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Efficacy of Coloured Overlays and Lenses for the Treatment of Reading Difficulty: An
Overview of Systematic Reviews

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Background

Coloured overlays or lenses are widely available for use by children and adults with difficulties or discomfort while reading. In recent years, systematic reviews have been conducted in an attempt to establish the strength of the evidence base for this intervention. The aims of this overview is to systematically review these reviews.

Method

The methodology was published prospectively as a protocol (Prospero CRD42017059172). Online databases Medline, Cinahl, Ovid and the Cochrane library were searched for systematic reviews on the efficacy of coloured overlays or lenses for the alleviation of reading difficulty or discomfort. Included studies were appraised using the AMSTAR 2 checklist. Characteristics of included studies including aspects of methods, results and conclusions were recorded. Both processes were conducted independently by two reviewers and any discrepancies were resolved by discussion.

Results

Thirty-one studies were found via databases and other sources. After excluding duplicates and those not fitting the inclusion criteria, four reviews were included in the analysis. While all reviews were systematic, their methodology, results and conclusions differed. Three of the four concluded that there is insufficient good quality evidence to support the use of coloured overlays or lenses for reading difficulty, while one concluded that, despite research limitations, the evidence does support their use.

Conclusions

On balance, systematic reviews to date indicate that there is not yet a reliable evidence base on which to recommend coloured overlays or lenses for the alleviation of reading difficulty or discomfort. High quality, low bias research is needed to investigate their effectiveness in different forms of reading difficulty and discomfort for adults and children.

Coloured overlays and lenses are widely available for use by children and adults who experience a range of reading difficulties, including slow or inaccurate reading. Reading difficulties may be associated with perceived movement or other distortion of text and the presence of symptoms such as headache and eye strain.¹⁻³ Interest in the potential benefits of coloured filters began when Meares and Irlen found, independently, that in schoolchildren experiencing such difficulties, symptoms could be relieved by viewing text on coloured paper or through coloured overlays (transparent sheets placed over text).^{4,5} These findings formed the basis of research on the effects of coloured filters on comfort, accuracy and speed when reading, and of the provision of coloured overlays or coloured spectacle lenses for children and adults experiencing such symptoms.^{6,7} Research findings have indicated that blue or yellow filters, or a variety of individually-specific coloured filters may be beneficial for people with reading difficulties.⁸ Individuals whose symptoms or signs (such as slow reading speed) are improved when using a coloured filter are sometimes diagnosed with visual stress, Meares-Irlen or Scotopic Sensitivity syndrome. Research groups have tended to adopt one of these terms (e.g. Wilkins et al coined the term visual stress,⁹ while Irlen first used the term scotopic sensitivity syndrome) but they refer to the same set of reading difficulties or discomfort. Here, the term 'visual stress' will be used because much of the more recently published work has used this term. Recently, a consensus-based set of diagnostic indicators has been established³ which may offer more precision in identifying people with visual stress. However, in prior research visual stress has been diagnosed on the basis of any of a range of visual symptoms when reading, and the reduction of these symptoms when viewing through coloured filters.

The use of coloured overlays and lenses for reading difficulty is controversial for at least three reasons. First, as indicated above, different research groups do not agree on the range of beneficial colours (blue/yellow versus any colour on the spectrum^{10,11}). Second, to date there is a lack of consensus on the effectiveness of coloured filters, with some research findings indicating significant improvements in reading,^{8, 11-18} for example, while others find

no improvement.¹⁹⁻²¹ Third, a claim that coloured filters alleviate symptoms and/or enhance reading ability should be supported by an evidence base not only showing effectiveness but also explaining why the effect is found. In the case of coloured filters and their effect on reading, one hypothesis is that the visual cortex is hyperexcited by high contrast patterns of spatial frequency around 3 cycles per degree, and by black-white text around this frequency.²² However, results from functional magnetic resonance imaging (fMRI) and visual evoked potential (VEP) studies of subjects with visual stress have included small samples or have focused on people who have migraine as well as visual stress.²³⁻²⁶

In addition, it should be noted that people with reading difficulties may be keen to find a solution to their problem, and parents or carers of a child with visual stress are likely to welcome an intervention that could enhance their child's reading comfort and/or ability. In view of this, before suggesting coloured overlays or lenses for patients with reading difficulty, it is important to establish that the intervention has a solid, reliable evidence base demonstrating clinically significant efficacy.

