

Hyperhidrosis: oral glycopyrronium bromide

Evidence summary

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Key points from the evidence

The content of this evidence summary was up-to-date in July 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

There is weak evidence from case series that oral glycopyrronium bromide tablets reduce sweating in people with hyperhidrosis. The most commonly reported adverse effects are antimuscarinic, particularly dry mouth. There is no randomised controlled trial evidence of the use of oral glycopyrronium bromide for hyperhidrosis.

Regulatory status: unlicensed

<p>Effectiveness</p> <ul style="list-style-type: none"> • No randomised controlled trials were identified. • Across a number of case series, involving around 150 adults, children and young people, hyperhidrosis 'responded' to oral glycopyrronium bromide tablets in 67–90% of participants. 	<p>Safety</p> <ul style="list-style-type: none"> • Contraindicated in medical conditions that preclude antimuscarinic therapy. • Specific warnings about: <ul style="list-style-type: none"> – fever and heat stroke as a result of decreased sweating in high environmental temperatures, – diarrhoea, which may be an early symptom of incomplete intestinal obstruction.
<p>Patient factors</p> <ul style="list-style-type: none"> • Glycopyrronium bromide tablets and oral solution or suspension are imported or prepared by 'specials' manufacturers. • Dosage varies, ranging from 1 mg to a maximum 8 mg (in divided doses) daily in case series. • Across case series 29–79% of participants experienced adverse effects, most frequently dry mouth (affecting 16–63%). • In 3 case series, 26%, 20% and 3% of participants withdrew because of adverse effects. • In 2 case series, no withdrawals because of adverse effects were reported. 	<p>Resource implications</p> <ul style="list-style-type: none"> • The cost of glycopyrronium bromide tablets varies depending on the source and the dosage used. • In 2012 in England there were 21,600 items dispensed for oral glycopyrronium bromide at a net cost of £5,732,400 (indications not known). • Cost per item for tablets between £268.57 and £712.34 (number of tablets per item not known).

Key points

Glycopyrronium bromide is an antimuscarinic drug that prevents the stimulation of sweat glands. This evidence summary reviews the use of oral glycopyrronium bromide for treating hyperhidrosis, or excessive sweating.

Oral preparations of glycopyrronium bromide (tablets and solution or suspension) are not licensed or available in the UK for treating hyperhidrosis. Such preparations must be either imported or prepared by 'specials' manufacturers. Use for this indication would be unlicensed.

Glycopyrronium bromide powder for solution ([Robinul powder](#)) is currently licensed for the iontophoretic treatment (electromotive drug administration) of primary (idiopathic) hyperhidrosis of the palms of hands and soles of feet in children and adults.

No randomised controlled trials were identified. Five case series reported the use of oral glycopyrronium bromide tablets in people with hyperhidrosis: 3 in a total 100 adults with focal or generalised primary hyperhidrosis ([Bajaj and Langtry 2007](#); [Lee et al. 2012](#); [Walling 2012](#)); 1 case series in 31 children or young people with focal primary hyperhidrosis ([Paller et al. 2012](#)); and 1 case series in 19 adults or young people with compensatory hyperhidrosis following sympathectomy for focal primary hyperhidrosis ([Gong and Kim 2013](#)).

Dosages of oral glycopyrronium bromide in these case series ranged from 1 mg to a maximum 8 mg (in divided doses) daily, and treatment duration was variable or unreported. In all but 1 study, participants had tried previous treatments and either the condition had not responded, or they had been intolerant to the treatment.

Across these case series, hyperhidrosis responded to treatment in 67 to 90% of participants. These response rates were based on absolute responses to therapy as recorded in patient records, or on patient questionnaires, which could be subjective and do not appear to be validated.

Adverse effects affected between 29 and 79% of participants, the most frequent being dry mouth (affecting 16–63%). Two studies ([Bajaj and Langtry 2007](#); [Walling 2012](#)) reported that, respectively, 26% and 20% of participants stopped treatment because of adverse effects. [Paller et al. \(2012\)](#) reported that 1 child (3%) stopped because of palpitations. The other 2 studies reported no withdrawals because of adverse effects.

Additional safety information is included in the labelling of the oral glycopyrronium bromide products available in the USA but not licensed for hyperhidrosis (glycopyrrolate tablets, USP, Robinul and Robinul Forte; glycopyrrolate oral solution, Cuvposa). The tablets are contraindicated in medical conditions that preclude antimuscarinic therapy. There are also warnings about fever and heat stroke as a result of decreased sweating in high environmental temperatures, and diarrhoea, which may be an early symptom of incomplete intestinal obstruction. Listed adverse effects include dry mouth, urinary retention, blurred vision, palpitations, drowsiness, vomiting and constipation.

