to ensure that the key messages of this report are clear and effectively communicated.

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8. Glossary of terms

Acetylcholine
Acetylcholine is a chemical messenger (also known as a neurotransmitter) that plays an important role in involuntary muscle movements and other bodily functions. It is also involved in brain functions such as learning, memory, and attention.

Active comparator group
An active comparator refers to an existing treatment or intervention that is used as a reference point to evaluate the efficacy and safety of a new investigational product or treatment.

Alzheimer's disease
Alzheimer's disease is the most common cause of dementia. It is a physical illness where changes occur in the brain that are different to the changes seen with normal ageing. These changes include the build-up of two proteins, called amyloid and tau. These proteins damage brain cells over time and eventually cause dementia, affecting memory and thinking.

Anticholinergic drug/medicine
Anticholinergic drugs/medicines are substances that block the action of the acetylcholine, a chemical messenger in the nervous system that affects involuntary muscle movements and other functions. They are used to treat various conditions including urinary incontinence and overactive bladder.

Antimuscarinics
Antimuscarinics are a class of drugs or agents that blocks the action of the chemical messenger acetylcholine by binding to receptors known as muscarinic. They are also known as anticholinergics drugs.

Bias/biases
Bias in research refers to errors that can occur during the design, conduct, or interpretation of a study. It can have a significant impact on the completeness and accuracy of the findings of the study.

Bladder antimuscarinic
These are antimuscarinic drugs that are commonly used to treat overactive bladder by blocking antimuscarinic receptors in the bladder wall, which helps reduce the urge to urinate and the frequency of urination.

Blood brain barrier
The blood brain barrier is a tightly packed layer of cells that acts to regulates the passage of substances between the bloodstream and the brain. It acts to protect the brain from harmful substances while allowing essential nutrients to pass through.

Case-control study
A case-control study is a type of observational study in which a group of individuals with a specific condition (cases) are compared to those without the condition (controls). The main goal of this type of study is to determine whether certain exposures or characteristics are

more common in the case group compared to the control group, to identify potential risk factors.

Central nervous system
The central nervous system (CNS) is made up of the brain, spinal cord, and neurons. It controls how you think, feel, and respond to the world around you.

Channeling bias
Channeling bias may occur when drugs/medicines used to treat the same disease or condition may be more or less likely to be prescribed to a patient due to the patient's characteristics or severity of their illness. The known benefits or risks of drugs/medicines may also influence the treatment given to a patient resulting in a drug being more likely to be prescribed to someone suffering from a disease or medical condition. This results in the disease outcome being incorrectly attributed to the use of the drug/medicine.

Charlson Comorbidity Index
This is a medical tool that is used to predict mortality rates for patients based on the number and seriousness of various concurrent medical conditions they may have (comorbidities) such as heart disease, cancer and diabetes. The higher the score, the higher the risk of mortality (death). Researchers and clinicians commonly used this a scoring system to help inform their decisions around patient care and/or clinical outcomes.

Cholinergic receptors
Cholinergic receptors are proteins in cell membranes that are activated when they bind the chemical messenger, acetylcholine. There are two main types of cholinergic receptors, called muscarinic and nicotinic receptors – named after the drugs that work on them.

Clinical data or clinical studies
Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

Clinical Practice Research Datalink (CPRD)
The CPRD primary care database contains anonymised computerised longitudinal records of patients registered with contributing primary care practices across the UK. CPRD contains patient registration information, and all care events that general practice staff record. This includes demographic information, medical diagnoses, and prescriptions issued in primary care.
The CPRD GOLD database contains data from UK primary care practices using Vision® general practice patient management software.

Cognitive abilities
Intellectual or thinking skills.

Cohort study
In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Comorbidity/Comorbidities
Comorbidity means more than one disease or condition is present in the same person at the same time. Conditions described as comorbidities are often chronic or long-term conditions.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Contra-indicated/Contraindication
When a drug should not be used in a specific situation, condition or group of people because it may be harmful to the person.

Control group
The control group is defined as the group in an experiment or study that does not receive the substance, drug, treatment that is being tested and is used by the researchers as a benchmark to measure how the other tested subjects do.

Cystitis
Inflammation of the bladder, often caused by a urinary tract infection (UTI), leading to symptoms like painful urination and frequent urges to urinate.

Dysuria
Pain or a burning sensation when urinating.

Efficacy
In medicine, efficacy refers to the ability of a medicinal product or a treatment to provide a beneficial effect.

Epidemiological studies
Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

Hazard ratio (HR)
Hazard ratio (HR) is a measure of an effect of an intervention on an outcome of interest over time. Hazard ratio is reported most in time-to-event analysis or survival analysis (i.e. when we are interested in knowing how long it takes for a particular event/outcome to occur). A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and value less than 1 suggests a decreased risk. An adjusted hazard ratio is a measure of the effect that has taken into account other factors that may affect the relationship.

Healthcare databases
Healthcare databases are systems into which healthcare providers routinely enter clinical and laboratory data during usual practice as a record of the patient's care.

ICD-10
The International Classification of Diseases, Tenth Revision (ICD-10) is a system used by physicians to classify and code all diagnoses, symptoms and procedures.