Research evidence on the efficacy of health interventions such as coloured filters for reading may use a range of study designs involving comparison between the use of a coloured filter and a different filter, or no filter. Research can be subject to various forms of bias and in an intervention study these can be controlled to some extent by using a randomised controlled study design, in which a group of people with the target condition are randomly allocated to two or more groups, to investigate the effectiveness of a specific intervention. One group (the experimental group) receives the intervention under investigation, while a comparison or control group receives an alternative intervention, a dummy (placebo) intervention or no intervention at all. All groups are followed up, outcomes are measured at specific times and any differences between groups are assessed statistically. However, bias can still exist in randomised controlled studies and can be identified by appraising the quality of the research using standardised risk of bias tools. Systematic reviews of research on a particular question involve finding and appraising relevant research with the aim of answering the question.²⁷ If

the various pieces of research evidence are sufficiently comparable, a meta-analysis may be included to provide a pooled estimate of effectiveness. A systematic review offers advantages over a more narrative review in that it includes controls for an author's conscious or unconscious bias. Specifically, the systematic review includes a wide search of published and unpublished research using appropriate key words, at least two people independently checking relevance, and appraising each relevant study using a set of pre-determined criteria. Several reviews including some systematic reviews have now been conducted into questions related to the effectiveness of coloured overlays or lenses in reading difficulty and/or visual stress. The aim of this review is to provide an overview²⁸ and critical appraisal of the existing systematic reviews to determine whether coloured overlays or lenses are effective in alleviating reading difficulty or discomfort, including visual stress. A research question consistent with this aim was developed including the PICO components Patient or Problem (people with reading difficulties or discomfort), Intervention (coloured overlays or coloured spectacle lenses), Comparison (placebo or no comparison) and Outcome (alleviation of reading difficulties).

Methods

The protocol for this overview was prospectively published on the PROSPERO database (CRD42017059172; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017059172). The overview addressed the question 'Do coloured filters alleviate reading problems?' For this purpose, 'coloured filters' refers to both overlays and tinted lenses, and 'reading problems' includes any symptom affecting reading, including discomfort or perceptual distortion, and/or signs of reading difficulty such as slow reading. Systematic reviews that had addressed this question were eligible for inclusion in this overview. Studies that had searched more than one database and had conducted a critical analysis of their included studies were considered to be systematic reviews. The method adopted in this overview of systematic reviews followed the methodology described by Smith et al for the systematic review of

systematic reviews²⁸ and is aligned with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (<http://prisma-statement.org>).

Cinahl and Medline databases were searched via the EBSCOHost platform and Embase database was searched via the Ovid platform. In addition, the Cochrane library was searched. Searches were conducted on 17th March 2017 and were repeated on 29th June 2017 to check for any new studies. Within each database, the concepts 'reading', 'coloured filter' and 'review' were used. Within the concept 'reading', subject headings 'reading', 'reading disorder' and 'dyslexia' were searched. Keywords: 'visual stress', 'Meares-Irlen', 'Reading difficulty', 'Scotopic sensitivity' were searched separately. In the concept 'coloured filter' the subject heading 'coloured filter' was searched, and keywords 'coloured overlay', 'coloured lens', 'coloured filter', 'precision tint' were searched separately. In the concept 'review', the subject headings 'review', 'systematic review' and 'meta-analysis' were searched, and the same terms were searched separately as keywords. Throughout the search, wild cards and other symbols appropriate to each database were used to ensure that plural, other variations and non-English terms were captured. Within each concept, the results of the subject heading and keyword searches were combined using the OR Boolean operator. Results of the three concept searches were combined using the AND operator. The search was not limited by date or language except for the earliest year set by each database.

