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Overview of systematic reviews – a new type of study. Part II

Overview de revisões sistemáticas – um novo tipo de estudo. Parte II

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ABSTRACT

CONTEXT AND OBJECTIVE: Overviews of Systematic Reviews (OoRs) are a new type of study in which multiple evidence from systematic reviews (SRs) is compiled into an accessible and useful document. The aim here was to describe the state of the art and critically assess Cochrane OoRs that have been published.

DESIGN AND SETTING: Descriptive study conducted at a research center.

METHODS: The OoRs identified through the filter developed in Part I of this study were evaluated in five domains: methodological quality; quality of evidence; implications for practice; general profile of OoRs; and length of work.

RESULTS: All 13 OoRs included had high methodological quality. Some OoRs did not present sufficient data to judge the quality of evidence; using sensitivity analysis, the quality of evidence of the OoRs increased. Regarding implications for practice, 64% of the interventions were judged as beneficial or harmful, while 36% of them showed insufficient evidence for judgment. It is expected (with 95% confidence interval) that one OoR will include 9,462 to 64,469 patients, 9 to 29 systematic reviews and 80 to 344 primary studies, and assess 6 to 21 interventions; and that 50 to 92% of OoRs will produce meta-analysis. The OoRs generated 2 to 26 meta-analyses over a period of 18 to 31 months.

CONCLUSION: The OoRs presented high methodological quality; the quality of evidence tended to be moderate/high; most interventions were judged to be beneficial/harmful; the mean length of work was 24 months. The OoR profile adds power to decision-making.

RESUMO

CONTEXTO E OBJETIVO: *Overviews* de revisões sistemáticas (OoRs) representam um novo tipo de estudo que compila múltiplas evidências de revisões sistemáticas (SRs) em um documento acessível e útil. O objetivo foi de descrever o estado da arte e avaliar criticamente as OoRs Cochrane publicadas.

DESENHO E LOCAL: Estudo descritivo realizado em centro de pesquisa.

MÉTODOS: As OoRs identificadas através do filtro desenvolvido na parte I deste estudo foram avaliadas por cinco domínios: qualidade metodológica, qualidade da evidência, implicações para a prática, perfil geral das OoRs e tempo de execução.

RESULTADOS: As 13 OoRs incluídas apresentaram alta qualidade metodológica. Algumas OoRs não apresentavam dados suficientes para julgar a qualidade da evidência; com a análise de sensibilidade, a qualidade evidência nas OoRs aumentou. Implicações para prática foram julgadas como benéficas ou danosas em 64% das intervenções; em 36% das intervenções há evidências insuficientes para o julgamento. É esperado (com intervalo de confiança de 95%) que uma OoR inclua 9.462 a 64.469 pacientes, 9 a 29 revisões sistemáticas e 80 a 344 estudos primários, e avaliem entre 6 e 21 intervenções; que 50 a 92% das OoRs realizem metanálise. As OoRs geraram entre 2 e 26 metanálises em um período de 18 a 31 meses.

CONCLUSÃO: As OoRs apresentam alta qualidade metodológica; a qualidade da evidência tende a ser alta/moderada; as intervenções, em sua maioria, foram julgadas como benéficas/danosas; o tempo de execução foi de 24 meses em média. O perfil das OoRs potencializa a tomada de decisão.

INTRODUCTION

Overviews of Systematic Reviews (OoRs) are a new type of study that has been proposed by the Cochrane Collaboration in order to compile multiple evidence from systematic reviews (SRs) into a single document that is accessible and useful. Each OoR focuses on a problem or medical condition for which two or more SRs have addressed potential interventions and their outcomes.[1-6]

One SR rarely addresses all potential interventions for a condition, and healthcare policymakers may have difficulty in finding, evaluating, comparing and summarizing the information from all the relevant SRs.[3,4] Thus, the main objective of OoRs is to serve as a friendly front end for the Cochrane Collaboration with regard to healthcare decision-making. The relevant SRs are integrated and/or summarized into a single document, i.e. an OoR. This, in theory, allows the reader to have access to an integrated summary of a long list of studies included in Cochrane SRs.[1-6] Therefore, the primary audience for OoRs are healthcare decision-makers, such as healthcare professionals, policymakers and informed consumers who, through the Cochrane Library, seek evidence on treatments for various health conditions.[1,2]

The first part[1,2] of this series of three articles on OoRs focused on the growth of publications with the best level of evidence available for healthcare decision-making. It provided justifications for implementing this new type of study, as well as defining who the target audience are. Furthermore, a filter was created and applied in order to search for specific OoRs in the Cochrane Library.

This second part of the series continues to address this topic by describing the state of the art (state of knowledge) of Cochrane Collaboration OoRs, through a critical assessment of Cochrane OoRs. In Part III, a new hierarchy for the pyramid of evidence will be proposed, taking this new type of study into consideration.

OBJECTIVE

To critically assess Cochrane Overviews of Systematic Reviews, through analyzing the characteristics, approaches and methodological aspects of this type of study.