Immortal time bias
Immortal time bias is a type of bias that occurs in observational studies, it can occur when a study is designed so that the follow-up includes a period of time where participants in the exposed group cannot experience the outcome and are essentially 'immortal'. This may lead to distorted associations between the exposure and the outcome and result in an artificially low event rate.

Incidence/Incidence rate
The occurrence of new cases of a disease or condition in a population over a specified time period.

Indication
The disease or condition, or manifestation or symptoms, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

In-vitro study
An experiment or study, usually involving cells or tissues, which is conducted outside of a living organism in a controlled environment, such as a test tube or laboratory dish.

In-vivo study
A medical test, experiment or procedure that is done on (or in) a living organism, such as a laboratory animal or human.

Lipophilicity
Lipophilicity, often described as the "fat-loving" characteristic of a compound, indicates a drug's affinity for lipid environments and affects how well a drug can cross biological membranes, which are primarily composed of lipid bilayers.

Marketing authorisation holder
The company or other legal entity that has the authorisation to market a medicine in the UK.

Median
The median is an average that is found by listing the values in order and finding the middle value.

Meta-analysis
A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

Molecular size
The physical dimensions of the drug molecule, which is crucial for understanding its behaviour in the body. Smaller molecules can diffuse more quickly and have better solubility, while larger molecules face challenges in penetrating biological barriers.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Neurogenic bladder
Neurogenic bladder is a condition that causes loss of bladder function. It is usually caused by disease or by damage to your nervous system. Neurogenic bladder may cause urinary incontinence (trouble controlling urination) or urinary retention (trouble urinating).

Neurotransmitter
A chemical messenger that plays a role in transmitting signals between nerve cells (neurons) or between other cell types, such as muscle cells or gland cells. Neurotransmitters play a key role in bodily functions such as muscle movement, mood regulation and memory.

Neurons
Specialised nerve cells that receive, process and send electrical and chemical signals to communicate with each other in the brain and nervous system.

Nocturia
The need to wake up more than once during the night to urinate. It is a common condition, especially among older adults.

Non-clinical studies
In drug development, preclinical development, also named non-clinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected.

Odds ratio (OR)
A measure of risk (effect) for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than 1 suggests a decreased risk. An adjusted odds ratio is a measure of the effect that has taken into account other factors that may affect the relationship.

Overactive bladder
Overactive bladder is a very common condition where the bladder squeezes (contracts) suddenly without the person having control and when the bladder is not full. Symptoms of overactive bladder include an urgent feeling that you need to go to the toilet, needing to pass urine frequently and sometimes leaking urine before you can get to the toilet.

Patient Information Leaflet
Medicine packs include a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics

(SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Peripheral nervous system
The peripheral nervous system is system of nerves outside of the brain and spinal cord. It is responsible for relaying essential messages to and from the brain and spinal cord. These messages include those that allow you to move your muscles as well as ones that your brain uses to control vital, unconscious processes like your heartbeat and breathing.

Pharmacodynamics
The study of how drugs interact with the body to produce therapeutic effects. This includes how they interact with specific proteins on or inside cells called receptors.

Pharmacokinetics
Pharmacokinetics is the study of how medicines/drugs move into, through and out of the body. There are four main parameters, which are absorption (how the drug gets from the administration site to the place of action), distribution (how the drug travels via the bloodstream to different parts of body), metabolism (the process by which the drug breaks down), and excretion (the process by which the drug is removed from the body).

Pharmacovigilance Expert Advisory Group
The Pharmacovigilance Expert Advisory Group advises the Commission on Human Medicines (CHM) on all aspects of pharmacovigilance for human medicines (including herbal products) and vaccines. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
This includes advising the CHM on the public health importance of potential new safety signals; the confirmation of identified risks and their size and nature; how the risks should be managed including healthcare professional, patient and public communications.

Physicochemical properties
These relate to the physical or chemical properties of a drug/medicine that influence its absorption, distribution, metabolism, and excretion and in turn influence its overall therapeutic efficacy. These properties include lipophilicity, molecular size, polarity and solubility.

Polarity
The polarity of a drug refers to the distribution of electrical charge within its molecular structure, which affects its solubility in water-based body fluids and its ability to cross lipid-rich cell membranes.

Prevalence
The proportion of individuals in a defined population that have a disease or other health outcomes of interest at either a specified point in time (known as point prevalence) or during a specified period of time (period prevalence).

Prodromal
The prodromal stage of a disease is the period during which some early signs and non-specific symptoms start to appear. These early signs and symptoms indicate the beginning

of any disease, but the disease may not be diagnosed until more specific symptoms of the disease appear.

Prospective study
A prospective study asks a specific study question (usually about how a particular exposure affects an outcome), recruits appropriate participants, and looks at the exposures and outcomes of interest in these people over the following months or years.

Prostatitis
Prostatitis is inflammation of the prostate, which is a small gland found below the bladder in men.

Protopathic bias
Protopathic bias (also referred to as reverse causation) can affect epidemiological studies when a medicine is prescribed for symptoms that are an early sign of the onset of the specific illness or condition that is being studied. This creates an artefactual excess of cases in the group with prior use of the medicine and a tendency to overestimate the association between the medicine and the risk of the illness or condition.

p-value (p)
A measure of the statistical probability of an event occurring by chance. A smaller p-value suggests the event is less likely to be due to chance; a larger p-value suggests the event is more likely to have occurred by random chance.