Overall, the 5 case series provide weak evidence of the efficacy and safety of oral glycopyrronium bromide for treating hyperhidrosis.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Regulatory status of glycopyrronium bromide

Oral glycopyrronium bromide does not have marketing authorisation in the UK for treating hyperhidrosis in children, young people or adults. Glycopyrronium bromide is available in the UK as:

- a powder for solution licensed for iontophoretic treatment (electromotive drug administration) of idiopathic hyperhidrosis of the palms of hands and soles of feet in children and adults (Robinul powder, Amdipharm Mercury Company),

- a 200 microgram/ml solution for injection licensed for preoperative and intraoperative use in children and adults ([Amdipharm Mercury Company](#); [Accord Healthcare](#)), and
- a single-dose dry-powder inhaler licensed for maintenance therapy to relieve symptoms of chronic obstructive pulmonary disease in adults ([Seebri Breezhaler inhalation powder](#), Novartis Pharmaceuticals).

Oral preparations of glycopyrronium bromide (tablets and solution or suspension) are not licensed in the UK and must be either imported or prepared by specials manufacturers. Use of these preparations is unlicensed.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using oral glycopyrronium bromide outside its authorised indications.

Evidence statements

- No randomised controlled trials on the use of oral glycopyrronium bromide for treating hyperhidrosis were identified.
- Five case series reporting the use of oral glycopyrronium bromide tablets were identified: 3 in a total 100 adults with focal or generalised primary hyperhidrosis; 1 in 31 children or young people with focal primary hyperhidrosis; and 1 in 19 adults or young people with compensatory hyperhidrosis after sympathectomy for focal primary hyperhidrosis.
- Dosages of oral glycopyrronium bromide in case series ranged from 1 mg to a maximum 8 mg (in divided doses) daily, and treatment duration was variable or unreported. In all but 1 case series, participants had previously tried various treatments, and either the condition had not responded or they had been intolerant to the treatment.
- Across the 5 case series, hyperhidrosis responded to treatment in between 67 and 90% of participants. Response rates were based on absolute responses to therapy as recorded in patient records, or on patient questionnaires, which could be subjective and do not appear to be validated.
- Adverse effects were common, affecting between 29 and 79% of participants, the most frequent being dry mouth (affecting 16–63%). In 2 studies, around a quarter of participants stopped treatment because of adverse effects. In the study in children or

young people, 1 child stopped treatment because of palpitations.

- These case series provide weak evidence of the efficacy of oral glycopyrronium bromide for treating hyperhidrosis; the publication of well conducted randomised controlled trials would assist local decision making on this topic.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Efficacy

No randomised controlled trials were identified that had examined oral glycopyrronium bromide for treating primary or secondary hyperhidrosis in adults, children or young people.

Five case series reporting the use of oral glycopyrronium bromide tablets in people with hyperhidrosis were identified: 3 in a mainly adult population with focal or generalised primary hyperhidrosis ([Bajaj and Langtry 2007](#); [Lee et al. 2012](#); [Walling 2012](#)), 1 in children or young people with focal primary hyperhidrosis ([Paller et al. 2012](#)), and 1 in adults or young people with compensatory hyperhidrosis after sympathectomy for focal primary hyperhidrosis ([Gong and Kim 2013](#)).

Dosages of oral glycopyrronium bromide ranged from 1 mg to a maximum 8 mg (in divided doses) daily, and treatment duration was variable or unreported. In all but 1 case series ([Lee et al. 2012](#)) participants had tried previous treatments for hyperhidrosis and either the condition had not responded, or they had been intolerant of the treatment.

According to patients' case notes, in [Bajaj and Langtry \(2007\)](#) hyperhidrosis responded to treatment with oral glycopyrronium bromide (in terms of reduced sweating) in 79% (15 out of 19) adults, and in [Walling \(2012\)](#) the response rate was 67% (30 out of 45). In [Lee et al. \(2012\)](#) the response rate was 75%, with 27 out of 36 participants showing a decrease in sweating on the Keller scale. In children and young people, [Paller et al. \(2012\)](#) reported that hyperhidrosis responded to treatment with oral glycopyrronium bromide in 90% (28 out of 31) of participants, based on case notes or verbal interview. In people with compensatory hyperhidrosis after sympathectomy, [Gong and Kim \(2013\)](#) reported a response rate of 89% (17 out of 19) on the Milanez de Campos scale, which measures

everyday discomfort caused by hyperhidrosis.

Table 1 Summary of the 5 case series

	Oral glycopyrronium bromide tablets	Comment
<u>Bajaj and Langtry (2007)</u>		
Number	19 adults (24 adults received treatment; results reported only for 19 who attended follow-up)	Participants had focal or generalised primary hyperhidrosis and all but 13% (3/24) had tried previous treatments
Dosage and treatment duration	2 mg twice daily increased to 2 mg 3 times daily (4 mg twice daily in 1 person; 2 mg once daily in 1 person)	Duration of treatment not reported
Effect on hyperhidrosis	79% (15/19) responded ^a ; 4 stopped because of lack of efficacy	8 out of 19 completed LAS ^b before and after treatment: 'excellent' response in 3, 'improvement' in 4 and no improvement in 1
Adverse effects	79% (15/19)	Dry mouth affected 63% (12/19)
Withdrawal because of adverse effects	26% (5/19)	Reasons: dry mouth (n=3), erectile dysfunction (n=1), headaches and urinary retention (n=1)
<u>Lee et al. (2012)</u>		
Number	36 adults (66 adults received treatment; results reported only for 36 who completed all follow-up)	Participants had focal or generalised primary hyperhidrosis. None had received previous treatments

