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TABLE OF CONTENTS

[Intervention Review]

Interventions for improving adherence to ocular hypotensive therapy

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ABSTRACT

Background

Poor adherence to therapy is a significant healthcare issue, particularly in patients with chronic disease such as open-angle glaucoma. Treatment failure may necessitate unwarranted changes of medications, increased healthcare expenditure and risk to the patient if surgical intervention is required. Simplifying eye drop regimes, providing adequate information, teaching drop instillation technique and ongoing support according to the patient need may have a positive effect on improving adherence.

Objectives

To summarise the effects of interventions for improving adherence to ocular hypotensive therapy in people with ocular hypertension (OHT) or glaucoma.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 6), MEDLINE (June 1946 to June 2012), EMBASE (June 1980 to June 2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (June 1937 to June 2012), PsycINFO (1806 to June 2012), PsycEXTRA (1908 to June 2012), Web of Science (1970 to June 2012), ZETOC (1993 to June 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 26 June 2012. We did not search the National Research Register (NNR) as this resource has now been now archived. We contacted pharmaceutical manufacturers to request unpublished data and searched conference proceedings for the Association for Research in Vision and Ophthalmology (ARVO), and the Annual Congress for the Royal College of Ophthalmologists (RCO).

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs that compared interventions to improve adherence to ocular hypotensive therapy for patients with OHT or glaucoma.

Data collection and analysis

At least two authors independently assessed the search results for eligibility and extracted data for included trials onto specifically designed forms. We did not pool data due to clinical and methodological heterogeneity.

Main results

Sixteen trials (1565 participants) met the inclusion criteria. Seven studies investigated some form of patient education. In six of these studies this education was combined with other behavioural change interventions including tailoring daily routines to promote adherence to eye drops. Eight studies compared different drug regimens (one of these trials also compared open and masked monitoring) and one study investigated a reminder device. The studies were of variable quality and some were at considerable risk of bias; in general, the length of follow-up was short at less than six months with only two studies following up to 12 months. Different interventions and outcomes were reported and so it was not possible to produce an overall estimate of effect. There was some evidence from three studies that education combined with personalised interventions, that is, more complex interventions, improved adherence to ocular hypotensive therapy. There was less information on other outcomes such as persistence and intraocular pressure, and no information on visual field defects, quality of life and cost. There was weak evidence as to whether people on simpler drug regimens were more likely to adhere and persist with their ocular hypotensive therapy. A particular problem was the interpretation of cross-over studies, which in general were not reported correctly. One study investigated a reminder device and monitoring but the study was small and inconclusive.

Authors' conclusions

Although complex interventions consisting of patient education combined with personalised behavioural change interventions, including tailoring daily routines to promote adherence to eye drops, may improve adherence to glaucoma medication, overall there is insufficient evidence to recommend a particular intervention. The interventions varied between studies and none of the included studies reported on the cost of the intervention. Simplified drug regimens also could be of benefit but again the current published studies do not provide conclusive evidence. Future studies should follow up for at least one year, and could benefit from standardised outcomes.

PLAIN LANGUAGE SUMMARY

Interventions for helping people use eye drops as prescribed for raised eye pressure or glaucoma

A large number of people do not use eye drops as prescribed. Glaucoma is a slowly progressive eye disease, which can result in severe vision loss. Drops prescribed for raised eye pressure or glaucoma are aimed at lowering the pressure to assist in reducing the rate of progression, or preventing the conversion of raised eye pressure to glaucoma. It is important that these eye drops are used continually, usually for life. Approximately one-third of people who are prescribed eye drops for the first time fail to continue collecting prescriptions within the first year and even when patients collect prescriptions they do not always use the drops as frequently as they should. A number of reasons are thought to be the cause, for example, forgetfulness, being prescribed a large number of medications, difficulties instilling drops, lack of knowledge about glaucoma, a busy lifestyle and seeing no benefit.

This review is based on 16 studies (1565 participants) that tried out different methods to help people to use drops as prescribed. All the studies took place in industrialised countries (Belgium, Denmark, France, Greece, Iceland, Japan, Sweden, Switzerland, UK and USA) and recruited participants in outpatient clinics. The following interventions were included: simplifying drop routines, reminder devices, automated telephone service, providing information about glaucoma and offering advice regarding day to day issues with eye care. Those studies which combined the provision of information about glaucoma and eye drops with other interventions, such as helping people to fit instillation of eye drops into their daily routine, appear to be more successful. Unfortunately, not all of these studies were of high quality and, therefore, until more evidence is available we cannot recommend any particular method. Good quality research is needed in this area in order to develop a better understanding of patients' individual needs and to help us provide more effective eye care services.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Education and individualised care planning compared with standard care for improving adherence to ocular hypotensive therapy

Patient or population: people with glaucoma or ocular hypertension
Settings: outpatients
Intervention: education and individualised care planning
Comparison: standard care

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Adherence	902 (7)	⊕⊕◯◯ **low**[1]	3 studies found that people given education and individualised care planning were more adherent. Substantial improvements in adherence were observed in these studies. 4 studies did not find a difference, in these studies the intervention was less detailed. Different measures of adherence meant it was difficult to estimate overall treatment effect
Persistence	127 (1)	⊕⊕◯◯ **low**[2]	Only 1 trial reported this outcome in which 17/127 patients discontinued therapy (risk ratio for persistence 1.14, 95% CI 0.99 to 1.41)
Intraocular pressure	193 (2)	⊕⊕◯◯ **low**[3]	Only 2 trials reported this outcome. One trial reported this at 12 and 24 months and found no difference between the intervention groups. 1 trial reported at 3 months follow-up which may be too short a time period to observe an effect on intraocular pressure
Visual field defects			No data on this outcome
Quality of life			No data on this outcome
Adverse effects			No data on this outcome
Patient knowledge	390 (4)	⊕◯◯◯ **low**[4]	In Gray 2011 intervention improved patient knowledge (median knowledge score was 14 (range 2 to 18) for the intervention group and 6 (range 0 to 17)

		for the control group (Mann-Whitney P <0.001). 3 other studies reported no differences in patient knowledge between groups

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded to low because (i) the majority of the trials were not masked , (ii) there was inconsistency in trial results.
[2]We downgraded to low because (i) only one trial, (ii) imprecision in the estimate.
[3]We downgraded to low because (i) only one trial measured at reasonable length of follow-up, (ii) no pooled estimate so not enough numbers to detect moderate effects.
[4]We downgraded to low because (i) inconsistency in trial results, (ii) the majority of the trials were not masked.

BACKGROUND

There are a number of terms that describe whether medications are taken as prescribed. Adherence has superseded the term compliance and although synonymous with compliance, has fewer negative connotations and is intended to be non-judgemental (Haynes 1979; Horne 2006). Adherence will, therefore, be used throughout the review.

A useful taxonomy for describing adherence to medication helps to clarify the confusion surrounding the proliferation of ambiguous terms on medication adherence. In this taxonomy, non-adherence to medications is said to occur by late or non-initiation of prescribed treatment, by sub-optimal implementation of the regimen and by early discontinuation of therapy sometimes referred to as persistence (Vrijens 2012). Although persistence may be achieved by the patient collecting all dispensed prescriptions, it does not necessarily follow that the medication will be taken as prescribed. Because adherence is difficult to measure, persistence (which can be objectively measured) is often employed as an outcome for studies investigating adherence (Wilensky 2006; Yu 2005). Another term often confused with adherence is concordance. Concordance describes an agreement reached after negotiation between a patient and a healthcare professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines are to be taken. Although reciprocal, this is an alliance in which healthcare professionals recognise the primacy of the patient's decision about taking the recommended medications (Royal Pharmaceutical Society of Great Britain 1997).

Concordance is not synonymous with compliance or adherence. Concordance focuses on the consultation process rather than specific patient behaviour and has an underlying ethos of a shared approach to decision making (Weis 2003). The concept involves the pooling of patients' and health professionals' beliefs, experiences and expertise to arrive at mutually agreed goals (Bissell 2004). To ensure completeness for this review, our search strategy will incorporate the above terms and any other terminology associated with adherence.

Poor adherence most often leads to increased resource utilisation, owing to a reduction in effectiveness and associated increase in the risk of therapeutic failure (Urquhart 1999). Treatment failure may necessitate more frequent hospital appointments and diagnostic tests, unwarranted increases in doses or changes of medications, waste of unfinished pharmaceutical supplies, increased healthcare expenditure and risk to the patient if subsequent surgical intervention is required. Electronic monitoring devices are considered the gold standard for measuring adherence because they are an objective measure of behaviour but experimenter's bias may be a limitation. A systematic review of seven studies using this method reports that there are a sizeable group of 20% or less of patients who are defined as non-adherent (Reardon 2011). Other studies also identify from electronic monitoring that patients' behaviour can be grouped into such categories as fully adherent, non-per-

sistent, taking regular breaks/dosing holidays or erratic frequent missing of doses (Ajit 2010; Herman 2010). Research from a systematic review of medical chart reviews (six studies) indicates that at one year 67% (range 62% to 78%) of patients remained persistent with their anti-glaucoma medication (Reardon 2011).

In chronic, asymptomatic diseases such as open-angle glaucoma (OAG), adherence is a particular issue. The treatment for glaucoma aims to prevent disease progression, yet provides no subjective improvement in well-being, and may even cause ocular or systemic side effects, or both (Diggory 1995).

In a systematic review by Olthoff 2005 non-adherence ranged from 4.6% to 80% across 34 studies. A more recent review found the prevalence of non-adherence to glaucoma treatment to range from 23% to 60% over 12 months (Lu 2010). A variety of definitions for non-adherence and assessment methods were found to be in use. This emphasises our poor understanding and the poor classification of adherence.

Description of the condition

Glaucoma is an optic neuropathy characterised by an acquired loss of retinal ganglion cells, atrophy of the optic nerve and loss of visual field (Maier 2005). Increased intraocular pressure (IOP) may be present as in open-angle glaucoma (OAG) and angle-closure glaucoma (ACG). Glaucomatous optic neuropathy and field loss with normal IOP is known as normal tension glaucoma (NTG). Elevated IOP in the absence of glaucomatous appearance of the optic nerve head or visual field is known as ocular hypertension (OHT). Intraocular pressure control (reduction and control of fluctuations) has a role in preventing the onset (for patients with OHT) and reducing the rate of progression of glaucoma (Heijl 2002). It is routinely monitored in clinical practice in conjunction with other risk factors such as the structural appearance of the optic nerve head and visual field status (Spry 2005).

Glaucoma is the leading cause of irreversible blindness worldwide. A review of 34 studies involving patients with OAG and ACG estimated the prevalence of glaucoma to be 60.5 million by 2010 (74% with OAG) rising to nearly 80 million by 2020; with an ageing population accounting for a large proportion of this rise (Quigley 2006). A meta-analysis confirmed previous estimates that black populations had the highest prevalence of OAG at 4.2%, ranging from 2.9% at the age of 40 years to 16.9% at 80+ years (Rudnicka 2006). The prevalence for white populations was 2.1%, ranging from 0.4% at age 40 years to 6.6% at 80+ years, and for Asian populations was 1.4%, ranging from 0.6% to 3.8% for the same age range.

In its early stages, glaucoma is asymptomatic and approximately one in two people with the disease may be undiagnosed (Quigley 2006). In a north London-based cross-sectional survey, 74% of those found to have a definite diagnosis of glaucoma and 84% of suspected glaucoma cases were not known to an eye care service (Reidy 1998). People at risk of developing glaucoma are more likely to present late if they have no family history of glaucoma or do not visit an optometrist regularly (Fraser 1999). The majority of cases are detected during routine eye examination and, therefore, increasing public awareness of the disease may be valuable for early detection. Patients newly diagnosed with OHT or glaucoma should have the opportunity to make informed choices about their long-term care. Deokule 2004 found only 52% of patients could name their medication or frequency of instillation correctly. An Australian study reports that of 200 patients with glaucoma, 32% could not state their prescribed therapeutic regimen and that those with three or more prescribed eye drops were five times more likely not to know their medication (O'Hare 2009). Providing adequate information, advice and ongoing support according to patient need may have a positive effect on improving adherence.

Description of the intervention

Treatment of patients with OHT or glaucoma aims to prevent visual disability and preserve overall well-being (Burr 2012). Therapy focuses on lowering IOP levels in an attempt to slow the rate of disease progression or prevent the conversion of OHT to glaucoma within a person's lifetime (NICE 2009).

First-line treatment usually consists of mono-therapy, commencing with an uncomplicated regime of one drop per day. Even the simplest regimes are subject to poor persistence rates, as Vanelli 2009 found that it was medication-naive patients with prescribed non-oral medicines (diabetes mellitus, insulin; glaucoma, eye drops; asthma, inhalers) who were most at risk of discontinuation in the first 30 days of therapy compared with those who were more experienced. This supports the early provision of patient education and support in an attempt to prevent early discontinuation (Lunnela 2010). For many patients, multiple therapy is required and this has led to the introduction of fixed-combination drops (two active ingredients in a single drop) for patients requiring more than one preparation. The aim of fixed combination drops is to enable a more complex dosing regimen while allowing the patient to benefit from a once only dose which may improve adherence (Brown 1997). The previous version of our review (Gray 2009) shows that there were a few studies which have attempted to investigate this issue and, unfortunately, there was insufficient evidence to confirm this claim.

How the intervention might work

Although complicated regimes do appear to affect adherence, there is no evidence to date that indicates that there are any determinants, such as age, race or level of education, that can predict accurately potential patients who will not adhere. However, previous studies have found numerous patient-identified barriers to adherence with anti-glaucoma medication, such as communica-

tion difficulties between patient and physician, lack of knowledge about glaucoma and the purpose of eye drops, forgetfulness, lack of motivation, living alone, poor dexterity, a busy lifestyle and seeing no benefit (Granstrom 1982; Kholdebarin 2008; Lacey 2009; Patel 1995; Schwartz 2008; Taylor 2002; Tsai 2003). These factors would seem to be amenable to interventions.

Why it is important to do this review

A previous Cochrane review synthesised the evidence relating to adherence to a range of medications including oral and inhaled drugs (Haynes 2008). Topical eye drops, however, were not included. Olthoff 2005 published a systematic review relating to poor adherence with ocular hypotensive treatment. This review raised a number of interesting issues and did conclude that poor adherence is a considerable concern. The authors suggested that future research should take a more objective approach of measuring adherence by means of medication monitors. Olthoff 2005 excluded drug trials on the basis that drug use under everyday circumstances may differ completely from the situation in a clinical trial. We are aware of this, however, we believe drug studies should be included. Studies that compare adherence rates for patients on different drug regimes, such as daily combination drops versus twice or three times daily mono-therapy, may prove to be beneficial in informing future prescribing practices. Olthoff 2005 also excluded studies if they reported involuntary non-adherence, e.g. due to co-morbidity. Again, the authors of this review believe that such trials are important. If a patient is unable to adhere to a prescribed regime due to a co-existing condition such as Alzheimer's disease, this has implications for future service provision. This is an update of our original Cochrane review published in 2009 (Gray 2009).

OBJECTIVES

To summarise the effects of interventions for improving adherence to ocular hypotensive therapy in people with OHT or glaucoma.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi RCTs that compared interventions to improve adherence to ocular hypotensive therapy.

Types of participants

We included patients with a clinical diagnosis of glaucoma or OHT who were prescribed ocular hypotensive therapy. There were no age or gender limitations.

Types of interventions

We included any intervention that aimed to improve adherence to ocular hypotensive therapy versus other interventions or usual care. There were no restrictions on the type of ocular hypotensive medications used. Studies included were likely to match one of the following four comparisons:

1. Usual care versus adherence intervention and usual care.
2. Usual care versus adherence intervention alone.
3. Usual care and adherence intervention versus usual care and an alternative adherence intervention.
4. Adherence intervention versus an alternative adherence intervention.

Interventions may include, but are not exclusive to, the following:

- Patient education programmes.
- Verbal and written information.
- Follow-up support; telephone or postal reminders to collect prescriptions and/or medication reminder charts.
- Rescheduling of eye drop therapy; simplification of dosing, e.g. reducing the number of drops per day or tailoring regimes to daily activities.
- Eye drop instillation training.
- Identification of adherence barriers and individualised adherence plan.

Types of outcome measures

A gold standard for measuring adherence to glaucoma therapy does not exist; methods vary greatly. This review incorporated any measure for a study that met the inclusion criteria.

Primary outcomes

- Adherence to therapy measured as defined in each study; including, but not limited to patient interviews, questionnaires, patient diaries or electronic monitoring devices. This includes dichotomous (success/failure), nominal (reasons for non/poor adherence) and discrete data (proportions of missed doses over a specific time period).
- Persistence with therapy measured by repeat prescriptions (prescription refill) or dispensing counts, or both. This includes dichotomous (success/failure) and discrete data (proportions of uncollected prescriptions over a specific time period).

Secondary outcomes

- Intraocular pressure reduction measured via tonometry.

- Progression of optic nerve head damage as defined by each study.
- Progressive visual field loss as defined by each study.
- Quality of life
    - We collected quality of life data where available and where reported in association with adherence outcomes. Many recognised tools are available, such as the MOS SF36 (Iester 2002), IPQ-R (Moss-Morris 2002) or VFQ-25 (Mangione 2001; Spaeth 2006). We included any validated quality of life measure as reported in the trials.
- Adverse effects.
    - Serious adverse events (fatal, life-threatening or require hospitalisation).
    - Adverse events that result in discontinuation of treatment.
    - Any other adverse events.
- Patients' knowledge of glaucoma and its treatment.
- Costs.

Secondary outcome measures may involve the analysis of both continuous and ordinal data.

Follow-up

Studies measuring adherence and persistence may vary. We have included all studies meeting the criteria and categorised as follows:

- Short-term = < six months.
- Medium-term = six months to < one year.
- Long-term = ≥ one year.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 6, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 26 June 2012), MEDLINE (June 1946 to June 2012), EMBASE (June 1980 to June 2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (June 1937 to June 2012), PsycINFO (1806 to June 2012), PsycEXTRA (1908 to June 2012), Web of Science (1970 to June 2012), ZETOC (1993 to June 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 26 June 2012. We did not search the National Research Register (NNR) as this resource has now been now archived.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), CINAHL (Appendix 4), PsycINFO and PsycEXTRA (Appendix 5), Web of Science (Appendix 6), ZETOC (Appendix 7), OpenGrey (Appendix 8), *m*RCT (Appendix 9), ClinicalTrials.gov (Appendix 10) and the ICTRP (Appendix 11).