METHODS

This descriptive study was conducted at the research center of a federal university in Brazil and within one of its postgraduate study programs.

We performed a search for OoRs in the Cochrane Library, as described in Part I[1,2] of this series. The flowchart for the OoRs is shown in **Figure 1**. The inclusion criteria were that the studies needed to be OoRs and to have been published in the Cochrane Database of Systematic Reviews, which is one of the six directories of the Cochrane Library.[7] Protocols for Cochrane OoRs that have been published were excluded.

After OoR selection, two of the present authors (VS and AJG) read them, extracted data and assessed the quality. Differences in data collection information were resolved by reaching a consensus.

The data extracted from each OoR were organized using a specific form that sought information on the research question and objective, date of search, number of studies included, participants, interventions, main outcome, methodological quality of the review, quality of evidence and authors' conclusion.

We used five items to critically assess the OoRs: (1) methodological quality, using the AMSTAR tool (Assessing the Methodological Quality of Systematic Reviews);[8] (2) quality of evidence, assessed using the GRADE tool (Grades of Recommendation, Assessment, Development and Evaluation) or any other method reported through OoRs; (3) implications for practice (the evidence confirms that the intervention presents benefits; the evidence confirms that the intervention presents harm/risk; or absence of evidence for a recommendation); (4) general profile of OoRs included (patients/OoR, SRs/OoR, studies/OoR, interventions/OoR, meta-analysis/OoR and search strategy); (5) Length of work, i.e. the time taken to publish the OoR (in years), obtained from the date of registration of the title (via Archie), date of publication of the protocol (via the Cochrane Library) and date of publication of the OoR (via the Cochrane Library).

Data synthesis was performed using descriptive statistics. Contingency tables were used to summarize dichotomous data as frequencies and proportions. Quantitative data were summarized using the mean and standard deviation. Sensitivity analysis were performed to assess the robustness of the results.

RESULTS

The search filter for OoRs that was developed in Part I[1,2] of this study was updated, validated[9] [sensitivity = 1.00 (95% CI = 0.86 to 1.00); specificity = 0.99 (95% CI = 0.99 to 1.00)] and used (on November 5, 2013). Through this process, 1207 titles were retrieved, of which 95% were excluded because they had not been published in the Cochrane Database of Systematic Reviews. Ninety-three references were checked, but 52 of these were systematic reviews and were excluded; and another 26 potential OoRs[10-35] were excluded because they were at the protocol stage. At the end of the selection process, 13 OoRs[26,35-46] were included, were used for data extraction and were critically assessed. **Figure 1** presents the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart for the OoRs.

The characteristics of the thirteen OoRs[26,35-46] included in this study are described in detail in **Appendix 1**, which includes the main conclusions from the approaches used in each study. The synthesis on the data extracted from these 13 OoRs,[26,35-46] with the overall assessment, is presented in **Table 1**.

All the OoRs that were included[26,35-46] had high methodological quality, reaching between 9 and 11 points out of the 11 points possible in AMSTAR (**Table 1**). However, some OoRs lost points regarding methodological quality for the following reasons: they did not record the protocol[36] or, if it was cited, did not make it available;[38] they only included searches in the Cochrane Database of Systematic Reviews (CDSR);[26,35-37,39,43,44,46] they did not consider the quality of evidence in formulating conclusions;[46] they were unable to "meta-analyze" the data;[40,42,43,46] and they did not assess the risk of bias among the reviews included.[36]

With regard to judging the quality of evidence, it was found that many categories/studies were unclear, and thus the proportion of the categories/studies that presented high-quality evidence was low. If the OoRs[40,42,46] in which more than 10% of the studies/categories could not be clearly judged regarding the quality of evidence were excluded, the proportion of studies/categories that were of high quality doubled. The sensitivity analysis drastically altered the proportions of the other categories regarding the quality of evidence (**Table 1**).

Through the outcome of implications for practice, we found that about 64% of the interventions were judged to be beneficial or harmful. However, there was insufficient evidence to judge the interventions in 36% of them (**Table 1**).

Regarding general factors, with a 95% confidence interval, we expect that each new OoR will include between 9,462 and 64,469 patients, between 9 and 29 SRs and between 80 and 344 primary studies, and will assess between 6 and 21 interventions. Between 50 and 92% of OoRs that pool data qualitatively will generate between 2 and 26 meta-analyses. Additional details are analyzed in **Table 1**.