Dosage and treatment duration	1 mg twice daily increased by 2 mg daily to maximum 8 mg daily	Duration of treatment not reported
Effect on hyperhidrosis	75% (27/36) responded on the Keller scale ^c	Mean score reduction on Keller scale ^c from 60 to 35.9 (p<0.01) Mean score reduction on Milanez de Campos scale ^d from 57.9 to 38.7 (p<0.01)
Adverse effects	36% (13/36)	Dry mouth (n=10), palpitations (n=4), headache (n=1) and 'other' (n=3).
Withdrawal because of adverse effects	None	
<u>Walling (2012)</u>		
Number	45 adults	Participants had focal or generalised primary hyperhidrosis and had tried previous treatments (76% continued other treatments alongside oral glycopyrronium bromide tablets)
Dosage and treatment duration	1 mg once daily to 3 mg twice daily	Duration of treatment not reported
Effect on hyperhidrosis	67% (30/45) responded ^{a,e} 6 did not respond 9 withdrew because of adverse effects	14 out of 30 people who responded reported degree of improvement as 'great', 'excellent' or '>75%' (n=6), or 'some', 'moderate' or '>50%' (n=8)
Adverse effects	Not reported	Adverse effects are only reported for those who withdrew from treatment
Withdrawal because of adverse effects	20% (9/45)	Dry mouth (n=4), gastrointestinal disturbance (n=2), headache (n=1), rash (n=1) and mental health effects (n=1)
<u>Paller et al. (2012)</u>		

Number	31 children or young people	Participants had primary focal hyperhidrosis of the palms, soles and/or axillary area and had tried previous treatments
Dosage and treatment duration	1 mg once daily to 3 mg twice daily	Duration of treatment ranged from 4 months to 10 years in those who found improvement
Effect on hyperhidrosis	90% (28/31) responded ^f 3 did not respond	20 rated the response as 'major' and 8 as 'adequate'
Adverse effects	29% (9/31)	Dry mouth (n=8), dry eyes (n=3), blurred vision (n=1) and palpitations (n=1)
Withdrawal because of adverse effects	3% (1/31)	1 stopped treatment because of palpitations
<u>Gong and Kim (2013)</u>		
Number	19 adults or young people (age range 15 to 76 years)	Participants had compensatory hyperhidrosis after sympathectomy for primary hyperhidrosis
Dosage and treatment duration	1 mg twice daily to 8 mg daily	Questionnaire completed 1 month after treatment started
Effect on hyperhidrosis	89% (17/19) responded on the Milanez de Campos scale at 1 month ^d	Mean score reduced from 60.4 to 34.2 (p<0.05)
Adverse effects	42% (8/19)	Dry mouth (n=3), palpitations (n=3), headache (n=1) and constipation (n=1)
Withdrawal because of adverse effects	None	

Abbreviations: LAS, linear analogue scale.

^a The degree of treatment response could not be accurately assessed from the patients' case notes, so the absolute responses were recorded.

^b A patient-assessed LAS (0 to 10 points) of the severity of hyperhidrosis and quality of life. An 'excellent' response was an improvement of 9 points or more, and 'improved' was an improvement of up to 8 points.

^c The Keller scale examines hyperhidrosis symptoms. No further details of this scale are given.

^d The Milanez de Campos scale examines the discomfort level of hyperhidrosis in everyday life. No further details of this scale are given.

^e 'Non-responders' were defined as people who reported 'no', 'slight' or 'less than 50% improvement', or stopped treatment because of lack of efficacy.

^f Response was based on a review of case notes or verbal interview.

Safety

In case series of oral glycopyrronium bromide in people with hyperhidrosis, adverse effects have been common, the most frequent being dry mouth. In adults, [Bajaj and Langtry \(2007\)](#) (n=19) reported that 79% experienced adverse effects (63% dry mouth) and 26% stopped treatment because of adverse effects; in [Lee et al. \(2012\)](#) (n=36), 36% experienced adverse effects (28% dry mouth), though none stopped treatment as a result; and in [Walling \(2012\)](#) (n=45), 20% stopped treatment because of adverse effects (9% because of dry mouth). In children and young people, [Paller et al. \(2012\)](#) (n=31) reported adverse effects in 29% (dry mouth in 26%), and 1 child stopped treatment because of palpitations.

In people taking oral glycopyrronium bromide for compensatory hyperhidrosis after sympathectomy, [Gong and Kim \(2013\)](#) (n=19) reported adverse effects in 42% (dry mouth in 16%; palpitations in 16%), although no withdrawals because of adverse effects were reported.

Oral glycopyrronium bromide products (glycopyrrolate tablets, USP, [Robinul and Robinul Forte](#); and glycopyrrolate oral solution, [Cuvposa](#)) are available in the USA (not licensed for hyperhidrosis). The tablets are contraindicated in medical conditions that preclude antimuscarinic therapy, such as glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, unstable cardiovascular status in acute

haemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis and myasthenia gravis. There are also warnings about fever and heat stroke as a result of decreased sweating in high environmental temperatures, and diarrhoea, which may be an early symptom of incomplete intestinal obstruction. Listed adverse effects include dry mouth, decreased sweating, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, headaches, nervousness, mental confusion, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, constipation and impotence.