Searching other resources

We searched reference lists of identified trial reports to find additional trials. We contacted primary investigators of identified trials for details of additional trials. We also contacted pharmaceutical manufacturers of ocular hypotensive medications such as Pfizer, Allergan, Alcon and Merck Sharp and Dohme to request unpublished data that they were willing to release. We searched the following conference proceedings for relevant abstracts both electronically and by hand:

- Annual Meeting for the Association for Research in Vision and Ophthalmology (ARVO) (2000 to 2008).
- Annual Congress for the Royal College of Ophthalmologists (RCO) (1993 to 2008).

Data collection and analysis

Selection of studies

Two review authors working independently assessed the titles and abstracts of all reports identified by the electronic and manual searches as per 'Criteria for considering studies for this review'. We obtained full reports for potentially eligible studies and for those where we had insufficient information. Review authors were not masked to names of the investigators, the institutions, journal of publication or results when making their assessments. In cases where additional information was needed before a decision could be made as to whether to include a trial, we attempted to obtain this information by contacting investigators. We resolved disagreements by consensus. We scrutinised results for duplicate publications from the same data set. Details of excluded studies have been retained and reasons for exclusion are documented in the 'Characteristics of excluded studies' table.

Data extraction and management

Extraction of study characteristics

At least two authors independently extracted the data from each paper onto data extraction forms, designed specifically for the review with guidance from the Cochrane Eyes and Vision Group. We compared the extracted data for differences and discrepancies were resolved by discussion.

Data entry

Data was entered by one author into Review Manager 5 (RevMan 2012) (JE) and subsequently checked by another author (HW). We approached the investigators for more information where data were missing or difficult to determine from a trial report. We designed study-specific data collection forms to capture data that were not available from the published report.

Assessment of risk of bias in included studies

At least two authors independently assessed each study for risk of bias, using the Cochrane Collaboration tool for assessing the risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion. We graded the following items as low risk of bias, high risk of bias or unclear. We sought additional information from the authors of any study graded unclear.

1. Selection bias

We assessed the generation of the allocation sequence and allocation concealment.

2. Performance bias

We assessed the extent to which participant and care providers were masked to the treatment group (blinding).

3. Detection bias

We assessed whether the outcome assessor was masked to the intervention group.

4. Attrition bias

We recorded the amount of missing data and whether participants were analysed in the groups to which they were originally randomly allocated.

Assessment of heterogeneity

There was considerable clinical heterogeneity with respect to the type of intervention and methodological heterogeneity with respect to the measurement of outcomes so we did not perform any meta-analyses.

Data synthesis

We did not conduct any data synthesis but tabulated data from the different studies according to type of intervention.

Sensitivity analysis

We did not plan any sensitivity analyses.

RESULTS

Description of studies

Results of the search

For the original review published in 2009, the electronic searches identified a total of 1519 titles and abstracts. We did not find any additional references by searching conference abstracts or by contacting pharmaceutical companies. One further study was identified by someone who peer reviewed the review. We assessed the titles and abstracts and agreed to look at 68 full-text papers. We rejected 31 papers for lack of relevance to the review as many were discussion papers and not studies. A further 27 were excluded for not meeting one or more inclusion criteria. Details of these 27 studies are included in the 'Characteristics of excluded studies' table). Ten publications reporting 11 studies were considered eligible for inclusion. Three of these studies were ongoing (see 'Characteristics of ongoing studies' table). The remaining eight completed studies (Laibovitz 1996; Laster 1996; Norell 1979; Sakai 2005; Schenker 1999; Sheppard 2003; Sverrisson 1999 USA; Sverrisson 1999 Europe) are compared in detail below and further details can be found in the 'Characteristics of included studies' table.

An update search was run in June 2012 which retrieved a further 654 records. The Trials Search Co-ordinator scanned the search results and removed 476 records which were not relevant to the scope of the review. We assessed the titles and abstracts of the remaining 178 records for potential inclusion in the review. We rejected 144 records. There were 13 reports of ongoing studies (see 'Characteristics of ongoing studies' for trial details). We obtained the full text of 21 publications for further assessment. We included the following eight studies in the review: Gray 2011; Hermann 2011a; Hermann 2011b; I-SIGHT; Muir 2012; Nakakura 2012; Okeke 2009; Ring 2011. We excluded the following 13 studies: Gulkilik 2011; Inoue 2011; Inoue 2012; Lorenz 2011; NCT00230763; NCT00262626; NCT00328835; NCT00329095; NCT00348062; NCT01415401; Rolle 2012; Rossi 2011; Sanchez-Pulgarin 2011.

Included studies

See Table 1 for a summary and individual tables for each included trial ('Characteristics of included studies').

We attempted to contact the study authors as a number of details were missing for all included studies. Where contact was made

we sent study-specific data collection forms via e-mail or post. The information below is based on a combination of published evidence and correspondence with authors. We have reviewed and analysed Sverrisson 1999 USA and Sverrisson 1999 Europe as two separate studies as the results were presented separately by the study authors, although published within the same paper.

Study design

There were 14 RCTs and two quasi-RCTs (Ring 2011; Sakai 2005). Although not specified in the published article, Sakai 2005 conducted randomisation by rotation.

Five studies were cross-over studies (Laibovitz 1996; Laster 1996; Schenker 1999; Sverrisson 1999 USA; Sverrisson 1999 Europe) and the rest were parallel-group designs.

There were six multi-centre studies (I-SIGHT; Okeke 2009; Nakakura 2012; Schenker 1999; Sverrisson 1999 Europe; Sverrisson 1999 USA) and the rest were single-centre.

All the studies were conducted in industrialised countries (Belgium, Denmark, France, Greece, Iceland, Japan, Sweden, Switzerland, UK and USA) and recruited participants in outpatient clinics.

Four studies were commercially sponsored by Merck & Co (Laibovitz 1996; Schenker 1999; Sverrisson 1999 USA; Sverrisson 1999 Europe), one study was part-funded by Pfizer (Gray 2011) and one by Alcon (Okeke 2009), five studies were funded or part-funded by government or charitable organisations (I-SIGHT; Laster 1996; Muir 2012; Okeke 2009; Ring 2011); and six did not state funding sources or had no funding (Hermann 2011a; Hermann 2011b; Nakakura 2012; Norell 1979; Sakai 2005; Sheppard 2003).

Participants

The 16 studies involved 1565 participants. The studies were relatively small: the median trial size was 74; the largest trial recruited 312 participants (I-SIGHT); and the smallest study recruited 13 participants (Laster 1996).

The average age of participants included in these studies ranged from 55 to 73 (median value 66 years). The range of ages went from 18 to 91. In the 15 studies reporting gender, the proportion of women ranged from 1% to 85%, with a median value of 58%. Eleven studies reported ethnicity: the proportion of the study population who were white ranged from 9% (I-SIGHT) to 100% (Hermann 2011a; Hermann 2011b), the proportion black ranged from 0% to 91% (I-SIGHT) and the proportion Asian ranged from 0% (five studies) to 10% (Ring 2011). Nakakura 2012 and Sakai 2005 were conducted in Japan but ethnic group was not specifically reported.

Almost all studies included people diagnosed with OAG or OHT and prescribed ocular hypotensive eye drops. The exception was the Japanese trial (Sakai 2005) which recruited people diagnosed with primary angle-closure glaucoma.

Interventions

The interventions varied considerably, although there were a few common themes as categorised below. For most studies the follow-up period was categorised as short-term (less than six months). The exception to this was Muir 2012 which followed up to six months and Gray 2011 and I-SIGHT followed up to 12 months. Gray 2011 also collected some follow-up data at 24 months.

Education or education combined with behavioural change interventions

There were seven studies which had employed some form of educational programme to improve adherence (Gray 2011; I-SIGHT; Muir 2012; Norell 1979; Okeke 2009; Ring 2011; Sheppard 2003).

In Gray 2011 patients were allocated to receive either individualised patient care in addition to standard care or standard care alone. Individualised patient care was provided by a glaucoma trained nurse and involved an assessment of healthcare needs and beliefs about illness and medicines (lasting approximately 45 minutes), an educational session (of approximately 20 minutes duration) and an interactive training session, to learn the technique of instilling eye drops (lasting approximately 10 minutes). Frequency and purpose of follow-up visits or telephone calls over one year was agreed with patients. It was expected that the duration of intervention activities would vary according to patient need.

In I-SIGHT the intervention group was given a tailored automated telephone intervention and tailored printed materials. The telephone intervention was delivered using interactive voice recognition technology and consisted of individually tailored messages to encourage adherence. This covered taking medication, keeping appointments, obtaining refills as well as information on glaucoma. The participant received 12 telephone calls over a nine-month period. After each telephone call, written materials were sent to the participants. The control group was given usual care.

In Muir 2012 participants received an educational intervention. This was a 20-minute individual session with the study co-ordinator (who had a background in ophthalmic research but was not a clinician). The participants watched a video about glaucoma which explained the structure of the eye and glaucoma and showed how to instil drops. The language used in the video, and other printed material, was tailored to the participants' literacy which was measured using the Test of Functional Health Literacy in Adults (Parker 1995). The control group received standard care as usual from an ophthalmologist.

Norell 1979 implemented a 30-minute education and tailoring programme using a parallel-group design which took place as part of the clinic appointment. The intervention group received basic information on glaucoma and its treatment supplied by a tape-slide show and leaflet, then patients' knowledge and understanding was checked by an ophthalmic assistant and insufficiently mastered information was re-emphasised; participants were encouraged to

ask questions and discuss problems with medication. This was followed by 'tailoring' which consisted of a patient interview with an ophthalmic assistant to ascertain daily routine and to advise on best times to instil eye drops within the daily routine. Advice was also given on storage of drops. Finally, times and drop routines were written for each patient. No description was given regarding the control group apart from the fact that the participants did not receive the intervention. The intervention was implemented after the first 20 days of monitoring. Patients were then followed up for a further 20 days post intervention to evaluate the difference between the periods and the groups.

The intervention in Okeke 2009 consisted of a 10-minute educational video, a structured discussion with the study co-ordinator, reminder telephone calls and a dosing aid. The educational content *"stressed the importance of regular drop-taking, its rationale and expected effects, alternatives to eyedrops, and methods to maximize cooperation, such as linking drops to a daily activity, keeping a drop-taking calendar diary, and using family members to help in reminding them"*. The discussion with the study co-ordinator aimed "*to develop a strategy for improving adherence that included finding the best time of day to take the medication, distributing a blank calendar diary and going over details of how to keep it, and discussing individual patient barriers to taking the medication*". The telephone calls were made once per week for the first follow-up month and then every other week for the next two months and included a questionnaire *"about drop-taking behavior, difficulty with drops, side effects, and eliciting questions about therapy"* and the dosing aid had audible and visible alarms. The control group were told it was important to take drops as prescribed.

In Ring 2011 the intervention group watched a *"specifically designed patient education film"* and received standard written educational material. The control group received standard written educational material alone. Patients were followed up three months later to evaluate the difference in outcomes between the two groups.

Sheppard 2003 evaluated the effectiveness of a glaucoma monitoring nurse-led clinic using a parallel-group design, involving consultations of 15 minutes duration divided into two parts. Part one consisted of a standard assessment designed to monitor and record health details, such as current health status and recent ocular history and eye examinations including visual acuity, visual field test and IOP test using Goldmann's applanation tonometry. Part two comprised of a semi-structured educational session tailored to individual patient needs (details not provided). The control group attended a general ophthalmic clinic involving consultations of 10 minutes duration which included the standard assessment and eye examinations as above, a fundus examination and the remainder of time utilised according to each individual clinician (details not provided). Differences in patient outcomes were followed up at 12 weeks.

Reminder devices

Laster 1996 monitored participants using a medication alarm (the Prescript TimeCap) reminder device which comprised of a cap fitted onto a pre-weighed drop bottle. This device comprised of:

- a digital display that showed the time and day of the week when the container was last opened (the display reminded the patient when the most recent dose of medication was taken);
- an alarm that beeped when a dose was due and if the beep was ignored the digital face flashed to provide a visual reminder that a dose had been missed.

Patients undergoing the control period used a pre-weighed drop bottle without the TimeCap. As this was a cross-over study each patient acted as their own control. Patients were monitored for two periods of 30 days.

Drug comparisons

Drug studies that compared ocular hypotensive therapy met the inclusion criteria if the dosage frequencies differed and adherence was compared between the two frequencies

- Hermann 2011a compared brimonidine twice daily with brimonidine three times daily over four weeks with open and masked monitoring of adherence.
- Hermann 2011b compared brimonidine twice daily with brimonidine three times daily over four weeks.
- Laibovitz 1996 compared 2% dorzolamide three times daily with 2% pilocarpine four times daily using a cross-over design. Both groups continued to receive 0.5 timolol twice daily. Patients were monitored for two periods of 14 days.
- Nakakura 2012 compared latanoprost 0.005%/timolol 0.5% plus brinzolamide 1% with dorzolamide 1%/timolol 0.5% plus latanoprost 0.005%.
- Sakai 2005 compared latanoprost mono-therapy once daily with multi-therapy of 0.5% timolol twice daily and 1% dorzolamide three times daily using a parallel-group design. Participants were monitored for 12 weeks.
- Schenker 1999 compared 0.5% timolol gel once daily with 0.5% timolol solution twice daily using a cross-over design; patients were monitored for two periods of six weeks.
- Sverrisson 1999 USA and Sverrisson 1999 Europe compared 2% dorzolamide/0.5% timolol combination therapy twice daily with 2% pilocarpine four times daily and 0.5% timolol twice daily using a cross-over design. Participants were monitored for two periods of 14 days.

Outcomes

Adherence

All studies measured adherence. There were four main ways of measuring adherence: by self report, by electronic monitoring, prescription refills or weighing bottles.

Data on adherence were collected via self report in 10 studies (Gray 2011; I-SIGHT; Laibovitz 1996; Laster 1996; Nakakura 2012; Sakai 2005; Schenker 1999; Sheppard 2003; Sverrisson 1999 Europe; Sverrisson 1999 USA). Questionnaires were administered via an interviewer and were delivered at baseline in four studies (Laibovitz 1996; Sheppard 2003; Sverrisson 1999 USA; Sverrisson 1999 Europe) and on the last day of each cross-over period for the cross-over studies (Laibovitz 1996; Laster 1996; Schenker 1999; Sverrisson 1999 USA; Sverrisson 1999 Europe). The remainder assessed at the end of the study period.

Three studies used the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire (Laibovitz 1996; Sverrisson 1999 USA; Sverrisson 1999 Europe) which aims to measure common side effects of ocular hypertensive therapy and the extent to which these side effects affect health-related quality of life, compliance and patient satisfaction (Barber 1997). The questionnaire includes one adherence question: *"How often did you miss one or more drops*?" Patients were asked to mark on a scale from 0 to 6; 0 = never and 6 = always.

Gray 2011 measured adherence based on the Reported Adherence to Medication Scale (Horne 1999) using the following questions.

1. *"Some people say that it is easy to forget drops. Do you agree or disagree with the following statement: I sometimes forget to use my drops"*
2. *"How often do you forget drops?"*
3. *"Some people miss drops out, stop taking them for a while or adjust the times to suit their needs. Do you agree or disagree with the following statement: I sometimes miss out drops or alter the times to suit my own needs".*
4. *"How often do you miss/stop using drops or adjust the times to suit your own needs?"*

Patients were then asked to approximate how many drops they missed per month. Answers were scored using an ordinal scale of none, 1 to 3, 4 to 6 and 7 or more. Patients were also asked what the longest period without administering drops was and what caused them to omit doses. These questions were entered as free text.

I-SIGHT defined non-adherence as self report of missing doses of any glaucoma medication within one month of the interview. They also asked about missed doses within seven days and two weeks.

Laster 1996 asked patients to report the percentage of time (0% to 100%) they adhered to their eye drop therapy for each of the two 30-day phases studied.

Nakakura 2012 asked the following question: *"How often do you forget administration per week?"* (never/within two times per week/more than three times per week).

Sakai 2005 asked patients how many times they had forgotten to apply the eye drops, and responses were classified into four groups: less than once a week, once a week, two or three times a week, and four or more times a week.

Schenker 1999 measured adherence using the following question: *"During the last two weeks, how often did you miss one or more doses of test medication"* with the answer classified as never/rarely/occasionally/frequently/always

Sheppard 2003 conducted structured telephone interviews. Adherence was measured using an 11-point response scale (0 = never uses drops, 10 = always uses drops) but did not state over what time period. Participants were also asked if they encountered problems instilling drops and the reasons for not instilling drops.

Adherence was measured by electronic monitoring in four studies:

- Hermann 2011a and Hermann 2011b used an electronic monitoring device that was reported to detect eye drop usage with a sensitivity of 99% and specificity of 98% (confidence interval not given) (Hermann 2006). In Hermann 2011a patients were randomised to either a group which were aware or not aware of adherence monitoring to test whether masking this information has an effect on adherence whereas in Hermann 2011b no patients were told that their adherence was being monitored.
- Norell 1979 used a medication monitor. The monitor consisted of a plastic box with a holder for a 25 ml bottle. The holder was designed to protect the bottle and to facilitate replacement of the eye dropper cap. An elastic flap linked to a micro switch inside the box signalled to the electronic part of the monitor whether the cap was on or off. A sliding lid in the bottom of the monitor could be removed to exchange the bottle and battery but it was sealed when the monitor was given to the patients. The electronic system recorded information on whether or not the bottle had been opened during the last hour. When the monitor was connected to a separate read-out device, this information, together with the time signal was displayed on an electrocardiographic recorder. Patients were not told the purpose of the medication monitor until after data collection was complete.
- Okeke 2009 used a dosing aid that recorded the time and date of delivery on an internal, battery-operated chip and had been previously evaluated to have acceptable accuracy (Friedman 2007). Patients were aware that the devices recorded their drop-taking.