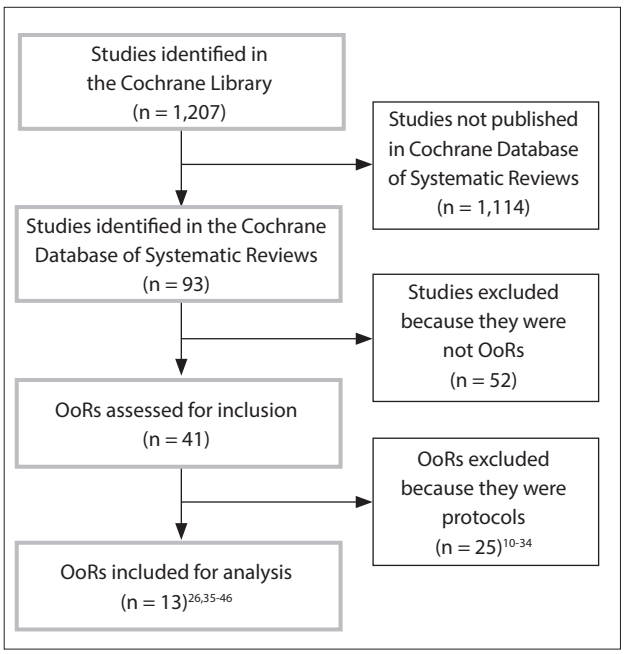

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart for Cochrane Overviews of Systematic Reviews (OoRs).

Most of the OoRs (62%) conducted searches for systematic reviews only in the Cochrane Database of Systematic Reviews (CDSR). However, those that conducted external searches, in addition to searching in the CDSR, used between one and ten databases (**Table 1**).

Table 1 also shows that, from the date when the OoR title was registered, the authors spent about two years (about one year for planning/preparing the protocol and another year for implementing the full study) until the date of publication.

Table 1. Overall assessment of Cochrane Overviews of Systematic Review (OoRs)

	Overall assessment	
Methodological quality[a]	**Classification of quality**	**General analysis**
	% (n/N)	**Mean (SD); range; N**
High (8 to 11)	100% (13/13)	
Moderate (4 to 7)	0% (0/13)	9.8 (0.9); 8-11; 13
Low (≤ 3)	0% (0/13)	
Quality of evidence[b]	**General analysis % (n/N)**	**Sensitivity analysis[c] % (n/N)**
High	11% (232/2141)	21% (171/801)
Moderate	16% (348/2141)	30% (242/801)
Low	20% (425/2141)	31% (251/801)
Very low	11% (246/2141)	16% (128/801)
Not clear to judge	42% (890/2141)	1% (9/801)
Implication for practice[d]	**% (n/N)**	
Beneficial intervention	52% (26/50)	
Harmful intervention	12% (6/50)	
Insufficient evidence	36% (18/50)	
General profile	**Mean (SD); range; N**	
Patients/OoR[e]	36965.7 (40939.6); 2323-117501; 11	
Studies/OoR[e]	211.9 (207.8); 21-700; 12	
SRs/OoR[e]	18.9 (16.3); 3-54; 12	
Interventions/OoR	13.3 (10.2); 3-38; 13	
Meta-analysis/OoR	**% (n/N)**	**Mean (SD); range; N[f]**
	76.9% (10/13)	13.5 (14.4); 5-46; 8
Additional search in CDSR[g]	**% (n/N)**	**Mean (SD); range; N[h]**
	39% (5/13)	5.8 (3.5); 2-11; 5
Length of work (months)	**Mean (SD); range; N**	
Total time taken to publish	24.5 (10.3); 8-43; 13	
Time taken to publish the protocol[i]	13.8 (8.4); 5-30; 11	
Time taken to publish the OoR[i]	12.4 (8.4); 3-25; 11	

[a]AMSTAR conducted;[8] [b]frequency based on the number of outcomes or studies assessed; [c]OoRs[41,43,48] in which more than 10% of the studies/categories could not be clearly judged regarding the quality of the evidence were excluded from the sensitivity analysis; [d]judgments based on main outcome conclusion; [e]some data could not be determined (patients/OoR,[39,41] SRs/OoR[42] and studies/OoR[41]), even by looking for results tables in the OoRs or SRs included, thus reducing the number of OoRs in the analysis; [f]studies in which no meta-analysis was conducted[37,41,43-45] were not included; [g]CDSR is the abbreviation for Cochrane Database of Systematic Reviews; [h]only OoRs[39,41-43,46] in which additional searches in the CDSR were conducted were included in the analysis; [i]the protocols for these OoRs[37,39] were not found in the Cochrane Library or in Archie, thus reducing the number of OoRs in the analysis;
SD = standard deviation; range = minimum to maximum;
SR = systematic review.

Only 23% (3/13) of the OoRs did not identify the study type in the title. The same also occurred in the protocols for OoRs (6/28).

DISCUSSION

The Cochrane Collaboration's OoRs are supervised by one of the 16 methods groups, the Comparing Multiple Interventions Methods Group. This methods group of the Cochrane Collaboration was established in 2004 and initially was called the Umbrella Reviews Working Group.[47]

Other milestones during the development of the OoRs methodology occurred in 1996, 1997, 1998 and 2005. Between February 1997 and December 1998, the first series of OoRs,[48-51] four reviews relating to pregnancy were published as a partnership between researchers from the UK Cochrane Centre and the World Health Organization. In 1996, Julian Higgins and Anne Whitehead published the first article to describe the standard Bayesian approach towards multiple-treatment meta-analysis (MTM).[52] In 2005, in the 13th Cochrane Colloquium in Melbourne, Georgia Salanti made a presentation on MTM methodology,[53] co-authored with Julian Higgins and Valeria Marinho. This won the prize for best oral presentation and helped to popularize the technique.