Cost effectiveness and cost

No cost-effectiveness studies of oral glycopyrronium bromide for use in hyperhidrosis were identified.

The [NHS Electronic Drug Tariff \(May 2013\)](#) lists the following prices for glycopyrronium bromide oral solution and suspension in Part VIII B, Arrangements for payment for specials and imported unlicensed medicines:

- glycopyrronium bromide 1 mg/5 ml oral solution/suspension: £150.92 for minimal volume of 100 ml plus £0.01 for each extra ml
- glycopyrronium bromide 2 mg/5 ml oral solution: £262.61 for minimal volume of 100 ml plus £0.14 for each extra ml
- glycopyrronium bromide 2 mg/5 ml oral suspension: £197.59 for minimal volume of 100 ml plus £0.15 for each extra ml.

No price is listed for glycopyrronium bromide oral tablets, and the cost of these will differ depending on the source. [NHS Prescription Cost Analysis for England 2012](#) reported that various glycopyrronium bromide tablets cost between £268.57 and £712.34 per item (the number of tablets per item is not known).

Relevance to NICE guidance programmes

This unlicensed use of oral glycopyrronium bromide for hyperhidrosis is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

No NICE guidance relevant to the treatment of hyperhidrosis or to the use of oral

glycopyrronium bromide was identified.

Intervention and alternatives

Glycopyrronium bromide is an antimuscarinic drug that prevents the stimulation of sweat glands and does not cross the blood brain barrier. Glycopyrronium bromide powder for solution ([Robinul powder](#)) is currently licensed for the iontophoretic treatment (electromotive drug administration) of primary (idiopathic) hyperhidrosis of the plantar (soles of feet) and palmar (palms of hands) skin.

Glycopyrronium bromide is also licensed as solution for [injection](#) for preoperative and intraoperative use, and in a single-dose dry-powder [inhaler](#) for treating chronic obstructive pulmonary disease.

No oral preparations (tablets and solution or suspension) of glycopyrronium bromide are licensed in the UK. The use of imported oral preparations or those prepared by special manufacturers for treating hyperhidrosis in adults and children is unlicensed.

Glycopyrronium bromide (glycopyrrolate) tablets 1 mg and 2 mg ([Robinul and Robinul Forte](#)) are available in the USA, licensed for adjunctive therapy in the treatment of peptic ulcer. Glycopyrronium bromide (glycopyrrolate) 1 mg/5 ml oral solution ([Cuvposa](#)) was licensed in the USA in 2010 to reduce chronic severe drooling in children and young people aged 3–16 years with a neurological condition associated with problem drooling, such as cerebral palsy.

Condition

Hyperhidrosis is a condition in which sweating is in excess of that necessary to maintain normal body temperature. Primary (idiopathic) hyperhidrosis has no recognised cause and mainly affects focal areas of the body such as the soles of the feet (plantar hyperhidrosis) and palms of the hands (palmar hyperhidrosis), underarms (axillary area), or face and scalp. Onset of primary hyperhidrosis is usually before the age of 18 years. Primary hyperhidrosis affects males and females equally ([Hyperhidrosis: CKS 2009](#)).

Secondary hyperhidrosis is caused by another condition, such as hyperthyroidism or diabetes, neuropathy, or spinal disease or injury, or can be a side effect of a drug. Secondary hyperhidrosis can be generalised, affecting the whole body, or can affect only

focal areas, similar to primary hyperhidrosis ([Hyperhidrosis: CKS 2009](#)).

Alternative treatment options

The first-line approach to treating primary hyperhidrosis usually involves self-help measures, such as personal care and use of antiperspirants containing 20% aluminium chloride hexahydrate ([Hyperhidrosis: CKS 2009](#)). Treating any underlying anxiety, which may be an exacerbating factor, should also be considered, with referral to a dermatologist if these measures are inadequate or unacceptable ([Hyperhidrosis: CKS 2009](#)).

Second-line treatments include:

- iontophoresis (either tap water iontophoresis, or with glycopyrronium bromide [[Robinul powder](#)], which is licensed for primary hyperhidrosis of the hands and feet, added to the water)
- botulinum toxin type A ([Botox](#) injection, which is licensed for treating severe hyperhidrosis of the axillae, which has not responded to topical treatment with antiperspirants)
- oral antimuscarinics: propantheline bromide ([Pro-Banthine](#) tablets, which are licensed for hyperhidrosis), glycopyrronium bromide (unlicensed), oxybutynin (off-label)
- surgery: resection or endoscopic thoracic sympathectomy
- topical glycopyrronium bromide (unlicensed)
- emollients and topical corticosteroids for treating irritation, different strengths of aluminium salts (up to 50%), and topical glutaraldehyde or formaldehyde
- other treatments: clonidine, diltiazem, or benzodiazepines.

Managing secondary hyperhidrosis generally involves history taking, examination, and investigations to look for an underlying cause ([Hyperhidrosis: CKS 2009](#)).