Gray 2011 measured prescription refill and used this to measure adherence. It was not stated whether patients were aware of being monitored for prescription refill adherence. I-SIGHT defined refill non-adherence as *"failure to refill any glaucoma medication prescription within a 1-month period after it was prescribed"* as indicated in pharmacy records, or as a physician note on refill non-adherence. No information was provided on whether patients knew for what reason prescription data was to be collected. Muir 2012 reviewed pharmacy records and determined the *"number of days without medication"* which was defined as *"the difference between the number of days that medication was available to the subject according to the pharmacy records and the prescribed dosing and the*

number of days that medication was required over the study period". Again, no information is provided on whether patients knew for what reason prescription data were to be collected.

Two studies weighed the eye drop bottle to measure adherence. Ring 2011 measured adherence by weighing bottles**.** The weight of eye drop bottle was taken before and after the study period and the target weight as per prescription was compared to actual weight afterwards. Laster 1996 weighed each bottle before the intervention and weighed it again on return so the amount of medication could be calculated. It is unclear in either study whether patients were told that bottles would be weighed to calculate adherence to eye drop therapy.

Persistence

In Gray 2011 patients who discontinued therapy and did not restart during the study period were defined as not being persistent. Laibovitz 1996; Sverrisson 1999 Europe and Sverrisson 1999 USA reported the numbers of patients who continued or completed treatment.

Intraocular pressure

Only a few studies declared how they measured IOP. Those that did reported they used Goldman's Applanation Tonometer. For Gray 2011 measurements were taken from the medical records of patients at 12 months immediately after the follow-up period and then at 24 months. In Nakakura 2012 an experienced ophthalmologist measured IOP at baseline, four weeks and 12 weeks. Okeke 2009 provided little information other than reporting that intraocular pressure was measured before and after the intervention. Measurements were taken at each visit between 10am and noon prior to washout, at baseline and at four-week intervals for Sakai 2005. For Schenker 1999 they were taken immediately before instillation (trough/0 hour), and two hours after instillation (peak) of morning medication at three-week intervals. Measurements were taken at trough and peak at baseline and the beginning and end of each cross-over period for Laibovitz 1996, Sverrisson 1999 USA and Sverrisson 1999 Europe.

Visual field defects

Four studies assessed for visual field defects (Laibovitz 1996; Sakai 2005; Sverrisson 1999 USA; Sverrisson 1999 Europe) using the Humphrey Field Analyser, except in Sverrisson 1999 Europe where some sites used an Octopus perimeter. All tested at baseline and at the end of the treatment period.

Quality of life measures

Three studies (Laibovitz 1996; Sverrisson 1999 USA; Sverrisson 1999 Europe) measured the effect of eye drops on quality of life as part of the COMTol questionnaire (Barber 1997). Patients were asked whether their quality of life was interfered with by side effects and activity limitations. Responses were marked on a scale of 0 to 5; 0 = not at all, 5 = extremely. This was measured at baseline and after each treatment period.

Adverse events

Only the drug comparison studies reported adverse events. In the three studies using the ComTol questionnaire *(*Laibovitz 1996; Sverrisson 1999 USA; Sverrisson 1999 Europe) participants were asked about ocular symptoms (burning/stinging; red, itchy, dry eyes; discharge; swelling; tearing), taste (bitter/unusual), vision (blurred vision, dimming of vision, trouble seeing at night), accommodation (trouble reading, trouble focusing near-to-far) and brow ache. Participants were asked how frequently any of the above symptoms occurred on a scale of 0 to 6 (0 = never, 6 = always) and how bothersome the symptoms were also on a scale of 0 to 6 (0 = not bothered, 6 = extremely bothered). In addition, headache was reported by participants in both studies. Sakai 2005 did not specify the questions asked to determine adverse events, yet reported that the following ocular adverse effects were observed: mild irritation, conjunctival hyperaemia, superficial punctate keratitis and eye lid pigmentation. The authors also reported the systemic adverse events of bradycardia and orthostatic hypertension. Schenker 1999 also did not specify the questions asked, yet reported the following symptoms: upper respiratory infection, blurred vision, eye burning/stinging, headache, conjunctival injection and eye itching. Nakakura 2012 asked about stinging/burning, foreign body administration, blurred vision, conjunctival hyperaemia and "comfortableness". Conjunctival hyperaemia and superficial punctate keratopathy were also assessed clinically.

Patients' knowledge of glaucoma

Four studies measured patients' knowledge or understanding of glaucoma (Gray 2011; Okeke 2009; Ring 2011; Sheppard 2003). Three of the studies used different measures. Gray 2011 compared patients' knowledge of glaucoma between the intervention group and control group administering a questionnaire (the Revised Glaucoma Adherence Questionnaire, GAQ-R, Gray 2010) by interview at the end of the 12-month follow-up period. Ring 2011 asked 10 questions on patients' knowledge of glaucoma (Appendix 12) at baseline and three months after the intervention. Sheppard 2003 assessed patients' understanding of glaucoma by two questions: *"What is glaucoma?"* and *"How does glaucoma affect the eye?"* using a multiple choice format before and after the intervention. No information was provided in Okeke 2009 about how knowledge of glaucoma was measured. Muir 2012 stated that they collected data on *"self-reported disease knowledge"* but did not report this outcome.

Costs

None of the studies reported the costs of the interventions.

Other outcomes

Gray 2011 measured other outcomes including patients' perception of glaucoma as an illness, the Revised Illness Perception Questionnaire, their beliefs about glaucoma (Moss-Morris 2002), Beliefs about Medicines Questionnaire (Horne 1999) and patients' satisfaction with quality of care, the Patient Enablement Instrument (Howie 1998). I-SIGHT assessed patients as non-adherent to appointments if physicians had made a record as such in notes or if there were no rescheduling of appointment within three months.

Excluded studies

Reasons for excluding studies are presented in the 'Characteristics of excluded studies' table. The majority of studies were not randomised trials and those that were did not measure adherence. These were mainly drug trials. One drug trial (Shibuya 2003) did measure adherence, however, the two ocular hypotensive therapies being compared were instilled via the same frequency ('once a day') and, therefore, we could not include this study. The authors of this study did not find a significant difference in adherence between the two ophthalmic solutions. We contacted authors of five studies for more information before a decision regarding eligibility could be made. A French study (Bron 2004) did question patients about their adherence level but did not publish the results. When asked for the results the authors stated that, *"such an evaluation is unreliable"*. Very little information was available regarding a study by Hunter 1999, found via the UK National Research Register. As there was no published paper and we were unsuccessful in contacting the author, we could not proceed further with this study.

Risk of bias in included studies

Details of 'Risk of bias' assessments for individual trials are presented in the 'Risk of bias' tables and figures (Figure 1; Figure 2).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

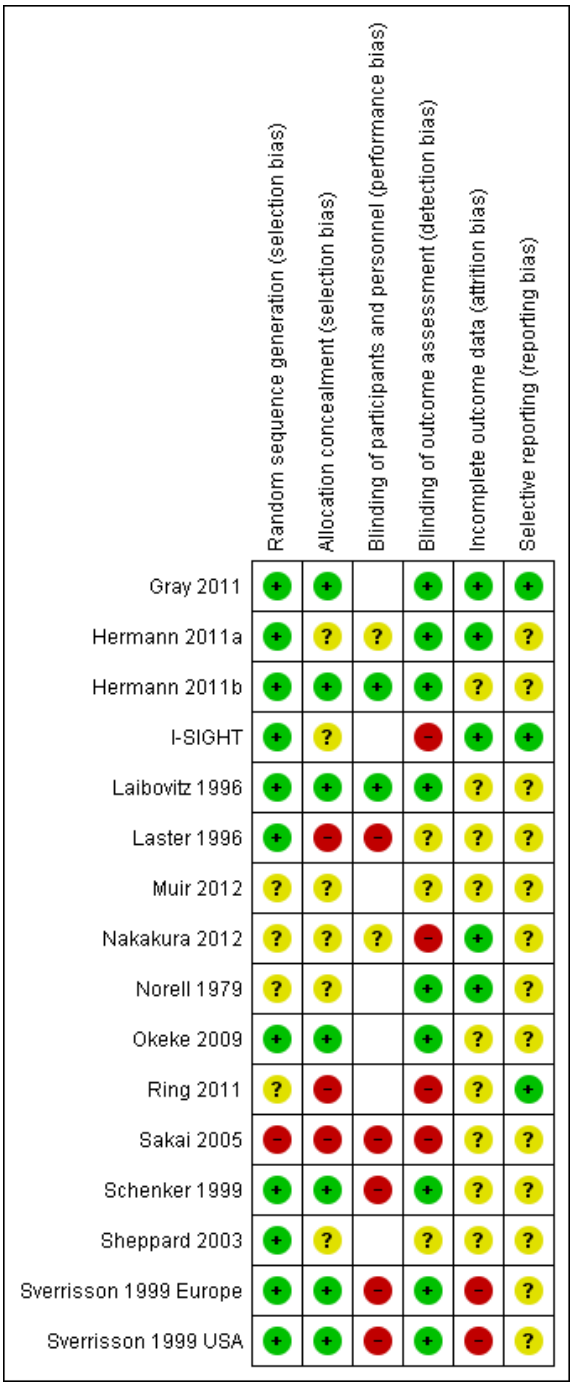
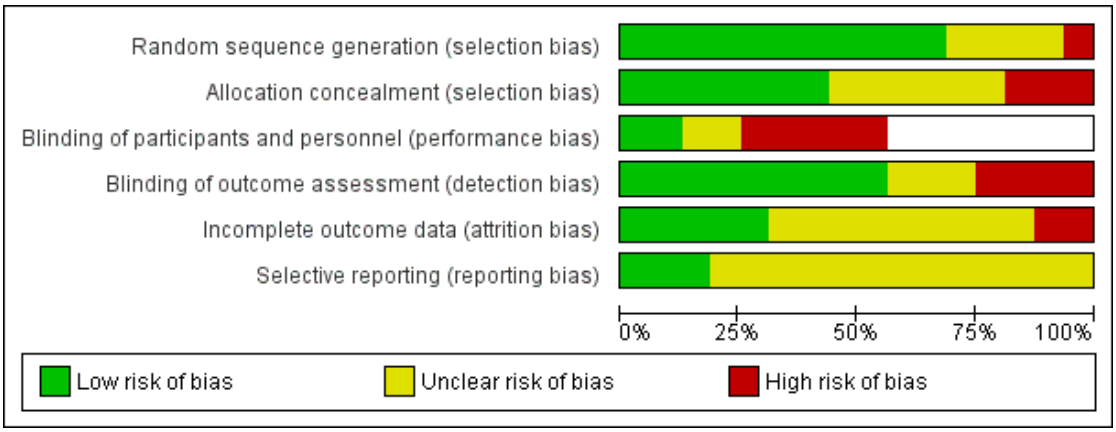


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Within the published papers, information was sparse concerning sequence and allocation concealment. Only a minority of studies reported adequate methods of sequence generation (Gray 2011; Hermann 2011a; Hermann 2011b; I-SIGHT; Okeke 2009; Sheppard 2003) and only Gray 2011, Hermann 2011b and Okeke 2009 reported adequate methods to conceal allocation prior to assignment. Following contact with authors, we were able to judge more accurately for some studies. A further five studies (Laibovitz 1996; Laster 1996; Schenker 1999; Sverrisson 1999 USA; Sverrisson 1999 Europe) described adequate sequence generation, either by using a computer-generated system or by drawing lots. We judged one quasi-randomised study (Sakai 2005) as high risk for using a rotation method, one trial (Norell 1979) as unclear, for not providing adequate information, and Ring 2011 ran the educational film on random days, rather than randomly allocating participants.

Six studies concealed allocations adequately until assignment using sealed opaque envelopes (Gray 2011; Hermann 2011b, Laibovitz 1996;Okeke 2009; Schenker 1999; Sverrisson 1999 USA; Sverrisson 1999 Europe). We graded three studies as high risk (Laster 1996; Ring 2011; Sakai 2005) for not concealing allocations and the rest were unclear (Hermann 2011a; Norell 1979; Sheppard 2003), as we could not obtain adequate information.

Blinding

We assessed masking according to those involved, e.g. the participants, study personnel involved in data collection such as interviewers and outcome assessors involved in data analysis. Much of the information regarding masking was obtained through contacting authors rather than the published evidence. Due to the nature of the included studies it was particularly difficult to mask participants. It could be argued that for drug trials, placebo drops could be used so that the frequency of instillation was the same for both groups, but since the hypothesis is that adherence may be related to the frequency of drop instillation this would be counterproductive.

For the studies involving interventions such as education, individualised care planning and reminder devices, 'performance bias' is an integral part of the intervention so we did not grade these studies for this parameter.

With respect to detection bias, Gray 2011, Hermann 2011a, Hermann 2011b, Laibovitz 1996, Norell 1979, Okeke 2009, Schenker 1999, Sverrisson 1999 USA and Sverrisson 1999 Europe reported that their studies were observer-masked or used techniques such as electronic monitoring where masking was not relevant. The remaining studies did not state any masking details which made judgements difficult. We judged four studies as high risk for detection bias; three (Laster 1996; Nakakura 2012; Ring 2011) had no masking procedures in place and the other (Sakai 2005) masked the interviewer but not the outcome assessor. We classified Sheppard 2003 as unclear.

Incomplete outcome data

We judged five studies as low risk for incomplete outcome data; for either having no missing data or adequately addressing missing outcome data, with attrition rates of less than 20% (Gray 2011; Hermann 2011a; I-SIGHT; Nakakura 2012; Norell 1979). We judged two studies as high risk (Sverrisson 1999 Europe; Sverrisson 1999 USA). For Sverrisson 1999 USA and Sverrisson 1999 Europe, the attrition rates were unclear from the paper and no further clarification was provided by study authors. The number of participants excluded from analyses varied across outcomes. The European study (Sverrisson 1999 Europe) suffered the greatest number of exclusions (22/93 (24%)) for the quality of life data. The numbers of participants involved in intraocular pressure and visual field analyses were unavailable for this study and, therefore, may also have exceeded 20%. In the remaining studies it was difficult to judge the impact of missing data and we graded these as unclear.

Selective reporting

As we did not have access to study protocols we could not judge studies as low or high risk of bias for this aspect. We marked all studies as unclear for selective reporting due to insufficient evidence, with the exception of Gray 2011 where it was clear from the report that all outcomes were reported.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: education and individualised care planning; **Summary of findings 2** Summary of findings: drug regimen

We did not perform a meta-analysis because there was clinical heterogeneity with respect to the interventions, and methodological heterogeneity with respect to the measurement of outcomes.

Adherence

Patient education or patient education combined with other behavioural change interventions

Table 2 summarises the effect of patient education or patient education combined with other behavioural change interventions on adherence to ocular hypotensive therapy.

Gray 2011, Norell 1979 and Okeke 2009 reported that adherence changed significantly with education and other behavioural change interventions. In Gray 2011 the proportion of people who were classified as adherent during the one-year follow-up was 70% in the intervention group compared to 43% in the control group. In Norell 1979 13% of the time patients exceeded eight-hour dose intervals in the intervention group compared to 24% in the control group during a 20-day period. In Okeke 2009 there was a higher adherence rate in the intervention group over three months (0.73) compared to the control group (0.51). All these differences were clinically and statistically significant.

I-SIGHT, Muir 2012, Ring 2011 and Sheppard 2003 did not find any statistical differences between the intervention and control. In I-SIGHT 30% of the intervention group and 27% of the control group did not report missing drops in the last month. In Muir 2012 the intervention group had, on average, 63 days without medication compared to 65 in the control group over six months. In Ring 2011 adherence as defined in the study (eye drop bottles within 10% of target weight) was similar between intervention and control groups. In Sheppard 2003 it was difficult to judge as no data were presented to support the statement that there were no differences between intervention and control groups.

Reminder devices

Laster 1996 was a cross-over study that reported data without providing information on the cross-over periods. Out of 13 participants, five people reported being adherent (100% compliance over 30 days) when using the TimeCap reminder device, one participant reported being adherent when not using the TimeCap device and seven were not adherent irrespective of whether using the device or not. It is difficult to interpret these data without knowing more information as to the time periods when the data were collected. Laster 1996 also reported that people using the TimeCap instilled approximately 3 grams more (mean difference (MD) 2.87, 95% confidence interval (CI) 1.70 to 4.03, $P < 0.001$) of eye drops over a 30-day period than those without.

Comparison of different drug regimens

Table 3 summarises the effect of drug regimen on adherence. The 'simpler' dosing regimen is classified as the intervention in this table. The specific dosing regimens are summarised in Table 1.

Two studies measured adherence using an electronic monitoring device (Hermann 2011a; Hermann 2011b) and the other six studies measured adherence using self report.

The table shows that in all eight studies the simpler dosing regimen was associated with greater adherence, although these differences were not always statistically significant, There were some uncertainties as to the analysis of the cross-over studies because in all cases they reported data for both periods combined. In addition, in most studies there were also differences in the type of drug used which may mean that drawing conclusions as to the association between adherence and simpler drug regimens may be too simplistic.

Monitoring

Hermann 2011a compared open and masked monitoring and measured adherence using an electronic monitor. They found little effect of type of monitoring on adherence (see table 3 of trial report on page e303). The adherence rate in people taking brimonidine

twice daily was 69.5% (standard deviation (SD) 17%) in people who were informed that they were being monitored compared to 77.1% (SD 6.0%) in people who did not know that they were being monitored. In people taking brimonidine three times daily the open monitoring group had an adherence rate of 65.3% (SD 14%) compared to people in the masked monitoring group who had an adherence rate of 62.4% (SD 9.1%).

Persistence

There were fewer data reported on persistence.

Patient education or patient education combined with other behavioural change interventions

In Gray 2011 persistence was defined when patients who discontinued therapy did not restart during the study period. Overall there were 17/127 patients who did not persist. In the intervention group 59/64 persisted compared to 51/63 in the standard care group (risk ratio 1.14, 95% CI 0.99 to 1.31).

Comparison of different drug regimens

In Laibovitz 1996 72/75 (96.0%) patients continued with the simpler regimen (dorzolamide three times daily) and 51/74 (68.9%) continued with the more complicated regimen (pilocarpine four times daily). However, these data represent the two periods of this cross-over study combined - in fact 75 patients in total were recruited into the study but no information on persistence in the different time periods was reported.

Sverrisson 1999 Europe did not find much difference between two groups; 87/92 (94.6) completed treatment with the simpler regimen (combination treatment with dorzolamide/timolol) compared to 84/91 (92.3%) who completed treatment with the more complex regimen. Again the cross-over design has been ignored in this analysis. In the US study (Sverrisson 1999 USA) the results were different: 90/93 (96.8%) completed treatment with the simpler combination regimen compared to 60/95 (63.2%) with the more complex regimen.