Residual confounding
Residual confounding occurs when a risk factor has not been adequately adjusted for in the statistical analysis. The consequence is that the estimated association is not the same as the true effect.

Retrospective study
A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

Risk factor
A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Risk Ratio/Relative Risk (RR)
A risk ratio (RR), also called relative risk, is a measure of effect and compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than 1 suggests a decreased risk. An adjusted risk ratio/relative risk is a measure of the effect that has taken into account other factors that may affect the relationship.

Sensitivity analysis/analyses
Sensitivity analysis is a way to test how changing one or more factors in a model affects the outcome.

Standard deviation (SD)
A measure of the amount of variation of a set of values. A low standard deviation indicates that the values tend to be close to the mean (the average) of the set, while a high standard deviation indicates that the values are spread out over a wider range.

Statistical analysis
Statistical analysis is the collection and interpretation of data to uncover patterns and trends.

Statistical significance
A statistical interpretation of data that indicates that a result is unlikely to have occurred by chance.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Suspected adverse drug reactions
Also known as side effects. All medicines or vaccines can cause adverse reactions in some people. Adverse drug reactions reported to the MHRA are looked at and used to assess the balance of risks and benefits of medicines and vaccines.

Urethritis
Urethritis is when the tube that carries urine from the bladder out of the body (urethra) becomes swollen and sore.

Urinary frequency
Urinary frequency refers to the need to urinate more often than is usual, which can disrupt daily activities and may indicate an underlying health issue.

Urinary incontinence
This is a loss of bladder control, which means you sometimes urinate unintentionally. There may also be increased urgency to urinate, leading to increased frequency of urination.

Urinary urgency
When you suddenly need to go to the toilet. If you do not, urine may leak.

Vesical supra-pubic pain
This is a type of pain that occurs in the lower central region of the abdomen, specifically above the pubic bone. It is caused by various conditions including urinary tract infections and bladder conditions.

Yellow Card scheme
The MHRA's scheme for healthcare professionals and members of the public to report suspected adverse reactions of a medicine or vaccine, as well as medical devices and other products.

9. Annexes

Annex 1 –Bladder Anticholinergics class: Studies with a non-use control

Studies conducted in UK

Richardson and colleagues (2018) conducted a nested case-control study in CPRD to estimate the association between chronic anticholinergic drug use and future dementia incidence and to also explore whether any observed effect was specific to a particular drug class. Patients were aged 65-99 years with a recorded diagnosis of dementia (Read codes for dementia as diagnosis, symptom or referral or a prescription for a cognitive enhancer if a code for a diagnosis of dementia was recorded within 12 months) made between April 2006 and July 2015. At least 6 years of data before a diagnosis was required to allow for a 4-year delay before a diagnosis of dementia. In addition, at least one year of drug exposure period was required as well as data for one year before drug exposure period to ascertain covariates. Each case was matched to a maximum of seven controls on sex, year of birth (within three years), years of up to standard data history, and area level deprivation. Secondary prespecified analyses included: disaggregation of exposure by drug class; testing the effect of exposure 4-10, 10-15, and 15-20 years before the index date. The median drug exposure period was 7.1 years (interquartile range 4.1-11.3, range 1-16). When analysed by class, there was a significant association between dementia incidence and any prescription of antidepressant, antiparkinson, or bladder anticholinergics with an anticholinergic burden score of 3, but no association with antispasmodic, antipsychotic, antihistamine, or other drugs with an anticholinergic burden score of 3. The bladder anticholinergics included in this study, which represented more than 1% of the prescription within anticholinergic burden 3 group were oxybutynin, tolterodine and solifenacin accounting for 7%, 7% and 1% of prescriptions, respectively. Associations with prescriptions for drugs with an anticholinergic burden score of 3, including bladder anticholinergics, were consistent across the drug exposure period, with a significantly increased risk of dementia with bladder anticholinergics also being observed for exposure 15-20 years before dementia diagnosis. Associations with drugs with an anticholinergic burden score or 1 and 2 were more apparent closer to the index date. The authors also conducted sensitivity analyses that examined the association in new users (excluding patients with a prescription for a drug with anticholinergic burden score of 2 or 3 in the 12 months before the drug exposure period) and this analysis also showed that bladder anticholinergics with an anticholinergic burden score of 3 were associated with an increased risk of dementia.

Iyen and colleagues (2024) conducted a nested case-control study in CPRD GOLD and examined the risk of dementia in patients aged ≥55 years who received bladder

anticholinergics during the period January 2006 and February 2022. Each case was matched with up to five controls, by age, sex, general practice, and calendar time (same time period of follow-up) with incidence density sampling and allowing for replacement of controls. The index date was defined as the earliest recorded date of a diagnosis of dementia (or date of the first prescription of a drug treatment for dementia) for cases, whereas controls were assigned the date of the diagnosis of dementia of their matched case. Cases and controls were included only if they had at least 13 years of electronic health data recorded before the index date, so that there was a minimum period of 10 years of use of bladder anticholinergics (excluding the three-year period before the index date). The most commonly used bladder anticholinergics in cases and controls were oxybutynin, tolterodine and solifenacin. The adjusted odds ratio (aOR) for dementia associated with the use of any bladder anticholinergic compared with no use of these drug treatments was 1.18 (95% CI 1.16 to 1.20). In separate subgroup analyses in men and women, the odds ratio for dementia associated with the use of any anticholinergic drug was higher in men (aOR: 1.22, 95% CI 1.18 to 1.26) than in women (aOR: 1.16, 1.13 to 1.19).