Evidence review: efficacy

No randomised controlled trials examining the effectiveness of oral glycopyrronium bromide for treating hyperhidrosis were identified.

Four case series were identified which examined the use of oral glycopyrronium bromide in people with primary (idiopathic) hyperhidrosis (3 in mainly adult populations and 1 in children or young people), and 1 case series that examined oral glycopyrronium bromide in people with compensatory hyperhidrosis after thoracic or lumbar sympathectomy.

Bajaj and Langtry (2007) retrospectively reviewed the case notes of 24 adults with primary hyperhidrosis (mean age 33 [range 19–62 years]; 70% female) who had been treated with oral glycopyrronium bromide between 2001 and 2004 at Sunderland Royal Hospital. Hyperhidrosis was focal in 15 people (most commonly axillae in 9 people, and palms of hands or soles of feet in 6 people) and generalised in 9. Previous treatments (aluminium chloride in 17, beta-blockers in 7, diltiazem in 4, clonidine in 3 and propantheline in 2) were either ineffective or not tolerated. Three people had tried no previous treatment.

Oral glycopyrronium bromide tablets were given at a dose of 2 mg twice daily initially and increased to 2 mg 3 times daily depending on response and tolerability. One person took 4 mg twice daily and 1 person took 2 mg once daily. Duration of treatment is not reported.

Follow-up was available for 19 people, 15 of whom (79%) had hyperhidrosis that responded to glycopyrronium bromide according to their case notes. The degree of treatment response could not be accurately assessed from the patients' case notes, so the absolute responses were recorded. Four people stopped treatment because of lack of effectiveness. Eight of the 19 people completed a 10-point linear analogue scale reporting the severity of their hyperhidrosis and quality of life before and after treatment. Response was rated as excellent (an improvement of 9 points or more) in 3 people, improved (an improvement of up to 8 points) in 4 people and no improvement in 1 person.

Lee et al. (2012) retrospectively reviewed the case notes of 36 people with primary hyperhidrosis (mean age 28 ± 14.9 years; 58% female) who had attended a pain clinic in South Korea between 2007 and 2009, and had accepted treatment with oral glycopyrronium bromide. Participants were newly diagnosed with hyperhidrosis and had received no previous treatment for this condition. Fifty-three per cent of participants had symptoms in 3 or more body areas, 28% in 2 areas and 19% in only 1 area of the body.

Oral glycopyrronium bromide tablets were given at a dose of 1 mg twice daily initially and increased by 2 mg per day, depending on response and tolerability, up to a maximum of 8 mg daily. Response to treatment was assessed by questionnaire before and after treatment. This included questions from the Keller scale and Milanez de Campos scale, which examined any improvement in hyperhidrosis symptoms. The Beck Depression

Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to assess psychological effects, and Short Form 36 (SF-36) was used to assess effects on quality of life. The function of the autonomic nervous system was assessed on a 90-question test (the Autonomic Nervous System [ANS] scale). Duration of treatment was not reported.

A total of 66 people were given oral glycopyrronium bromide; results are only reported for the 36 who completed follow-up and all questions on the questionnaire. After treatment, 75% of 36 people showed a decrease in sweating on the Keller scale. The mean score reduced from 60 before treatment to 35.9 after treatment ($p < 0.01$). No further details are reported on this scale, such as what the total score is or the change in score that would indicate a clinically significant improvement. The mean score on the Milanez de Campos scale reduced from 57.9 before treatment to 38.7 after treatment ($p < 0.01$). The authors reported that this scale measures the discomfort level of hyperhidrosis in everyday life, but no further details on this scale were given. Glycopyrronium bromide had no effect on BDI or ANS scores, but improved BAI scores (mean score change from 12.1 to 9.7; $p = 0.03$). SF-36 results were not reported.

Walling (2012) retrospectively reviewed the case notes of 59 people (mean age 29 [range 14–59 years]; 63% female) who had been treated with oral therapy for primary hyperhidrosis at the University of Iowa's Department of Dermatology between 1993 and 2005. A total 71 people had been treated with oral medications during this time; 59 had follow-up data available (mean duration 19.5 months) and were included in the analysis. Seventy-one per cent of the 59 participants ($n = 42$) had focal hyperhidrosis of the axillae, palms or soles; 14% ($n = 8$) had focal hyperhidrosis of the face and scalp; and 15% ($n = 9$) had generalised hyperhidrosis. In 95% of participants ($n = 56$), their condition had failed to respond to other treatments, including aluminium chloride ($n = 55$); iontophoresis ($n = 13$); oral medications, such as propranolol, clonidine, benzodiazepines, and in 3 people glycopyrronium bromide ($n = 13$), botulinum toxin ($n = 1$) and sympathectomy ($n = 1$).

Of the 59 participants who had been treated with oral therapy in this case review, 45 had received oral glycopyrronium bromide tablets. Three-quarters of those treated ($n = 34$) took this in addition to other treatment (including aluminium chloride, botulinum toxin and iontophoresis).