Intraocular pressure

Intraocular pressure was found to be significantly reduced in only one of the four studies that measured this outcome (Sakai 2005). They found a mean difference of -2.30 (95% CI -3.85 to -0.75, P = 0.004). This difference is likely to be independent of the adherence results as there was no difference in adherence between the two groups as reported above. There was no difference in intraocular pressure for three studies. Laibovitz 1996 measured at peak at the end of each study period (MD 0.10, 95% CI -0.43 to 0.63, P = 0.71) and Schenker 1999 also measured at peak at the end of each study period (MD -0.10, 95% CI -0.79 to 0.59, P = 0.78). Although both studies measured intraocular pressure at several intervals, we have reported the peak measurement as this result was presented by both studies. We could not analyse intraocular pressure for the remaining two studies (Sverrisson 1999 USA; Sverrisson 1999 Europe), as the number of participants involved was not stated in the paper and the authors could not provide these data when contacted. According to the published results, however, a significant difference was not found between treatment groups in both studies.

Of the new studies included in the current update, Hermann 2011a reported baseline intraocular pressure only and Gray 2011 found no difference in intraocular pressure between the two groups at 12 months and 24 months, but there was some suggestion of decreased "fluctuation" in the intervention group at over 24 months (Table 4). Okeke 2009 found no difference between the intervention groups with respect to intraocular pressure but did not report the actual data. They also did not find any association between adherence rate and intraocular pressure. Nakakura 2012 found very similar intraocular pressure in both groups (14.1 mmHg (SD 2.7) versus 14.2 mmHg (SD 2.7).

Visual field defects

We could only analyse the results of one study (Sakai 2005) for visual field defects, and we did not find a significant difference between the two groups (MD 0.90, 95% CI -3.85 to 2.05, P = 0.55). We could not analyse the results for Laibovitz 1996 as paired data were not presented and for Sverrisson 1999 USA and Sverrisson 1999 Europe due to missing data (as above, we could not obtain data for the number of participants involved in visual field testing). The study authors for all three studies did not find a significant difference for emerging or worsening of defects. None of the new studies included in this 2012 update (Gray 2011; Hermann 2011a; Okeke 2009; Ring 2011) reported visual field defects.

Quality of life

Quality of life was analysed in three studies via the self report COMTol tool (Barber 1997). Side effects for patients prescribed pilocarpine drops alone or pilocarpine plus timolol drops interfered with quality of life; both of these regimes required drops to be instilled four times a day (Laibovitz 1996: MD -1.60, 95% CI -2.04 to -1.16, P < 0.001; Sverrisson 1999 USA and Sverrisson 1999 Europe: MD 1.10, 95% CI -1.35 to -0.85, P < 0.001, I^2 = 60%). There were also more reported activity limitations when the frequency of drop instillation increased (Laibovitz 1996: MD -1.60, 95% CI -2.04 to -1.16, P < 0.001; Sverrisson 1999 USA and Sverrisson 1999 Europe: MD -0.72, 95% CI -0.97 to -0.47, P < 0.001, I^2 = 92%). Patients instilling drops less frequently, dorzolamide three times a day (Laibovitz 1996) or dorzolamide/timolol combination drops (Sverrisson 1999 USA; Sverrisson 1999 Europe) twice a day, reported significantly less interference to their quality of life by side effects or activity limitations.

Patient knowledge

Gray 2011 found that patients who received education combined with an individualised package had better knowledge of glaucoma and its treatment compared to those who received standard care. The median knowledge score (Gray 2010) was 14 (range 2 to 18) for the intervention group and 6 (range 0 to 17) for the control group (Mann-Whitney P < 0.001).

Data on patient knowledge were provided by Ring 2011. For two out of the 10 questions, the control group showed greater improvement in knowledge over the three-month period (i.e. answered questions correctly). However, for most questions the differences between intervention and control groups three months after the intervention were not statistically significant.

Okeke 2009 and Sheppard 2003 reported no differences between intervention and control groups with respect to patient knowledge, but Okeke 2009 did not report the actual data. Muir 2012 collected but did not report data on patient knowledge.

Costs

No data were reported on the cost of the interventions.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Simplified drug regimen for improving adherence to ocular hypotensive therapy

Patient or population: people with glaucoma or ocular hypertension
Settings: outpatients
Intervention: simplified drug regimen
Comparison: standard care

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Adherence	650 (8)	⊕◯◯◯ **very low**[1]	All studies reported a better adherence rate in the group with the simpler drug regimen; in 3 studies this difference was statistically significant. Different measures of adherence meant it was difficult to estimate overall treatment effect
Persistence	265 (3)	⊕◯◯◯ **very low**[1]	2 out of 3 studies found that the people using the simpler drug regimen had a higher persistence, however all 3 studies were short-term cross-over studies and time periods were not reported
Intraocular pressure	503 (5)	⊕◯◯◯ **very low**[1]	Overall there was little evidence of any effect on IOP
Visual field defects	301 (4)	⊕◯◯◯ **very low**[1]	None of the studies found significant effects on visual fields but were of short duration
Quality of life	265 (3)	⊕◯◯◯ **very low**[1]	In all 3 studies quality of life was assessed using the COMTol questionnaire. There were more reported activity limitations when the frequency of drop instillation increased
Adverse effects	650 (8)	⊕◯◯◯ **very low**[1]	Interventions too different to come to a consensus as to adverse effects

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to

change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded to very low because (i) trials were at risk of performance and other biases, (ii) data from cross-over trials had not been analysed appropriately, and (iii) there was inconsistency in trial results.

DISCUSSION

Summary of main results

There was some evidence that patient education combined with other more complex behavioural change interventions improved adherence to ocular hypotensive therapy (Summary of findings for the main comparison), however overall the findings were not conclusive. The studies were variable quality; some studies were at considerable risk of bias, and in general the length of follow-up was short, i.e. less than six months. Only three studies followed up for six months or more.

It was not possible to combine the results of different studies due to differences in reporting outcomes. In three studies, people who received patient education combined with other more complex behavioural change interventions to improve adherence to eye drops were more likely to take their medication as prescribed. However, in four studies no effect was observed. The intervention was more complex and individually tailored in the studies that showed an effect. There was less information on other outcomes such as persistence and intraocular pressure, and no information on visual field defects and quality of life.

There was weak evidence as to whether people on simpler drug regimens were more likely to adhere and persist with their ocular hypotensive therapy (Summary of findings 2). Again studies were of variable quality and short-term. A particular problem was the interpretation of cross-over studies which in general were not reported correctly.

One study investigated a reminder device and monitoring. However, this study was small and inconclusive.

Overall completeness and applicability of evidence

Follow-up and duration of intervention

Follow-up of patient outcome in the studies which incorporated an educational intervention ranged from 20 days to one year (24 months for a few outcomes) with the most being around three months. Reardon 2011 found that persistence significantly diminishes at the end of the first year for patients newly prescribed ocular hypotensive therapy. Arguably, a longer follow-up period would be most efficacious in understanding the long-term effects of these types of interventions. Similarly, the reminder device (Laster 1996) was tested for only two periods of 30 days. Monitoring for a longer period of time may have given a more accurate picture of the device's true effect and may have produced a different result.

Some of the interventions focusing on education were of extremely short duration. One (Norell 1979) lasted 30 minutes and the other (Sheppard 2003) 15 minutes. In Ring 2011 intervention lasted for as long as the video (not specified). More recent studies have designed interventions which have lasted for longer periods, incorporating long-term support: Okeke 2009 provided reminders for up to three months, Gray 2011 provided nursing support for up to one year and I-SIGHT provided advice and reminders via an automated tailored health communication over nine months. More and better designed studies are required in order to understand the effectiveness of short versus long-term interventions.

'Hawthorne effect'

For Sheppard 2003, a significant difference was not found between the groups. When scores were compared to baseline results, however, both groups were found to have significant improvement in adherence levels. This result potentially masks the true effect of the intervention and may reflect the 'study effect' often termed the 'Hawthorne effect' (Leonard 2006; Leonard 2008; Mangione-Smith 2002). Both groups may have changed behaviour as a result of being involved in a research study due to the additional attention received. Specific details for care received by the control group were limited for this study; the authors stated that, *"time was utilised according to each individual clinician"*. A number of factors may be involved; control group patients may have become more interested in their disease and asked more questions than they would have done normally. Adherence was assessed at baseline and at completion and, therefore, patients may have changed their behaviour by adhering to their drop regime, knowing that they would be questioned about their adherence level

again at the end of the study as they had been at the beginning. Doctors may have spent more time than usual discussing eye drop therapy and adherence issues with control group patients knowing that they were also being observed. If the study had been of longer duration, for example, with a one-year follow-up period, the 'Hawthorne effect' may have subsided over time. Whilst the Hawthorne effect may be particularly pertinent to Sheppard 2003, it may also have been a factor in the outcomes of the other studies. This is with regard to what researchers tell participants about the study, especially concerning what and how the outcomes are to be measured. In the case of this review, it is unclear in many of the studies whether patients knew in advance how adherence was to be measured objectively if they knew at all. Usually, good ethical practice demands transparency with patients but this may have the potential to cause reactivity bias. As reported in this review, Hermann 2011a found that there was no significant difference in adherence between those patients masked and unmasked to adherence monitoring. Although more research is needed to further our understanding of this issue.

Measures of adherence

Ten studies measured adherence via self report.This is said to be unreliable as patients tend to over-estimate their adherence level, as Rotchford 1998 found when self report results were compared with prescription refill rates. The subjective measure of self report, however, is the most utilised method for assessing adherence in glaucoma as in other long-term conditions (Chang 1991; Nelson 2006; Senior 2004; Ulrik 2006). Three of the studies (Laibovitz 1996; Sverrisson 1999 USA; Sverrisson 1999 Europe) in our review used the previously validated COMTol tool (Barber 1997). Gray 2011 and Schenker 1999 validated the reliability of the questionnaire used during their studies and the remainder did not discuss validation of the tool used. All were numerical scales which allowed patients to mark along the scale where they thought their answer should be, without judgemental or leading questions. Numerical and Likert scales are frequently used (Ross 2004; Treharne 2004) and have been validated (DiMatteo 1993; Horne 1999; Moss-Morris 2002; Wetzels 2006) for adherence studies involving patients with long-term conditions. They can provide a constructive measure, yet one must bear in mind that positive findings are likely to over-estimate the true effect. Sakai 2005 appeared to have the least robust tool which asked patients whether they forgot drops on a narrow scale, ranging from less than once a week to four or more times a week. The categories used may have led patients to answer 'less than once a week'. This study compared the least frequent dosage (once a day) with a rather complicated regime of one drop three times a day and another drop twice a day and found no difference between the groups. It may well have been the assessment tool that produced such positive results for both groups rather than the interventions being compared.

Measures of persistence

Prescription refill rates and dispensing counts are objective methods for assessing patients' continuity of therapy and have been used successfully in ophthalmology (Reardon 2004; Reardon 2011; Rotchford 1998). While these methods accurately measure persistence, they do pose some problems; an accurate measurement of prescribed drops can usually be obtained via the patient's doctor - obtaining dispensing information is sometimes more difficult if patients use several pharmacies. Also, patients may obtain repeat prescriptions for a number of medications and, therefore, receive their eye drops as part of their regularly repeated supply. This does not necessarily mean that the drops will be used as prescribed or used at all. Combining both adherence and persistence measures may help to combat the latter issue.

Monitoring device

The monitoring devices used by Norell 1979 and Okeke 2009 could be viewed as the most reliable tools. It is particularly unfortunate that we could not assess the risk of bias effectively for Norell 1979 in order to provide a more comprehensive assessment of methodological quality. A monitoring and reminder device has been developed (Boden 2006; Flowers 2006). This is a container that houses a drop bottle and records the handle on the device being depressed to indicate drop instillation. There is also a visual and auditory function to act as a reminder for patients to instil drops. This appears to be an updated version of the device used in the Laster 1996 study and, therefore, has similar issues regarding monitoring and for patients wishing to travel. The device has been designed for use with travoprost drops only, however the software for this device has been withdrawn from the UK and is no longer available.

Another device (Hermann 2006) fitted with a microprocessor is designed to attach to a normal size bottle to record tilting and squeezing of the bottle. The advantages this has over the previous designs are that it is smaller; the microprocessor has increased data safety, data can be downloaded onto a personal computer and patients can carry the device around easily. The device is hidden under a drop bottle creating a normal bottle appearance, thereby increasing the likelihood of patients being unaware of monitoring. This device does appear to be promising, but until more accurate, cost-effective monitoring devices like this are available, methods of self report and prescription refill used independently, or in combination, will continue to be the standard assessment tools for measuring drop usage.

Another device available is the Medication Events Monitoring System (MEMS, http://www.aardexgroup.com), a white plastic container with a screw top in which the eye drop bottle is stored until needed for drop instillation, that is, it is a bottle in a bottle and therefore it is easy to tip out the drop bottle when there is a need to instil eye drops. An electronic record is made every time the top is unscrewed. The battery is reported to last for 36 months. There

are various sizes of the MEMS so it is quite probable it will store all types of glaucoma eye drop bottles. The MEMS has been used successfully to measure adherence to glaucoma treatment (Sleath 2012). The device is relatively cheap to purchase and it is easy to train patients in its use. The drawbacks of the MEMS include, on the one hand, that it may act as a reminder to patients and on the other that it could be a barrier to taking medicines as prescribed. This is because it requires an additional action (unscrewing the bottle) which could be sufficient to put off some people. Also, there is no way of knowing whether the patient actually instils the eye drops once unscrewed and, vice versa, patients could leave off the screw top but still be putting in eye drops. To date no RCT has reported using the MEMS to measure adherence to ocular hypotensive medication, however its potential is worthy of exploration in future studies.

Co-morbidity

We stated in the protocol that we would include studies that reported involuntary non-adherence, e.g. due to co-morbidity. Three studies (Gray 2011; Okeke 2009; Sheppard 2003) reported that they asked participants what problems they had instilling drops.

Clinical outcomes

Most of the studies measuring education or reminder interventions did not assess clinical outcomes. As these studies were short-term it is unlikely that changes in clinical outcomes such as intraocular pressure, visual field defects or optic nerve head changes would have been significantly different between groups. A study (Sakai 2005) that did assess clinical outcomes found evidence that one drug was more efficacious in terms of reducing intraocular pressure. This study, however, did not find a significant difference between the groups regarding adherence to therapy and, therefore, as previously discussed the difference in pressures was likely to be unrelated to the adherence level and more related to the drug, whilst the adherence results may be due to the measuring tool used. The remaining four studies (Laibovitz 1996; Schenker 1999; Sverrisson 1999 Europe; Sverrisson 1999 USA) found no evidence that patients' intraocular pressures were significantly reduced in the groups with better reported adherence levels. Gray 2011 report no difference in intraocular pressure between the intervention and control group but did find a statistical difference in intraocular pressure fluctuations at 24 months in that it was lower in the intervention group.

Sakai 2005 had sufficiently robust data with which to identify that there were no differences in visual field defects between the two groups. As mentioned above, the data from the remaining three studies could not be analysed (Laibovitz 1996, Sverrisson 1999 Europe; Sverrisson 1999 USA). Only one study (Okeke 2009) measured the optic disc but the categories were not exclusive.

Quality of the evidence

The overall quality of the evidence for the different outcomes is summarised for the main comparisons in Summary of findings for the main comparison and Summary of findings 2.

In general we graded the evidence as 'low' or 'very low' (Gordon 2008). This is because we considered the included trials to be at risk of bias in one or more parameters, there was inconsistency in the findings between trials, and in some cases sufficiently sparse data such that the findings were imprecise. This means that future research is likely to have an important impact on the estimates of effect and in some cases we are very uncertain about the estimates of effect.

Potential biases in the review process

It is possible that unfavourable findings did not reach publication. A failure to publish unfavourable results leads to an accumulation of literature favouring benefits. Bias distorts systematic reviews and meta-analyses and encourages the use of questionable treatments (Dwan 2008). This is less of an issue for our review since we have not found sufficient evidence yet to make definitive recommendations. For completeness, we invite readers to send us any published or unpublished studies that meet our inclusion criteria, that we may have missed.

Publication bias may be less of a problem in the future with the use of trial registries. For this update we searched the clinical trial registries and have a total of 16 unpublished and ongoing studies that will be included in future updates of this review.

Agreements and disagreements with other studies or reviews

A systematic review by Olthoff 2005 found the quality of experimental studies to be poor, as did the first version of our review (Gray 2009). However since then the quality of some studies appears to have improved, albeit no definitive trial has yet been published. Five intervention studies were included; three of these were RCTs (Gray 2011; Norell 1979; Ring 2011) and, therefore, are included in our review. Norell 1979 was the only one to be judged as good quality by Olthoff 2005 who also found the education and tailoring intervention to be the most convincing. Unfortunately, Norell was the only author amongst our included studies that we could not contact for more information regarding missing methodology information and, therefore, we could not judge the study as good quality.

A recent update of a Cochrane review (Haynes 2008) found that interventions for chronic health conditions were mostly complex and not very effective; even the most effective did not lead to large improvements in adherence and clinical outcomes. Haynes 2008 also found a plethora of interventions which could not be combined into a meta-analysis. As for our review, most of the studies

suffered from low power due to small sample size. Haynes 2008 recommended that high priority should be given to fundamental and applied research, concerning innovations to assist patients in following prescriptions for long-term medical disorders.

We found only limited evidence to support the effectiveness of simplifying medication regimes, in contrast to van Dulmen 2007 who found that simplification of the medication regimen led to better adherence following a review of 36 systematic adherence reviews in specialities other than ophthalmology. The difference may be accounted for by the larger number of studies and resulting higher number of patients involved, or that the method of administration may have had an effect (oral versus eye drop).

AUTHORS' CONCLUSIONS

Implications for practice

Although the findings of this review suggest that patient education combined with more complex behavioural change interventions may improve adherence to ocular hypotensive therapy, there is insufficient evidence to advocate any particular intervention at present. Educating patients about their condition, teaching them how to instil eye drops, providing reminders and working individually with patients to help them manage their eye drop routines are all aspects of care which have provided positive findings for improving adherence levels. In addition to the above, simplifying drop regimes may also be beneficial, but until there are more convincing results, we are unable to make more substantial clinical recommendations. However, in the absence of robust estimates of effectiveness, and in particular any evidence of effect on progression of the disease, it is not possible to address the issue as to whether investment in improving adherence is warranted, although in theory it would seem to be a sensible strategy.