Coupland and colleagues (2019) conducted a nested case-control study within a cohort of patients registered to practices in England contributing to the QResearch database. They examined the risk of dementia in patients aged ≥55 years who received anticholinergic drugs during the period January 2004 and January 2016. Cases were patients diagnosed with dementia (unspecified clinical codes in practice records, ONS death records or patients with prescriptions for acetylcholinesterase inhibiting drugs) during the follow-up period. Each case was matched to 5 controls by age (within 1 year), sex, general practice and calendar time using incidence density sampling. Cases and controls were only included if they had at least 11 years of recorded data prior to the index date (excluding the 1-year period prior to the index date) so that anticholinergic drug exposure could be assessed over a complete period of 10 years. The study examined the risk of dementia in association with anticholinergic exposure, which was categorised as follows: 0, 1-90, 91-365, 366-1095 and >1095 total standardised daily doses. Associations were also assessed for 11 separate types of anticholinergic drug, including bladder anticholinergics. The most frequently prescribed types of anticholinergic drugs were antidepressants (27.1% of cases, 23.3% of controls), antivertigo/antiemetic drugs (23.8% of cases, 21.7% of controls), and bladder anticholinergics (11.7% of cases, 8.3% of controls). Oxybutynin, tolterodine and solifenacin were the most frequently prescribed bladder anticholinergics in both cases and controls. Analyses examining the risk of dementia with specific types of anticholinergic drug showed increased risks in association with antidepressants, anti-parkinson drugs, antipsychotics, bladder anticholinergics, and epilepsy drugs. The risk of dementia with bladder anticholinergics was significantly increased across all dose categories and increased with greater cumulative use. Patterns of risk were similar in the 3- to 13 year and 5- to 20 year-exposure windows. For the other drug classes where an increased risk of dementia was observed the findings were also suggestive of a dose-dependent risk but for the

antiepileptics it was only the highest total standardised daily dose (TSSD) of >1095 where the increased risk was statistically significant.

Studies conducted in European Union

Malcher and colleagues (2022) conducted a nested case-control study in the French Health Data Hub (this combines health insurance and hospital discharge data) and examined the association between the use of bladder anticholinergics and the risk of dementia in patients ≥ 60 years of age. The study period was between 2006 and 2018, with an observation period that allowed for a 5-year exposure period and a lag-time period of 2 years. Cases were individuals with incident dementia identified by at least 1 of the following criteria: 1) an ICD-10 code related to dementia, 2) at least 1 long-term disease information report associated with the ICD-10 code for dementia, and 3) reimbursable anti-dementia drugs dispensed at least twice. The index date was defined as the first date that identified the case. For each case, 5 controls were randomly selected from the eligible population and matched cases based on sex, age ±2 years, and special reimbursement systems for low-income persons. Bladder anticholinergic exposure was analysed using two different methods: 1) user (at least 1 dispensing over the period) vs nonuser, and 2) exposure levels with clinically relevant thresholds: 0 cDDD, 1-90 cDDDs, 91-365 cDDDs, and >365 cDDDs. They found that the use of any bladder anticholinergic over a 5-year period was associated with an increased risk of dementia: adjusted OR: 1.23 (95% CI: 1.10-1.37) and the risk increased with higher doses. Interaction for sex and age (binary and ordinal exposure) only showed a significant interaction for ordinal exposure.

Pourhadi and colleagues (2025) conducted a nested case-control study within a Danish nationwide cohort. The primary cohort included the general population aged 60-75 years with no previous history of dementia and this cohort was used to examine the risk compared with bladder anticholinergic users. The secondary cohort was a population of new users of bladder drugs where they compared anticholinergic bladder drugs with the β3 agonist bladder drug, mirabegron, and the associated risk of dementia; an active comparator, new user study design. Case-control population was nested within each of the two cohorts, generating two matched populations of incident cases of dementia and a set of controls for each incident case. Cases of dementia were identified from registered diagnoses of dementia syndrome of any aetiology or from prescriptions for antidementia drug treatment, whichever came first. On the date of incident dementia (index date) each case was matched by age and sex to five controls with no dementia from the respective source cohort. The number of defined daily doses (DDDs) and cumulative use was calculated for bladder anticholinergic use and categorised as 1-90, 91-365 and >365 DDDs. Timing of use of bladder anticholinergics compared with non-use were categorised as: current user (within

one year of index date), recent user (1-5 years before index date) or past user (>5 years before index date).

The primary cohort was followed up for up to 23 years from 1st January 2000 until the occurrence of dementia, emigration, death, a filled prescription for mirabegron, of the end of follow-up (31 December 2022). Compared with non-use in the general population, ever use of bladder anticholinergics was associated with an increased incidence rate ratio for all cause dementia of 1.44 (95% CI 1.40 to 1.48) that increased with increasing cumulative use. The rate of dementia was highest for current users (incidence rate ratio 2.18, 95% CI 2.11 to 2.25) and lowest for past users (1.24, 1.20 to 1.28). The sensitivity analysis without a lag time gave overall higher rates of dementia with use of bladder anticholinergics than the main analysis with a lag time of five years.