Thirty out of 45 participants (67%) had hyperhidrosis that responded to treatment with oral glycopyrronium bromide according to their case notes. Absolute responses to therapy were recorded because degrees of response could not be determined from most patient records. The dose of glycopyrronium bromide was titrated depending on response and

tolerability. Among 'responders' the most common dose was 1 mg once daily (n=12), followed by 1 mg twice daily (n=6), 2 mg twice daily (n=5), 2 mg once daily (n=4), 3 mg once daily (n=2) and 3 mg twice daily (n=1).

Of the 30 'responders', 14 people reported a degree of improvement. This was reported as 'great', 'excellent' or 'more than 75%' in 6 people and 'some', 'moderate' or 'more than 50%' in 8 people. Of the 15 people whose condition did not respond to treatment with oral glycopyrronium bromide, 6 out of 45 (13%) were defined as 'non-responders' (a person who reported 'no', 'slight' or 'less than 50% improvement', or stopped treatment because of lack of efficacy) and 9 out of 45 (20%) had experienced adverse effects leading to treatment withdrawal.

Paller et al. (2012) retrospectively reviewed the case notes of 31 children or young people (aged 3–17 years; mean age at hyperhidrosis onset 10.3 years; mean age when prescribed oral glycopyrronium bromide 14.8 years; 74% female) with primary hyperhidrosis focal to the palms, soles and/or axillary areas (greater than 6 months duration and of a severity that interfered with daily activity), who were treated with at least 1 dose of oral glycopyrronium bromide between 2001 and 2010 at a children's hospital in Chicago. Almost all children (97%) had tried previous topical therapy with 20% aluminium chloride, 11% had tried botulinum toxin and 7% iontophoresis.

Oral glycopyrronium bromide tablets were given at a dose of 1 mg once or twice daily initially and increased by 1 mg per day, depending on response and tolerability, to a maximum of 3 mg twice daily (2 mg twice daily if less than 12 years of age). Thereafter the dose was tapered to maintain control. The mean daily dose was 2.2 ± 1.3 mg. Just over a quarter of children continued with aluminium chloride intermittently as needed to maintain control.

Overall 90% (28) of 31 children or young people experienced an improvement in hyperhidrosis with oral glycopyrronium bromide treatment. Based on case notes or verbal interview, this was defined as 'major improvement' in 20 children or young people and 'adequate improvement' in 8. Three children (10%) had no improvement but the condition worsened in none. The duration of treatment ranged from 4 months to 10 years in children who found improvement, and less than 1 month in the 3 who found it ineffective. In all children, the response was lost within a day or 2 of stopping glycopyrronium bromide treatment.

Gong and Kim (2013) retrospectively reviewed the case notes of 19 adults or young people

(age range 15–76 years) who had received oral glycopyrronium bromide to treat compensatory hyperhidrosis after thoracic or lumbar sympathectomy at a pain clinic in South Korea between 2007 and 2012 and had complete follow-up available. Compensatory hyperhidrosis develops in other parts of the body unrelated to the area treated by surgery. The site of primary hyperhidrosis varied (hand, foot, face, neck or axillae), as did the site of compensatory hyperhidrosis, which included the chest, back, abdomen and thighs.

Oral glycopyrronium bromide tablets were given at a dose of 1 mg twice daily initially and increased by 2 mg per day depending on response and tolerability up to a maximum of 8 mg daily. Response to treatment was assessed by questionnaire at baseline and after 1 month of treatment. This included the Milanez de Campos scale, which measures the everyday discomfort from hyperhidrosis symptoms, the modified Beck Depression and Anxiety Inventories (mBDI and BAI) to assess psychological effects, and the ANS scale, to assess the function of the autonomic nervous system.

At 1 month, 17 of the 19 participants (89%) who received oral glycopyrronium bromide and had complete follow-up had a reduction in Milanez de Campos score from baseline (mean score reduced from 60.4 to 34.2; $p < 0.05$). The mBDI score also decreased in 89% of participants (mean score reduced from 17.8 to 12.8; $p < 0.05$) and the BAI score decreased in 79% of participants (mean score reduced from 12.5 to 9.3; $p < 0.05$). There was no statistically significant effect on the ANS scale.

Evidence review: safety

Adverse effects of oral glycopyrronium bromide in case series

Bajaj and Langtry (2007) reported that 15 of the 19 people who completed follow-up (79%) experienced adverse effects with oral glycopyrronium bromide. Dry mouth was the most common and affected 12 people. Five of the 19 people stopped treatment because of adverse effects: 3 because of dry mouth, 1 because of erectile dysfunction, and 1 because of headaches and urinary retention.

Lee et al. (2012) reported that 36% of 36 people experienced adverse effects with oral glycopyrronium bromide treatment, the most common of which was dry mouth (affecting 10 people [28%]). Other adverse effects reported were palpitations ($n=4$), headache ($n=1$)

and 'other' (n=3).

Walling (2012) reported that 9 out of 45 people treated with oral glycopyrronium bromide (20%) stopped treatment because of adverse effects. Reasons for stopping were dry mouth (n=4), gastrointestinal disturbance (n=2), headache (n=1), rash (n=1) and mental health effects (n=1).

Paller et al. (2012) reported that adverse effects were experienced by 9 out of 31 children or young people (29%). The most common adverse effect was dry mouth, which was experienced by 8 people, 3 of whom also had dry eyes, and 1 of whom had blurred vision. Dryness was dose related and improved when the dosage was reduced. One other person experienced palpitations and stopped treatment because of this adverse effect.

