Section: Physiology

Systematic Review Article

GLYCOPYRROLATE IN HYPERHIDROSIS: A SYSTEMATIC ANALYSIS TO INTROSPECT INTO THE PHYSIOLOGICAL BASIS OF ITS PHARMACO-KINETICS AND DYNAMICS

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ABSTRACT

Background: This systematic review examines the pharmacokinetics, pharmacodynamics, efficacy, and safety of glycopyrrolate, with a particular focus on its topical formulation for the treatment of primary hyperhidrosis. Glycopyrrolate, a synthetic muscarinic anticholinergic agent, exhibits structural differences from atropine, resulting in limited blood-brain barrier penetration and reduced central nervous system side effects. Originally synthesized in 1960, glycopyrrolate has evolved from oral and intravenous use for peptic ulcer disease and pre-operative medication to a promising topical therapy for hyperhidrosis.

The study reviewed 21 PubMed-indexed articles from 2018 to 2024, using standardized guidelines for systematic analysis. The findings highlight glycopyrrolate's competitive antagonism at muscarinic acetylcholine receptors, with a notable affinity for the M1 subtype. Key clinical trials, including the ATMOS-1 and ATMOS-2 studies, demonstrate the efficacy of glycopyrronium tosylate in reducing axillary sweat production with minimal systemic side effects. Patient-reported outcomes indicate improvements in sweating severity and quality of life metrics with once-daily topical application.

While systemic absorption of glycopyrrolate remains low, ensuring safety, rare side effects such as dry mouth, mydriasis, and skin irritation were noted. Limitations of existing studies include short trial durations and restricted age ranges of participants. Emerging alternatives, such as sofpironium bromide, show potential as adjunct or alternative therapies, pending comparative trials.

In conclusion, topical glycopyrrolate offers an effective and well-tolerated option for managing primary hyperhidrosis. Its targeted action minimizes systemic exposure, aligning with the physiological basis of sweat gland regulation. Further research on long-term use and comparative effectiveness with other agents will strengthen its role in clinical practice.

INTRODUCTION

3-[(Cyclopentilehydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidiniumbromide is popularly known as glycopyrronium bromide or glycopyrrolate. It is a synthetic muscarinic anti-cholinergic drug with structural similarity to atropine, a well-known naturally occurring anti-muscarinic agent. Glycopyrrolate was first synthesized in 1960. It is a racemic mixture of 3R,2S and 3S,2R stereo-isomers.[1,2] Glycopyrronium has a permanently charged quaternary amine function, in contrast to tertiary amine structure of atropine and scopolamine. Due to this structure, it is less bioavailable through oral intake and also has reduced permeability through the blood-brain barrier. This property helps in reducing systemic and especially CNS-related adverse effects on oral administration.[3]

Before moving into the pharmacokinetics and pharmacodynamics of glycopyrrolate, here is a brief recapitulation of anti-cholinergic receptors. [Table 1] After being identified as a possible neurotransmitter in 1914 by Henry Dale, in 1930s, acetylcholine (ACh) has been found to bind either to the nicotinic or the muscarinic receptor to exert its physiological effect.

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Table 1: Brief description of Acetylcholine receptors.[4-6]

Type	Mode of action	Sub-type	Location	Mode of Action	Function
Muscarinic (Post-ganglionic parasympathetic neuron and sympathetic cholinergic neuron to some sweat glands)	Through G protein-coupled receptors	M1	CNS, gastric parietal cells, salivary glands	Coupled to G_q protein	CNS stimulation, gastric and salivary secretion
		M2	Cardiac myocytes	Coupled to G_i protein	Cardiac inhibition
		M3	Exocrine glands and smooth muscles	Coupled to G_q protein	Sweating and salivation
		M4	CNS	Coupled to G_i protein	Inhibitory auto-receptors for acetylcholine
		M5	CNS	Coupled to G_q protein	Regulation of dopamine release in the brain and in rewarding brain stimulation
Nicotinic	Regulation of ligand-gated channel		Pre-synaptic	Ligand-gated ionic flux	Muscle contraction
			Axonal		
			Post-synaptic		