Studies conducted in Asia

Two studies were conducted in national health insurance databases in Taiwan (Wang and others, 2019; Harnod and others, 2021) and examined the risk of dementia in association with use of bladder anticholinergics in patients aged ≥ 50 years and ≥ 55 years, respectively.

The study by Wang and colleagues (2019) was a retrospective population-based cohort study and the primary outcome was the occurrence of dementia, defined as a patient who had at least three outpatient visits or one inpatient admission for a principal diagnosis of dementia (ICD-9-CM 290.0–290.4 and 331.0) after the first diagnosis of lower urinary tract symptoms. Patients with at least three outpatient visits or one inpatient admission with a principal diagnosis of lower urinary tract symptoms were identified from January 2001 to December 2005; the date of initial lower urinary tract symptoms diagnosis was chosen as the index date. The use of bladder anticholinergics was stratified into four levels based on cumulative daily defined doses (cDDS): < 28, 28–84, 85–336, and ≥ 337 cDDDs. Patients with newly diagnosed dementia within the first year after the index date were excluded. Patients were followed up until development of dementia or until the end of 2012. At the end of the follow-up period, 1666 patients had dementia. The mean (SD) and median (IQR) follow-up time to dementia was 9.0 (2.2) years and 9.2 (8.0–10.7) years respectively for all patients and were all longer than 9 years in each cDDDs group. The incidence of dementia was significantly related to higher cumulative doses of anticholinergic use in patients with lower urinary tract symptoms. As a sensitivity analysis patients diagnosed with dementia 2,3, or 4 years after index date were excluded and this showed similar results to the main analysis.

The study by Harnod and colleagues (2021) was a case-control study. Cases were patients with dementia (ICD-9 codes) and diagnosed by a neurologist or a general physician during

2000-2013 and the first dementia diagnosis date was used as an index date. Controls were subjects without dementia that were randomly selected from the database. The controls were assigned the same index year as their matched cases with respect to age, sex, comorbidities, and certain medications. The use of bladder anticholinergics was evaluated in the period before the index date and categorised according to duration of use (medium (1–3 years), long (4–7 years), and prolonged use (> 7 years)) and cumulative dose (non-use, low-dose (≤ 207), medium-dose (207–3271), and high-dose (> 3271) users). Propensity score matching was used to match cases with controls. After adjusting for potential confounders, bladder anticholinergic users had a 2.46-fold increased risk of dementia compared with that in non-users (95% CI = 2.22–2.73). In patients who had been taking bladder anticholinergics a medium duration before the index date, an increased daily defined dose was associated with an increased risk of developing dementia compared with that in the controls. A dose-dependent risk of developing dementia was not observed in association with long or prolonged use of bladder anticholinergics.

Joung and colleagues (2019) used the Korean National Health Insurance Service (NHIS) elderly cohort, which includes medical information on elderly people (aged 60-119), and examined whether use of anticholinergics (strong and weak) is associated with an increased risk of Alzheimer's disease. New users of strong anticholinergic medicines (those who did not use a strong anticholinergic medicine in the year before study start or only filled a few prescriptions (1-9 doses/year) were followed up for incident Alzheimer's disease from 2005 to 2013. Subjects were categorised into four classes according to prescribed amount of strong anticholinergics: 0-9 doses/year, 10-49 doses/year, 50-119 doses/year, and ≥120 doses/year. Among the strong anticholinergic drug classes, the most commonly prescribed were antihistamines, antidepressants and bladder anticholinergics. The study showed the risk of Alzheimer's disease was significantly higher in subjects exposed to ≥50 doses/year of strong anticholinergics than in the reference group in both the crude and the adjusted models (Model I partially and Model II fully adjusted). The study also examined the risk of Alzheimer's disease in those exposed to weak anticholinergics and this did not support an increased risk across the different dose categories (fully adjusted model). Like the main analyses, for the specific classes of anticholinergic medicines, the study showed an increased risk for Alzheimer's disease when subjects are exposed to greater amounts of bladder anticholinergics (adjusted Hazard Ratio 1.31 (95% CI 1.24 to 1.38).

Okita and colleagues (2023) conducted a nested case-control study using data from the Longevity Improvement and Fair Evidence (LIFE) Study (Fukuda and others) and evaluated the association between the use of anticholinergic drugs and risk of dementia in older adults (≥ 65 years of age). The primary exposure variable was the total cumulative exposure to anticholinergic drug, which was categorised into 5 groups – non-use, 1-10, 11-30, 31-90 and >90 total standardised daily doses (TSDDs). Association for different types of anticholinergic drug classes were also examined using three categories (non-use, 1-30 and >30 TSDDs). Cases were patients diagnosed with dementia (ICD-10 codes) during follow-up. Controls

were subjects without dementia that were randomly selected from the database and five controls for each case were matched on age at cohort entry, sex, municipality year of cohort entry. Individuals who were prescribed anticholinergic drugs had a greater risk of being diagnosed with dementia (adjusted odds ratio 1.50 (95% CI, 1.47–1.54)). The risk increased with increasing cumulative use of any type of anticholinergic drug – adjusted odds ratio increased from 1.46 (95% CI, 1.42–1.50) for 1–10 TSDDs to 1.72 (95% CI, 1.63–1.82) for >90 TSDDs (P for trend <0.001). Among specific types of anticholinergic drugs, a significant increase in risk was observed with the use of antidepressants, antiparkinsonian drugs, antipsychotics, and bladder anticholinergics in a fully multivariable-adjusted model. For the bladder anticholinergics there was an increased risk of dementia for both the 1-30 and >30 TSDDs categories compared with non-use and a test for trend showed this dose-response was statistically significant.