In addition to searches via these electronic databases, grey literature (e.g. conference abstracts and unpublished theses) was identified via the Bielefeld Academic Search Engine (<https://www.base-search.net/about/en/>; BASE) and Open Grey (<http://www.opengrey.eu/>) databases. The Prospero database (<http://www.crd.york.ac.uk/PROSPERO>) was searched for ongoing systematic reviews. The reference lists of included studies (see below) were searched for relevant systematic reviews. The American Academy of Optometry and Association for Research in Vision and Ophthalmology conference Abstracts were searched

for the ten years from 2007 to 2017. Finally, key experts in the field were contacted to ask about any systematic reviews not identified in the above process.

Two authors (MC and CS) independently reviewed the list of results and identified studies that were systematic reviews relevant to the efficacy of coloured overlays or lenses for any form of reading difficulty including visual stress. This decision was based on the title of each study and, when unclear from the title, the Abstract or full text. Studies that were not considered relevant were excluded and those considered relevant were included for further analysis. Once this process was completed independently, the two reviewers met to compare their results and to agree on a final list of included and excluded studies. When planning this overview, a scoping review revealed a small number of systematic reviews which had included different populations (different age ranges and types of reading difficulty) and it seemed unlikely that it would be possible to quantitatively synthesise the data. For this reason a qualitative synthesis only was planned.

Characteristics of each included systematic review were reviewed independently by authors MC and CS to identify methodology, results and conclusions of each review. Data extraction for this purpose was conducted using a template which was drafted and piloted before application, to ensure all relevant aspects of methods were addressed. Any differences between characteristics extracted by the two authors were resolved by discussion.

Initially, the AMSTAR checklist^{29,30} was used to appraise the included reviews. During this process, a new checklist, AMSTAR 2,³¹ was published. Since the latter was developed to overcome limitations of the original version^{32,33} the new checklist was applied instead. Note that the PROSPERO protocol for this review indicates that AMSTAR would be used and includes additional information stating that the AMSTAR 2 was used instead. The included reviews were appraised by MC and CS independently. For each systematic review, the 16 questions included on the AMSTAR 2 checklist were considered along with the checklist guidelines and answered with 'yes', 'partial yes', 'no' or in some cases 'not applicable'.

Again, once this process had been completed independently the two reviewers met to agree

on their final appraisal for each study by consensus. It is possible to generate a score using this test, but this may be misleading²⁹⁻³³ and in the present study the checklist was used as a qualitative rather than quantitative indicator.

Results

Twenty-six studies were identified in the database search and a further five through other sources. After exclusion of duplicates and articles that did not fit the inclusion criteria, four studies were included. Figure 1 is a PRISMA diagram showing the number of studies identified at each stage of the search and selection process. Studies that were excluded due to not fitting the criteria, and the reasons for exclusion, are provided in Table 1.^{3,17,34-46}

Table 2 provides a summary of the included studies and their characteristics, results of any quantitative analysis, and conclusions. Three^{47,48,50} of the four studies focused on coloured overlays and lenses, while one⁴⁹ included this form of intervention along with a range of others. They had been published from 2008 to 2016. While all four focused on the effects of coloured filters on forms of reading difficulty, one was specifically on these effects in visual stress.⁴⁸ The reviews all included studies on these effects in children; three of the four also included adults,^{47,48,50} while one included adolescents but not adults.⁴⁹ Unsurprisingly, given the range of methods and scope, conclusions differed to some extent. All four systematic reviews found that studies on the efficacy of coloured filters for alleviating reading difficulty have limitations; three of the four concluded that the evidence is not sufficient to confirm any beneficial effect of coloured filters,^{47,49,50} while one concluded that the evidence does suggest a beneficial effect.⁴⁸

Figure 2 shows, for each of the 16 questions included in the AMSTAR 2 checklist, whether each of the four systematic reviews included here satisfied the criteria and gives a brief explanation for each decision.

All of the four reviews included research questions and inclusion criteria that were aligned with PICO, and the review authors acknowledged any of their own conflicts of interest.

Conversely, none of the reviews referred to an *a priori* protocol. On this question, the AMSTAR 2 tool indicates that the review should state that a protocol was developed and ideally registered prior to conducting the review, and that any deviations from it should be justified. The lack of an *a priori* protocol leaves the methods open to modification during the review process..