Implications for research

This review identified three problems with the published literature on this topic:

1. Generally, published studies are too short, although more recent studies have had longer follow-up of outcomes: they do not provide useful information on whether interventions to improve and maintain adherence to therapy are effective over the long term. Glaucoma and ocular hypertension are chronic conditions: adherence to therapy needs to be maintained over the long term. We suggest that patients should be followed up for at least one year.

2. Standardised outcomes are needed: this review has been limited by the fact that a wide range of outcomes were reported. This has meant that it was not possible to pool data between studies and produce reliable estimates of treatment effect. Ideally a core outcome set should be developed that would include the views of people who take these medications on a regular basis.

3. Better reporting of studies is needed: we encountered difficulties with the reporting and interpretation of the cross-over studies in particular. We recommend that authors follow standard reporting guidelines, for example, CONSORT guidance has been produced to assist in the writing of RCTs (Schulz 2010).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gray 2011

Methods	Randomised, single-centre, observer masked, parallel-group study Duration: 24 months
Participants	Country: UK Setting: hospital outpatient clinic Target number of participants: 127 Gender: 64 men, 63 women Age range: 30 to 91, mean age 66 years Ethnicity: 114 (90%) white, 8 (6%) black, 5 (4%) other Inclusion criteria: patients newly prescribed ocular hypotensive eye drops with a diagnosis of OAG, normal tension glaucoma, pseudo-exfoliation glaucoma, pigment dispersion glaucoma or OHT Exclusion criteria: patients unable to give informed consent or patients already prescribed a complicated drop regime for another eye condition
Interventions	Intervention group: individualised programme of care carried out by an ophthalmic-trained nurse based on an assessment that takes into account factors such as other medical conditions, additional medications, independence with daily living activities, potential problems managing an eye drop regime and beliefs about medications. Patients also continue to receive the information, advice and training they would normally be given within the outpatients department Control group: usual care; patients receive the information, advice and training they would normally be given within the outpatients department Follow-up: 1 year
Outcomes	Persistence of therapy measured by counting prescription and dispensing data Adherence to therapy assessed through self report via interviewer-administered questionnaire Beliefs about illness and medicines assessed through self report via previously validated, interviewer-administered questionnaires Patient enablement assessed through self report via previously validated, interviewer-administered questionnaires Intraocular pressure
Notes	Funding sources: part-funded by Pfizer http://www.controlled-trials.com/ISRCTN13706134

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"Computer-generated randomisation was conducted by a statistician with no involvement in data collection. Patients were allo-*

		cated to receive either individualised patient care in addition to standard care or standard care alone. Stratified random sampling ensured equal proportions of patients within each arm from specialist glaucoma and general ophthalmic clinics, to reduce the risk of confounding factors from potential clinical management inequalities" Page 257
Allocation concealment (selection bias)	Low risk	*"Allocations were concealed in opaque sealed envelopes by personnel with no involvement in the study. Envelopes were then passed onto a study coordinator with minimal involvement in the study. The study coordinator was responsible for opening envelopes as patients were recruited and contacting the intervention nurse to inform her as new patients were randomised to the intervention-arm."* Page 257
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The researcher and outcome assessor were masked to allocations until study completion.* " Figure 1 page 409
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes at 12 months: data for 63/64 of intervention group and 60/63 of control group. Reasons for incomplete outcome data supplied. Figure 2 page 412
Selective reporting (reporting bias)	Low risk	There were some modifications from the protocol but this was additional data collection (clinical outcomes data and knowledge and self report adherence measures). All data collected were available for this review

Hermann 2011a

Methods	Randomised, single-centre, observer masked, parallel-group study Duration: 4 weeks
Participants	Country: Greece Setting: hospital outpatient clinic Number of participants: 36 Gender: 11 men, 25 women Age range: 26 to 76, mean age 55.1 +/- 14 Ethnicity: Caucasian 61% ocular hypertension Inclusion criteria: age more than 18 years; diagnosis of primary open-angle glaucoma

	or ocular hypertension; established topical hypotensive therapy with brimonidine; no history of ocular surgery in the past 6 months Exclusion criteria: none
Interventions	Open or masked monitoring and brimonidine twice daily or 3 times daily
Outcomes	Dosing interval, applications per day, adherence rate, coverage. Assessed using an electronic monitoring device
Notes	Funding sources: not reported. This statement was included in the published paper *"The authors did not receive support from a for-profit organization."*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"Patients were then assigned to open or masked monitoring and to brimonidine BID or TID using permuted block randomization and randomization envelopes."* Page e301
Allocation concealment (selection bias)	Unclear risk	*"Patients were then assigned to open or masked monitoring and to brimonidine BID or TID using permuted block randomization and randomization envelopes."* Page e301 Not enough detail about the envelopes reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	*"Subjects received the study medication with attached monitoring devices free of charge and were familiarized with the usage of the bottles. Patients with masked monitoring were not informed about the electronic adherence monitoring. Instead, these patients were told, the electronic devices would continuously record the temperature of the medication. Patients assigned to open monitoring were fully informed about the monitoring of adherence to topical therapy."* Page e301 It is not clear if the personnel or participants were masked
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Subjects received the study medication with attached monitoring devices free of charge and were familiarized with the usage of the bottles. Patients with masked monitoring were not informed about the electronic adherence monitoring. Instead, these patients were told, the*

Hermann 2011a (*Continued*)

		electronic devices would continuously record the temperature of the medication. Patients assigned to open monitoring were fully informed about the monitoring of adherence to topical therapy." Page e301 The above statement suggests the participants might have been masked, but not clear as to personnel or outcome assessors. However, as the outcome measures were based on electronic recording, lack of masking was considered not to be a source of bias here
Incomplete outcome data (attrition bias) All outcomes	Low risk	36/37 participants completed the study
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Hermann 2011b

Methods	Randomised, single-centre, observer masked, parallel-group study Duration: 4 weeks
Participants	Country: France Setting: hospital outpatient clinic Number of participants: 75 Gender: 44 men, 31 women Age range: 42 to 89 years, mean age 70.0 +/- 11.2 years Ethnicity: 100% white Inclusion criteria: 18 years of age or older taking topical therapy for open-angle glaucoma, chronic angle-closure glaucoma, or ocular hypertension; no history of ocular surgery in the past 3 months; minimum of 12 months experience with topical glaucoma therapy Exclusion criteria: none
Interventions	Brimonidine twice daily and 3 times daily
Outcomes	Electronic monitoring Dosing interval Applications per day Adherence rate % Coverage % Medication used per dosing Drops per dosing
Notes	Funding sources: *"The authors did not receive support from a for-profit organization."*
Risk of bias	

Hermann 2011b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Patients were then randomly assigned to brimonidine bid or tid using permuted block randomization with randomization envelopes and received the study medication with attached monitoring devices free of charge.*" Page 503
Allocation concealment (selection bias)	Low risk	*"Patients were then randomly assigned to brimonidine bid or tid using permuted block randomization with randomization envelopes and received the study medication with attached monitoring devices free of charge.*" Page 503
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"According to the study protocol electronic adherence monitoring was accomplished in a masked fashion. Patients were informed about the electronic monitoring only to the point that the temperature of the medication would be recorded.*" Page 502
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"According to the study protocol electronic adherence monitoring was accomplished in a masked fashion. Patients were informed about the electronic monitoring only to the point that the temperature of the medication would be recorded.*" Page 502
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	*"A total of 75 patients [...] were enrolled in the study; 67 (89%) completed the study and were included in the statistical analysis. Seven patients (9.3%) did not complete the study owing to adverse effects (migraine, dry eye, redness, allergy). One bottle (1.3%) was not recollected.*" Unclear which group 7 patients were in. Page 504.
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with information available

I-SIGHT

Methods	Randomised, multi-centre, observer masked, parallel-group study Duration: 12 months
Participants	Country: USA Setting: outpatient clinic Number of participants: 312 Gender: 195 men, 117 women Age range: 18 to 80 years, mean age 62.6 years Study participants were patients with glaucoma considered to non-adherent *"because they did not take their medication, refill their medication, and/or keep their appointments"* Inclusion criteria: receive treatment for their eye condition at 1 of the 2 participating eye clinics; be between the ages of 18 and 80 years; be white or black/African American; have a home or cellular telephone; speak and understand English; be diagnosed with glaucoma or ocular hypertension for at least 1 year; be prescribed daily doses of topical glaucoma treatments for at least the past year; not have had eye surgery within the past 3 months; have better than 20/200 vision in at least 1 eye; and be able to read or have someone who can help them with reading printed materials Patients also had to acknowledge non-adherence in the past year with medication taking, obtaining refills or clinic appointments
Interventions	Intervention group: 12 telephone calls over 9 months delivered automatically including tailored information on adherence and glaucoma. The intervention was *"individually tailored to a participant's knowledge, attitudes, and behaviors; psychosocial predictors of adherence; health literacy; race and culture; and prescribed medication regimen."* Control group: usual care
Outcomes	Adherence (self report of missed doses) Prescription refills (pharmacy records) Appointment keeping Sources of information: interviews, medical record review, appointment records and pharmacy data
Notes	http://clinicaltrials.gov/ct2/show/NCT00794170

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"After completing the baseline interview, each participant was randomized into either the control or intervention group (with a 1:1 ratio). A random number generator was used in Excel (Microsoft), and participants were randomized in blocks of 10. The sequence was generated in advance by the research project manager, and participants were assigned in the order that they were enrolled. Randomization was stratified by clinical site because of expected differences in sex, race, and edu-*

I-SIGHT (*Continued*)

		cational level between the sites. " Page E2
Allocation concealment (selection bias)	Unclear risk	*"Research interviewers were not masked to assignment because it was necessary to determine treatment group participants' preferences for intervention delivery (eg, preferred telephone number and time of day)"* Page E2 Unclear if this applies to recruitment as well as outcome assessment
Blinding of outcome assessment (detection bias) All outcomes	High risk	*"Adherence data from data abstractions were coded independently by 2 raters who met in cases of disagreement to resolve discrepancies"* Page E3 *"Research interviewers were not masked to assignment because it was necessary to determine treatment group participants' preferences for intervention delivery (eg, preferred telephone number and time of day)"* Page E2
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intervention group: 150/157 (96%) interviewed at 12 months Intervention group: 152/155 (98%) interviewed at 12 months Figure page E4
Selective reporting (reporting bias)	Low risk	Investigator confirmed that all outcome data specified in protocol and collected in the study were published

Laibovitz 1996

Methods	Randomised, single-centre, observer masked, 2-period cross-over study Duration: 4 weeks
Participants	Country: USA Setting: outpatient clinic Number of participants: 75 Gender: 36 men, 39 women Age range: 24 to 88 years, mean age 55.7 years Ethnicity: white: 29/312 (9.3%), black 283/312 (90.7%) Inclusion criteria: men and women aged 18 years or older with OAG or OHT who were clinically suitable for adjunctive therapy. Patients treated with an ophthalmic beta-blocker for at least 3 weeks prior to randomisation Exclusion criteria: patients prescribed dorzolamide or pilocarpine in the past, visual acuity of worse than 20/80 in both eyes, history or evidence of acute or chronic ACG, insufficient pupillary dilation for an adequate retinal examination, history or presence of uveitis or retinal detachment. Patients with asthma or chronic obstructive pulmonary disease,

Laibovitz 1996 (*Continued*)

	clinically significant renal disease, severe physical disability or any contraindication to the use of dorzolamide, timolol or pilocarpine ophthalmic solution
Interventions	Group A: 2% dorzolamide 3 times daily during period 1 and 2% pilocarpine 4 times daily during period 2 Group B: 2% pilocarpine 4 times daily during period 1 and 2% dorzolamide 3 times daily during period 2 Both groups continued to receive 0.5% timolol twice daily throughout the study Follow-up: short-term; 14 days per period
Outcomes	Adherence assessed through self report via interviewer-administered questionnaire using previously validated tool (COMTol). Patients were asked how often they missed eye drops. Responses were marked on a scale of 0 to 6: 0 = never, 6 = always Quality of life assessed via interviewer-administered questionnaire (COMTol). Patients asked whether quality of life was interfered with by side effects or activity limitations. Responses were marked on a scale of 0 to 5: 0 = not at all, 5 = extremely IOP reduction assessed with Goldmann applanation tonometer Visual field defects assessed with Humphrey Field Analyser 24-2 programme
Notes	Funding Sources: Sponsored by Merck & Co

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random number generator used
Allocation concealment (selection bias)	Low risk	Central allocation used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"Because one purpose of our study was to determine patient preference between the two ophthalmic medications, and dosing regimen is an integral part of such preference, we deliberately did not mask the treatment regimens to the patients or study physician. However, the interviewer administering the COMTol questionnaire was masked to the patient's regimen, interviews were conducted in a brightly lit room (to induce miosis in all patients), and patients were instructed not to disclose their dosing frequency to the interviewer."* Page 823
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Because one purpose of our study was to determine patient preference between the two ophthalmic medications, and dosing regimen is an integral part of such preference, we deliberately did not mask the treatment regimens*

Laibovitz 1996 (*Continued*)

		to the patients or study physician. However, the interviewer administering the COMTol questionnaire was masked to the patient's regimen, interviews were conducted in a brightly lit room (to induce miosis in all patients), and patients were instructed not to disclose their dosing frequency to the interviewer." Page 823
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	*"Of the 75 patients who entered the study, 51 completed both treatment periods (Table III) . A total of 21 patients discontinued therapy due to adverse experiences while receiving pilocarpine (12 from group A and 9 from group B), whereas only 2 patients discontinued therapy due to adverse experiences while receiving dorzolamide (both from group B).[...] Only 1 patient, who was lost to follow-up during the first period, discontinued dorzolamide and did not enter the second period."* Page 825
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Laster 1996

Methods	Randomised, single-centre, 2-period cross-over study Duration: 60 days
Participants	Country: USA Setting: university-based glaucoma clinic Number of participants: 13 Gender: 2 men, 11 women Age range and mean age: data unavailable Ethnicity: data unavailable Inclusion criteria: patients diagnosed with OAG who were prescribed pilocarpine solution 4 times a day Exclusion criteria: not stated
Interventions	Group 1: pre-weighed bottle of pilocarpine of appropriate concentration (according to prescription) in a medication vial fitted with the Prescript TimeCap in period 1 and pre-weighed bottle of pilocarpine of appropriate concentration (according to prescription) without the vial or cap in period 2 Group 2: pre-weighed bottle of pilocarpine of appropriate concentration (according to prescription) without the vial or cap in period 1 and pre-weighed bottle of pilocarpine of appropriate concentration (according to prescription) in a medication vial fitted with the TimeCap in period 2 Follow-up: short-term; 30 days per period

Laster 1996 (*Continued*)

Outcomes	Adherence assessed by weighing the drop bottle at the end of each 30-day period and also through self report via a patient questionnaire completed at the end of each period	
Notes	Funding sources: non-commercially funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Drawing of lots (each participant was randomly given a number using a statistical table then numbers were drawn to assign to either group 1 or group 2)
Allocation concealment (selection bias)	High risk	Open random allocation schedule used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were not masked. The effects may vary with outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"*A total of 13 patients were [..] able to complete the study*" Page 655 This suggests that more people could have been enrolled and not reported
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Muir 2012

Methods	Randomised, single-centre, parallel-group study Duration: 6 months
Participants	Country: USA Setting: medical centre Number of participants: 127 (131 enrolled, 4 withdrew) Gender: 126 men, 1 woman Age range 43 to 87 years; mean age: 66 years (SD 9.6) Ethnicity: 29% white, 80% African American, 1% other Inclusion criteria: score of 18 or higher on Mini Mental State Examination patients diagnosed with OAG who were prescribed pilocarpine solution 4 times a day Exclusion criteria: best-corrected visual acuity in the better seeing eye < 20/200; eye surgery in the past month

Muir 2012 (*Continued*)

Interventions	Educational intervention lasting 20 minutes (one-on-one session) including "informational video". Language of video varied according to participants' tested health literacy level Standard care
Outcomes	Number of days without medication Medication possession ratio Self reported disease knowledge Satisfaction with care
Notes	Funding sources: non-commercially funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	*"Subjects were randomized in a one-to-one fashion to standard care or an educational intervention."* Page 161
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	131 enrolled, 4 withdrew, no other information on follow-up
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Nakakura 2012

Methods	Randomised, multi-centre, parallel-group study Duration: 12 weeks
Participants	Country: Japan Setting: hospital Number of participants: 36 (39 enrolled, 3 withdrew) Gender: 19 men, 17 women Average age: 71 years Ethnicity: not reported, assumed Japanese Inclusion criteria: primary open-angle glaucoma; exhibition of a stable intraocular pressure for more than 3 months; no history of fixed-combination therapy; treated with 3 antiglaucoma eye drops (various preparations of prostaglandin F2-alpha analogues + beta-blockers + carbonic anhydrase inhibitors) Exclusion criteria: congenital or narrow-angle glaucoma; ocular surgery including laser

Nakakura 2012 (*Continued*)

	surgery within the previous 6 months; any previous glaucoma surgery; ocular inflammation, neovascular glaucoma or steroid-induced glaucoma; any other conditions that prevent use of the Goldmann applanation tonometer; at risk of visual acuity and visual fields worsening during this study; allergy to preservatives
Interventions	Latanoprost 0.005%/timolol 0.5% plus brinzolamide 1% Dorzolamide 1%/timolol 0.5% plus latanoprost 0.005%
Outcomes	Intraocular pressure Questionnaire including question *"How often do you forget administration per week?"* Adverse effects If both eyes included, right eye analysed
Notes	Funding not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	20/21 participants in *latanoprost/timolol plus brinzolamide* group followed up compared to 16/18 in *dorzolamide/timolol plus latanoprost*
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Norell 1979

Methods	Randomised, single-centre, 2-period, parallel-group study. Randomisation stratified by age Duration: 40 days

Norell 1979 (*Continued*)