In this context, the present systematic review describes how far the knowledge of the select group of Cochrane OoRs[26,35-46] published in the CDSR has reached. Although we only included 13 OoRs,[26,35-46] these studies published in the CDSR by the Cochrane Collaboration stand out through their methodological rigor. This was highlighted in two studies[54,55] that compared the methodological rigor of Cochrane systematic reviews with non-Cochrane systematic reviews. On January 24, 2011, in recognition of the contribution to healthcare that the Cochrane Collaboration has made,[56] the World Health Organization lauded the Collaboration as a non-governmental organization, with a seat in the World Health Assembly and voting rights, in order to help manage healthcare worldwide.

As examples of Cochrane systematic reviews,[54,55] all the OoRs included in this review[35-46] had high methodological quality and therefore less risk of bias, according to the results obtained through AMSTAR.[8] However, the reasons why not all the OoRs included obtained the maximum score need to be discussed:

1. The protocols for two OoRs[36,38] were not found in the Cochrane Library or in Archie, even though one of them cited the protocol.[38] Registration of the protocols for OoR, just as for clinical trials and systematic reviews, allows assessment of methodological quality, provides transparency in conducting the study and minimizes occurrences of publication bias or selective reporting of outcomes.
2. Eight OoRs[26,35-37,39,43,44,46] restricted the search to only one database, i.e. the CDSR. Moreover, we did not consider this to be a potential source of bias, taking the view that the search methods for systematic reviews in the CDSR are rigorous and comprehensive (including no restrictions on date, publication status or language), and therefore that there was a high probability of including all the relevant primary studies.
3. Four OoRs[40,42,43,46] could not match any of the systematic reviews included in their quantitative data synthesis, through either direct or indirect meta-analysis, and therefore summarized and integrated the evidence qualitatively.
4. One OoR[36] did not evaluate or discuss the risk of publication bias among the systematic reviews included.

Although AMSTAR[8] was developed to assess the methodological quality of systematic reviews, it needs to be borne in mind that many of the items that it assesses are also present in OoRs, even though OoRs are different studies. Thus, AMSTAR[8] can be considered to be an analogous tool for assessing OoRs, in which external validity is preserved. Development of an instrument for judging the methodological rigor and consistency of OoRs will be important for reducing the uncertainties in decision-making from these studies.

One challenge identified in the present study was the lack of standardization in the method for assessing the quality of evidence. OoRs[26,35-46] have used various methods of assessment (e.g. GRADE,[57] Cochrane risk of bias tool,[58,59] Jadad et al.,[60] or even review-specific criteria) or, when using the same method, have described it in different ways, thereby making the judgment uncertain. In this context, two OoRs[40,42] can be highlighted. Despite the high methodological quality of the study by Ryan et al.,[40] it only described how the systematic reviews included had assessed the quality of evidence, thus making it difficult to assess this outcome. Many studies (890/2141) may not have made judgments regarding the quality of evidence. In the second of these OoRs, Jones et al.[42] used the Cochrane risk of bias tool[58,61] to assess the quality of the evidence in Cochrane reviews, while for non-Cochrane reviews they used Jadad et al.[60] Despite the differences in the concepts of quality of evidence and methodological quality (which were not among the objectives of this discussion), these authors reported the proportion of studies that presented high quality. Thus, the description was not sufficiently clear or standardized for a judgment to be made regarding the overall quality of evidence.

To assess the quality of evidence, the most consistently used method among the OoRs assessed[26,35-46] was the GRADE approach.[57] Basically, this tool classifies evidence into four levels: (1) high quality — it is unlikely that future research will change the estimated effect; (2) moderate quality — future research may have a major impact on the estimated effect and change the result; (3) low quality — further research is very likely to have

an important impact on the estimated effect and change the results; and (4) very low quality — there is no certainty in the estimated effect. In the GRADE approach to the classification of evidence, the assessment can be lowered or raised according to certain methodological factors. Methodological limitations, inconsistent results, imputations of evidence, imprecision of results and publication bias diminish the quality of evidence. The magnitude of the effect, controlling for confounders and dose-response gradients are methodological factors that may raise the level of evidence.

Even though there has been criticism regarding the lack of methodological rigor in this type of study,[62,63] all the Cochrane OoRs[35-46] assessed methodological quality, thus allowing judgment of the effects of interventions based on the main outcomes found. About two-thirds of the OoRs[26,35-46] presented evidence to judge how beneficial or harmful the main outcomes were. These results are based on various systematic reviews and thus integrate and summarize evidence from several interventions relating to a given condition, from a high number of clinical trials and patients. The evidence in these OoRs[26,35-46] was released over a period of about two years from the time of registration of the title to the date of publication. In the future, it will be important to also determine the time taken to update the OoRs.