Annex 2 –Bladder Anticholinergics class: Studies with an active comparator control

Studies conducted in Canada and the US

Welk and colleagues (2020) conducted a retrospective, matched-cohort study using population-based data from the province of Ontario, Canada and examined the risk of dementia in individuals aged >65 years who were prescribed bladder anticholinergics compared with those prescribed a β-3 agonist (mirabegron). The index date was the date of the first eligible prescription during the study period and patients were followed up until the date of the outcome. Dementia was the primary outcome and was defined using a validated definition that uses hospital admission ICD-10 codes, ≥2 physician billing claims for dementia, or a new prescription of a cholinesterase medication. Patients were matched based on age (±2 years), gender, baseline antidepressant use and the logit of the propensity score. In the primary analysis, an approximately 1.2-fold increased risk of dementia was found among bladder anticholinergic users compared to β-3 agonist users. Secondary analyses included one in which the first matched sets were excluded where any member had <90 days of follow-up and another where results were stratified by gender and age group and tested for effect modification using interaction terms. The secondary analyses that examined risk in those with a longer duration of bladder anticholinergic use (≥ 3 months of continuous use) showed a similar result to the main analysis.

Barthold and colleagues (2020) conducted a retrospective cohort study using a random 20% sample of patients drawn from the US Medicare beneficiaries enrolled in Medicare. They examined the risk of Alzheimer's disease and related dementias (ADRD) in individuals aged 65 years and older who were prescribed non-selective bladder anticholinergics (fesoterodine, flavoxate, oxybutynin, tolterodine, and trospium) versus the risk those prescribed M3-selective bladder anticholinergics (darifenacin and solifenacin). Individuals' use of bladder anticholinergics was measured according to total standardised daily dose (TSDD) and categorised into the following categories 1–364, 365–729, 730–1094, and >1094 daily doses, which correspond years of exposure during the 3-year exposure period. Non-selective bladder anticholinergic use, compared to M3 selective bladder anticholinergic use was not significantly associated with ADRD incidence. This was true at all four levels of exposure (1–364, 365–729, 730–1094, and >1094 TSDD), and for sub analyses by sex and race/ethnicity. Sensitivity analyses also showed the results were not influenced by switching between bladder anticholinergic types. In a secondary analysis, the relationship between overall bladder anticholinergic use and ADRD incidence was evaluated. These analyses compared people who used any bladder anticholinergics at higher exposures to a reference

group who used them at lower exposure (1–364 TSDD). This showed that those in the 730-1094 (odds ratio 1.11 (95% CI 1.05-1.17)) and the >1094 (odds ratio 1.10 (95% CI 1.04-1.15)) categories had an increased risk of dementia but not those in the 365-729 category (odds ratio 1.05 (0.99-1.10)). It is of note that some patients may have used both non-selective and M3-selective bladder anticholinergics during the exposure period, which could obscure differences in ADRD risk. This uncertainty is also highlighted by the sensitivity analyses where the sample was restricted to patients who only used one type of bladder anticholinergic.

Matta and colleagues (2022) conducted a population-based case-control study in Canadian linked administrative health datasets and examined the risk of dementia in patients ≥66 years of age who were exposed to bladder anticholinergics compared with patients exposed to mirabegron. In the primary adjusted analysis, use of any bladder anticholinergic was not associated with an increased risk of dementia. Cases were identified using a modified validated algorithm for dementia and Alzheimer's disease based on hospital admission codes, prescription claims for a cholinesterase inhibitor, or ≥2 physician billing claims for dementia. Cases were matched up to four controls on index year, age ± 2 years, and sex. In the primary analysis, the effect of bladder anticholinergic exposure on incident dementia was evaluated using multivariable conditional logistic regression and the increased risk observed just failed to reach statistical significance (adjusted odds ratio 1.12 (95% CI 0.98-1.27)). A sensitivity analysis was conducted to address protopathic bias (lag period of 6 months) and this also reported an increased risk of dementia in association with any bladder anticholinergic exposure (adjusted odds ratio 1.29 (95% CI 1.09-1.54)).

Li and colleagues (2025) conducted a retrospective, propensity-weighted cohort study using population-based data from Ontario, Canada and examined the risk of dementia in adult patients aged <65 years who were new users of bladder anticholinergics compared with those prescribed a β-3 agonist (mirabegron). The index date was the date of the first eligible prescription during the study period (01/02/2012 and 31/12/2020) and patients were followed up until the date of the outcome, a censoring event or study end date. Dementia was the primary outcome and was defined using a validated definition that uses hospital admission ICD-10 codes, ≥2 physician billing claims for dementia, a new prescription of a cholinesterase medication, or two or more visits within 6 months to community healthcare with an associated ICD-10 diagnosis code for dementia. A propensity score model was developed using the type of overactive bladder medication as the dependent variable and all base-line variables as independent variables, including patient demographics, baseline comorbidities, health care utilisation, and medications. Charlson Comorbidity Index, number of hospitalisations, number of emergency department visits, number of general practitioner visits, and count of potent anticholinergic medications as a measure of the anticholinergic burden were categorical variables. In the primary analysis, there was no significant differences in the association between new onset of dementia and the class of overactive bladder medication used (adjusted hazard ratio 0.99, 95% CI 0.86 – 1.15). Post-hoc

analyses included an analysis that restricted the cohort to those aged > 48 years, and an analysis that excluded those who filled their bladder anticholinergic prescription between 2012 and 2014. The latter was done to address the potential effect of differential follow-up time and prescribing practices by including bladder anticholinergic users prior to the introduction of mirabegron and the findings were very similar to the primary analysis (adjusted hazard ratio 0.87, 95% CI 0.73-1.04, p=0.02)