All four reviews provided information about the included studies, but key details were lacking. The reader of these systematic reviews would need to refer back to the individual studies in order to understand aspects of methods such as the information given to the participants within the study setting. One study⁴⁹ gave no information on the outcomes (e.g. rate of reading) in each of the included studies.

All four reviews assessed risk of bias but three⁴⁷⁻⁴⁹ did not describe consideration of one or more recognised risk of bias indicators such as selective reporting of results.

Two of the four reviews^{47,49} included meta analyses. Both considered and discussed heterogeneity among the included studies, but neither justified the inclusion of individual studies with high risk of bias. In both cases, the review found that the studies were not of sufficient quality to support the use of coloured filters for reading, yet the data were included in the meta analysis. Poor quality data included in the analysis raises questions about the validity and interpretation of the analysis, but both reviews did discuss the risk of bias and quality of the included studies within their discussion and took quality into account when drawing conclusions.

One study⁴⁸ made a qualitative assessment of bias of included studies and several limitations were identified, but despite these, and acknowledging poor quality, the authors concluded that “the balance of evidence suggests that coloured filters can alleviate symptoms or improve performance” in people with visual stress. This seems surprising in view of the acknowledged limitations of the evidence. However, the conclusion did include acknowledgement of the cost to the patient in terms of time, money and raised hopes.

Discussion

Coloured overlays and lenses are widely recommended for use by people with various forms of reading difficulty including those with or without a formal diagnosis of dyslexia. Parents of children with reading difficulty or discomfort may find claims of effective treatment appealing since they offer help during a period of life in which reading is important to achieve their full academic potential. Of the four systematic reviews found in this overview, three conclude that evidence is not sufficient to recommend the use of coloured overlays and lenses for reading difficulty. One systematic review⁴⁸ acknowledged limitations to research quality in this area, but concluded that despite these the available evidence suggests that coloured overlays or lenses can alleviate symptoms in people with visual stress. The authors noted that the quality of evidence was lower than would be needed for medical interventions, but “coloured filters are a safer form of intervention.” In making any clinical recommendation, there is always a trade-off between benefits and harms. Strong recommendations based on a body of evidence usually require that the desirable effects clearly outweigh the undesirable effects.⁵¹ Undesirable effects could be psychological as well as physical. To take one hypothetical example of a child whose teachers have identified a reluctance to read and possibly a reading difficulty; the child’s teachers or parents may be aware of coloured overlays or lenses being helpful for some children with reading difficulty, and may seek information independently. Information and resources are widely available via the Internet (e.g. <http://www.crossboweducation.com/visual-stress-resources>; <http://www.bdadyslexia.org.uk/dyslexic/eyes-and-dyslexia>) and children or parents may seek advice via a general practitioner or optometrist. Clearly, it is vital that all health practitioners,

including optometrists, make use of the best (highest quality) available evidence, tailored to the patient's needs, wishes and circumstances, as a basis for any such advice or recommendation.^{39,40} The patient and/or parent may have a strong expectation and wish for coloured overlays/lenses to significantly improve reading, and this raises two concerns. One is a high likelihood of a placebo effect when reading is tested with and without colour, meaning that the effect (such as reduced symptoms, or faster reading through colour) may be influenced by a wish or expectation, rather than any real effect on the visual system. It could perhaps be argued that any positive effect is good, even if it is a placebo effect. However, this effect is not likely to deal with any neurophysiological basis of reading difficulty.⁵⁴

The second concern is that, if the information gathered and the professional advice indicates that the intervention is likely to be effective, the patient and/or parent will have raised expectations. They will be encouraged to spend time and money on the intervention and will expect it to have a positive effect on reading ability. Thus, as well as a financial cost there are costs in terms of raised hopes which, if the intervention is not likely to deal with the problem, may result in disappointment. This is clearly a concern in light of the conclusions of three of the four systematic reviews, that there is not sufficient evidence to recommend coloured overlays or lenses for the alleviation of reading difficulty or associated symptoms.

Figure 2 highlights the differences between the systematic reviews in terms of factors affecting quality as defined by AMSTAR 2.. None of the four published a protocol before conducting the review. Without an *a priori* protocol, it is not possible to know whether the methods were fixed throughout the process based on the research question, or whether the methods or the question were modified in any way as the review progressed.

The critical appraisal process identified several other limitations. For example, risk of bias of the included studies was not taken into account when combining studies in a meta-analysis, reducing the reliability of the analysis findings. Not all reviews indicated that study selection was conducted independently by more than one researcher with discussion to resolve any

disagreement between their findings, or provided details of excluded studies. Not all studies specified when their search was conducted, or what restrictions (e.g. language) were imposed. It is possible that some of the apparent limitations reflect incomplete reporting, but in our review process we assumed, as recommended in the AMSTAR 2 guidance,³¹ that the reporting reflected the actual process.

Overall, the finding of this overview of systematic reviews is that the available evidence is not sufficiently reliable to conclude that coloured filters are effective in the alleviation of reading difficulty or discomfort. Since clinical decisions should be made on the basis of the best available evidence, this implies that coloured filters should not be recommended for this purpose until reliable evidence is available to demonstrate clearly that they are likely to be effective. As concluded by Evans and Allen,⁴⁸ this type of intervention is unlikely to cause harm in terms of the patient's health. In the absence of potential for harm, the clinician might consider prescribing this intervention for the benefit of a placebo effect. It is important, however, to consider the implications for the patient in terms of financial cost and raised expectations, in addition perhaps to neglecting other interventions in favour of this one. Public awareness of and interest in coloured filters and their use for reading seems high, based on anecdotal clinical experience and on their visibility via the internet and media. It is possible that they are effective, but a lack of reliable research to date means that this is not yet known. Therefore a clear implication for research is that high level, carefully conducted, unbiased research is needed to test effectiveness of coloured filters for different forms of reading difficulty and discomfort, in children and adults.

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Captions

Figure 1: PRISMA diagram, showing the number of systematic reviews at each stage from the search to the final selection of included studies.

Figure 2: Each of the 16 criteria on the Amstar 2 checklist are shown for each of the four included systematic reviews. Colour coding indicates whether the study satisfied each of these criteria. Red = No, Green = Yes, Yellow = Partial yes; Grey = Not applicable.

Table 1: Details of excluded studies, including whether the full text was assessed (if not, the study was excluded on the basis of information in the title or Abstract) and why it was excluded.

Table 2: Characteristics of the four included systematic reviews.

Table 1

Author(s) and year	Full text assessed	Primary reason for exclusion
Evans BJ and Drasdo N (1991) Tinted lenses and related therapies for learning disabilities – a review. ³⁴	Yes	Not a systematic review
Evans BJW, Patel R, Wilkins AJ, Lightstone A, Eperjesi F et al (1999) A review of the management of 323 consecutive patients seen in a specific learning difficulties clinic ¹⁷	No	Not a systematic review
Evans BJW, Allen PM and Wilkins AJ (2016) A Delphi study to develop practical diagnostic guidelines for visual stress (pattern-related visual stress) ³	No	Not a systematic review
Gray J (1998) Visual perceptual difficulties and reading behaviour Irlen syndrome and eye colour ³⁵	No	Not a systematic review
Griffiths PG (2015) Using coloured filters to reduce the symptoms of visual stress in children with reading delay ³⁶	No	Not a systematic review
Handler SM and Fierson WM (2011) Learning disabilities, dyslexia and vision ³⁷	Yes	Not a systematic review
Harle DE and Evans BJW (2004) The optometric correlates of migraine ³⁸	Yes	Not a systematic review
Kavale K (1982) Meta-analysis of the relationship between visual perceptual skills and reading achievement ³⁹	No	Not including coloured filters
Mumford C (2012) Coloured filters and literary progress ⁴⁰	No	Not a systematic review
Ritchie SJ (2010) Reading Disability, Visual Stress, and Coloured Filters: A Randomised Controlled Trial ⁴¹	No	Not a systematic review