With this wide arena of physiological activity of ACh through different receptors, various anticholinergic drugs are on trial or in use for varied conditions including Parkinson's disease (PD), overactive bladder (OAB), chronic obstructive pulmonary disease (COPD), nausea and vomiting, peptic ulcer disease (PUD), depression and psychosis, and also pre-operative reduction in salivary and gastrointestinal secretions, as well as primary axillary hyperhidrosis.[7-11] Nicotinic receptor-antagonist either act as skeletal muscle relaxant (e.g. atracurium, tubocurarine, α-conotoxin), or on autonomic ganglion and adrenal medulla (e.g. trimethaphan, mecamylamine), or on CNS (e.g. mecamylamine, erysodine and α-conotoxin); whereas anti-muscarinic anti-cholinergic (e.g. natural alkaloids: atropine or scopolamine, and semi-synthetic/synthetic derivatives: ipratropium, triatropium, tolterodine) acts mainly as bronchodilators, urinary or gastro-intestinal anti-spasmodic, as mydriatic or in Parkinsonism. Glycopyrrolate is a member of anti-muscarinic group.[12-17]

Glycopyrrolate, a competitive antagonist of muscarinic acetylcholine receptor with high binding affinity to all 5 subtypes.[18] Although radio-ligand binding assay revealed the highest affinity to M1 subtype, and then M4, M5, M3 and M2 subtypes in seriatim.[19]

In 1961, glycopyrrolate was first marketed for oral use in tablet form for the treatment of peptic ulcer disease. Intravenous glycopyrrolate was tried in the 70s as a pre-medication before surgery in substitution of atropine.[20,21] During surgery, glycopyrrolate has been in use since long for its antisilogauge effect to reduce salivary secretion, also to reduce per operative respiratory secretion, and to prevent reflex bradycardia. In a study by Rumler MJ et al in 2014, significant ($P < 0.01$) reversal of reflex bradycardia (HR >70 bpm) and increase in respiratory rate were noted. Marked and sustained delay in the frequency of bowel movements (1.1 ± 0.2 h [saline group] vs. 6.0 ± 2.0 h [GLY group]) were also reported.[22] Topical formulation as cream or shower lotion containing 0.5-1% glycopyrrolate were investigated in the early 1970s as a treatment of primary hyperhidrosis.[20,23] Inhaled glycopyrrolate has been found to have long-acting bronchodilator effect.[24] In Canada and South Korea, glycopyrrolate has been approved as pads and wipes for primary hyperhidrosis. Topical glycopyrronium tosylate has received USFDA approval for the treatment of primary axillary hyperhidrosis.[25] Glycopyrrolate and its derivative, sofpironium bromide, are currently being investigated in clinical trials for primary axillary hyperhidrosis (NCT03658616, NCT03037788, NCT03627468, NCT02682238, NCT03024255).

Based on this background knowledge, our present study was designed to conduct a systematic review of the articles published on glycopyrrolate in PubMed-indexed journals spanning through 2018 to 2024.

MATERIALS AND METHODS

In order to explore the efficacy, mechanism of action and safety of glycopyrrolate as an anti-perspirant agent to treat hyperhidrosis, we have embarked on this literature search and systematic review of it, as depicted in the flowchart below (Flowchart 1).

Literature search for the meta-analysis was done solely in PubMed database, from the year 2018 till July 2024, and free full texts were selected for the systematic review (described in the following flowchart). The database was last searched and articles accessed on November 24th, 2024. Data and information from other review articles, RCT reports, and the June 2018 USFDA report were also used, but solely for review of literature and discussion sections.[25-30]