Furthermore, comparing the results from this descriptive systematic review of published studies with other OoRs[62,63] that assessed this new type of study, the Cochrane OoRs seem to have higher quality and methodological rigor than non-Cochrane OoRs. To reduce the inconsistency of OoRs, it is important that authors follow the existing methodological recommendations.[3,5,61]

When extracting data, attention was drawn to two factors: (1) three studies[37,39,43] did not declare the type of study, i.e. "overview of reviews" (there was a similar proportion with regard to protocols for OoRs: 6/28), which may be a limiting factor in that it becomes more difficult for readers to easily identify the type of study; (2) Singh et al.[41] only included primary studies from the list of references of systematic reviews and conducted search strategies in bibliographic databases.

Another feature that may pose a challenge in conducting this type of study is the complex statistical methods required for integrate and summarizing the evidence. The methodological basis for network meta-analysis, also known as multiple-treatment meta-analysis and mixed-treatment comparisons, was established in 1996.[52] In view of the challenge of implementing these statistical techniques, a special issue of Research Synthesis Methods was published on this topic in 2012 (see volume 3, number 2). For researchers who wish to conduct an OoR, it is highly recommended that the information provided by the Cochrane Comparing Multiple Interventions Methods Group, the Multiple-Treatment Meta-analysis website <http://www.mtm.uoi.gr/> and the special issue of Research Synthesis Methods should be consulted.

This new type of study certainly attracts everyone's attention, as demonstrated from data in Evidence-Based Child Health.[5] In 2009, OoRs were downloaded 3.05 times more than other types of study. There has also been a tendency towards growth of this frequency over the years (2006 versus 2009), by a rate of 1.84 times. The importance of this type of study can be understood through the great interest of its audience.

Despite the limitation of the small number of OoRs included and the absence of some information that could not be obtained, it could be seen that this type of study presents the following potential benefits: (1) it allows consumers to know about and understand the concepts and application of such studies and their ability to integrate and summarize various interventions for a disease or health condition; (2) for healthcare policymakers, summarizing all interventions into a single document allows them to keep up to date in the era of information globalization[1,2] and, thus, this type of study serves as a friendly front end for healthcare decision-making based on the best available evidence, thereby changing professional practice and healthcare policies; and (3) it allows researchers to address the gaps, weaknesses and strengths of each study and think about future research strategies based on what still needs to be explored.

In Part III, a new hierarchy for the pyramid of evidence will be proposed, taking this new type of study into consideration.

CONCLUSION

OoRs have high methodological quality and high quality of evidence, as assessed in general. Moreover, about two-thirds of the conclusions had sufficient evidence to judge that the implications for practice were either beneficial or harmful. In order to do this, the mean length of work required was 24 months.

The profile of OoRs reduces uncertainty in decision-making. This new type of study demonstrates the ability to compile multiple evidence from systematic reviews in one handy and useful document that is able to address all potential interventions for a condition, thereby allowing decision-makers to locate, evaluate, compare and summarize the evidence from systematic reviews or primary studies.

Although OoRs are able to integrate and summarize multiple interventions for a problem in a single document, there is still a need to standardize the methods for this new type of study.

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Appendix 1. Characteristics of Cochrane Overviews of Systematic Reviews (OoRs) that were included.

Singh et al.[35]	
Review question/objective:	What are the efficacy and safety of biologics for rheumatoid arthritis?
Search methods:	Search date up to May 30, 2009. Databases: Cochrane Database of Systematic Reviews.
Studies included:	Six Cochrane systematic reviews.
Participants:	Adults 18 years or older, with rheumatoid arthritis meeting the 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis.
Interventions:	Biological disease-modifying anti-rheumatic drugs (DMARDs) (including abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab and other biological DMARDs) used alone in standard approved doses or in combination with other biological/traditional DMARDs, compared with placebo alone or with placebo plus biological/traditional DMARD.
Main outcomes:	ACR50, defined as 50% improvement in both tender and swollen joint counts and 50% improvement in three of the following five variables: patient overall assessment, physician overall assessments, pain scores, Health Assessment Questionnaire (HAQ) score and acute-phase reactants: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). ACR50 was chosen because clinical and statistical evidence shows that this is the preferred endpoint for contemporary rheumatoid arthritis clinical trials; withdrawal due to adverse events was used as a proxy measurement of safety.
Quality of the OoR:	High quality (10 points in AMSTAR).
Quality of the evidence:	The results were graded as 'moderate' using the GRADE approach.
Authors' conclusion:	In the absence of direct comparisons of biological DMARDs in patients with rheumatoid arthritis, practitioners are faced with a dilemma when choosing biological DMARDs. Anakinra was less efficacious than the other five biologics and etanercept led to lower withdrawal rates due to adverse events, compared with adalimumab, anakinra and infliximab. Future randomized controlled trials should use direct head-to-head comparisons of biological agents in patients with rheumatoid arthritis.
Keus et al.[36]	
Review question/objective:	What is the efficacy of different techniques for cholecystectomy for patients with symptomatic cholecystolithiasis?
Search methods:	Up to Issue 4, 2009 (CSDR and DARE).
Studies included:	Three systematic reviews.
Participants:	Patients suffering from symptomatic cholecystolithiasis.
Interventions:	Only surgical treatments. Three different techniques for cholecystectomy were recognized: open, small-incision and laparoscopic cholecystectomy.
Main outcomes:	Mortality; complications (including subcategories); symptom relief.
Quality of the OoR:	High quality (8 points in AMSTAR).
Quality of the evidence:	The overall quality of the randomized trials included varied given that most of the trials had several methodological deficiencies.
Authors' conclusion:	No statistically significant differences in the outcome measurements of mortality and complications were found between open, small-incision and laparoscopic cholecystectomy. There were no data on symptom relief. Complications from elective cholecystectomy are high. The quicker recovery of both laparoscopic and small-incision cholecystectomy patients, compared with patients undergoing open cholecystectomy, justifies using these two approaches. Research should concentrate on outcomes that are relevant to patients instead of focusing on outcomes that are of interest mainly to surgeons.
Amato et al.[37]	
Review question/objective:	What are the efficacy and safety of pharmacological interventions for treating Alcohol Withdrawal Syndrome?
Search methods:	December 30, 2010.
Studies included:	Five systematic reviews.
Participants:	Alcohol-dependent patients diagnosed in accordance with appropriate standardized criteria.
Interventions:	Pharmacological interventions alone or in combination with other drugs or placebo; and other pharmacological interventions.
Main outcomes:	Alcohol withdrawal seizures; alcohol withdrawal delirium; alcohol withdrawal symptoms as measured using pre-specified scales (such as the CIWA-Ar score); craving as measured using validated scales; adverse events; and severe, life-threatening adverse events.
Quality of the OoR:	High quality (10 points in AMSTAR).
Quality of the evidence:	The majority of study results were graded as very low or low quality using the GRADE approach.
Authors' conclusion:	Between the four treatments considered, benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures. Further studies should test alternative drugs, and should investigate which benzodiazepine performed best for treating alcohol withdrawal syndrome and the relative dose-response effect.