Studies conducted in the European Union

In a secondary cohort of new users of bladder drugs, Pourhadi and colleagues (2025) compared use of any bladder anticholinergic to use of mirabegron and reported that ever use of a bladder anticholinergic was not associated with an increased risk of dementia adjusted odds ratio 0.82 (95% CI 0.74-0.91) and this was true across all the dose categories studied. Timing of use of bladder anticholinergics compared with non-use were categorised as: current user (within one year of index date), recent user (1-5 years before index date) or past user (>5 years before index date) and the incidence rate of dementia was highest for current users and lowest for past users. Further details about the data source and the conduct of this study can be found in Annex 1.

Studies conducted in Asia

Park and colleagues (2024) conducted a cohort study in Korean national health insurance databases and examined the risk of dementia in patients who were newly diagnosed with overactive bladder and were new users of either bladder anticholinergics alone, mirabegron alone or a bladder anticholinergic in combination with mirabegron. The index date was the first overactive bladder medication prescription during the study period. The most frequently used bladder anticholinergics were solifenacin (42.9%), propiverine (28.5%), and tolterodine (14.5%). Along with analyses by overall drug exposure, analyses were stratified based on cumulative defined daily doses (cDDD) and for solifenacin and mirabegron cDDD was categorised as low-, medium- and high cDDD. The primary outcome was dementia, which was identified using ICD-10 codes or a new prescription of a cholinesterase medication. There was an increased risk of dementia for user of bladder anticholinergics alone (adjusted hazard ratio = 1.213; 95% CI, 1.195–1.232) and those taking a combination treatment (adjusted hazard ratio = 1.345; 95% CI, 1.323–1.366) compared with the users of mirabegron. Similar results were observed when the buffer period was set to 1 year (bladder anticholinergics adjusted hazard ratio: 1.186 (95% CI, 1.164-1.209), combination therapy adjusted hazard ratio: 1.346, 95% CI, 1.320-1.372). The findings of this study also suggest the possibility of an increased incidence of dementia with the use of mirabegron alone. After

multiple adjustments, the increase in cDDDs of mirabegron was proportional to the increased risk of dementia (adjusted hazard ratio = 1.062; 95% CI, 1.021–1.106 for the medium cDDD mirabegron group (28-120 cDDDs), and adjusted hazard ratio = 1.044; 95% CI, 1.004–1.084 for the high-cDDD mirabegron group (≥121 cDDDs) compared with the low cDDD mirabegron group (≤27 cDDDs)).

Okita and colleagues (2025) conducted a retrospective cohort study using data from the LIFE Study and examined the association between the dementia risk and bladder anticholinergics compared to β-3 agonists (mirabegron and vibegron) in older adults (≥ 65 years of age) with overactive bladder in Japan. Patients diagnosed with dementia were identified using ICD-10 codes. Participants were analysed in groups, wherein the initially prescribed overactive bladder medication was followed in the same group, and prescription from the other group was not followed during the observation period. Stratified analyses according to sex and age groups (aged < 75, 75–85, and ≥ 85 years) were conducted with adjustment for potential confounders. Bladder anticholinergic use was associated with an increased risk of dementia compared to β-3 agonist use and the stratified analysis by sex and age group showed no significant interaction between drug groups and dementia risk. The sensitivity analyses (lag time 6-month, ITT analysis and an analysis to reduce bias due to patient background) showed similar results to the main analysis.

Annex 3 – Key results for individual Bladder Anticholinergics

Table 6: Key results from studies examining risk with individual bladder anticholinergics versus non-use control

Study	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin	Propiverine	Solifenacin	Tolterodine	Tropsium
Yang and others 2017 Cohort study (Taiwan)	n/a	n/a	n/a	**2.35** (95% CI 1.96 – 2.81)	n/a	**2.16** (95% CI 1.81-2.58)	**2.24** (95% CI 1.85 – 2.73)	n/a
Malcher and others 2022 Case-control study (France)	n/a	1.12 (95% CI 0.52-2.43)	0.92 (95% CI 0.57-1.49)	**1.28** (95% CI 1.09-1.50)	n/a	**1.29** (95% CI 1.08-1.53)	n/a	1.17 (95% CI 1.00-1.37)
Pourhadi and others 2025 Case-control study (Denmark)	n/a	**1.48** (95% CI 1.26-1.74)	n/a	n/a	n/a	**1.37** (95% CI 1.29-1.46)	**1.43** (95% CI 1.38-1.49)	**1.52* (95% CI 1.37-1.37)**

Key: n/a = not applicable as either not studied or too few patients to provide data for individual drug substance;

* These confidence intervals (CIs) are incorrect but as reported in the paper.