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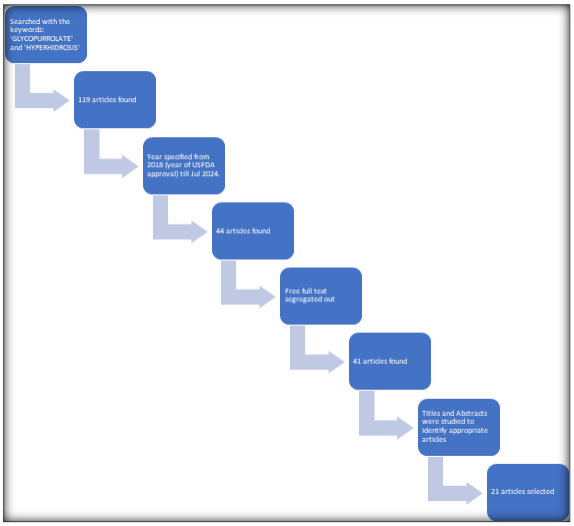

Flowchart 1: Methods of selecting articles for the systematic analysis

After thorough reading of the selected articles, significant findings (positive and/or negative) from these 21 PubMed-indexed articles were tabulated, and analysed. Relevant articles and reports referred in these articles were also accessed to make this article more inclusive.

To avoid any bias, three authors individually noted one-liner comments for these articles, and discussed to reach unanimously to the findings as stated below. Standard guidelines for systematic review were followed, but to provide a more extensive and encompassing view on the subject, databases like EMBASE, SCOPUS, etc should also be accessed and analysed

RESULTS

Based on the individual observations of all three authors, the unanimous findings were stated in the following table. The findings were assessed, analysed, correlated, and discussed.

All of the 21 selected articles were tabulated under the headings of title of the article, author(s), date of publication, reference, type of article and crucial findings. Crucial findings were incorporated through unanimous decision of the three authors after thorough discussions on their individual observations

Table 2: Observation and Findings of the Systematic Analysis

Sl No.	Title of the article	Author(s)	Date of publication	Reference	Type of article	Crucial findings
1	**Hyperhidrosis: Management Options**	John R. McConaghy & Daniel Fosselman	**2018/6**	31	**Review Article**	Suggested topical glycopyrrolate for cranio-fascial hyperhidrosis, but Inj botulinum toxin was said to have been used for palmar, plantar and axillary as well.
2	**Hyperhidrosis: disease aetiology, classification and management in the light of modern treatment modalities**	A Kisielnicka, A Szczerkowska-Dobosz, D Purzycka-Bohdan & RJ Nowicki	**2021/3**	32	**Review Article**	Whilst describing medical, surgical and pharmacological management modalities for hyperhidrosis, the ADRs (mild-moderate cholinergic effects) were also mentioned, along with the increased efficacy and limited reaction due to the retro-metabolic drug design
3	**Glycopyrronium Tosylate (Qbrexza) for Hyperhidrosis**	CE Nwannunu, AL Limmer, K Coleman, R Shah, RR Patel, UN Mui, SK Tyring	**2019/4**	33	**Review Article**	Review of the phase studies, ATMOS studies, clinical trials, focusing on the outcome, efficacy and safety of 2.5% glycopyrronium-soaked cloth for topical management of hyperhidrosis.
4	**Evaluation of Efficacy and Safety of Low Dose Glycopyrrolate in Management of Primary Hyperhidrosis---An Open Label Single Arm Study**	K Vyas, R Singh, A Kumari, M Balai	**2020/11**	34	**Letter to the Editor**	Following an open-label single arm study over a limited study population, authors concluded glycopyrrolate to be an effective, cost effective and safe treatment option for primary hyperhidrosis
5	**Management Strategies Of Palmar Hyperhidrosis: Challenges And Solutions**	S Gregoriou, P Sidiropoulou, G Kontochristopoulos, D Rigopoulos.	**2019/12**	35	**Review Article**	Whilst discussing all available treatment options for palmar hyperhidrosis, oral glycopyrrolate along with its efficacy and probable ADRs were also discussed
6	**Topical Glycopyrronium**	YN Lamb	**2019/11**	36	**Review Article**	Discussed the increased effectivity, decreased adverse

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	Tosylate in Primary Axillary Hyperhidrosis: A Profile of Its Use					events of glycopyrronium tosylate, vis-à-vis recommending its usage in both adults and children. Also, discussed about the mode of action, pharmacokinetics, and the two ATMOS studies.
7	**Hyperhidrosis: A Review of Recent Advances in Treatment with Topical Anticholinergics**	NS Wong, TM Adlam, GA Potts, M Farshchian	**2022/11**	37	**Review Article**	Discussed the clinical properties, mode of action and trial findings of topical anticholinergic treatment options for primary hyperhidrosis, with a positive outlook regarding USFDA-approved glycopyrronium tosylate
8	**Glycopyrronium (Qbrexza) Topical Wipes for Hyperhidrosis**	MJ Arnold, C O'Conner	**2019/9**	38	**Review Article**	Despite the great results of glycopyrronium tosylate in terms of efficacy, safety, tolerability, the steep price tag does call for it to not be used as first choice treatment for hyperhidrosis.
9	**Residual limb hyperhidrosis successfully managed with topical glycopyrrolate**	P Kotitsas, A Tsiogka, E Agiasofitou, V Markantoni, S Gregoriou, E Platsidaki, D Rigopoulos, G Kontochristopoulos	**2022/2**	39	**Letter to the Editor**	>75% improvement in residual limb hyperhidrosis with 2% glycopyrronium bromide. Besides emphasizing on the ADRs of systemic anticholinergic usage, topical agents has been identified as 'cost-effective and easily appliable'. Other than USFDA approved glycopyrronium tosylate, oxybutynine and glycopyrrolate (in various forms) 'have shown promising results'.
10	**Oral glycopyrrolate for primary focal hyperhidrosis in a pediatric population: A cross-sectional study**	HH Park, RRZ Conic, S Zhang, A Lieu, M Haft, GK Hightower	**2021/7**	40	**Letter to the Editor**	Better results are observed on usage of oral glycopyrrolate in patients, when topical therapy is inadequate.
11	**Limited Systemic Exposure with Topical Glycopyrronium Tosylate in Primary Axillary Hyperhidrosis**	DM Pariser, EL Lain, RD Mamelok, J Drew, DR Mould	**2021/1**	41	**Clinical Trial**	Focuses on reduced systemic absorption, thus reduced ADRs following topical application of GT
12	**Topical Glycopyrronium Tosylate for the Treatment of Primary Axillary Hyperhidrosis: Patient-Reported Outcomes from the ATMOS-1 and ATMOS-2 Phase III Randomized Controlled Trials**	DM Pariser, AA Hebert, J Drew, J Quiring, R Gopalan, DA Glaser	**2019/2**	42	**Clinical Trial**	PROs showed significant improvement in ASDD, PGIC, DLQI, HDSS and WI items following application of GT. This is based on the Phase III RCTs.
13	**Glycopyrronium tosylate in pediatric primary axillary hyperhidrosis: Post hoc analysis of efficacy and safety findings by age from two phase three randomized controlled trials**	AA Hebert, DA Glaser, L Green, WP Werschler, DW Forsha, J Drew, R Gopalan, DM Pariser	**2019/1**	43	**Clinical trial**	Topical GT (OD usage) gave promising results amongst all age groups, with significantly less ADRs, at par with various anticholinergics

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14	**A glycopyrronium bromide 1% cream for topical treatment of primary axillary hyperhidrosis: efficacy and safety results from a phase IIIa randomized controlled trial**	C Abels, M Soeberdt, A Kilic, H Reich, U Knie, C Jourdan, K Schramm, S Heimstaedt-Muskett, C Masur, R-M Szeimies	**2021/8**	44	**Clinical Trial**	Topical 1% GPB in PAHH shows increased efficacy and decreased ADR.
15	**Topical glycopyrronium tosylate in Japanese patients with primary axillary hyperhidrosis: A randomized, double-blind, vehicle-controlled study**	H Yokozeki, T Fujimoto, S Wanatabe, S Ogawa, C Fujii	**2022/1**	45	**Clinical Trial**	Following the USFDA approval of topical GT in PAHH, similar trial was undertaken in a multi-centric fashion in Japan, which also revealed a similar result of better outcome with a reasonable risk-benefit profile
16	**A dramatic case of diabetic gustatory hyperhidrosis successfully treated with topical glycopyrrolate**	V Patel, K Rudningen, B Shields	**2021/10**	46	**Case Report**	Resolution of DGH on application of topical 2% GPB. Although there is a dilemma regarding GPB's local effect and systemic absorption since effective amount of drug used per month in topical usage is many times higher than oral medication, irt ADRs author used the phrase 'atleast no worse than with the oral dosing'. Author also emphasized on the huge financial burden it would incur on the patient.
17	**Topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: Results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials**	DA Glaser, AA Hebert, A Nast, WP Werschler, L Green, R Mamelok, J Drew, J Quiring, DM Pariser	**2019/1**	47		Report based on the ATMOS studies suggests increased efficacy of GT with mild-moderate ADRs and negligible study discontinuation among participants.
18	**Long-term efficacy and safety of topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: Post hoc pediatric subgroup analysis from a 44-week open-label extension study**	AA Hebert, DA Glaser, L Green, C Hull, J Cather, J Drew, R Gopalan, DM Pariser	**2020/5**	48	**RCT**	With no TEAEs and 33% LSRs, long-term GT usage for primary axillary hyperhidrosis (PAH) showed fairly high tolerance rate
19	**A 44-Week Open-Label Study Evaluating Safety and Efficacy of Topical Glycopyrronium Tosylate in Patients with Primary Axillary Hyperhidrosis**	DA Glaser, AA Hebert, A Nast, WP Werschler, L Green, RD Mamelok, J Quiring, J Drew, DM Pariser	**2019/8**	49	**Clinical Trial**	48-month long-term usage of GT was fairly tolerated with high efficacy and negligible safety issues.
20	**Treatment of Axillary Bromhidrosis with Topical 2% Glycopyrronium Bromide Cream: A Prospective, Non-randomized, Open-label Study**	S Gregoriou, V Markantoni, A Campanati, E Martina, A Offidani, A Kouris, E Platsidaki, H Bokotas, A Stratigos, D Rigopoulos, G Kontochristopoulos	**2021/11**	50	**Clinical Trial**	Emphasizes on effectiveness and of 2% GPB upon 8-week usage for axillary bromhidrosis

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21	**Cost-effectiveness of topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis**	LM Bloudek, KK Gillard, VB Nguyen, SZ Klein	**2021**	51	**Clinical Trial**	GT was found to be cost-effective compared to aluminium chloride, considering cost per QALY gain

After preparing the above table very meticulously through intensive critical judgements by all three authors, extensive discussions were made on the issue, as detailed in the following section.

DISCUSSION

Through systematic analysis of all the literature under our study domain, it is indicative that GT is effective in primary axillary hyperhidrosis with very less systemic adverse effect. ATMOS studies 1 and 2 are very specific in this regard as phase III RCT to study patient-reported outcomes (PROs). ATMOS 1 and 2 were basically phase III randomized double-blind, vehicle controlled, parallel group, 4-week trials of GT 3.75% (2.4% glycopyrronium equivalent), of which ATMOS 1 was conducted in USA and Germany and ATMOS 2 in USA only. 344 patients were recruited in ATMOS 1 and 353 in ATMOS 2; of which more than 90% completed the 4-week trials. The cohort consisted of ≥ 9 years aged non-pregnant females and males with primary axillary hyperhidrosis for ≥6 months with score of ≥4 on the 11-point scale of ASDD and grade 3-4 on the 4-point scale of HDSS, and gravimetrically ≥50mg/5min axillary sweat production.[52,53] Axillary Sweating Daily Diary (ASDD), Hyperhidrosis Disease Severity Scale (HDSS), 6-weekly impact (WI) items, Patient Global Impression of Change (PGIC) and Dermatology Life Quality Index (DLQI) were utilized to evaluate PROs in these trials. Cochran-Mantel-Haenszel (CMH) test was used to analyse the data statistically. Greater improvement with GT compared to vehicle was observed through different items of PROs. Major limitation of either ATMOS trials was relatively short duration (4-weeks) of study for such a chronic condition; to overcome this, Glaser et al conducted a 44-week study.[49] Another drawback was that participants under 16 years of age did not complete ASDD item 3 and 4, WI items or the PGIC, but both the trials concluded positively regarding once daily application of GT as a non-invasive and well-tolerated treatment option for primary axillary hyperhidrosis.[42]

Though rare, mydriasis could be found in some of its users – usually bilateral; but unilateral particularly non-paediatric participants of <16 years of age. It had been thought that these participants might have touched one eye with finger after application of GT.[41,42,53] Very rarely few cases of dryness of mouth or urinary retention were reported.[47,49] Slight oedema and more persistent erythema were reported.[55] Elston (2018) suspected a link between long-term use of drugs with anti-cholinergic effect and dementia;[56] but for topical glycopyrrolate it is rarely possible as discussed below.

Penetration of glycopyrronium was low with 2% and 7% concentrations after 30 and 100 minutes as it moderately penetrates through the skin to reach the target receptors of the sweat glands, but overall permeation through the stratum corneum is very little to have any biologically relevant systemic exposure. Hence, glycopyrronium tosylate is a well-tolerated molecule on topical application for PAH.

Glycopyrrolate was first approved by USFDA in 1961 for adjunctive use in peptic ulcer disease in adults, and since 1975 as pre-operative or intra-operative medication in children >2 years and adults, to reduce salivary, tracheobronchial and pharyngeal secretions. Oral, intravenous, inhalational administration have been supplemented, recently over the last few years, with topical application. In June 2018, USFDA approved GT in the form of clothes for topical treatment of primary axillary hyperhidrosis in children >9 years of age and in adults.[47,49]

There are few other topical agents for treating hyperhidrosis, like aluminium salts, oxybutynin, etc. Aluminium chloride hexahydrate and aluminium zirconium tetrachlorohydrex are common aluminium salts used in cosmetic preparations as anti-perspirants. They act by precipitating with muco-polysaccharides to form superficial plugs causing mechanical obstruction to the distal eccrine sweat gland ducts.[57] Long-term blockage of these ducts eventually degenerates the eccrine cells both functionally and structurally; thus, yielding in long-term reduction in hyperhidrosis severity over time.[58] Except some mild and transient skin irritation,[59] these are basically safe and are not found to be related to Alzheimer's disease, breast cancer, or to have any genotoxic or carcinogenic effect.[60] 3% oxybutynin topical gel has longer duration of action as anti-perspirant in axillary region. Irritation being the common local side-effect, serious side-effects are rarely observed as trans-dermal application, as it bypasses the hepatic and gastro-intestinal first pass metabolism leading to less formation of inactive metabolite, N-desethyloxybutynin (N-DEO). Hence, more availability of oxybutynin in system results in higher incidences of anti-cholinergic side effects like xerostomia, blurred vision, constipation, difficulty in urination, cognitive and memory deficiency.[61] It could also passively defuse as gel form across stratum corneum.[62]

Sofpironium bromide, a newer derivative of glycopyrrolate, underwent a latest phase II double-blind RCT with 0.05, 0.1, 0.15 concentrations of active ingredient in gel form. It yielded in good efficacy of this derivative as antiperspirant in PAH with mild to moderate SE. It could be promising

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alternative to GT if a head-to-head trial be undertaken.[19,32,63]

CONCLUSION

Glycopyrrolate is in use as oral, parenteral and inhalational drug forms for various indications. Inhalational use in obstructive airway disease and as intramuscular injection in pre-anaesthetic medication are regularly done in India. Depending on the route of administration, pharmacokinetics of glycopyrrolate – its absorption, distribution, metabolism and excretion – vary widely. Systemic side-effects are also observed at different levels according to the route of administration and dosage. These aspects need separate systematic analysis in greater details for better understanding of the pharmacokinetics and pharmacodynamics of the molecule. In the present article we could conclude that once daily topical application of GT even at single location could control primary axillary hyperhidrosis in both armpits among susceptible population. These could have been possible only because minimum absorption of topical GT could block the relevant muscarinic receptors of sweat glands in contralateral axilla also, without exerting any significant side-effect. Thus, topical GT could be recommended as a good pharmacotherapy in PAH, conforming to the physiology of hyperhidrosis.

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