Continues

Appendix 1. Continuation

Flodgren et al.[38]	
Review question/objective:	What is the impact of financial incentives on professional behavior and patient outcomes?
Search methods:	January 2010.
Studies included:	Four systematic reviews.
Participants:	Physicians, dentists, nurses and allied healthcare professions (such as physiotherapists, speech therapists, etc.) involved in providing direct patient care. Healthcare providers could be targeted individually or at the level of the organization within which they worked.
Interventions:	Payment for working for a specified time period (e.g. a salary or sessional payment); payment for each service, episode or visit (fee-for-service); payment for providing care for a patient or specific population (e.g. capitation); payment for providing a pre-specified level or change in activity or quality of care (e.g. target payments or bonuses); and mixed and other systems (comprising more than one of the above groups, or not classifiable).
Main outcomes:	Measurements of healthcare professionals' clinical behavior such as the rates of performing preventive actions, diagnosis and treatment (e.g. immunization, blood pressure measurement, prescription and referral); measurements of health service use by patients, such as participation rates in immunization schemes or mammography screening programs; healthcare costs, either combined with measurements of healthcare professional behavior, quality of care or health outcomes to produce measurements of efficiency, or uncombined; including costs of (i) introducing the incentives; (ii) the transaction; (iii) the information systems required to implement the financial incentive; and (iv) monitoring.
Quality of the OoR:	High quality (10 points in AMSTAR).
Quality of the evidence:	The results were graded as low to moderate using interpretations of the studies included in the systematic reviews.
Authors' conclusion:	Financial incentives may be effective in changing healthcare professional practice. The evidence has serious methodological limitations and is also very limited in its completeness and generalizability. There is no evidence regarding the effect of financial incentives on patient outcomes. Future studies should use robust designs and include bias, data and economic evaluations.
Moore et al.[39]	
Review question/objective:	What is the efficacy of pharmaceutical interventions for acute pain in adults after surgery?
Search methods:	Not stated.
Studies included:	35 systematic reviews.
Participants:	Adult participants with pain of at least moderate intensity that became established after surgery.
Interventions:	Mild analgesics, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and celecoxib; weaker opioids such as codeine; and strong opioids such as oxycodone and fentanyl.
Main outcomes:	Total pain relief (TOTPAR); remedication time; and adverse events.
Quality of the OoR:	High quality (10 points in AMSTAR).
Quality of the evidence:	The quality of the evidence was good.
Authors' conclusion:	The major implication for practice is the knowledge that there is a body of reliable evidence about the efficacy of 46 drug/dose combinations for treating acute pain. There will be few circumstances in which such a body of information exists in such a clinically homogenous dataset, and it might appear to be an ideal opportunity to test new methods for meta-analysis, like network meta-analysis.
Ryan et al.[40]	
Review question/objective:	What are the effects of consumer-oriented interventions for evidence-based prescribing and medicine use?
Search methods:	Up to issue 3, 2008 (CSDR and DARE).
Studies included:	37 systematic reviews.
Participants:	Consumers, defined as any person using medicine(s), who might be patients, careers, or both, and targeted as individuals or as a group. Healthcare professionals who prescribed or monitored medicines were also included.
Interventions:	Providing information or education; facilitating communication and/or decision-making; acquiring skills and competencies; supporting behavioral change; support; minimizing risk or harm; improving quality; and consumer system participation.
Main outcomes:	Consumer-oriented outcomes, such as knowledge and understanding, skills acquisition and health status and wellbeing; provider-oriented outcomes, including knowledge and understanding and evaluation of care; health service-oriented outcomes, including service use outcomes and costs.
Quality of the OoR:	High quality (10 points in AMSTAR).
Quality of the evidence:	Overall, the studies included were of variable methodological quality and this may in some cases have predisposed the results to bias. Where reviews had obvious methodological shortcomings, attempts were made to adjust for this by downgrading the effectiveness statements.
Authors' conclusion:	What is clear from this accumulated evidence is that there is no single approach that appears effective across all clinical situations or for all outcomes. Similarly, not all complex interventions are more effective than simple strategies for improving the use of medicines. Further research is needed on a range of additional interventions, in order to improve safe and effective medicine use by and for consumers.