Robinson R, Boyle P and Garvey P (2015) Ocular interventions, excluding correction of significant refractive error, for specific reading disorder ⁴²	No	Protocol only (withdrawn)
Uccula A, Enna M and Mulatti C (2014) Colors, colored overlays, and reading skills ⁴³	No	Not a systematic review
Virgili G, Acosta R, Grover LL, Bentley SA and Giacomelli G. (2013) Reading aids for adults with low vision ⁴⁴	Yes	Not including visual stress
Wilkins A, Huang J and Cao Y (2007) Prevention of visual stress and migraine with precision spectral filters ⁴⁵	No	Not a systematic review
Wilkins A (2002) Coloured overlays and their effect on reading speed: a review ⁴⁶	Yes	Not a systematic review

Table 2

Authors, Country, Year of publication	Type of reading difficulty	Type of intervention	Databases searched	Included study designs	Included age range	Number of included studies	Quantitative results	Conclusions
Albon, Adi, Hyde, UK, 2008 ⁴⁷	reading disorder, reading disability, reading difficulty, dyslexia	Coloured overlays and coloured lenses	Cochrane, Medline, Embase, Cinahl, PsycInfo, Social Science Citation Index, Science Citation Index	SRs, RCTs, comparative studies.	Adults and children aged 7 or older	24	Meta-analysis shows no effect of coloured filters on reading accuracy or speed, but marginal effect on comprehension.	“It was not possible to comment on whether coloured filters can improve symptoms... due to a lack of available evidence”.
Evans, Allen, UK, 2016 ⁴⁸	Visual stress (Irlen syndrome, Meares-Irlen syndrome or Scotopic sensitivity syndrome) diagnosis by at least one of:	Coloured overlays or lenses	PubMed, ERIC, Cochrane Central Register of Controlled Trials, PubPsych	Randomised controlled trial, quasi-experimental study, population-based cross-sectional study, observational study using a	Over 5 years	12	None	“Despite the limitations of the research... evidence suggests that coloured filters can alleviate symptoms or improve performance...”

	Questionnaire based rating scales; pattern glare test positive; sustained greater than 2 weeks overlay use; improvement in reading or task with IO			comparison group (prospective or retrospective)				
Galuschka, Ise, Krick, Schulte-Korne, Germany, 2014 ⁴⁹	Reading disability specified in search as dyslexia, developmental reading disorder, developmental dyslexia, developmental reading disability, reading disorder, word blindness, spelling disorder.	Phonemic awareness instruction, phonics instruction, reading fluency training, reading comprehension training, auditory training, medical treatment, coloured overlays (filters/overlays)	ERIC, PsycInfo, Pubmed, Cochrane, Pro Quest, Clinical trials.com	Randomised controlled trials only.	Children and adolescents (age cut-off not specified)	22; 4 specifically on coloured filters or overlays	Meta-analysis includes 4 studies using coloured overlay or tint. In each case, no significant effect.	"This finding confirms earlier systematic reviews that could not prove any positive effect of coloured lenses..."
Griffiths, Taylor, Henderson,	Any form of 'reading difficulty' or	Coloured overlays and coloured lenses	Medline, PsycInfo, Embase	Experimental studies, reading	Adults and children (age range	51	None	"...the use of coloured overlays and

Barrett, UK, 2016 ⁵⁰	'reading disability' as described by study authors			ability measure, effect of coloured filters, with control group.	not specified)			lenses to ameliorate reading difficulties cannot be endorsed".
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Figure 1



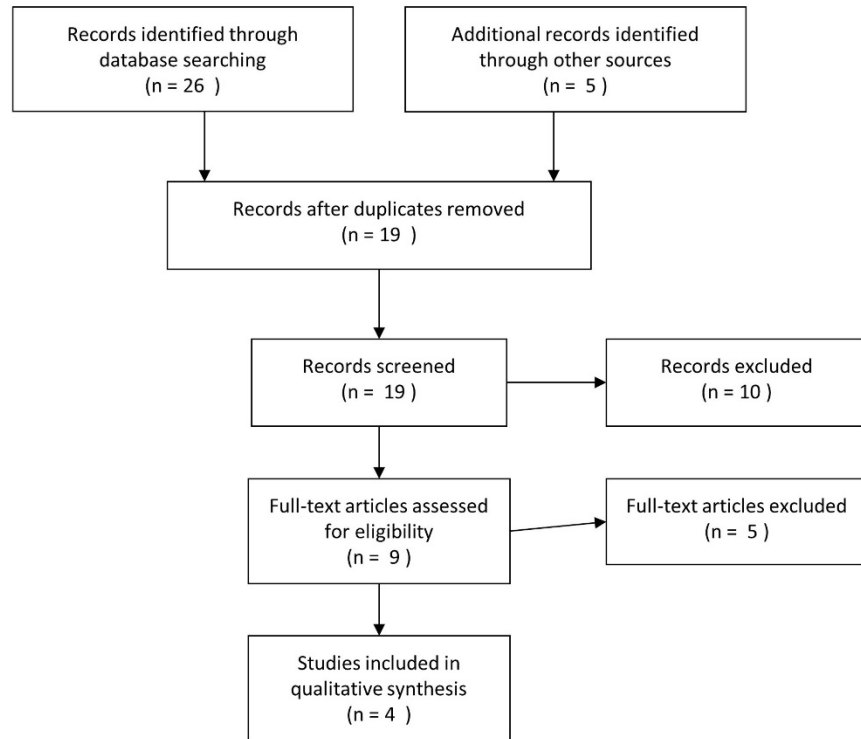





Figure 2

AMSTAR 2 checklist question	Albon et al 2008 ⁴⁷	Evans and Allen 2016 ⁴⁸	Galushka et al 2014 ⁴⁹	Griffiths et al 2016 ⁵⁰	Explanation
1. Research question and inclusion criteria aligned with PICO	Yes	Yes	Yes	Yes	Research focused on specific problem, intervention, comparator and outcome
2. <i>a priori</i> protocol	No	No	No	No	No verifiable written protocol established or registered prior to review
3. Study design selection explained	No	Yes	Yes	Yes	⁴⁷ selected reviews, RCTs and other comparative studies but did not explain/justify this selection
4. Comprehensive search	Partial Yes	No	No	Partial Yes	^{48,49} did not search trial registries; ^{47,50} did not specify/justify search restrictions
5. Duplicate study selection	No	No	Yes	Partial Yes	^{47,48} did not specify independence; ⁵⁰ did not specify consensus
6. Duplicate data extraction	Yes	No	No	Yes	⁴⁸ data extraction process was not explained
7. List and justification of excluded studies	Yes	No	No	Yes	^{48,49} no list of excluded studies provided
8. Included studies described in adequate detail	Partial Yes	Partial Yes	Partial Yes	Partial Yes	⁴⁹ did not describe outcomes or research designs. ^{47,48,50} insufficient detail to understand study methods
9. technique for assessment of risk of bias	Partial Yes	No	Partial Yes	Yes	^{47,49} did not appraise all commonly recognised risk of bias domains
10. Sources of funding of included studies reported in review	Yes	No	No	Yes	^{48,49} did not appraise whether the included studies acknowledged conflicts of interest
11. If meta analysis: Justified combination of data	Yes	Not applicable	Yes	Not applicable	^{47,49} grouped similar studies and used random effects model used to accommodate statistical heterogeneity
12. If meta analysis: risk of bias of included studies taken into account	No	Not applicable	No	Not applicable	^{47,49} included studies with high risk of bias in meta analysis
13. Risk of bias taken into account in interpretation and discussion	Yes	No	Yes	Yes	⁴⁸ acknowledged high risk of bias but concluded that despite this the evidence suggests efficacy
14. Satisfactory explanation for any heterogeneity	Yes	Yes	Yes	Yes	All reviews discussed heterogeneity in the included studies
15. Publication bias in included studies assessed	Yes	Not applicable	Yes	Not applicable	⁴⁷ did consider publication bias in discussion but too few studies to conduct a formal assessment
16. Review authors report on any of their own conflicts of interest	Yes	Yes	Yes	Yes	Statement made regarding conflicts of interest

Yes	
Partial Yes	
No	
Not applicable	