Participants	Country: Sweden Setting: hospital outpatient clinic Number of participants: 73 (82 recruited, 9 excluded from analysis) Gender: 45 men, 37 women Age range: 50 to 90 years, median age 73 years Ethnicity: not stated Inclusion criteria: patients with chronic simple glaucoma, glaucomatous visual field defect, cupping of optic disc, raised IOP and prescribed pilocarpine eye drops 3 times a day in an eye with visual acuity of least 2/60 Exclusion criteria: not stated
Interventions	Experimental group: no intervention for the first 20-day monitoring period, then 30-minute education and tailoring programme implemented at clinic appointment and monitoring continued for a further 20 days. Education involved basic information on glaucoma and its treatment, supplied by a tape-slide show and leaflet. Patients' knowledge and understanding was then checked by ophthalmology assistant and insufficiently mastered information re-emphasised. Patients were encouraged to ask questions and discuss problems with medication. Tailoring involved patient interview with an ophthalmology assistant to ascertain daily routine and to advise on best times to instil eye drops within daily routine. Advice given re: storage of drops. Times and drop routine written for each patient Control group: monitoring for 2 x 20-day periods, no intervention Follow-up: short-term; 20 days per period
Outcomes	Adherence to therapy assessed with a medication monitor which recorded the date and hour each time the medication bottle was opened
Notes	Funding sources: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	*"They were stratified for age and randomly allocated to an experimental group or a control group."* Page 1031
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Patients were not told the purpose of the monitor until we had finished collecting all the data."* Page 1032 Electronic outcome monitoring considered at low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	73/82 (89%) participants provided complete data

Norell 1979 (*Continued*)

		"The second monitor record was lost in nine cases-one patient suffered acute heart disease, two were admitted to hospital for long-term care, in two cases the monitor was lost or broken, and in four no record was obtained because the monitor battery was defective." Page 1032
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Okeke 2009

Methods	Randomised, 2-centre, 2-period, parallel-group study Duration: 3 months
Participants	Country: USA Setting: Glaucoma Services of the Wilmer Eye Institute and the Scheie Eye Institute Number of participants: 66 Gender:3 6 men, 30 women Age range: mean age 66.1 in intervention group; 63.8 in the control group Ethnicity: 40 black, 25 white, 1 Asian Inclusion criteria: people with glaucoma being treated with a prostaglandin analogue in 1 or both eyes Exclusion criteria: people were excluded if they were unable to understand the study, they did not put in their own drops, or they could not use the dosing aid
Interventions	The intervention consisted of the following: • 10-minute educational video • structured discussion • reminder telephone calls • activation of the audible and visible alarms on the dosing aid People in the control group received usual care, i.e. were told that it is important to take their eye drops as prescribed but had no other intervention
Outcomes	Adherence rate as measured by a dosing aid device and a questionnaire Intraocular pressure
Notes	Funding sources: supported in part by the National Institutes of Health, charitable grants and Alcon http://clinicaltrials.gov/ct2/show/NCT00333463

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"To perform the randomization procedure, a string of random numbers was selected from*

Okeke 2009 (*Continued*)

		a random numbers table...." Page 2287
Allocation concealment (selection bias)	Low risk	*"...The numbers were placed into envelopes and then sealed and initialed across the seal. The envelopes were numbered consecutively starting with 1. When an eligible patient was identified, an envelope was opened; if the envelope contained an even number then the participant received the intervention.*" Page 2287
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking was not described and intervention/control group received very different interventions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All 66 patients randomised were apparently assessed for adherence at 3 months, however the following statement implies there were some dropouts in the intervention group. *"For the 35 patients randomized to the intervention group, telephone calls were made at weeks 1 to 5, 7, 9, and 11. The number of patients contacted was highest at week 1 (100%), and over the remaining weeks there was a decline in the number successfully contacted (week 11, 63%). Reasons for the decline included early dropout from study, inability to contact patients, and early final visit.*" Page 2289
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Ring 2011

Methods	Quasi-experimental, single-centre study Duration: 3 months
Participants	Country: UK Setting: hospital outpatient clinic Number of participants: 124 (127 recruited, 2 withdrew and 1 died) Gender: 47 men, 77 women Age range: 40 to over 80, mean age = 71 years (calculated from frequencies on table 5, page 32), median age 73 years Ethnicity: 101 white, 12 Asian, 8 black, 3 other Inclusion criteria: people diagnosed with open-angle glaucoma, ocular hypertension, normal tension glaucoma on ocular hypotensive drops Exclusion criteria: people who were unable to understand and sign and informed consent form, people who could not see the film clearly

Interventions	Educational intervention: specially developed film
Outcomes	Questionnaire Weight of eye drop bottles
Notes	Funding Sources: International Glaucoma Association

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	*"The participants were randomly allocated to either the control group or the intervention group. The allocation can be referred to as random because the film was shown on various days and no prior knowledge of when the participants were attending their routine clinic appointment was known."* Page 27 Further information from investigator: *"The participants were allocated into each group purely by attending an outpatient appointment on different days. The control or test intervention was set for different days and the participants arrived according to their outpatient appointment. This was considered random allocation as the student researcher had no influence over which participant arrived on which day."*
Allocation concealment (selection bias)	High risk	Information from investigator: *"The person recruiting the participants was the student researcher as outlined in the dissertation. This person was aware of which group the participant was allocated to."*
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	*"A total of 127 participants were enrolled into the study over a four week period; 2 participants withdrew without a specific reason and 1 participant died before the 3 month data was collected. All results are based on a cohort of responding participants (n=124). 110 participants completed the study (88.7%). 14 of the original cohort did not respond to the 3 month postal questionnaire (non-response*

		rate of 11.3%).” Page 32
Selective reporting (reporting bias)	Low risk	Investigator confirmed all data collected were reported

Sakai 2005

Methods	Quasi-randomised, single-centre, parallel-group study Duration: 12 weeks
Participants	Country: Japan Setting: university-based ophthalmology clinic Number of participants: 36 (40 recruited, 2 withdrew after randomisation, 2 excluded after washout period as IOP < 20 mmHg and, therefore, no longer met criteria) Gender: 14 men, 22 women Age range: 45 to 75 years, mean age 64 years Ethnicity: Asian 100% Inclusion criteria: patients with primary ACG diagnosed by indentation gonioscopy and UBM, existence of synechial angle closure, released pupillary block by LPI at least 3 months before the study and a history of elevated IOP > 21 mmHg without any treatment with antiglaucoma medications Exclusion criteria: previous ocular surgery other than LPI, acute PAC, use of oral acetazolamide because of poor IOP control, suspected secondary angle closure related to uveal effusion, uveitis, lens subtractions or trauma. Patients who were already scheduled for surgery that would affect IOP such as trabeculectomy or phacoemulsification. Patients prescribed medicines for hypertension, cardiovascular disease, bronchial asthma and allergy to any of the study medication
Interventions	Latanoprost (L) group: monotherapy with latanoprost once daily Timolol/dorzolamide (T/D) group: unfixed combination therapy with 0.5% timolol maleate twice daily and 1% dorzolamide 3 times daily Follow-up: short-term; 12 weeks
Outcomes	Adherence assessed though self report via patient questionnaire at 12 weeks. Patients were asked how many times they had forgotten to apply their drops. Pre-defined responses were; less than once a week, once a week, 2 or 3 times a week and 4 or more times a week IOP reduction assessed with Goldmann applanation tonometer Visual field defects assessed with Humphrey Field Analyser, automated perimetry full-threshold 30-2 programme
Notes	Funding sources: none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sakai 2005 (*Continued*)

Random sequence generation (selection bias)	High risk	*"All but 1 of the remaining 36 patients were randomly allocated to ..."* Page 484 Assigned by rotation. 1 patient not randomised but assigned to latanoprost group to minimise possible side effects of timolol administration due to a pulse rate of 59/min at first evaluation
Allocation concealment (selection bias)	High risk	Open random allocation schedule used *"One patient was assigned.. to the latanoprost group to eliminate the risk of side effects."* Correspondence with investigator: *"It was open labelled and allocation schedule was not concealed prior to the assignment to the subjects. Two subjects were dropped out by their own will, may be because of the allocation."*
Blinding of participants and personnel (performance bias) All outcomes	High risk	Difficult to mask participants as dosing frequency differed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Correspondence with investigator: *"It was open labelled, and the number of the eye drop (s) was different."*
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data available for 4 patients; 2o withdrew after randomisation and 2 were excluded after washout period Attrition rate: 10%
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Schenker 1999

Methods	Randomised, multi-centre, 2-period, cross-over study Duration: 12 weeks
Participants	Country: USA Setting: hospital outpatient clinic Number of participants: 202 Gender: 77 men, 125 women Mean age: 59.4 years Ethnicity: white 142 (70%), black 47 (23%), Hispanic 13 (6%) Inclusion criteria: patients with a diagnosis of OAG or OHT. IOP $\geq$ 22 mmHg in at least 1 eye after a 3-week washout period Exclusion criteria: contact lens use within 3 weeks of study start, a history of acute

Schenker 1999 (*Continued*)

	or chronic ACG, occludable angles, a history of recent ocular inflammation or foreign body, a history of uveitis, concomitant use of systemic medications known to affect IOP, contraindications to beta-blockers and existing renal disease
Interventions	Group A: timolol gel once daily during period 1 followed by timolol solution twice daily during period 2 Group B: timolol solution twice daily during period 1 followed by timolol gel once daily during period 2 Follow-up: short-term; 6 weeks per period
Outcomes	Adherence assessed through self report via interviewer-administered questionnaire. Patients were asked how often they missed 1 or 2 doses of test medication during the last 2 weeks. Pre-defined responses were scored on a scale of 1 to 5: never = 1, rarely = 2, occasionally = 3, frequently = 4, always = 5 IOP reduction assessed with Goldmann applanation tonometer
Notes	Funding sources: sponsored by Merck & Co.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"... were enrolled in this 12-week, randomized observer-masked, two-period cross-over study."* Page 138 *"This was an open-label, multicenter, randomized, observer-masked, two-period crossover study ..."* Page 139 Correspondence with investigators: *"Subjects were randomized 1:1 to one of two sequences of treatment (tgel/ts or ts/tgel); randomization done within each center in blocks of 4."*
Allocation concealment (selection bias)	Low risk	Correspondence with investigators: *"Allocation completed by use of sealed envelopes opened at the time of enrollment"*
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and care providers deliberately not masked. Difficult to mask participants as dosing frequencies were different
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"A member of the clinic staff who was masked to the treatment the patient was receiving administered an anti-glaucoma patient-preference questionnaire."* Page 139 Correspondence with investigators: *"Inves-*

Schenker 1999 (*Continued*)

		tigator office staff was blinded until after the analysis was reported."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 patients did not complete both periods, a further 8 patients were excluded from the questionnaire analysis because of other protocol violations. Attrition rate: 9%. A further 4 patients (11%) did not respond to the adherence question 99/102 group A and 93/100 group B completed the study. Reasons for non-completion described well and summarised here: Adverse event: n = 5, 4 probably related to medication, 1 unrelated Other reason: 3 lost to follow-up, 1 withdrew consent, 1 for personal reasons
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Sheppard 2003

Methods	Randomised, single-centre, parallel-group study Duration: 3 months
Participants	Country: UK Setting: hospital outpatient clinic Number of participants: 73 (92 recruited, 19 withdrew) Gender: not stated Mean age 73 years (SD 11.6) Ethnicity: not stated Inclusion criteria: patients with a diagnosis of long-term chronic stable glaucoma Exclusion criteria: no telephone access, difficulties using the phone, diagnosis of cognitive impairment
Interventions	Intervention: glaucoma monitoring nurse-led clinic involving consultations of 15 minutes duration divided into 2 parts. The first part was a standard assessment designed to monitor and record health details, such as current health status and recent ocular history. Eye examinations included visual acuity, visual field test and IOP test using Goldmann's applanation tonometry. The second part was a semi-structure educational session tailored to individual patient needs Control: general ophthalmic clinic involving consultations of 10 minutes duration which included the standard assessment, a fundus examination and remainder of time utilised according to each individual clinician
Outcomes	Adherence assessed through self report patient questionnaire during a structured telephone interview

Sheppard 2003 (*Continued*)

Notes	Funding sources: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"The patients who consented to take part were allocated [...] using a computerised randomisation table"*. Page 17
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	92 participants: 36/42 (86%) nurse-led and 37/50 (74%) doctor clinic *"There was no difference in age, length of time diagnosed with glaucoma or the questionnaire measures between the participants who dropped out and those who remained in the study."* Page 18
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

Sverrisson 1999 Europe

Methods	Randomised, multi-centre, observer masked, 2-period, cross-over study Duration: 38 days
Participants	Countries: 8 sites in 5 European countries: Belgium, Denmark, Iceland, Sweden and Switzerland Setting: outpatient clinics Number of participants: 93 Gender: 35 men, 58 women Age range: 44 to 87 years, mean age: 69.5 Ethnicity: white 92 (98.9%), other 1 (1.1%) Inclusion criteria: patients 18+ years with a diagnosis of OAG or OHT in both eyes. IOP of $\geq$ 22 mmHg 2 hrs after the morning dose of timolol maleate on study day 1 after run-in Exclusion criteria: patients previously treated with dorzolamide or pilocarpine. Visual acuity of worse than 20/80 in both eyes, evidence of ACG, current use of contact lenses, intraocular surgery or significant trauma within 6 months or intraocular laser surgery within 3 months of initiation of the study, history or presence of retinal detachment or

Sverrisson 1999 Europe (*Continued*)

	other conditions for which pilocarpine might be appropriate. Asthma, chronic obstructive pulmonary disease, renal disease, severe physical disabilities or any contraindications to the use of pilocarpine, dorzolamide or timolol ophthalmic solutions
Interventions	Group A: 2% dorzolamide/0.5% timolol combination twice daily during period 1 and 2% pilocarpine 4 times daily plus 0.5% timolol twice daily during period 2 Group B: 2% pilocarpine 4 times daily plus 0.5% timolol twice daily during period 1 and 2% dorzolamide/0.5% timolol combination twice daily during period 2 Follow-up: short-term; 14 days per period
Outcomes	Adherence assessed through self report via interviewer-administered questionnaire using previously validated tool (COMTol). Patients were asked how often they missed their drops. Responses were marked on a scale of 0 to 6: 0 = never, 6 = always Quality of life assessed via interviewer-administered questionnaire (COMTol). Patients asked whether quality of life was interfered with by side effects or activity limitations. Responses were marked on a scale of 0 to 5: 0 = not at all, 5 = extremely IOP reduction assessed with Goldman applanation tonometer Visual field defects assessed with Humphrey Field Analyser at all US sites and some European sites. The other European sites used an Octopus perimeter
Notes	Funding sources: sponsored by Merck & Co.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random number generator used
Allocation concealment (selection bias)	Low risk	Central allocation used
Blinding of participants and personnel (performance bias) All outcomes	High risk	*"Because the purpose of the studies was to determine patient preference between two therapeutic regimes and dose regimen is an integral part of such preference, the treatment regimens were deliberately not masked to the patients or the study physician. However, the interviewer administering the COMTol questionnaire was masked to the patient's regimen, interviews were conducted in a brightly lit room (to induce miosis in all patients), and patients were instructed not to disclose their dose frequency to the interviewer."* Page 823
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Because the purpose of the studies was to determine patient preference between two therapeutic regimes and dose regimen is an integral part of such preference, the treatment regimens were deliberately not masked to the*

Sverrisson 1999 Europe (*Continued*)

		patients or the study physician. However, the interviewer administering the COMTol questionnaire was masked to the patient's regimen, interviews were conducted in a brightly lit room (to induce miosis in all patients), and patients were instructed not to disclose their dose frequency to the interviewer." Page 823
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient information to permit judgement. Difficult to assess attrition rate from paper and following contact with author. 18 patients (19%) were excluded from the adherence analysis, 19 (20%) from quality of life analysis concerning side effects and 22 (24%) from quality of life analysis concerning activity limitations. Numbers of patients involved in IOP and visual field test analysis were not published and could not be obtained from authors
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Sverrisson 1999 USA

Methods	Randomised, multi-centre, observer masked, 2-period cross-over study Duration: 38 days
Participants	Countries: USA (10 sites) Setting: outpatient clinics Number of participants: 97 Gender: 41 men, 56 women Age range: 27 to 83 years, mean age 60.4 years Ethnicity: white 70 (72.2%), black 18 (18.6%), other 9 (9.3%) Inclusion criteria: patients 18+ years with a diagnosis of OAG or OHT in both eyes. IOP of $\geq$ 22 mmHg 2 hours after the morning dose of timolol maleate on study day 1 after run-in Exclusion criteria: patients previously treated with dorzolamide or pilocarpine. Visual acuity of worse than 20/80 in both eyes, evidence of ACG, current use of contact lenses, intraocular surgery or significant trauma within 6 months or intraocular laser surgery within 3 months of initiation of the study, history or presence of retinal detachment or other conditions for which pilocarpine might be appropriate. Asthma, chronic obstructive pulmonary disease, renal disease, severe physical disabilities or any contraindications to the use of pilocarpine, dorzolamide or timolol ophthalmic solutions
Interventions	Group A: 2% dorzolamide/0.5% timolol combination twice daily during period 1 and 2% pilocarpine 4 times daily plus 0.5% timolol twice daily during period 2 Group B: 2% pilocarpine 4 times daily plus 0.5% timolol twice daily during period 1 and 2% dorzolamide/0.5% timolol combination twice daily during period 2

Sverrisson 1999 USA (*Continued*)