Continues

Appendix 1. Continuation

Singh et al.[41]	
Review question/objective:	What are the adverse effects of biologics?
Search methods:	January 2010.
Studies included:	46 open-label extension studies; 160 randomized controlled trials.
Participants:	Adults (aged 16 years or older) with any disease (except HIV/AIDS).
Interventions:	Abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab alone or in combination with other therapies for any medical condition (other than HIV/AIDS), compared with any other therapy or placebo.
Main outcomes:	Number of serious adverse events; withdrawals due to adverse events; number of adverse events; number of serious infections; tuberculosis; leukemia or lymphoma; and congestive heart failure.
Quality of the OoR:	High quality (11 points in AMSTAR).
Quality of the evidence:	The results were graded as 'moderate' using the GRADE approach.
Authors' conclusion:	The findings should be interpreted with caution, given the study limitations. In short-term randomized controlled trials (median duration six months), the overall use of biologics was associated with a statistically significantly higher risk of total adverse events, withdrawals due to adverse events, serious infections and tuberculosis reactivation, compared with the control. There is an urgent need for more research regarding the long-term safety of biologics and comparative safety of different biologics.
Jones et al.[42]	
Review question/objective:	What are the efficacy and safety of non-pharmacological and pharmacological interventions to manage labor pain?
Search methods:	Up to issue 5; 2011 (CSDR and DARE).
Studies included:	18 systematic reviews.
Participants:	Women in pain during labor.
Interventions:	Hypnosis; biofeedback; intracutaneous or subcutaneous sterile water injection; immersion in water; aromatherapy; relaxation techniques (yoga, music or audio); acupuncture or acupressure; massage, reflexology and other manual methods; transcutaneous electrical nerve stimulation (TENS); inhaled analgesia; opioids; non-opioid drugs; local anesthetic nerve blocks; and epidural anesthesia.
Main outcomes:	Pain intensity; satisfaction with pain relief; sense of control during labor; satisfaction with childbirth experience; effect (negative) on mother/baby interaction; breastfeeding; assisted vaginal birth; cesarean section; adverse effect; admission to special care baby unit/neonatal intensive care unit; Apgar score less than seven at five minutes; and poor infant outcomes over long-term follow-up.
Quality of the OoR:	High quality (10 points in AMSTAR).
Quality of the evidence:	Most of the fifteen Cochrane systematic reviews presented a low risk of bias. Most of the three non-Cochrane review scores had a low risk of bias.
Authors' conclusion:	Most methods for non-pharmacological pain management are noninvasive and appear to be safe for the mother and baby. However, their effectiveness is unclear because of the limited high-quality evidence. There is more evidence confirming that pharmacological methods are efficacious, but these also have better-known adverse effects. Thus, epidural analgesia provides effective pain relief but at the cost of increased medical intervention, including increased incidence of instrumental vaginal birth. Further trials are needed, particularly for non-pharmacological methods of pain management.
Payne et al.[43]	
Review question/objective:	What is the efficacy of the interventions used in managing fatigue and/or unintentional weight loss in adults with advanced progressive illness?
Search methods:	Up to issue 8; 2010 (CSDR and DARE).
Studies included:	27 systematic reviews.
Participants:	Adults aged 18 years or older with an advanced progressive illness that is known to have clinically significant fatigue and/or weight loss in the latter stages of illness.
Interventions:	Pharmacological interventions and non-pharmacological interventions.
Main outcomes:	Clinically significant improvements in fatigue and/or unintentional weight loss; improvements in quality of life among people who have fatigue and/or unintentional weight loss; and withdrawals due to adverse events.
Quality of the OoR:	High quality (9 points in AMSTAR).
Quality of the evidence:	Only one review was judged to present high quality and the authors were unable to judge the remaining reviews.
Authors' conclusion:	There is a lack of robust evidence for interventions to manage fatigue and/or unintentional weight loss in the advanced stage of progressive illnesses such as advanced cancer, heart failure, lung failure, cystic fibrosis, multiple sclerosis, motor neuron disease, Parkinson's disease, dementia and AIDS. Researchers could improve the methodological quality of future studies by blinding the outcome assessors. Adopting uniform reporting mechanisms for fatigue and weight loss outcome measurements would also enable opportunities for meta-analysis on small studies.