Gong and Kim (2013) reported that 8 out of 19 people (42%) who received oral glycopyrronium bromide to treat compensatory hyperhidrosis and had complete follow-up experienced adverse effects. These included dry mouth (n=3), palpitations (n=3), headache (n=1) and constipation (n=1). No participants stopped medication because of adverse effects.

Additional safety information from US products

Oral glycopyrronium bromide products are available in the USA (glycopyrrolate tablets, USP, Robinul and Robinul Forte; and glycopyrrolate oral solution, Cuvposa). Neither of these products is licensed for hyperhidrosis but their labelling provides useful safety information.

Robinul and Robinul Forte are contraindicated in medical conditions that preclude antimuscarinic therapy, such as glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, unstable cardiovascular status in acute haemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis and myasthenia gravis. There are also warnings about fever and heat stroke as a result of decreased sweating in high environmental temperatures, and diarrhoea, which may be an early symptom of incomplete intestinal obstruction. Listed adverse effects include dry mouth, decreased sweating, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, headaches, nervousness, mental confusion, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, constipation, and impotence.

Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies of oral glycopyrronium bromide for use in hyperhidrosis were identified.

Cost

The [NHS Electronic Drug Tariff \(May 2013\)](#) lists the following prices for glycopyrronium bromide oral solution or suspension in Part VIII B, Arrangements for payment for specials and imported unlicensed medicines:

- glycopyrronium bromide 1 mg/5 ml oral solution/suspension: £150.92 for minimal volume of 100 ml plus £0.01 for each extra ml
- glycopyrronium bromide 2 mg/5 ml oral solution: £262.61 for minimal volume of 100 ml plus £0.14 for each extra ml
- glycopyrronium bromide 2 mg/5 ml oral suspension: £197.59 for minimal volume of 100 ml plus £0.15 for each extra ml.

No price is listed for glycopyrronium bromide oral tablets, and the cost of these will differ depending on the source. [NHS Prescription Cost Analysis for England 2012](#) reported that various glycopyrronium bromide tablets cost between £268.57 and £712.34 per item (the number of tablets per item is not known).

Current drug usage

[NHS Prescription Cost Analysis for England 2012](#) reported that the following items were dispensed, inclusive of items that were imported in 2012:

- Glycopyrronium bromide 200 micrograms/5 ml liquid special: 400 items at a net cost of £138,200.
- Glycopyrronium bromide 500 micrograms /5 ml liquid special: 300 items at a net cost of £112,000.

- Glycopyrronium bromide 2 mg/5 ml liquid special: 800 items at a net cost of £212,100.
- Glycopyrronium bromide 5 mg/5 ml liquid special: 700 items at a net cost of £196,900.
- Glycopyrronium bromide 1 mg/5 ml oral solution: 5800 items at a net cost of £966,000.
- Glycopyrronium bromide 1 mg/5 ml oral suspension: 1000 items at a net cost of £164,400.
- Glycopyrronium bromide 1 mg tablets: 8300 items at net cost of £2,239,400.
- Glycopyrronium bromide 2 mg tablets: 3500 items at a net cost of £1,199,900.
- Robinul 1 mg tablets (import): 500 items at a net cost of £314,400.
- Robinul Forte 2 mg tablets (import): 200 items at a net cost of £136,100.

The total number of items dispensed for oral glycopyrronium bromide was 21,600 at a net cost of £5,732,400. It is not known for which indications these items were prescribed.

No data were identified on the extent of oral use of solution for injection in UK clinical practice.

Evidence strengths and limitations

No randomised controlled trials were identified comparing oral glycopyrronium bromide with placebo or with alternative treatment for hyperhidrosis (primary or secondary) in adults, young people or children.

This evidence summary was limited to a retrospective review of case series of people who had been treated with oral glycopyrronium bromide tablets. This included 3 case series of mainly adults with primary hyperhidrosis ([Bajaj and Langtry 2007](#); [Lee et al. 2012](#); [Walling 2012](#); reporting results for a total of 100 adults), 1 of children or young people with primary hyperhidrosis ([Paller et al. 2012](#), n=31), and 1 of adults or young people with compensatory hyperhidrosis following sympathectomy ([Gong and Kim 2013](#), n=19).

Dosages of oral glycopyrronium bromide in case series ranged from 1 mg to a maximum 8 mg (in divided doses) daily, and treatment duration was variable or unreported. In all but 1 case series, participants had tried previous treatments and either the condition had not responded, or they had been intolerant to the treatment.

These case series provide weak evidence on the efficacy and safety of oral glycopyrronium bromide for treating hyperhidrosis in children, young people and adults. Response rates were based on absolute responses to therapy as recorded in patient records, or on patient questionnaires, which could be subjective and do not appear to be validated. Randomised controlled trials comparing oral glycopyrronium bromide with placebo or alternative treatments on validated measures of hyperhidrosis are needed.