	Follow-up: short-term; 14 days per period
Outcomes	Adherence assessed through self report via interviewer-administered questionnaire using previously validated tool (COMTol). Patients were asked how often they missed their drops. Responses were marked on a scale of 0 to 6: 0 = never, 6 = always Quality of life assessed via interviewer-administered questionnaire (COMTol). Patients asked whether quality of life was interfered with by side effects or activity limitations. Responses were marked on a scale of 0 to 5: 0 = not at all, 5 = extremely IOP reduction assessed with Goldman applanation tonometer Visual field defects assessed with Humphrey Field Analyser at all US sites and some European sites. The other European sites used an Octopus perimeter
Notes	Funding sources: sponsored by Merck & Co.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random number generator used (contact with trialists) *"[...] patients who met the inclusion criteria and who had none of the exclusion criteria on study day 1 were randomly assigned to group A or group B."* Page 316
Allocation concealment (selection bias)	Low risk	Central allocation used (contact with trialists)
Blinding of participants and personnel (performance bias) All outcomes	High risk	*"Because the purpose of the studies was to determine patient preference between two therapeutic regimes and dose regimen is an integral part of such preference, the treatment regimens were deliberately not masked to the patients or the study physician. However, the interviewer administering the COMTol questionnaire was masked to the patient's regimen, interviews were conducted in a brightly lit room (to induce miosis in all patients), and patients were instructed not to disclose their dose frequency to the interviewer."* Page 823
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Because the purpose of the studies was to determine patient preference between two therapeutic regimes and dose regimen is an integral part of such preference, the treatment regimens were deliberately not masked to the patients or the study physician. However, the interviewer administering the COMTol questionnaire was masked to the patient's regimen,*

		interviews were conducted in a brightly lit room (to induce miosis in all patients), and patients were instructed not to disclose their dose frequency to the interviewer." Page 823
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient information to permit judgement. Difficult to assess attrition rate from paper and following contact with author. 12 patients (13%) were excluded from the adherence analysis, 8 (8%) from the quality of life analysis concerning side effects and 9 (9%) from the quality of life analysis concerning activity limitations. Numbers of patients involved in IOP and visual field test analysis were not published and could not be obtained from authors See table 5. Lower follow-up in timolol plus pilocarpine group (63%) compared to combination group (97%), however, in international study good follow-up, 95% and 92%, in both groups
Selective reporting (reporting bias)	Unclear risk	Difficult to judge without access to protocol; no immediate cause for concern

ACG: angle closure glaucoma
COMTol: Comparison of Ophthalmic Medications for Tolerability
IOP: intraocular pressure
LPI: laser peripheral iridotomy
OAG: open-angle glaucoma
OHT: ocular hypertension
SD: standard deviation
UBM: ultrasound biomicroscopy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akafo 1995	Did not measure adherence
Amon 1990	Not a randomised study
Bayer 2004	Not a randomised study, adherence not measured
Bhojwani 1981	Not a randomised study, adherence not measured

(*Continued*)

Blair 2001	Not a randomised study
Blair 2004	Not a randomised study
Bron 2004	Measured adherence but did not publish results. Author contacted and gave reason, *"such an evaluation of compliance is not reliable"*.
Chang 1991	Not a randomised study
Derick 1992	Adherence not measured
Dunker 2007	Not a randomised study
Flowers 2006	Single-arm study
Ghinato 1996	Unclear whether participants were randomised to 1 of 2 groups. No reply from author
Goni 2005	Did not measure adherence
Granstrom 1982	Not a randomised study
Gulkilik 2011	Did not measure adherence
Hasegawa 2005	Not a randomised study
Hughes 2005	Did not measure adherence
Hunter 1999	Very little information available, no paper, no other evidence of study found. Several attempts made to contact author without success
Inoue 2011	Not a controlled trial
Inoue 2012	Not a controlled trial
Kass 1987	Not a randomised study
Klein 2003	Not a randomised study, adherence not measured
Konstas 2001	Did not measure adherence
Kurtz 2004	Did not measure adherence
Lorenz 2011	Did not measure adherence
March 2000	Did not measure adherence
NCT00230763	Non-randomised study

(*Continued*)

NCT00262626	Non-randomised study
NCT00328835	Non-randomised study not assessing adherence
NCT00329095	Non-randomised study
NCT00348062	Non-randomised study
NCT01415401	Non-randomised
Novack 1988	Did not measure adherence
Rolle 2012	Not a controlled trial
Rossi 2011	Not a controlled trial
Sanchez-Pulgarin 2011	Not a controlled trial
Sclar 1991	Not a randomised study, adherence not measured
Shibuya 2003	Adherence measured although the 2 types of drops being compared were instilled with the same dosage frequency of once daily
Wandel 1986	Not a randomised study, adherence not measured
Yie 2000	Not a randomised study, adherence not measured

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN25754048

Trial name or title	Glaucoma compliance aids research project
Methods	Randomised, single-centre, parallel-group study
Participants	Country: UK Setting: hospital outpatient clinic Target number of participants: 100 Inclusion criteria: patients with a diagnosis of OAG, using anti-glaucoma eye drops, able to instil drops independently Exclusion criteria: patients prescribed more than 1 eye drop, patients with other eye problems, patients unable to give informed consent, patients < 40 years
Interventions	Intervention group: adherence aid and usual care which involves glaucoma assessment followed by assessment for appropriate adherence aid with instruction on how to use it; patients also continue to receive the usual care normally provided within the outpatients department

ISRCTN25754048 (*Continued*)

	Control group: glaucoma assessment and usual care normally provided within the outpatients department
Outcomes	Adherence to therapy assessed through self report via patient questionnaire
Starting date	September 2006
Contact information	See trial register entry
Notes	http://www.controlled-trials.com/ISRCTN25754048

ISRCTN31673586

Trial name or title	Comparing the after-use sensation and safety of long acting (LA) carteolol 2 % versus timolol LA 0.5 % in simple intra-ocular hypertension and glaucoma
Methods	Randomised controlled trial, parallel-group
Participants	People with unilateral or bilateral ocular hypertension or primary open-angle glaucoma and intra-ocular pressure controlled with beta-blocker monotherapy: pressure < 21mmHg and visual field stable
Interventions	Carteolol long-acting 2%: daily, 1 drop at 8 am in the eye(s) to be treated over 3 months Timolol long-acting 0.5%: daily, 1 drop at 8 am in the eye(s) to be treated over 3 months
Outcomes	Compliance, reported at 1 and 3 months was one of the secondary outcomes for this study
Starting date	December 2007
Contact information	See trial register entry
Notes	http://www.controlled-trials.com/ISRCTN31673586

ISRCTN89683704

Trial name or title	Helping adherence with glaucoma treatment
Methods	Randomised, single-centre, parallel-group study Duration: 2 years
Participants	Country: UK Setting: hospital outpatient clinic Target number of patients: 200 Inclusion criteria: newly diagnosed or previously untreated glaucoma patients (using established standard criteria as documented in the European Glaucoma Society Guidelines), prescribed travoprost only, male or female, > 18 years of age Exclusion criteria: those who cannot speak English fluently (to eliminate any potential bias by poor interpretation of information by a translator), those whose drops will be applied by care home staff/carers/home-helpers

ISRCTN89683704 (*Continued*)

Interventions	Intervention group: the intervention group will spend time with a Glaucoma Support Assistant (GSA) who will discuss/provide general aspects relating to glaucoma and anti-glaucomatous therapy, advice and practical help with drop application techniques, advice on taking eye drops within their own schedule/routine and an invitation for the participant to ask any questions about anything they are unsure of. In addition, patients will be asked to discuss their normal routine and a mutually agreeable time and place will be decided upon for patients to administer their drops. Patients will be advised to take their drops before a given point in their routine, to leave their drops where this "event" normally happens (e.g. by their toothbrush holder). A helpline number will also be given so that participants or their carers can call the on-call GSA at any time during clinic hours for additional information about glaucoma and drop application. The initial intervention group appointment is expected to last about 30 minutes Standard care group/control group: the control group will receive information in the form of our expected standard care and a leaflet about glaucoma with their ophthalmologist. Expected standard care consists of a brief explanation about glaucoma and the degree to which the particular patient has the condition, a summary of the proposed future management for that patient, including how frequently and when drop administration should be carried out and the importance of the condition with respect to driving and future vision. In addition, they will receive a contact telephone number for the glaucoma research unit in case of any problems with the electronic device or adverse events Follow-up: 32 weeks
Outcomes	Patient adherence, measured by an electronic dosing monitor to give a % adherence and persistence score Self perception of adherence will be measured using self rating questionnaires Level of knowledge about glaucoma will be measured using self rating questionnaires The individual components of the intervention will be assessed using questionnaires so as to identify which components are in most demand for a given population A cost-effectiveness approach will determine the additional cost associated with the additional benefits. In this way, the 'fixed' (staff, overheads etc) and 'variable' costs of the intervention protocol will be estimated per patient. Resource utilisation and variance by individual patient will be monitored prospectively. Social demographic and medical history data recorded will be used in the socio-economic and health analyses
Starting date	November 2009
Contact information	See trial register entry
Notes	http://www.controlled-trials.com/ISRCTN89683704

NCT00376974

Trial name or title	The effect of education on patient compliance
Methods	Randomised controlled trial, parallel-group
Participants	People with glaucoma attending for routine examination
Interventions	Educational video

NCT00376974 (*Continued*)

Outcomes	Intraocular pressure Score on glaucoma educational test
Starting date	March 2005
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00376974

NCT00454922

Trial name or title	Effect of glaucoma educators on adherence to prescribed therapeutic regimens in glaucoma patients
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: single-blind (outcomes assessor) Primary purpose: prevention
Participants	100
Interventions	Education versus standard care
Outcomes	Primary outcome measures: primary outcome is adherence (time frame: 6 months) Secondary outcome measures: differences between patients randomised to standard of care and education intervention (time frame: 6 months) Differences between dropouts and non-dropouts (time frame: 6 months)
Starting date	*From clinical trals.gov* Start date: October 2007; end date: May 2008 *From contact with investigators December 2011* *"Our study evaluating the "Effect of Glaucoma Educators on Adherence to Prescribed Therapeutic Regimens in Glaucoma Patients" (http://clinicaltrials.gov/show/NCT00454922) just started a few months ago and is still recruiting participants. We won't have outcomes to report for another 12-18 months."*
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/show/NCT00454922

NCT00465803

Trial name or title	Compliance study comparing DuoTrav to TRAVATAN plus timolol using the dosing aid
Methods	Randomised controlled trial, parallel-group
Participants	People with open-angle glaucoma or ocular hypertension

NCT00465803 (*Continued*)

Interventions	DuoTrav Travatan/timolol
Outcomes	Patient compliance
Starting date	March 2007
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00465803

NCT00508469

Trial name or title	Adherence assessment with Travalert dosing aid
Methods	Parallel-group randomised controlled trial
Participants	People diagnosed with glaucoma or ocular hypertension
Interventions	Dosing aid device
Outcomes	*From ClinicalTrials.gov* Primary outcome measures: the primary objective is to compare patients adherence using Travalert® device in the different treatment groups (time frame: use) (designated as safety issue: no) Secondary outcome measures: safety and satisfaction (time frame: use) (designated as safety issue: no)
Starting date	July 2007
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00508469

NCT00573638

Trial name or title	Effects of Xal-Ease on patient compliance with Xalatan
Methods	Intervention model: single group assignment Masking: open label Primary purpose: treatment
Participants	50
Interventions	Device: Xal-Ease device to be used with Xalatan eye drops

NCT00573638 (*Continued*)

Outcomes	Primary outcome measures: the primary outcome measure is compliance with the medication Xalatan using and not using the Xal-Ease delivery aid for their glaucoma treatment (time frame: 6 months) Secondary outcome measures: to determine if any of the other factors mentioned in the survey affect compliance to their medical regimen (time frame: 6 months) To see whether or not the Xal-Ease device helps patients conserve medication, i.e. - aids in drops not distilled in the eye (time frame: 6 months)
Starting date	February 2005
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00573638

NCT00626067

Trial name or title	Study of patient use and perception of the Travatan dosing aid Pilot study of patient acceptance and impact of the new Travatan™ compliance monitoring dispenser (Travatan™ dosing aid)
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: single group assignment (but has 3 interventions) Masking: double-blind (subject, investigator) Primary purpose: supportive care
Participants	45
Interventions	Travatan compliance monitoring dispenser Fully functioning, partially functioning and non-functioning
Outcomes	From clinicatrials.gov Primary outcome measures: assess patients' opinions regarding new Travatan compliance monitoring dispenser (time frame: 6 weeks) (designated as safety issue: no) Secondary outcome measures: pilot study of the impact of physician monitoring of compliance on patient compliance (time frame: 6 weeks) (designated as safety issue: no)
Starting date	September 2006 Investigator indicates manuscript in preparation
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/show/NCT00626067

NCT00676637

Trial name or title	GAS - Glaucoma Adherence Study
Methods	Allocation: non-randomised Intervention model: single group assignment Masking: open-label
Participants	100
Interventions	TravAlert dosing aid
Outcomes	Mean change from baseline in intraocular pressure at 4 months
Starting date	May 2008
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/show/NCT00676637%20%C2%A0

NCT00756184

Trial name or title	1-year randomized control trial investigating the value of an intervention to enhance adherence in glaucoma patients receiving prostaglandin monotherapy and in patients who are candidates for adjunctive therapy
Methods	Parallel-group randomised controlled trial
Participants	People with newly diagnosed open-angle glaucoma, or ocular hypertensive subjects naive to medical therapy and people who have failed monotherapy with any prostaglandin analogue
Interventions	Intensive glaucoma adherence and education during the course of 1 year compared to intensive, equal-time eye care education without any direct adherence or glaucoma specific education
Outcomes	Adherence rate (% of days patient used the medication) as monitored by a dosing aid electronic device, intraocular pressure (morning) and persistency to therapy Follow-up time: 1, 3, 6, 9 and 12 months
Starting date	September 2007
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00756184

NCT00767793

Trial name or title	A multi-center, double-masked, randomized, placebo-controlled, ascending dose study of INS117548 ophthalmic solution in subjects with bilateral ocular hypertension or early primary open angle glaucoma
Methods	Randomised controlled trial, parallel-group
Participants	People with primary open-angle glaucoma or ocular hypertension
Interventions	INS117548 at various concentrations Placebo
Outcomes	Include compliance and rate of discontinuation
Starting date	September 2008
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00767793

NCT00887029

Trial name or title	A 12 week comparison of DuoTrav and Xalacom at 24 hours post-dose in the treatment of open-angle glaucoma (the DVX study)
Methods	Randomised controlled trial, cross-over
Participants	People with primary open-angle glaucoma or ocular hypertension
Interventions	DuoTrav Xalacom
Outcomes	Intraocular pressure Compliance and patient preference
Starting date	January 2009
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT00887029

NCT01125306

Trial name or title	Efficiency of Xal-Ease device in glaucoma and/or ocular hypertension (OHT) patients, treated with Xalatan or Xalacom
Methods	Intervention model: single group assignment Masking: open-label Primary purpose: supportive care

NCT01125306 (*Continued*)

Participants	50
Interventions	Device: Xal-Ease
Outcomes	Primary outcome measures: consumption of Xalatan/Xalacom bottles per year per patient (time frame: 12 months) Secondary outcome measures: evaluating cost of Xalatan/Xalacom eye drops use per year with Xal-Ease (time frame: 12 months) Characterising the optimal conditions for proper usage of the Xal-Ease device (time frame: 12 months)
Starting date	June 2009
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/ct2/show/NCT01125306

NCT01409421

Trial name or title	Research protocol: glaucoma treatment adherence and persistence
Methods	Parallel-group randomised controlled trial
Participants	People with glaucoma
Interventions	Motivational interviewing, reminder calls and standard care
Outcomes	*From ClinicalTrials.gov* Primary outcome measures: MEMS-based medication adherence and persistence (time frame: 1 month) (designated as safety issue: no) comparing adherence and persistence between the intervention and control groups. Medication Event Monitoring Systems record the date and time a pill bottle is opened, evaluating the percentage of prescribed doses taken during one-week intervals, but will augment it by also considering a more fine-grained percentage of prescribed doses taken in required dosing window (defined as within 3 hours before or after the scheduled time) as a second primary outcome measure. Secondary outcome measures: counsellor-rated medication adherence (time frame: 1 month) (designated as safety issue: no). Will supplement MEMS-based adherence metrics with a counsellor rating of adherence completed by the glaucoma educator during each in-person or telephone contact with intervention group participants. The interview also measures patients' perceived reasons for non-adherence, including treatment cost, lack of commitment based on low perceived benefits of treatment and fear of potential adverse drug events (ADEs)
Starting date	April 2011
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/show/NCT01409421

NCT01417689

Trial name or title	Eyedrop Instillation Technique
Methods	Parallel-group randomised controlled trial
Participants	People with glaucoma or suspected glaucoma
Interventions	Standard eye drop instillation compared to experimental technique of eye drop instillation
Outcomes	*From ClinicalTrials.gov* Primary outcome measures: complete success (time frame: day 1, immediately after intervention) (designated as safety issue: no). Total success is defined as: patient manages to instil 1 eye drop into the eye spending only 1 eye drop. Difference in the proportion of patients achieving successful eye drop instillation in each of the 2 groups. For the main analysis the results of the first eye (right or left randomly determined will be used) a mixed model with both eyes in the analysis will also be presented for sensitivity analysis. Secondary outcome measures: qualified success (time frame: day 1, same day as intervention) (designated as safety issue: no). Qualified success is defined as: patient manages to instil 1 eye drop into the eye regardless of the amount of drops spent. Difference in the proportion of patients achieving successful eye drop instillation in each of the 2 groups. For the main analysis the results of the first eye (right or left randomly determined will be used) a mixed model with both eyes in the analysis will also be presented for sensitivity analysis. Number of drops (time frame: day 1) (designated as safety issue: no). Number of eye drops spent on attempted instillation in the first eye (randomly assigned). The average number of drops spent on each of the groups will be compared. Mixed models with data from both eyes will also be presented for sensitivity analysis
Starting date	August 2011
Contact information	See trial register entry
Notes	http://clinicaltrials.gov/show/NCT01417689

OAG: open-angle glaucoma
OHT: ocular hypertension

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Study design, interventions and outcomes in included studies

	Study	RCT type	Intervention	Control group	Length of follow-up	Main outcome measures	Comments
1	Gray 2011	Parallel-group	Education and tailoring programme	Usual care	12 months and 24 months	Adherence (prescription data and questionnaire) Persistence (prescription and dispensing data) Intraocular pressure Patient knowledge	-
2	Hermann 2011	Parallel-group, factorial	Brimonidine twice daily Masked monitoring	Brimonidine 3 times daily Open monitoring	1 month	Adherence (electronic monitoring device)	-
3	Herman 2011a	Parallel-group	Brimonidine twice daily	Brimonidine 3 times daily	4 weeks	Adherence (electronic monitoring)	-
4	I-SIGHT	Parallel-group	Telephone automated education and tailoring programme	Usual care	12 months	Adherence (self report of missed doses) Prescription refills (pharmacy records) Appointment keeping Sources of information: interviews, medical record review, appointment records, and pharmacy data	-

Table 1. Study design, interventions and outcomes in included studies (*Continued*)