Figures in bold are those that reached statistical significance

Table 7 Key results from studies examining risk with individual bladder anticholinergics and active comparator (active comparator used either as reference group or included as another group)

Study	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin	Propiverine	Solifenacin	Tolterodine	Tropsium	Active
Welk and others 2020 Cohort study (Canada)	n/a	n/a	n/a	Reference	n/a	1.01 (95% CI 0.87-1.19)	0.93 (95% CI 0.82-1.16)	n/a	Oxybutynin - reference
Matta and others 2022 Case-control study (Canada)	**1.30** (95% CI 1.08-1.56)	1.09 (95% CI 0.93-1.29)	n/a	1.05 (95% CI 0.92-1.21)	n/a	**1.24** (95% CI 1.08-1.43)	1.04 (95% CI 0.91-1.18)	1.05 (95% CI 0.72-1.53)	β3-agonist (mirabegron) - reference
Iyen and others 2024 Case-control study (UK)	No increased risk at any dose	No increased risk at any dose	Marginally increased risk with >1095 TSDDs 1.71 (95% CI 1.00-2.96)	**Dose response** **1-90 TSDD 1.04** (95% CI 1.01-1.07) to **>1095 TSDDs 1.28** (95% CI 1.15-1.43)	No increased risk at any dose	**Dose response** 1-90 TSDD 1.02 (95% CI 0.97-1.08) to **>1095 TSDDs 1.29** (95% CI 1.19-1.39)	**Dose response** **1-90 TSDD 1.05** (95% CI 1.01-1.09) to **>1095 TSDDs 1.25** (95% CI 1.17-1.34)	Increased risk only at 366-1095 TSDDs **1.31** (95% CI 1.13-1.52)	β3-agonist (mirabegron); Included as group not as reference vs non-use Increased risk at **91-365 TSDDs 1.27** (95% CI 1.04-1.56) and **366-1095 TSDDs 1.62** (95% CI 1.30-2.03)
Park and others 2024 Cohort study (Korea)	n/a	**mono 1.178** (95% CI 1.139-1.218) **combi 1.226** (95% CI 1.170-1.285)	mono 0.861 (95% CI 0.831-0.892) combi 0.989 (95% CI 0.927-1.054)	mono 1.024 (95% CI 0.975-1.075) **combi 1.136** (95% CI 1.006-1.283)	**mono 1.196** (95% CI 1.171-1.220) **combi 1.216** (95% CI 1.181-1252)	**mono 1.173** (95% CI 1.151-1.196) **combi 1.231** (95% CI 1.205-1.258)	**mono 1.170** (95% CI 1.140-1.200) **combi 1.228** (95% CI 1.175-1.285)	mono 1.067 (95% CI 0.967-1.176) **combi 1.300** (95% CI 1.128-1.498)	β3-agonist (mirabegron) – reference

Study	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin	Propiverine	Solifenacin	Tolterodine	Tropsium	Active
Pourhadi and others 2025l Case-control study (Denmark)	n/a	0.96 (95% CI 0.65-1.43)	n/a	n/a	n/a	**0.82** (95% CI 0.71-0.96)	**0.77** (95% CI 0.67-0.89)	0.79 (95% CI 0.59-1.05)	B-3 agonist (mirabegron)-reference
Sheyn and others 2025 Cohort study (USA)	Increased risk for following age groups **40-59 years 5.57** (95% CI 1.85-16.8) **60-79 years 2.27** (95% CI 1.29-4.00)	No increased risk for any age group	n/a	Increased risk seen across all age groups except >80 years **18-39 years 2.23** (95% CI 1.39-3.59) **40-59 years 2.22** (95% CI 1.85-2.66) **60-79 years 1.44** (95% CI 1.34-1.55) ≥ 80 years 1.06 (95% CI 0.96-1.17)	n/a	Increased risk for following age groups **40-59 years 1.92** (95% CI 1.17-3.15) **60-79 years 1.7** (95% CI 1.43-2.01)	Increased risk seen across all age groups except >80 years **18-39 years 4.16** (95% CI 1.54-11.2) **40-59 years 2.49** (95% CI 1.44-4.28) **60-79 years 1.55** (95% CI 1.30-1.85) ≥ 80 years 1.18 (95% CI 0.94-1.49)	Increased risk for following age groups **40-59 years 3.08** (95% CI 1.29-7.34) **60-79 years 2.53** (95% CI 1.92-3.33)	β3-agonist (mirabegron); Included as group not as reference vs non-use Increased risk for following age groups **40-59 years 2.51** (95% CI 1.58-4.00) **60-79 years 2.1** (95% CI 1.82-2.42)
Okita and others 2025 Cohort study (Japan)	n/a	**1.21** (95% CI 1.06-1.38)	n/a	1.14 (95% CI 0.90-1.45)	**1.20** (95% CI 1.01-1.43)	**1.28** (95% CI 1.18-1.39)	1.09 (95% CI 0.78-1.52)	n/a	β3-agonists (mirabegron and vibegron) - reference

Key: n/a = not applicable as either not studied or too few patients to provide data for individual drug substance; CI = confidence interval; TSDDs = total standardised daily doses. Figures in bold are those that reached statistical significance