A Cochrane review protocol on interventions for excessive sweating of unknown cause (Shams et al. 2011) states that, 'Quantifying hyperhidrosis remains challenging in the absence of a widely acceptable definition of the condition. Attempts at finding a quantitative cut-off for hyperhidrosis are marred by a high degree of variability of sweating in the same individual that depends on their level of physical activity, the ambient temperature, their emotional state, and even the type of food consumed, amongst other factors. As a result, a diagnosis of hyperhidrosis is often made subjectively by the physician depending on the individual circumstances, aided sometimes by different means of quantification of sweating. The main modes of quantification are objective (e.g. gravimetry, starch-iodine testing, vaporimetry), subjective (e.g. visual analogue scales), and the overall impact on the person affected (e.g. by the Hyperhidrosis Disease Severity Scale).

The validated Dermatology Life Quality Index (DLQI) is frequently used in dermatology and in clinical trials to assess the impact of skin conditions on the participant. It is also used when assessing hyperhidrosis. The Hyperhidrosis Disease Severity Scale and Hyperhidrosis Impact Questionnaire specifically measure the impact of hyperhidrosis on those affected. There is a high degree of variation in terms of the level of sweating which causes problems for an individual, and, thus, purely quantitative methods of measuring hyperhidrosis fail to adequately record the impact the condition has on the individual affected. Therefore, it has been suggested that the inclusion of a functional assessment of hyperhidrosis, i.e. the impact it has on the sufferer, may more accurately reflect the condition's severity rather than isolated quantitative measurements of sweat production.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

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Shams K, Rzany BJ, Prescott LE et al. [Interventions for excessive sweating of unknown cause](#). Cochrane review protocol DOI: 10.1002/14651858.CD002953.pub2, published online: 5 Oct 2011

Walling HW (2012) [Systemic therapy for primary hyperhidrosis: a retrospective study of 59 patients treated with glycopyrrolate or clonidine](#). *Journal of the American Academy of Dermatology* 66: 387–92

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- [NICE Evidence Services](#)
- [NICE](#)
- [Euroscan](#)
- Broad internet search: [Google](#) e.g.: allintitle: glycopyrronium OR glycopyrrolate OR Robinul OR Cuvposa "hyperhidrosis" filetype:pdf
- [Scirus](#)

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1. Glycopyrrolate/ (651)
2. (Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul).mp. (947)

3. 1 or 2 (947)
4. hyperhidrosis.tw. (2300)
5. ((abnormal\$ or excess\$) adj3 (sweat\$ or perspir\$)).tw. (734)
6. Sweating/ (5415)
7. exp Hyperhidrosis/ (2734)
8. 4 or 5 or 6 or 7 (8907)
9. 3 and 8 (50)
10. limit 9 to english language (45)

Embase (via Ovid)

Database: Embase <1988 to 2013 April 15>

Search Strategy:

1. Glycopyrronium bromide/ (3251)
2. (Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul).tw. (815)
3. 1 or 2 (3348)
4. hyperhidrosis.tw. (2541)
5. ((abnormal\$ or excess\$) adj3 (sweat\$ or perspir\$)).tw. (809)
6. Hyperhidrosis/ (4815)
7. sweating/ (11869)
8. 4 or 5 or 6 or 7 (16597)
9. 3 and 8 (129)
10. limit 9 to english language (120)

11. limit 10 to exclude medline journals (19)

Cochrane Central Register of Controlled Trials (CENTRAL)

ID Search Hits

#1 MeSH descriptor: [Glycopyrrolate] explode all trees 197

#2 Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul:ti,ab,kw (Word variations have been searched) 411

#3 #1 or #2 411

#4 MeSH descriptor: [Hyperhidrosis] explode all trees 133

#5 "hyperhidrosis":ti,ab,kw (Word variations have been searched) 215

#6 #4 or #5 233

#7 #3 and #6 in Trials 9

CRD HTA, DARE and EED database

MeSH DESCRIPTOR glycopyrrolate 2

(Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul) 8

MeSH DESCRIPTOR hyperhidrosis EXPLODE ALL TREES 8

(hyperhidrosis or sweating or perspiration) 71

#1 OR #2 8

#3 OR #4 71

#5 AND #6 0

Grey literature and ongoing trials

- [FDA](#)
- [EMA](#)
- [MHRA](#)
- [Scottish Medicines Consortium](#)
- [All Wales Medicine Strategy Group](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

Manufacturers' websites

[Merz](#)

[Shionogi](#)

[Robinul](#)

[Mercury Pharma](#)

Evidence selection

Our literature search identified no randomised controlled trials examining the effectiveness of oral glycopyrronium bromide for treating hyperhidrosis. The search retrieved case series reporting various populations using different methods of administration of glycopyrronium bromide. No evidence was submitted from the manufacturer for this indication.

We reviewed the 5 case series that have evaluated the use of oral glycopyrronium bromide in people with primary (idiopathic) or secondary hyperhidrosis.

We excluded case series and 1 small randomised controlled crossover trial (n=13) assessing the topical application of glycopyrronium bromide solution/lotion/cream in people with primary or secondary hyperhidrosis. We also excluded case series evaluating the effect of glycopyrronium bromide for the iontophoretic treatment of the plantar and

palmar skin (the licensed indication).

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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