Continues

Appendix 1. Continuation

Cahill et al.[46]	
Review question/objective:	What are the efficacy and safety of pharmacological interventions designed to support attempts to quit smoking?
Search methods:	Up to volume 11; 2012 (CDSR).
Studies included:	12 systematic reviews.
Participants:	Adult smokers who were undergoing any pharmacological treatment for quitting smoking.
Interventions:	Interventions included nicotine replacement therapy (NRT), antidepressants (bupropion and nortriptyline), nicotine receptor partial agonists (varenicline and cytisine), anxiolytics, selective type A cannabinoid receptor antagonist (rimonabant), clonidine, lobeline, dianicline, mecamylamine, nicobrevin, opioid antagonists, nicotine vaccine and silver acetate; alone or in combination.
Main outcomes:	Withdrawal from smoking for six months or more, reduction in symptoms of relapse and reduction of the desire to smoke.
Quality of the OoR:	High quality (11 points in AMSTAR)
Quality of the evidence:	High quality; 81% of the reviews included were classified as having low risk of bias and all were of high quality in AMSTAR.
Authors' conclusion:	The efficacy of treatments with bupropion and varenicline has been well established by high-quality evidence. There is little evidence on cytisine and nortriptyline, but the present results indicate that they also improve the chances of quitting smoking. The profiles of adverse events are less defined and depend more on monitoring and surveillance systems than on data from clinical studies.
O'Connell et al.[26]	
Review question/objective:	What is the efficacy of any intervention used to reduce pain and dysfunction in adults with complex regional pain syndrome?
Search methods:	Up to October 2011 in the DARE, MEDLINE, EMBASE, CINAHL, LILACS and PEDro databases.
Studies included:	19 systematic reviews.
Participants:	Adults with complex regional pain syndrome.
Interventions:	Any intervention to reduce pain, dysfunction, or both, in patients with complex regional pain syndrome.
Main outcomes:	Pain intensity or severity; dysfunction with serious adverse events.
Quality of the OoR:	High quality (11 points in AMSTAR).
Quality of the evidence:	Low or very low for most studies, using GRADE.
Authors' conclusion:	There is low or very low quality evidence regarding the efficacy of various therapies for chronic regional pain syndrome. Both the positive and the negative evidence needs to be interpreted with caution. This evidence does not help in clinical decision-making.
Cates et al.[45]	
Review question/objective:	How safe is regular formoterol or salmeterol as monotherapy or as combination therapy for children with asthma?
Search methods:	Up to volume 5; 2012 (CDSR).
Studies included:	Six systematic reviews.
Participants:	Children with asthma.
Interventions:	1. Regular formoterol monotherapy versus placebo 2. Regular salmeterol monotherapy versus placebo 3. Regular formoterol in combination with inhaled corticosteroids (ICS) compared with same dose of ICS 4. Salmeterol in combination with regular ICS, compared with same dose of ICS 5. Regular formoterol versus regular salmeterol 6. Regular formoterol in combination with ICS versus salmeterol in combination with ICS.
Main outcomes:	Mortality from all causes or non-fatal serious adverse events. Asthma related to non-fatal adverse events and death or asthma unrelated to non-fatal adverse events.
Quality of the OoR:	High quality (11 points in AMSTAR)
Quality of the evidence:	High quality using AMSTAR and low risk of bias using the risk of bias tool.
Authors' conclusion:	Monotherapy with formoterol or salmeterol is no longer advocated in guidelines. If separate inhalers for long-action beta agonist (LABA) and ICS are used, children who are at risk should stop taking ICS and continue taking LABA. Regular combination therapy is likely to be safer than monotherapy in children with asthma, but it cannot be said that the combination is risk-free. It is likely that three out of every 1000 children will suffer a serious nonfatal adverse event over a three-month period, using the combination therapy, in comparison with ICS. This is currently the best estimate for the risk of using combination LABA among children, and it has to be balanced with the symptomatic benefit obtained for each child.
Farquhar et al.[44]	
Review question/objective:	What procedures and treatment options are available to infertile couples undergoing assisted reproductive technology?
Search methods:	Up to 2012 (CDSR).
Studies included:	54 systematic reviews.
Participants:	Women with endometriosis, women with previous low response or recurrent pregnancy loss and couples undergoing cycles of frozen embryo replacement, donation cycles, or both.
Interventions:	Comments from in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).
Main outcomes:	Birth, clinical pregnancy, multiple pregnancy, ovarian hyperstimulation syndrome and abortion.
Quality of the OoR:	High quality (11 points in AMSTAR).
Quality of the evidence:	47 reviews presented high quality in AMSTAR.
Authors' conclusion:	This overview can be used in writing guidelines for fertilization with the goal of improving clinical practice.

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; AMSTAR = A Measurement Tool to Assess Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects.