Received: 13 July 2023 | Accepted: 6 October 2023

DOI: 10.1111/opo.13245

OPO THE COLLEGE OF OPTOMETRISTS

REVIEW ARTICLE

Barriers and enablers to medication adherence in glaucoma: A systematic review of modifiable factors using the Theoretical Domains Framework

Deborah Bott | **Ahalya Subramanian** | **David Edgar** | **John G. Lawrenson** | **Peter Campbell**

Department of Optometry and Visual Sciences, School of Health and Psychological Sciences, City, University of London, London, UK

Correspondence
Deborah Bott, Department of Optometry and Visual Sciences, School of Health and Psychological Sciences, City, University of London, London, UK.
Email: deborah.bott.1@city.ac.uk

Funding information
College of Optometrists

Abstract

Purpose: Nonadherence to medication reduces treatment effectiveness, and in chronic conditions it can significantly reduce health outcomes. In glaucoma, suboptimal adherence can lead to sight loss, which places a greater financial burden on society and reduces patients' quality of life. Interventions to improve adherence have so far had limited success and lack robust theoretical underpinnings. A better understanding of the determinants of medication adherence behaviour is needed in order to develop interventions that can target these factors more effectively. This systematic review aims to identify modifiable barriers and enablers to glaucoma medication adherence and identify factors most likely to influence adherence behaviour.

Recent Findings: We searched CINAHL, MEDLINE, PsycINFO, EMBASE, the Cochrane Library and sources of grey literature up to August 2022 for studies reporting determinants of glaucoma medication adherence. Data describing modifiable barriers/enablers to adherence were extracted and analysed using the Theoretical Domains Framework (TDF), a behavioural framework consisting of 14 domains representing theoretical factors that most likely influence behaviour. Data were deductively coded into one of the TDF domains and inductively analysed to generate themes. Key behavioural domains influencing medication adherence were identified by frequency of study coding, level of elaboration and expressed importance. Eighty-three studies were included in the final synthesis. Four key domains influencing glaucoma medication adherence were identified: 'Environmental Context and Resources', 'Knowledge', 'Skills' and 'Memory, Attention and decision processes'. Frequently reported barriers included complex eyedrop regimens, lack of patient understanding of their condition, forgetfulness and difficulties administering eyedrops. Whereas simplified treatments, knowledgeable educated patients and good patient–practitioner relationships were enablers to adherence.

Summary: We identified multiple barriers and enablers affecting glaucoma medication adherence. Four theoretical domains were found to be key in influencing adherence behaviour. These findings can be used to underpin the development of behaviour change interventions that aim to improve medication adherence.

KEYWORDS
barriers, determinants of health behaviour, enablers, glaucoma, treatment adherence and compliance

INTRODUCTION

Glaucoma is characterised by a group of optic neuropathies that, if left untreated, leads to progressive irreversible sight loss. In 2020, glaucoma was the second most common cause of global blindness.[1] With a projected worldwide increase in the prevalence to 111.8 million people by 2040,[2] it is likely the number of individuals visually impaired from glaucoma will also increase.

The only proven treatment to slow or halt disease progression is lowering intraocular pressure (IOP).[3] Therapy is frequently achieved by the instillation of daily eyedrops on a lifelong basis, but to achieve therapeutic benefits, ongoing medication adherence is required. For example, if medication is not routinely administered, it will not be effective, potentially leading to sight loss. Traditionally, the term compliance has been used to describe the extent to which a patient follows practitioner recommendations. However, due to a better understanding of patient–practitioner dynamics, compliance has largely been superseded by the term 'adherence'. Compliance suggests a passive act by the patient to follow orders, whereas adherence implies a behavioural change, in response to an agreed plan, to achieve actual medication use.[4] Adhering to ocular hypotensive medication involves four key steps requiring a change in patient health-related behaviour[5]: (a) obtain repeat prescriptions; (b) correctly instil eyedrops; (c) instil eyedrops every day and (d) at the appropriate time.[6] Nonadherence can occur at any of these four steps.

Nonadherence to long-term medication, especially in chronic diseases, is known to be significant (e.g., in systemic hypertension), and in developed countries it averages 50%.[6] Studies reporting glaucoma nonadherence rates report variable estimates, for example, 5%–80%[7] and 30%–70%,[8] depending on how adherence is measured or defined. With an ageing global population[9] at increased risk of developing glaucoma, together with advancements in technology and diagnostic roles, more cases are likely to be diagnosed and managed. It is imperative that those commencing treatment are adherent since suboptimal adherence is related to poor clinical, social and economic outcomes for both patients and society.[10-14] It is equally important that clinicians understand the factors that influence patients taking eyedrops in order to provide more tailored strategies to improve medication adherence.

Interventions to improve adherence have been utilised in health conditions by targeting a change in patient behaviour.[15] However, in glaucoma they have had limited success and lack a robust theoretical underpinning.[15-18] An intervention to improve adherence is more likely to be effective if it addresses the causal determinants of medication adherence behaviour.[19] Determinants can be enablers, barriers or mixed: an enabler facilitates taking medication, a barrier hinders medication taking and mixed determinants can facilitate or hinder medication taking.

Key points

- A multifactorial perspective is required to understand what influences medication adherence.
- Theoretical determinants (barriers/enablers) operating at the level of patient, healthcare professional and healthcare system were identified for glaucoma medication adherence.
- The theory-driven influences we identified in glaucoma medication adherence can be used to inform the development of behaviour change interventions that seek to improve adherence.

The Theoretical Domains Framework (TDF) provides a consensus framework for understanding behaviour change and informing intervention design.[20] The TDF, a validated framework developed by experts in health and behavioural science, consists of a synthesis of a number of behaviour change theories clustered into 14 overarching theoretical domains. Each domain represents a set of related constructs that explain potential determinants of behaviour. For example, the 'Knowledge' domain includes the constructs 'knowledge (including knowledge of condition/scientific rationale)', 'procedural knowledge' and 'knowledge of task environment'.

The TDF benefits from being linked to evidence-based behaviour change techniques.[21] Hence, the TDF key determinants of adherence behaviour, which are suitable for targeting with a behaviour change intervention, can be identified and mapped to appropriate behaviour change techniques to aid intervention development.

The TDF has been used in systematic reviews within eyecare,[22-24] and reviews investigating determinants of medication adherence in diseases such as bipolar disorder,[25] but to date, it has not been used in the context of glaucoma medication adherence.

The aim of this review was to identify factors affecting glaucoma medication adherence. The specific objectives were to: (a) systematically review the evidence that identifies modifiable behavioural determinants (barriers/enablers) of adherence to prescribed glaucoma medication; (b) extract the reported modifiable determinants and categorise them according to TDF domains and (c) identify the most important domains that influence adherence using pre-determined criteria.

METHOD

The study protocol was pre-registered with PROSPERO (CRD42022330637) and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=330637.

Eligibility criteria

Primary studies of any empirical design, describing modifiable determinants of glaucoma medication adherence in adults were included. Non-primary studies, systematic or non-systematic reviews, conference abstracts, commentaries, editorials, studies relating to non-prescribed medications, studies reporting on unmodifiable factors (e.g., age, race) or factors not modifiable within an ophthalmology setting (e.g., treatment for depression) were excluded.

Search strategy

Five bibliographic databases were searched—CINAHL Complete, MEDLINE Complete, PsycINFO (via EBSCO*host*), EMBASE and the Cochrane Library (via OVID). The search terms were classified into three concepts: 'barrier or enabler', 'adherence' and 'glaucoma medication' and adapted for each database accordingly. An example search strategy for MEDLINE is provided in Appendix S1. The search was restricted to studies reported in English and conducted from inception to August 2022.

Grey literature was identified using the following strategy: Google (limited to the first five pages of results), searching the National Grey literature collection (http://allcatsrgrey.org.uk/wp/) and the patient experience library (https://www.patientlibrary.net/cgi-bin/library.cgi?page=Welcome;prevref=).

Screening

Retrieved studies were uploaded to Zotero (https://www.zotero.org/), an online reference management tool where duplicates were removed. Following the elimination of duplicates, one author (DB) screened the abstracts of all identified records against pre-determined inclusion/exclusion criteria. One hundred records (approximately 25%) were rescreened by a second author (PC) to check for screening reliability. Cohen's kappa was calculated as 0.89, which represents high agreement.[26] The remaining eligible records had their full texts retrieved and screened by one reviewer (DB). Full-text screen reliability was calculated for 39 studies (28%) between DB and a second author (DE) with a similarly high agreement (Cohen's kappa = 0.78). Throughout the screening process, any uncertainty regarding eligibility was resolved by consensus or, if needed, discussed with a third reviewer (PC or DE).

Data extraction and analysis

Data analysis followed a standard four-step method using a content and framework analysis approach (see Figure 1), as described in previous systematic reviews using the TDF.[22,23]

Step 1: Data extraction

Data extraction was piloted on five studies and discussed by the whole review team. Two authors (DB and DE) then extracted data from the remaining studies and uploaded the results to Microsoft Excel (Microsoft.com). The extracted data included author, date, study aims and design, country, patient demographics, conditions treated, medications, duration of follow-up, adherence measures, extent of adherence, data collection methods, data analyses and modifiable determinants of adherence. Extracted determinants comprised participant quotations from qualitative studies, statistical analysis findings from quantitative studies or authors' interpretations of study results. Eighteen studies (22%) had data extraction reassessed by another reviewer (PC), and any minor disagreements found were resolved by discussion.

Step 2: Deductive analysis (TDF coding)

The extracted data were mapped to one of the 14 TDF domains. To aid mapping decisions, a codebook including definitions for each domain was developed (see Appendix S2). The codebook went through several iterations to reflect the increased knowledge gained from exposure to more studies. Three reviewers (DB, PC and DE) collaboratively piloted coding for five studies, using the codebook as a guide.

The remaining studies were independently coded by two reviewers (DB and DE). Data were only coded in the single most salient domain. Finally, DB and DE reviewed their co-reviewers' coding decisions for each study, and any disagreements were discussed until consensus was achieved, with input from a third reviewer (PC) if required.

Step 3: Inductive analysis (thematic synthesis)

One reviewer (DB) sifted and sorted the data coded for each TDF domain, grouping determinants of medication adherence into overarching themes/subthemes representing similar patterns. DE reviewed and verified all generated themes/subthemes. Any disagreements were resolved by discussion or, if needed, with another reviewer (PC).

Step 4: Identification of important domains

The importance of each domain, as identified in step 2, in influencing glaucoma medication adherence was determined using a previously established set of importance criteria:[22] (a) frequency (the number of studies identified per domain and the number of barriers/enablers identified per domain); (b) level of elaboration (number of themes/subthemes generated within each domain) and (c) expressed importance (denoted by study authors' comments

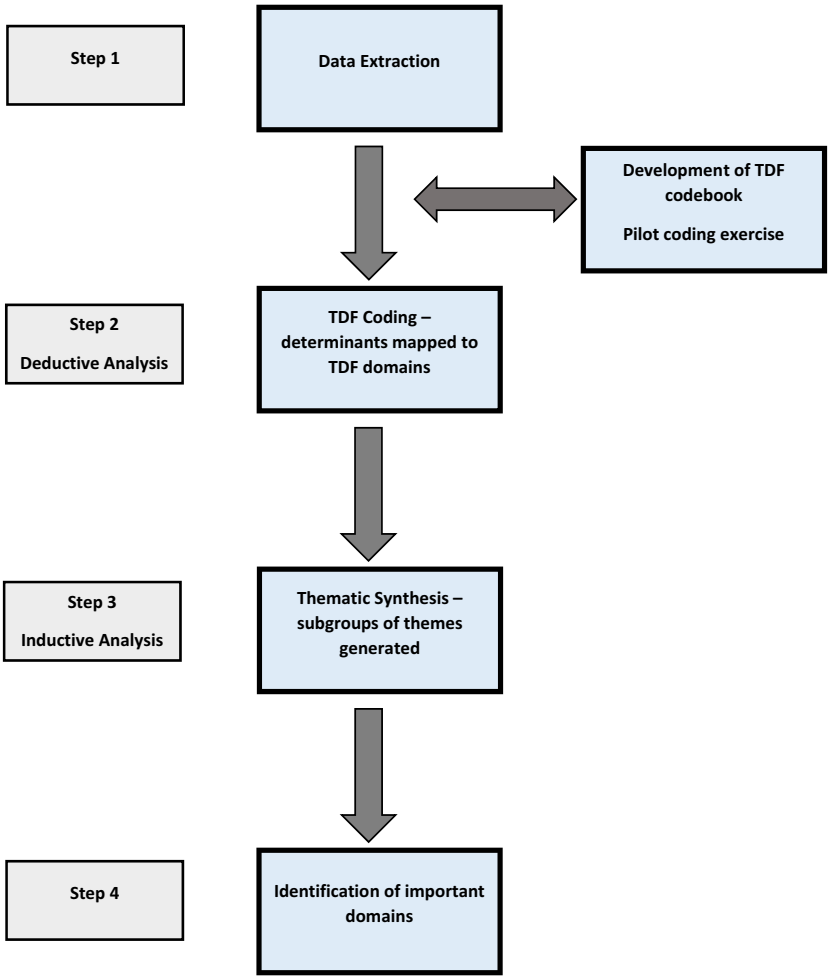

FIGURE 1 Flow chart representing the four-step method of data analysis. Abbreviation: TDF, Theoretical Domains Framework.

in discussion and quotations from study participants signifying importance or statistically significant findings).

Quality assessment

The Mixed Methods Appraisal Tool (MMAT) version 2018 was used to assess study quality as it is a single tool, with good content validity, that enables concomitant appraisal of different study designs.[27] Initially, four reviewers (DB, DE, PC and JGL) appraised 10 studies (12%) as a training exercise. Two of these reviewers (DB and DE) then quality assessed the remaining studies independently. Any disagreements in study quality were resolved by discussion until consensus was achieved, with input from a third reviewer (PC) if necessary.

RESULTS

From the initial total of 565 identified records (comprising 553 from the database search and 12 from other sources such as grey literature), 167 duplicates were removed, and after screening the titles and abstracts, 150 were eligible for full-text screening. From these 150 records, 83 were included in the final synthesis. Overall, the main reason for excluding records was that the reported determinants were non-modifiable. Figure 2 outlines the process of identifying included eligible studies.

Study characteristics

Nearly half of the eligible studies ($n = 34$, 41%) were conducted in the United States, 15 studies (18%) were from developing countries (as defined by the Organisation for Economic Co-operation and Development[28]) and 3 studies (4%) were conducted in more than one country. Most studies ($n = 75$, 90%) reported determinants from a patient perspective, and 7 (8%) were multiperspective in scope, describing determinants from both patient and practitioner viewpoints. No studies reported determinants from a carer's perspective.

Of the 71 studies that reported medication adherence levels, 48 (68%) measured adherence subjectively, either by questionnaire, survey or interview, and 20 (28%) measured

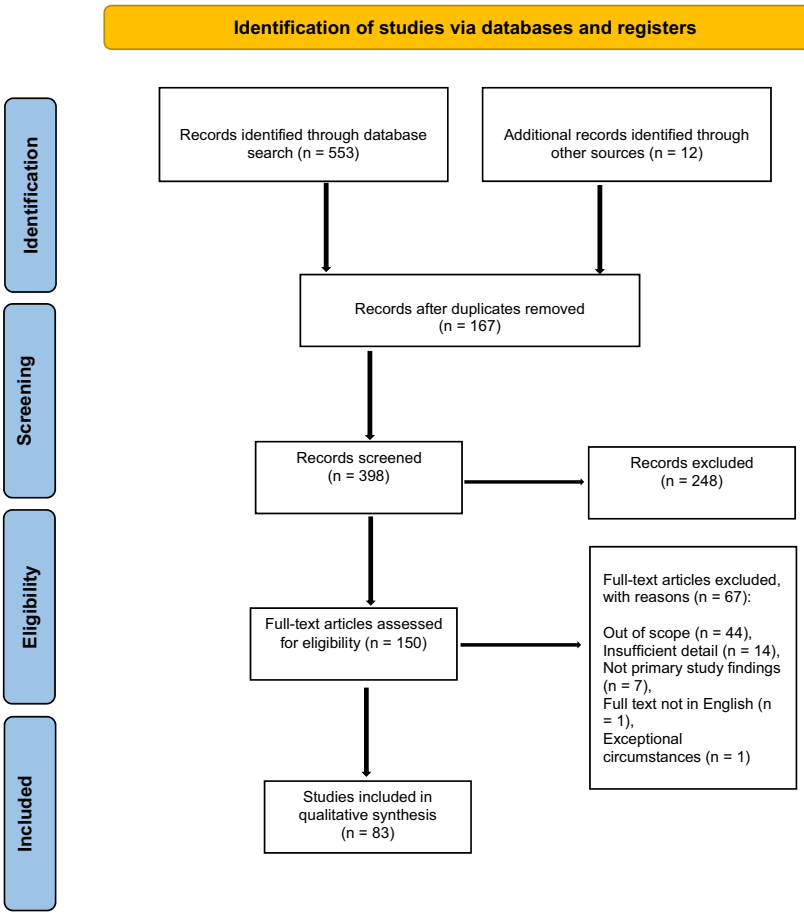

FIGURE 2 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram.

adherence objectively using pharmacy databases, electronic monitoring systems or weighing of the eyedrop bottle. Three studies (4%) measured adherence both subjectively and objectively. Sample sizes varied between 20 and 12,899. The included studies were published between 1977 and 2022.

An overview of the included study characteristics is shown in Table 1, with a more detailed analysis in Appendix S3.

Quality assessment

A summary of the overall quality of the included studies can be found in Table 2,[112] with a more detailed analysis provided in Appendix S4. In general, mixed methods and qualitative studies were reported as being of very high quality, while quantitative studies were of reasonable to high quality. The main sources of bias were due to adherence measurement tools not being validated or piloted prior to administration. Other sources of bias related to the sample not being representative of the target sample and lack of detailed information regarding participant selection processes or response rates, and these lead to several 'Cannot tell' decisions on quality.

Outcomes

Deductive analysis

In total, 579 units of data (234 modifiable enablers and 345 modifiable barriers) were extracted and coded to relevant TDF domains. For example, the extracted data 'non adherent patients were less aware of the permanent nature of glaucoma compared to adherent patients' was assigned to the *Knowledge* domain as a barrier. An example quotation from a qualitative study, 'I think it's when you go and do other things that take you away from the general routine, then you might forget it', was mapped to the *Environmental Context and Resources* domain as a barrier. Both enablers and barriers were extracted from the majority of studies ($n = 60$, 72%), whereas enablers only were extracted from 8 (10%) studies and barriers only from 15 (18%) studies. Overall, determinants spanned all 14 domains. For *Optimism*, no barriers were identified.

Inductive analysis

In total, 32 themes and 24 subthemes were generated from the coded determinants.

TABLE 1 An overview of the included study characteristics.

Study characteristics	Frequency *N* (%), Total number of studies *N* = 83
Study location[a]	
North America	37 (45)
Asia	22 (27)
Europe	18 (22)
Africa	7 (8)
Australia	6 (7)
Study design	
Quantitative	72 (87) of which 24 (33) were quantitative non-randomised and 48 (67) were quantitative descriptive
Qualitative	8 (10)
Mixed methods	3 (4)
Reported adherence rate[b]	
Subjectively	48 (68)
Objectively	20 (28)
Subjectively and Objectively	3 (4)
Determinants reported from	
Patient perspective	75 (90)
Practitioner perspective	1 (1)
Patient and practitioner perspective	7 (8)

[a]Three studies conducted in multiple countries.
[b]Seventy-one studies reported adherence rate.

TABLE 2 Summary of the quality of the included studies.

Study	Quality *	**	***	****	*****
Qualitative studies					
Dreer et al.[29]					*****
Lacey et al.[30]					*****
Mansberger et al.[31]					*****
Newman-Casey et al.[32]					*****
Nordmann et al.[33]					*****
Park et al.[34]					*****
Taylor et al.[35]					*****
Tsai et al.[36]					*****
Quantitative non-randomised studies					
Barker et al.[37]				****	
Boland et al.[38]				****	
Carpenter et al.[39]				****	
Castel et al.[40]					*****
Cook et al.[41]			***		
Dasgupta et al.[42]				****	
Djafari et al.[43]			***		
Friedman et al.[44]			***		
Gurwitz et al.[45]				****	
Gurwitz et al.[46]					*****
Hwang et al.[47]					*****
Kashiwagi et al.[48]				****	
Newman-Casey et al.[49]					*****
Nordstrom et al.[50]					*****
Norell et al.[51]				****	
Owen et al.[52]					*****
Reardon et al.[53]					*****
Sanchez et al.[54]				****	
Shirai et al.[55]				****	
Sleath et al.[56]				****	
Sleath et al.[57]				****	
Stein et al.[58]					*****
Welge-Lussen et al.[59]			***		
Zhu et al.[60]				****	
Quantitative descriptive studies					
Anbesse et al.[61]				****	
Balkrishnan et al.[62]				****	
Bloch et al.[63]				****	
Chen et al.[64]			***		
Day et al.[65]					*****
Effendi et al.[66]		**			
Friedman et al.[67]			***		
Gelb et al.[68]			***		
Gray et al.[69]					*****
Guven et al.[70]				****	

Identification of important domains

The following three criteria were used to identify the important domains influencing glaucoma medication adherence, and details are given in Table 3.

1. *Frequency*: TDF domains scored according to the number of studies and determinants identified per domain. The highest number of studies ($n = 70$) were mapped to the *Environmental Context and Resources* domain, which also generated the greatest number of barriers ($n = 146$) and enablers ($n = 51$). This was followed by the *Skills* and *Knowledge* domains, which contained similar numbers of studies ($n = 45$ and $n = 49$, respectively) and total number of determinants ($n = 90$ and $n = 81$, respectively).
2. *Level of elaboration*: TDF domains scored according to the number of themes and subthemes identified. Again, the *Environmental Context and Resources* domain generated most themes/subthemes ($n = 6/n = 7$). *Knowledge*, *Skills* and *Beliefs about consequences* were the next highest-ranked domains.
3. *Expressed importance*: TDF domains scored according to the number of times authors/participants expressed a

TABLE 2 (Continued)

Study	Quality *	**	***	****	*****
Hoevenaars et al.[71]				****	
Kawai-Tsuboi et al.[72]			***		
Kayode et al.[73]				****	
Khaled et al.[74]		**			
Khandekar et al.[75]					*****
Kholdebarin et al.[76]				****	
Kim et al.[77]			***		
Konstas et al.[78]			***		
Lai et al.[79,a]		**			
Loon et al.[80]			***		
Lunnela et al.[81]				****	
Mansouri et al.[82]				****	
Masoud et al.[83]		**			
McClelland et al.[84]				****	
Mehari et al.[85]					*****
Mowatt et al.[86]			***		
Newman-Casey et al.[87]					*****
O'Hare et al.[88]			***		
Olthoff et al.[89]					*****
Omolase et al.[90]			***		
Onwubiko et al.[91]			***		
Osman et al.[92]			***		
Patel et al.[93]	*				
Ramesh et al.[94]			***		
Rees et al.[95]				****	
Rees et al.[96]				****	
Schwartz et al.[97]				****	
Sleath et al.[98]			***		
Sleath et al.[99]				****	
Sleath et al.[100]			***		
Sleath et al.[101]		**			
Stewart et al.[102]			***		
Suet et al.[103]				****	
Stringham et al.[104]				****	
Tamrat et al.[105]			***		
Tshivhase et al.[106]					*****
Tsumura et al.[107]			***		
Wolfram et al.[108]		**			
Mixed Methods studies					
Gatwood et al.[109]				****	
Killeen et al.[110]					*****
Spencer et al.[111]					*****

Note: ***** denotes 100% quality criteria met; **** denotes 80% quality criteria met; *** denotes 60% quality criteria met; ** denotes 40% quality criteria met; * denotes 20% quality criteria met.

[a]The main study was a randomised control trial, but for this review, the relevant part was a pre-RCT questionnaire and classified as 'quantitative descriptive'.

level of importance. The expressed importance was determined by:

- Study authors' comments in discussion sections or throughout the paper, for example, 'another notable finding…', 'physicians most often identified…' or 'an important theme that arose…'.
- Direct quotations from study participants signifying importance, for example, 'the older you get, the more important it is to establish a routine'.
- Notable statistically significant findings not reflected in the study authors' comments, for example, 'having difficulties in reading the labels and identifying the eye drop bottles significantly affected adherence'.

Initially, the intention was to only use study authors' comments or participants' direct quotations to define expressed importance; however, this strategy was adapted post-hoc, and a number of the most notable, statistically significant findings were included, reflecting the preponderance of quantitative studies (87%) and the relative dearth of qualitative studies (8%). Extracted data items deemed to express a level of importance using the above criteria were assigned a point, and totals for each domain were calculated to determine the overall level of expressed importance. Again, the *Environmental Context and Resources* domain ranked highest, followed by *Knowledge*, *Skills*, and *Memory, Attention and decision processes*.

Combining results from frequency, level of elaboration and expressed importance, we identified the most important domains influencing glaucoma medication adherence as *Environmental Context and Resources*, *Knowledge*, *Skills*, and *Memory, Attention and decision processes* (See Table 4). Good convergence between all three importance criteria (frequency, level of elaboration and expressed importance) was demonstrated. Appendix S5 lists all TDF domains in order of importance.

The following narrative description documents theoretical domains and themes/subthemes of high importance that influence glaucoma medication adherence. (A tabular summary can be found in Table 5.) The remaining themes and corresponding TDF domains can be found in Appendix S6, together with illustrative examples.

Environmental Context and Resources

The main themes within this domain were treatment considerations, financial circumstances, patient-related factors, existence of side effects, eye clinic factors and pharmacy issues.

Treatment considerations, as identified in 46 studies, relate to the class/type of drug or eyedrop regimen. The type/class of drug prescribed either aided or hindered adherence. Consistently, prostaglandin analogues (PGAs)

TABLE 3 Theoretical Domains Framework (TDF) domains by level of frequency, level of elaboration and expressed importance.

	Frequency			Level of elaboration		
TDF domain	**Number of studies identifying domain**	**Number of barriers**	**Number of enablers**	**Number of themes**	**Number of subthemes**	**Expressed importance**
Knowledge	49	37	44	3	6	33
Skills	45	65	25	3	4	30
Social professional role and identity	7	2	5	2	0	5
Beliefs about capabilities	10	2	12	3	0	8
Optimism	1	0	1	1	0	0
Beliefs about consequences	25	25	20	2	4	15
Reinforcement	9	2	10	2	0	8
Intentions	3	1	3	1	0	0
Goals	5	2	4	1	0	4
Memory, Attention and decision processes	38	38	6	2	0	29
Environmental Context and Resources	70	146	51	6	7	57
Social influences	16	9	18	3	0	12
Emotion	19	12	16	2	0	10
Behavioural regulation	18	4	19	1	0	0

TABLE 4 The four most important Theoretical Domains Framework domains as identified by frequency, level of elaboration and expressed importance.

Frequency	**Level of elaboration**	**Expressed importance**	**Top four domains**
Environmental Context and Resources	Environmental Context and Resources	Environmental Context and Resources	Environmental Context and Resources
Skills	Knowledge	Knowledge	Knowledge
Knowledge	Skills	Skills	Skills
Memory, Attention and decision processes	Beliefs about consequences	Memory, Attention and decision processes	Memory, Attention and decision processes

were associated with better adherence than other types of IOP-lowering medication.[40,43,53] A large study, conducted in the United States with over 1000 participants, evaluated persistency rates with four different classes of glaucoma monotherapy in newly diagnosed patients and found those using PGAs were 'less likely to discontinue therapy than patients receiving β-blockers…, CAIs [Carbonic Anhydrase Inhibitors], …or brimonidine'.[42] Unpreserved medications were associated with better adherence levels compared with medications containing preservatives.[108]

Complex eyedrop regimens and issues with dosing schedules were barriers to adherence.[29,62,65] Midday was reported to be the most inconvenient administration time, as patients were often too busy to instil eyedrops.[35,51,111] The number of glaucoma medications to be administered had a mixed effect on adherence. One study[45] reported poorer adherence was associated with fewer eyedrops, whereas another investigation found improved adherence with fewer eyedrops.[55] Both patients and practitioners, in a multiperspective Japanese study, reported that a greater number of eyedrops and more frequent instillations negatively affected adherence.[107]

Finance, as identified in 28 studies, was a barrier to adherence. Difficulties paying for eyedrops[41,61,79]: self-funding,[85,94,105] high medication co-payments[49,58] or not having health insurance[36,92] contributed to poorer adherence. For example, a participant commented, 'They told me to use [the drops] for both eyes, but due to lack of money I used only for one [eye]. I used only for left eye; if [I was using it in both eyes] the drops would have run out long back'.[110] Studies conducted in countries where patients had health insurance plans covering all/the majority of their medical expenses (e.g., Japan, South Korea) reported good adherence rates.[48,77,82]

Patient-related factors were identified in 28 studies. Competing priorities (e.g., being away on holiday, caring for a family member, work commitments, life stresses) were commonly reported as obstacles to using eyedrops.[39,66,67] Patients not having eyedrops with them was also a barrier. In one study 15.9% of participants reported that sometimes

TABLE 5 An overview of generated themes/subthemes, with illustrative examples, from the four key Theoretical Domains Framework domains influencing glaucoma medication adherence.

	Enabler/Barrier/ Mixed	Illustrative examples
1. Environmental context and resources, *N* = 70		
1.1. Theme		
Treatment considerations, *N* = 46		
Subtheme		
Class/type of drug	Enabler	Persistence with a prostaglandin analogue was 'substantially higher than with any of the other classes'[50]
Eyedrop regimen	Barrier	'Patients on more glaucoma medications were less likely to take their doses on time'[57]
1.2. Theme		
Financial circumstances, *N* = 28	Barrier	'Those participants who pay for their medications by themselves were 79% less likely to be adherent to glaucoma topical medications as compared to those who were sponsored by family/employer'[61]
1.3. Theme		
Patient-related factors, *N* = 28		
Subtheme		
Dependency on carer/family member to instil eyedrops	Mixed	Lack of carer help was a reason for nonadherence[69] '…having someone to help in eye drops administration was a motivation to adhere to medication regimen…'[106]
Competing priorities	Barrier	Busy patient schedule was the second most common reason for non-compliance[34]
Drops not to hand	Barrier	'Sometimes the drops aren't with me when it is time to take them [48%]'[54]
1.4. Theme		
Existence of side effects, *N* = 18	Barrier	'Patients offered unsolicited information about barriers such as … side effects'[67]
1.5. Theme		
Eye clinic factors, *N* = 12		
Subtheme		
Demands during clinic	Barrier	'Physicians most often identified [their]… limited time to spend with patients (12%) as a major barrier to compliance'[68]
Follow-up appointment/ continuity of care	Barrier	Second most important factor associated with nonadherence was 'longer frequency of follow-up'[73]
1.6 Theme		
Pharmacy issues, *N* = 6	Barrier	[The pharmacists] say 'no one [comes] to buy this medicine except you. If it was for diabetes or blood pressure we could order it, but for [these eye drops] you have to go to Madurai city'[110]
2. Knowledge, *N* = 49		
2.1. Theme		
Patient understanding, *N* = 41		
Subtheme		
Lack of awareness/awareness of nature of glaucoma	Barrier	Nonadherent patients were 'less aware of the permanent nature of glaucoma'[70]
Lack of awareness/awareness of treatment rationale/regimen/ side effects	Barrier	'Compared with the adherent group, nonadherent participants were less likely to be able to name their glaucoma medications (61.4% vs. 82.2%; $p < 0.05$)'[38]
2.2. Theme		
Education, *N* = 17		
Subtheme		
Lack of desire/desire for more information	Enabler	'patients had a desire for more individualised information from their health care team to better understand their disease course, especially in the early stages'[109]
Source of educational information	Enabler	'very adherent people with glaucoma had also received information from other sources (69%, *n* = 81), such as opticians, leaflets, literature and the Internet'[81]

(Continues)

TABLE 5 (Continued)

	Enabler/Barrier/ Mixed	Illustrative examples
2.3. Theme		
Health care professional (HCP) role, *N* = 5		
Subtheme		
Practitioner–patient relationship	Enabler	Author comment, continuity of care was associated with persistence which 'implies better physician–patient relationship and communication, which may help improve patients' knowledge about their disease status and the importance of adherence'[47]
HCP awareness of adherence/ nonadherence	Enabler	'Better … appreciation among healthcare providers of the need for better compliance with treatment may also partly explain the improvements in persistence observed over time'[52]
3. Skills, *N* = 45		
3.1. Theme		
Ability to administer drops, *N* = 31		
Subtheme		
Practical skills	Barrier	'difficulty of drop application, [is] … highly associated with [low] adherence'[37]
Vision-related skills	Enabler	'Patients who could read the standard label information were three times more likely to recall their drops accurately compared with patients who were unable to read the standard label'[88]
3.2. Theme		
HCP skills, *N* = 22		
Subtheme		
Communication and educational skills	Enabler	'…patients said that they would be encouraged to continue their treatment if their physicians were willing to train them how to administer their medication…'[33]
Clinical skill to detect adherence/ nonadherence	Barrier	'Interviewed physicians … agreed that … the ability to detect and address nonadherence is limited'[68]
3.3. Theme		
Ability to obtain ongoing prescription supplies, *N* = 7	Barrier	'Patients who reported forgetting to refill their drops … were found to be less compliant'[104]
4. Memory, Attention and decision processes, *N* = 38		
4.1. Theme		
Forgetfulness, *N* = 34	Barrier	'Patients who reported difficulty remembering to take their glaucoma medications increased their odds of being less than 100% adherent during the previous week by 12-fold'[98]
4.2. Theme		
HCP treatment decision-making process *N* = 6	Enabler	Authors comment, 'result stresses the role of the physician's choice of medication in promoting adherence to glaucoma pharmacotherapy'[40]

Note: Barrier, hinders glaucoma medication adherence; Enabler, facilitates glaucoma medication adherence; Mixed, either facilitates or hinders glaucoma medication adherence; *N*, number of studies.

they did not use their drops because they did not have their medication to hand.[107]

Relying on someone else to instil medication had a mixed effect on adherence, depending on carer/family member availability. One participant commented 'When I was living alone I had problems taking my drops, now I live with my daughter and I have no problems'.[36] Whereas the authors from a Nigerian study observed that carers were often unavailable for days and, as a result, patients who had assistance administering their eye drops were more likely to be nonadherent.[91]

The existence of side effects, reported in 18 studies, was associated with poorer adherence[63,97,104] in all but one study. Surprisingly, this study found patients experiencing burning or stinging with their eyedrops had higher objectively measured adherence levels.[44]

Eye clinic factors were identified in 12 studies, with the main issue being the frequency of follow-up appointments. More regular clinic visits and seeing the same practitioner were found to promote adherence.[46,73,75] In one study, patients with more frequent follow-ups were found to have better adherence than those with less frequent follow-ups, and this difference in adherence was statistically significant.[105] Both patients and practitioners reported time constraints within the clinic as a barrier to adherence.[68,84] Busy clinics led to patients feeling reluctant to ask for help or practitioners

being unable to provide adequate advice due to lack of time. A UK study reported 'unsatisfactory hospital-led education was considered to be the direct result of the current NHS system, where doctors appeared too busy clinically to have time to provide adequate education'.[30] Another study found that clinic size was associated with the level of adherence.[107]

Issues obtaining eyedrops from the pharmacy were identified in six studies. One study, investigating adherence patterns over a 4-year period, reported that the use of mail order services to receive repeat prescriptions was an important factor in contributing towards better long-term adherence.[49] Difficulties obtaining medications,[109] with eyedrops either being out of stock at the pharmacy, not used commonly enough for the pharmacist to order stocks in[110] or prescription discrepancies,[69] were barriers to adherence. In a study from Nigeria, the distance patients had to travel to collect their eyedrops influenced adherence; living more than 5 km from a pharmacist was reported as a barrier.[91]

Knowledge

The main themes generated within *Knowledge* were patient understanding, education and role of the health care professional (HCP).

Patient understanding, as identified in 41 studies, covered awareness of the nature of glaucoma and/or its treatment. Poor understanding of glaucoma was consistently reported by patients and practitioners as a contributing factor to nonadherence.[33,95,106] One participant commented 'I kind of missed, you know, I, I wasn't, um, taking them the drops as regularly as I probably should have because I didn't know what glaucoma was'.[109] Another study in the United States that interviewed practitioners involved in the management of glaucoma reported that 'Physicians most often identified … lack of patient understanding about glaucoma … as a major barrier to compliance'.[68] Good glaucoma knowledge was associated with better adherence.[34,86,96] In one study, with high levels of self-reported and objectively measured adherence, the authors speculated this was due to patients being seen in a specialised glaucoma clinic rather than a general clinic, as a result of which they were more likely to be aware of their condition.[43]

Lack of understanding about treatment and its rationale was a barrier to adherence.[38,80,83] In a qualitative USA study, one participant remarked 'I stopped taking my drops because I did not understand initially that I need to take them forever'.[36] A 2022 study, in which glaucoma patients in China were interviewed, found higher self-reported adherence in those who better explained 'the side effects of eyedrops, … understood the side effects…and rationale for using eyedrops'.[64]

The subtheme of education arose in 17 studies and incorporated lack of desire/desire for more information and the source of educational information. Lack of education surrounding glaucoma and its treatment was a contributing factor to poor adherence, with patients commenting they wanted more information on glaucoma symptoms,[54] instillation techniques[89] and emerging treatments.[35] A study conducted in Saudi Arabia found that 76.2% of self-reported nonadherent participants lacked background information on glaucoma and its treatment.[74] Patients who reported not needing any more information were more likely to be adherent.[71]

Patients who researched glaucoma themselves, received more education from their provider, or obtained additional information from sources such as optometrists, leaflets or the internet were more likely to be adherent.[57,81] One study that interviewed participants across Europe noted that UK and German patients were more aware of support organisations providing additional information on glaucoma compared with patients from France, Italy or Spain.[102] Another study found reasons for nonadherence varied from patient-to-patient, leading authors to recommend patients receive personalised information, either electronically or face-to-face, depending on their needs.[87]

The theme of HCP role emerged from five studies and incorporated the practitioner–patient relationship and HCP awareness of adherence/nonadherence. Good practitioner–patient relationships, which support patient understanding of their condition, were found to facilitate medication adherence.[47] In contrast, relationships built on patients' passive dependence on their practitioner for information contributed to poorer adherence.[44] Better practitioner awareness of the importance of adherence resulted in improved long-term patient adherence.[52]

Skills

Within *Skills*, the themes that emerged were the ability to administer eyedrops, practitioner skills and patients' ability to obtain ongoing prescription supplies.

Practical or vision-related skills needed to instil eyedrops were identified in 31 studies. Problems with drop administration were associated with poorer adherence.[72,76,78] The more difficulties a patient reported, the less adherent they were likely to be.[98,100,101] A Canadian study, assessing patient instillation methods, found 33.8% 'demonstrated improper drop administration technique'.[76] HCPs were also aware of the problems patients experienced instilling eyedrops; in one qualitative study, ophthalmologists commented 'they [patients] find it hard to put them in themselves'.[33] The main problems patients described with instilling eyedrops were difficulty squeezing the bottle,[31] too many drops coming out or drops falling onto their cheeks.[90,99] Another factor hindering adherence was the inability to see print on the eyedrop bottle.[88] A Malaysian study found adherence was significantly affected by a

patient's ability to read the label and identify the eyedrop bottle.[103]

Health care professional skills emerged from 22 studies and were related to communication and education skills, or the skills required to detect adherence/nonadherence. The ability of HCPs to have meaningful conversations, inquire about adherence issues, discuss the rationale for treatment, counsel patients, teach administration techniques and provide education on the nature of glaucoma were associated with better adherence. One study interviewing practitioners reported that 'Physicians most often identified [their]… inability to communicate why compliance is important (15%)… as a major barrier to compliance'.[68] A multiperspective study exploring the relationship between practitioner–patient interactions found providers only offered education about treatment and its rationale at 14% and 17.6% of study clinic visits.[56] Several studies found patients struggled to instil their eyedrops, which led authors to recommend practitioners should not only assess patient technique but also demonstrate the correct method and offer practical assistance.[54,89] Practitioners' ability to detect nonadherence was consistently reported to be poor, with HCPs remarking that their own ability was limited.[68] One study found that '71.1% of patients thought by physicians to be nonadherent were actually adherent'.[43] To help improve practitioner detection skills, the authors from another study, conducted in Australia, suggested patients self-complete an adherence assessment questionnaire prior to their clinic visit.[84]

The subtheme based on the skill of obtaining continuous supplies of eyedrops emerged from seven studies, with patients inability to order repeat prescriptions contributing to poorer adherence.[36,104] One participant commented 'When I ran out I would think I'm going to get it reordered and then…it would be like a day or two before I remembered to call'.[109]

Memory, Attention and decision processes

The main themes within *Memory, Attention and decision processes* were forgetfulness and the HCP treatment decision process.

Forgetting to instil eyedrops, as identified in 34 studies, was commonly reported as a major barrier to adherence.[32,59,93] In one study, over 88% of nonadherent patients admitted they forgot to use their medication sometimes.[54] HCPs also recognised patients' inability to remember to instil eyedrops as a contributing factor to poorer adherence.[68]

Practitioners' decision-making process in selecting a relevant treatment was identified in six studies. The authors consistently reported that practitioners should consider prescribing simplified regimens, specifically once-daily treatments and unpreserved medications, to promote better adherence.[60,108]

DISCUSSION

The aim of this review was to identify systematically modifiable barriers and enablers influencing glaucoma medication adherence operating at a patient, HCP and healthcare system level using the TDF. The majority of determinants were reported from a patient perspective and assigned to four key TDF domains: *Environmental Context and Resources, Knowledge, Skills, and Memory, Attention and decision processes*. The domains *Goals, Intentions* and *Optimism* were found to have the least impact on adherence behaviour. The large number of barriers and enablers identified reflects the complex nature of medication adherence.

Having identified the modifiable influences on medication adherence, the next stage will be to use this information to develop behaviour change interventions to improve adherence that could operate at either the patient, HCP or organisational level. The TDF benefits from being linked to two frameworks that can be used to potentially change behaviour: the behaviour change wheel[113] and the behaviour change technique taxonomy.[114] The behaviour change wheel allows key TDF domains that influence behaviour to be mapped to intervention functions (e.g., education, training and environmental restructuring) and policy categories that can be used to support an intervention (e.g., legislation, service provision and guidelines). The behaviour change technique taxonomy provides language to describe the 'active ingredients' of behaviour change interventions (e.g., action planning, prompts/cues, motivation). The recently developed 'Theory and Techniques Tool' is an interactive resource that provides links between specific behaviour change techniques and their respective theoretical domains to support intervention design.[115] Using this approach to develop an intervention to improve glaucoma medication adherence will help address the fact that interventions currently have limited success. They lack a robust theoretical underpinning, since strategies to improve suboptimal adherence are more likely to be effective if they focus on the theoretical determinants of behaviour and the mechanisms involved in behaviour change.

Implications for practice

The main barriers influencing glaucoma medication adherence are related to treatment characteristics, lack of patient understanding, forgetfulness and difficulties administrating eyedrops, whereas the main facilitators included simplified treatments, knowledgeable educated patients and good patient–practitioner relationships. Based on these findings, we propose that three key recommendations are implemented into practice:

1. Choice of treatment regimen;
2. Promotion of glaucoma awareness and education among patients and HCPs;
3. Promote better patient relationships with HCPs.

Choice of treatment regimen

Deciding on a treatment regimen is an important factor influencing patient adherence. In this review, monotherapy (typically with PGAs) was associated with better adherence. Non-PGAs, multiple glaucoma drops and preserved preparations were associated with poorer adherence. Patients found complex regimens requiring multiple daily instillations of one or more glaucoma medications, especially instillations around the middle of the day, disrupted their lifestyle leading to poorer adherence. The existence of side effects was often a barrier to adherence. Hence, practitioners should consider reducing the burden of instilling eyedrops by simplifying dosing regimens, prescribing fixed combination regimes where possible, and using preservative-free preparations when there are signs of preservative toxicity.[116] A successful choice of therapy is likely to promote better long-term adherence with fewer medication changes and fewer new prescription collections for patients.[50]

Practitioners are encouraged to follow recommended guidelines in relation to treatment choices for glaucoma and ocular hypertension (OHT), such as the UK National Institute for Health and Care Excellence (NICE), the European Glaucoma Society, the American Academy of Ophthalmology and the Asia Pacific Glaucoma guidelines. Up to January 2022, NICE guidance in England and Wales recommended offering patients with OHT, suspect glaucoma or chronic open angle glaucoma (COAG) who are at risk of visual loss during their lifetime a generic PGA as first-line drug therapy.[117] PGAs have good efficacy at reducing IOP, require a convenient once a day dosing regime and are well tolerated with limited systemic side effects.[118] Since glaucoma is a chronic condition requiring long-term treatment, patient acceptability of using eyedrops is important for long-term persistence. Preservative-free prostaglandin preparations, which are available in either single unit or multidose containers, often have greater patient satisfaction and tolerability than unpreserved versions,[119] although at increased cost.[116] Studies have shown patients can use individual unit dose vials just as well as multidose bottles,[120-122] but they can be more difficult to store due to the extra packaging and produce more plastic waste.[123]

Another option to consider when deciding on IOP-lowering treatment is selective laser trabeculoplasty (SLT). This is a safe, repeatable, clinically-effective and cost-effective treatment for OAG and OHT.[124,125] Since January 2022, NICE has recommended offering SLT to newly diagnosed COAG or OHT patients (where the IOP is >23 mmHg and they are at risk of visual impairment within their lifetime) as first-line treatment.[117] Similar recommendations have been advocated by the United States and Europe.[126,127] As an initial treatment, SLT can delay the need for eyedrops in approximately 70% of patients for up to 6 years.[125] In patients already on treatment but with uncontrolled IOP, SLT can potentially reduce the need for further medications or delay more invasive procedures (e.g., surgery). Difficulties paying for and obtaining medications, especially in developing countries, were reported as barriers to adherence, and in these cases SLT may be a more suitable option. However, SLT may not be successful in every case, IOP reduction may not be sufficient or sustained,[128] and while uncommon, severe complications can arise.[129,130]

To overcome patients forgetting instillation times either due to poor memory or competing priorities, practitioners can recommend patients develop a routine that becomes habit forming (e.g., instilling eyedrops at the same time as taking other medication), use visual or practical cues as reminders (e.g., placing eyedrops next to their toothbrush) or use reminder aids (e.g., mobile phone alarm, medication reminder apps). Reminder strategies can also be recommended to patients who struggle to remember to order repeat prescriptions (e.g., creating an alert in a mobile phone diary or physically writing on a calendar). Using mail-order services to deliver eyedrops should be promoted since this was found to facilitate long-term adherence.[49]

Promotion of glaucoma awareness and education

Poor awareness of glaucoma and its treatment was reported by both patients and HCPs as a barrier to adherence. Patients who had good knowledge of glaucoma and its symptoms, an understanding of the rationale for treatment, were aware of the consequences of non-adherence, and could accurately describe their medication regimen were more likely to be adherent. To improve glaucoma knowledge, the implementation of a structured national group educational programme, similar to the DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) scheme, which has proved effective in improving patients' knowledge and behaviours in people with type 2 diabetes,[131] is recommended.

Educational interventions in the form of tailored counselling sessions, educational videos, the use of illustrative pictures and information leaflets provided by pharmacists, nurses or research assistants have all proved beneficial in improving glaucoma medication adherence.[132-135] Providing patients with regular training programmes reviewing, updating and reinforcing information is desirable.[136] Group educational sessions, tailored to the individual needs of attendees, could also be considered since they have been found to be acceptable to glaucoma patients,[137] and may prove more cost-effective and time-efficient. Utilising the services of charities (e.g., Glaucoma UK: https://glaucoma.uk/) that are trusted by patients to provide information in a relatable, digestible manner is also recommended. Glaucoma UK issues patient information leaflets, educational videos, runs support groups and provides a dedicated telephone helpline for patient queries.

Issues with eyedrop administration were identified by both patients and HCPs as a barrier to adherence, with

patients reporting they would like more information on how to instil eyedrops correctly. Both hospital and community pharmacists can play a major role in raising awareness of instillation techniques. A UK pharmacist led '#KnowYourDrops' campaign, which delivered informal support events teaching administration techniques, demonstrating the use of compliance aids and addressing adherence issues, proved extremely successful with patients, carers and HCPs.[138] Community pharmacists are also ideally placed to review patient adherence concerns regularly, reiterate correct instillation techniques and offer further counselling as needed. Utilising services outside of the eye department addresses the issue of time constraints within the clinic. Patients reported busy clinics hindering their ability to ask for help, and practitioners felt unable to offer sufficient information due to a lack of time. Support staff, such as Eye Clinic Liaison Officers (ECLOs) in the UK, could also play an integral role in providing this service. ECLOs are able to offer practical and emotional support and provide information about a patient's condition while ensuring continuity of care in busy outpatient clinics.[139,140] However, consideration would need to be given to ensuring there were sufficient numbers of trained support staff to meet the demand.

To effectively manage nonadherence, HCPs need to be aware of the magnitude of the problem, be able to assess and identify poor adherence and recommend strategies to help. In this review, while practitioners appeared to be aware of the importance of adherence, their ability to detect cases of nonadherence was poor. To address this issue, providing training events for those involved in glaucoma care is recommended. Educational meetings can change professional practice,[141] and while they have been effective in supporting practitioners manage nonadherence issues in asthma, training for HCPs involved in medication adherence is generally lacking.[142] Arranging educational events at national/international conferences or local study days focussing on best adherence practice, practitioner communication skills and updating and refreshing glaucoma knowledge will provide HCPs with the tools to address adherence better in practice. Practitioners are also encouraged to follow professional body guidelines and recommendations to aid in prescribing and management decisions.

Promote better patient–practitioner relationships

Good patient–practitioner relationships supporting patient understanding and effective HCP communication were found to facilitate adherence. Medicines adherence guidance issued by NICE and the Royal Pharmaceutical Society Competency Framework for all prescribers advocates open, honest and non-judgemental conversations encouraging patient participation.[143,144] To promote an environment where patients can be honest about their adherence behaviour without the fear of feeling judged, HCPs need to have good communication skills and employ non-judgemental interview techniques to encourage a healthy patient–practitioner relationship.[145] UK practitioners are encouraged to follow NICE recommendations since informed and engaged patients tend to be more involved in shared decision-making, and hence are likely to be more adherent.[146]

Implications for future research

The Sight Loss and Vision Priority Setting Partnership (SLV-PSP), whose aim is to eradicate avoidable sight loss, has recognised the major issue of glaucoma medication nonadherence and identified improving adherence as a research priority within the UK.[147] To address this unmet need, future work should focus on intervention development, producing a scalable, low-cost intervention to improve adherence. Having identified the modifiable determinants of medication adherence, further research should use this information to develop theory-based interventions (the process described at the start of the discussion), which will then need assessing for effectiveness, acceptability and feasibility.

The majority of studies included in this review reported determinants from a patient perspective. To gain a more comprehensive understanding of what influences medication taking, future research should concentrate on studying HCPs' and carers' perspectives. HCPs are exposed to clinically diverse environments and so will perceive determinants that not only influence themselves but also patients and organisational processes. Similarly, a carer's point of view will add another dimension to understanding influences on medication adherence. Very few of the included studies were qualitative in design. Adherence is a complex, multifaceted behavioural issue, so exploring patients', HCPs' and carers' personal experiences with glaucoma medication to capture rich, in-depth information would provide a deeper understanding of the problem. Future work addressing this is recommended.

Known predictors of nonadherence include patients who are younger and less educated, patients from ethnic minorities and patients who are depressed.[11] Strategies to improve medication taking should ideally be targeted towards these 'at-risk' individuals. It was not, however, a specific objective of this review to identify theoretical domains that were important to these subsets of patients; hence, future research work exploring these issues is needed so that strategies can be targeted towards the highest-risk groups. Similarly, research focussing on different healthcare systems, especially those that are not universal, not publicly funded or have poor infrastructure, may be needed since factors influencing adherence may be different and more specific to these settings.

Strengths and limitations

This is the first systematic review to use the TDF within the context of glaucoma medication adherence, thus addressing a gap in the evidence. Only modifiable determinants were reported, since strategies to improve medication adherence are more likely to be effective if they target those factors that are amenable to change. A strength of using the TDF is that it is linked to evidence-based behaviour change techniques through the application of the behaviour change wheel. Therefore, it provides a theory-driven process for identifying determinants of glaucoma medication use that are suitable for targeting with a behaviour change intervention.

A second strength of the study was the extensive systematic reproducible search strategy, which included grey literature and studies of all designs (quantitative, qualitative and mixed methods). Another strength was the robust nature of the data analysis process, where all decisions (deductive and inductive) were reviewed and verified by a second reviewer. All data, extracted from the 83 included studies, were able to be coded to a TDF domain, demonstrating the comprehensive nature of the TDF framework in identifying determinants.

There are, however, some limitations of the review that need to be considered. Sixty-eight (82%) of the 83 included studies were conducted in developed countries. Medication adherence is lower in developing countries[7,148] due to limited access to healthcare, financial issues and low socio-economic status. The results of our review may not, therefore, be globally representative.

Second, there is no current universally accepted method for defining and measuring adherence.[17] The included studies used a range of definitions and measurement tools to report on adherence. Future work developing a standardised definition and approach to adherence measurement would be advantageous to aid the interpretation and application of heterogeneous results.

CONCLUSION

This review presents a comprehensive overview of modifiable determinants of glaucoma medication adherence. Multiple factors, from four theoretical domains, were identified as key in influencing adherence behaviour. Interventions targeting these domains are more likely to be effective in improving medication adherence. This review also highlights the impact treatment characteristics, lack of patient understanding, forgetfulness and administration difficulties have on adherence behaviour. Integrating multimodal strategies to address these specific issues may enhance the effectiveness of an intervention. Future research investigating barriers and facilitators influencing medication adherence from the perspective of a HCP, carer and different patient subgroups is recommended to encourage behavioural change where necessary. Findings from this research will further assist in intervention development, including the use of smartphone apps.

AUTHOR CONTRIBUTIONS

Deborah Bott: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (lead); validation (equal); visualization (equal); writing – original draft (lead); writing – review and editing (equal). **Ahalya Subramanian:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **David Edgar:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **John G. Lawrenson:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Peter Campbell:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal).

ACKNOWLEDGEMENTS

Deborah Bott is funded by a College of Optometrists Postgraduate Research Scholarship.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

ORCID

Deborah Bott https://orcid.org/0000-0002-5122-6697
Ahalya Subramanian https://orcid.org/0000-0001-8104-5312
David Edgar https://orcid.org/0000-0001-9004-264X
John G. Lawrenson https://orcid.org/0000-0002-2031-6390
Peter Campbell https://orcid.org/0000-0002-6019-1596

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bott D, Subramanian A, Edgar D, Lawrenson JG, Campbell P. Barriers and enablers to medication adherence in glaucoma: A systematic review of modifiable factors using the Theoretical Domains Framework. *Ophthalmic Physiol Opt*. 2023;00:1–19. https://doi.org/10.1111/opo.13245