5	Laibovitz 1996	Cross-over	2% dorzolamide three times daily	2% pilocarpine four times daily during period 1	14 days per period	Adherence (questionnaire - COMTol) Persistence (number of patients who continued treatment) Quality of life (questionnaire - COMTol) Intraocular pressure (Goldmann applanation tonometer) Visual field defects (Humphrey Field Analyser)	Both groups continued to receive 0.5% timolol twice daily throughout the study
6	Laster 1996	Cross-over	Pre-weighed bottle of pilocarpine in a medication vial fitted with the Prescript TimeCap	Pre-weighed bottle of pilocarpine in a medication vial fitted with the TimeCap	30 days per period	Adherence (weighing the drop bottle and questionnaire)	-
7	Muir 2012	Parallel-group	Educational intervention lasting 20 minutes (one-on-one session) including "informational video" delivered at varying literacy levels	Standard care	6 months	Adherence (number of days without medication) Self reported disease knowledge Satisfaction with care	Language of video varied according to participants' tested health literacy level
8	Nakakura 2012	Parallel-group	Latanoprost 0.005%/timolol 0.5% plus brinzolamide 1%	Dorzolamide 1%/timolol 0.5% plus latanoprost 0.005%	12 weeks	Intraocular pressure Adherence (self reported)	-
9	Norell 1979	Parallel-group	Education and tailoring programme	No intervention	20 days	Adherence (medication monitor)	-

Table 1. Study design, interventions and outcomes in included studies (*Continued*)

10	Okeke 2009	Parallel-group	Education and tailoring programme	No intervention	3 months	Adherence rate (dosing aid device) Intraocular pressure	-
12	Ring 2011	Quasi-experimental	Educational intervention (film)	No intervention	3 months	Adherence (return of bottles) Patient knowledge (questionnaire)	-
12	Sakai 2005	Quasi-experimental	Latanoprost once daily	0.5% timolol maleate twice daily and 1% dorzolamide 3 times daily	3 months	Adherence (questionnaire) Intraocular pressure (Goldmann applanation tonometer) Visual field defects (Humphrey Field Analyser)	-
13	Schenker 1999	Cross-over	Timolol gel once daily	Timolol solution twice daily	6 weeks per period	Adherence (questionnaire) Intraocular pressure (Goldmann applanation tonometer)	-
14	Sheppard 2003	Parallel-group	Education and tailoring	Usual care	3 months	Adherence (questionnaire) Patient knowledge (questionnaire)	-
15	Sverrisson 1999 Europe	Cross-over	2% dorzolamide/0.5% timolol combination twice daily	2% pilocarpine four times daily plus 0.5% timolol twice daily	14 days per period	Adherence (questionnaire COMTol) Persistence (number of patients who completed treatment) Quality of life (questionnaire	-

Table 1. Study design, interventions and outcomes in included studies (*Continued*)

						COMTol) Intraocular pressure (Goldman applanation tonometer) Visual field defects (Humphrey Field Analyser/ Octopus perimeter)	
16	Sverrisson USA	Cross-over	2% dorzolamide/0.5% timolol combination twice daily	2% pilocarpine 4 times daily plus 0.5% timolol twice daily	14 days per period	Adherence (questionnaire COMTol) Persistence (number of patients who completed treatment) Quality of life (questionnaire COMTol) Intraocular pressure (Goldman applanation tonometer) Visual field defects (Humphrey Field Analyser)	-

COMTol: Comparison of Ophthalmic Medications for Tolerability

Table 2. Effect of education and tailoring on adherence

Study	**Outcome measure**	**Follow-up period**	**Outcome measure variable type**	**Intervention n/N (%) *or* mean (SD)**	**Control n/N(%) *or* mean (SD)**	**Reported P value**	**Comments**
Gray 2011	Number of people who were adherent	12 months	Dichotomous	45/64 (70%)	27/63 (43%)	0.002	Data from page 185 of Gray PhD thesis "Refill ad-

Table 2. Effect of education and tailoring on adherence (*Continued*)

							herence" measured by contacting GPs and pharmacists for prescrip- tion and dispensing information during the 1-year follow-up. People who collected 100% of prescrip- tions were defined as adherent
I-SIGHT	Self reported medication adherence: number of people not reporting missing drops in 1 month	"last visit" which could be 6, 9 or 12 months	Dichotomous	30.2%	27.0%	"treatment x visit" interaction 0.18	Also reported a number of other measures of adherence (see table 3, page E5) including self reported refill adherence, self reported appointment adherence, chart report medication adherence, chart report refill adherence, chart report appointment adherence, none of which showed statistically significant differences between groups
Muir 2012	Days without medication	6 months	Continuous	63 (198) n = 67	65 (198) n = 60	0.955 (calculated from data t-test)	-

Table 2. Effect of education and tailoring on adherence (*Continued*)

Norell 1979	% of time exceeding 8-hour dose intervals % (number of missed doses)	20 days	Dichotomous (denominator not reported)	13% 6% (120)	24% 15% (338)	< 0.001	Table page 1032 Measured using a medication monitor Unit of analysis not same as unit of randomisation Reported P value tests difference in change between first time period (before intervention) and second time period (after intervention)
Okeke 2011	Adherence rate Change between pre-intervention 3 months and post-intervention 3 months	3 months	Continuous Continuous	0.73 (0.22) 0.19 (0.20)	0.51 (0.30) 0.06 (0.30)	0.001 0.01	Table 3 page 2289 Adherence rate measured using Travatan dosing aid device
*Ring 2011	Number of people who were adherent	3 months	Dichotomous	18/54 (33.3)	19/56 (33.9)	0.947 (calculated from data)	Page 44 of Ring MSc thesis People who returned bottles within 10% of target weight were defined as adherent
Sheppard 2003	Adherence	3 months	Continuous	"*No differences were found between the two groups on adherence using an ANCOVA with the pre-appointment score as a covariate*"			Page 19 Adherence measured by questionnaire using an 11-point

Table 2. Effect of education and tailoring on adherence (*Continued*)

						response scale: 0 "I never use my eye drops" to 10 "I always use my eye drops". Reported as a continuous variable in the paper but only pre-appointment mean (SD) reported. Also reported *"significantly fewer of the [intervention] group reported [specific problems with adherence] compared to [control group]."*

Adherence: taking medicine as prescribed
See text for description of education and tailoring packages in each study.
*Ring 2011 did not include any tailoring.

Table 3. Effect of drug regimen on adherence

Study	Outcome measure	Follow-up period	Outcome measure variable type	Intervention* n/N (%) *or* mean (SD)	Control n/N(%) *or* mean (SD)	Reported P value	Comments
Hermann 2011	Adherence rate (%)	4 weeks	Continuous	73.3 (13) n = 18	64.0 (12) n = 18	0.02	Table 3 page e302 Adherence rate defined as *"Ratio of recorded dosing events to intended dosing events for the observed time period."* A

Table 3. Effect of drug regimen on adherence (*Continued*)

							recorded dosing event was application of 1 or more drops within 30 minutes following the first application
Herman 2011a	Adherence rate (%)	4 weeks	Continuous	72.2 (19) n = 33	62.1 (16) n = 34	0.04	Text pages 504 and 505 Adherence rate defined as for Herman 2011 above
Laibovitz 1996	Reported missed doses	4 weeks	Continuous	0.8 (SE 0.18)	2.3 (SE 0.18)	< 0.001	COMTol questionnaire: *"How often did you miss one or more doses? "* Graded 0 (never) to 6 (always). Data are from crossover study but data from 2 time periods appear to have been pooled
Nakakura 2012	Forgot administration	12 weeks	Dichotomous	2/19	2/16	0.855 (calculated)	Question *"How often do you forget administration per week?"* Never/ within 2 times per week/ more than 3 times per week
Sakai 2005	Reported missed doses	3 months	Dichotomous	16/18 (88.9)	13/18 (72.2)	0.207 (calculated)	*"How many times patient has forgotten to apply the eye drop?"* An-

Table 3. Effect of drug regimen on adherence (*Continued*)

							swer less than once a week defined as adherent
Schenker 1999	Reported never missed dose	3 months	Dichotomous	141/180 (78.3)	123/182 (67.6)	0.021 (calculated)	Table V Page 144 Frequency of missed doses: never, rarely, occasionally, frequently, always Analysis ignores cross-over design
Sverrisson 1999 Europe	Reported missed doses	14 days	Continuous	0.1 (0.1)	1.4 (0.1)	-	COMTol questionnaire: *"How often did you miss one or more doses?"* Graded 0 (never) to 6 (always). Data are from cross-over study but data from 2 time periods appears to have been pooled
Sverrisson 1999 USA	Reported missed doses	14 days	Continuous	0.2 (0.1)	1.2 (0.1)	-	

COMTol: Comparison of Ophthalmic Medications for Tolerability
SE: standard error

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Glaucoma
#2 MeSH descriptor Ocular Hypertension
#3 MeSH descriptor Intraocular Pressure
#4 glaucoma*
#5 (intraocular or intra ocular) next pressure*
#6 ocular hypertensi*
#7 IOP or OHT
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Antihypertensive Agents
#10 antihypertensi*
#11 therap* or treat* or medicat* or drug* or drop*
#12 (#9 OR #10 OR #11)
#13 MeSH descriptor Attitude to Health
#14 MeSH descriptor Patient Compliance
#15 MeSH descriptor Patient Dropouts
#16 MeSH descriptor Treatment Refusal
#17 MeSH descriptor Patient Acceptance of Health Care
#18 MeSH descriptor Patient Satisfaction
#19 adhere* or non adhere* or complian* or non complian* or concordance or persistence or acceptance or coperat* or co operat* or conform*
#20 (discontinu* or abstention or abstain* or stop* or abandon*) near/4 (treat*)
#21 (discontinu* or abstention or abstain* or stop* or abandon*) near/4 (medic*)
#22 (discontinu* or abstention or abstain* or stop* or abandon*) near/4 (therap*)
#23 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24 (#8 AND #12 AND #23)

Appendix 2. MEDLINE (OvidSP) search strategy

1 randomized controlled trial.pt.
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp glaucoma/
14 exp ocular hypertension/
15 exp intraocular pressure/
16 glaucom$.tw.
17 ((intraocular or intra ocular) adj1 pressure$).tw.
18 ocular hypertensi$.tw.
19 (IOP or OHT).tw.
20 or/13-19
21 exp antihypertensive agents/

22 antihypertensi$.tw.
23 (therap$ or treat$ or medicat$ or drug$ or drop$).tw.
24 or/21-23
25 exp attitude to health/
26 exp patient compliance/
27 exp patient dropouts/
28 exp treatment refusal/
29 exp patient acceptance of health care/
30 exp patient satisfaction/
31 (adhere$ or non adhere$ or complian$ or non complian$ or concordance or persistence or acceptance or coperat$ or co operat$ or conform$).tw.
32 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 treat$).tw.
33 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 medic$).tw.
34 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 therap$).tw.
35 or/25-34
36 20 and 24 and 35
37 12 and 36
The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or prospectiv$ or volunteer$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)

32 11 or 24 or 31
33 exp glaucoma/
34 exp intraocular hypertension/
35 exp intraocular pressure/
36 glaucom$.tw.
37 ((intraocular or intra ocular) adj1 pressure$).tw.
38 ocular hypertensi$.tw.
39 (IOP or OHT).tw.
40 or/33-39
41 exp antihypertensive agent/
42 antihypertensi$.tw. (28653)
43 (therap$ or treat$ or medicat$ or drug$ or drop$).tw.
44 or/41-43
45 exp attitude to health/
46 exp patient compliance/
47 exp patient/
48 exp treatment refusal/
49 exp patient attitude/
50 exp patient satisfaction/
51 (adhere$ or non adhere$ or complian$ or non complian$ or concordance or persistence or acceptance or coperat$ or co operat$ or conform$).tw.
52 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 treat$).tw.
53 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 medic$).tw.
54 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 therap$).tw.
55 or/45-54
56 40 and 44 and 55
57 32 and 56

Appendix 4. CINAHL (EBSCO) search strategy

1 Randomized Controlled Trial.pt.
2 Controlled Clinical.pt.
3 Randomized Controlled Trials.sh.
4 Random Allocation.sh.
5 Double Blind Method.sh.
6 Single Blind Method.sh.
7 1 or 2 or 3 or 4 or 5 or 6
8 (Animals not Human).sh.
9 7 not 8
10 Clinical Trial.pt.
11 exp Clinical Trials/
12 (clin$ adj25 trial$).ti,ab.
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14 placebos.sh.
15 Placebo$.ti,ab.
16 random$.ti,ab.
17 Research Design.sh.
18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 18 not 8
20 19 not 9
21 Comparative Study.sh.
22 exp Evaluation studies/

23 Follow Up Studies.sh.
24 Prospectice Studies.sh.
25 (control$ or prospective$ or volunteer$).ti,ab.
26 21 or 22 or 23 or 24 or 25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28
30 exp GLAUCOMA/ or exp OCULAR HYPERTENSION/
31 exp INTRAOCULAR PRESSURE/
32 glaucoma$.mp.
33 (ocular adj1 hypertension).mp.
34 (intraocular adj1 pressur$).mp.
35 OHT.mp.
36 30 or 31 or 32 or 33 or 34 or 35
37 exp ATTITUDE TO HEALTH/ or exp PATIENT COMPLIANCE/ or exp TREATMENT REFUSAL/
38 exp PATIENT CARE PLANNING/ or exp PATIENT EDUCATION/
39 ((patient$ or user$) adj3 (acceptance or complian$ or non-complian$ or concordance or persisten$ or adher$ or non-adhere$ or co?operat$ or non-co?operat$ or conform$)).mp.
40 ((discontinu$ or abstention or abstain or stop$ or abandon$) adj3 (treatment$ or medication$ or medicine$ or therap$)).mp.
41 37 or 38 or 39 or 40
42 (therap$ or medicine$ or medication$ or treatment$ or drug$ or drop$).mp.
43 29 and 36 and 41 and 42

Appendix 5. PsycINFO and PsycEXTRA (OvidSP) search strategy

1 exp glaucoma/
2 glaucom$.tw.
3 ((intraocular or intra ocular) adj1 pressure$).tw.
4 ocular hypertensi$.tw.
5 (IOP or OHT).tw.
6 or/1-5
7 exp antihypertensive drugs/
8 antihypertensi$.tw.
9 (therap$ or treat$ or medicat$ or drug$ or drop$).tw.
10 or/7-9
11 exp compliance/
12 exp treatment compliance/
13 exp treatment dropouts/
14 exp treatment refusal/
15 exp health behavior/
16 exp health attitudes/
17 exp client attitudes/
18 exp Client Satisfaction/
19 (adhere$ or non adhere$ or complian$ or non complian$ or concordance or persistence or acceptance or coperat$ or co operat$ or conform$).tw.
20 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 treat$).tw.
21 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 medic$).tw.
22 ((discontinu$ or abstention or abstain$ or stop$ or abandon$) adj4 therap$).tw.
23 or/11-22
24 6 and 10 and 23

Appendix 6. Web of Science search strategy

Topic=(glaucoma* or ocular hypertension or IOP or OHT) AND Topic=(therap* or treat* or medic* or drug* or drop*) AND Topic=(adhere* or complian* or concordance)

Appendix 7. ZETOC search strategy

”glaucoma adherence“

Appendix 8. OpenGrey search strategy

Glaucoma AND (Adherence OR Compliance OR Concordance)

Appendix 9. metaRegister of Controlled Trials search strategy

(Adherence OR Compliance OR Concordance) AND Glaucoma

Appendix 10. ClinicalTrials.gov search strategy

(Adherence OR Compliance OR Concordance) AND Glaucoma

Appendix 11. ICTRP search strategy

Glaucoma = Condition AND Adherence OR Compliance OR Concordance = Intervention

Appendix 12. Questions on patient knowledge

The following questions were used in Ring 2011. The participants were required to answer true/false.

1. Glaucoma is a disease that affects the eyes and no other parts of the body
2. Glaucoma is always painful
3. Raised eye pressure can cause glaucoma
4. Treatment for glaucoma is life long
5. The most common treatment for glaucoma is surgery
6. Eye drops have side effects that affect other parts of the body
7. Most people have symptoms that warn them that glaucoma is getting worse
8. Glaucoma affects the central part of your vision before the sides
9. Regular check-ups are not necessary
10. Lowering the eye pressure reduces the risk of sight loss in glaucoma

WHAT'S NEW

Last assessed as up-to-date: 26 June 2012.

Date	Event	Description
28 June 2012	New search has been performed	Issue 4 2013: New searches have been conducted. One new co-author, Jennifer Evans, has joined the review team for the update
28 June 2012	New citation required and conclusions have changed	Issue 4 2013: Eight new trials have been included.

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 2, 2009

Date	Event	Description
1 September 2009	Amended	Issue 1, 2010: 'Results of the search' amended as the number of trials stated to be eligible for inclusion in the review was incorrect. Eleven trials were relevant for the review; three ongoing and eight completed
5 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: HW, DH

Designing the review: TG

Co-ordinating the review: TG, JE

Undertaking manual searches: TG

Screening search results: TG, LO, HW, JE

Organising retrieval of papers: TG

Screening retrieved papers against inclusion criteria: TG, HG, DH, RH, HW, JE

Appraising quality of papers: TG, HW, DH, RH, JE

Extracting data from papers: TG, HW, DH, RH, JE

Writing to authors of papers for additional information: TG, JE

Obtaining and screening data on unpublished studies: TG

Data management for the review: TG, JE

Entering data into RevMan: TG, JE

Analysis of data: TG, JE

Interpretation of data: TG, JE

Writing the review: TG, JE

Securing funding for the review: DH, HW

DECLARATIONS OF INTEREST

The authors of this review (with the exception of Jennifer Evans) were involved in one included study (Gray 2011).

SOURCES OF SUPPORT

Internal sources

- University of Manchester, UK.

External sources

- Central Manchester and Manchester Children's University Hospitals NHS Trust, UK.
- Pfizer Limited, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Cochrane Collaboration's new tool for assessing the risk of bias has been used in updates of this review. In the update in 2012, two new outcomes were added: patient's knowledge about glaucoma and costs.

INDEX TERMS

Medical Subject Headings (MeSH)

*Medication Adherence; Ocular Hypertension [*drug therapy]; Ophthalmic Solutions [administration & dosage]; Patient Education as Topic; Randomized Controlled Trials as Topic; Reminder Systems [instrumentation]

MeSH check words

Humans