pharmacypractice
FEATURE

JOURNAL SERIES:

Statistics Review Part 12: Systematic Reviews and Meta-analyses

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Objectives

1. Define narrative reviews, systematic reviews, and meta-analyses and assess appropriateness of use.
2. Describe the limitations of systematic reviews and meta-analyses.
3. Determine how to evaluate heterogeneity in meta-analyses.

Review articles are a mainstay to guide clinical practice and provide substantial information to answer clinical questions. They are often utilized to review medical literature and evaluate drug therapies. Systematic reviews are crucial as clinical decisions should be based on all available evidence rather than just one particular study. Due to the important role of systematic reviews, it is essential that clinicians understand how to critically analyze systematic reviews and to assess the limitations associated with this type of article.

Types of Review Articles

Narrative reviews are general reviews of a disease state or class of medications. However, they typically do not have predefined protocols and may include opinions, which may increase the risk of bias, in addition to evidence (e.g., clinical trials).[1] In contrast, systematic reviews begin with a specific clinical question, have a predefined protocol, and summarize literature by including all relevant trials to answer the clinical question. When determining the specific clinical question for a systematic review, the clinical question must be clearly stated and framed with selection criteria for the included studies, which is typically reported in the methods section. A meta-analysis is a systematic review that further utilizes statistical analyses and quantitative methods to mathematically summarize the information.[2,3]

Methods of a Systematic Review

As combining multiple studies has the potential to produce misleading results, it is important to follow a standardized protocol to ensure the most reliable inclusion and assessment of relevant research. The therapeutic question of a systematic review should include the following elements: a specific population, intervention, comparison, outcome, and study design (PICOS).[4,5] It is important to have clearly defined eligibility criteria for studies to be included in the review, as this enables readers to better understand the intervention, population, and potential biases in the final results. More than one database should be used to search for studies in an attempt to find all relevant research, and the inclusion of relevant unpublished work, also known as "gray literature", should also be pursued. Additionally, more than one investigator should conduct the literature search to increase the reproducibility of the

systematic review and to minimize the risk of subjective bias in study inclusion.

Reviewers should agree on how to assess trial quality *a priori*. The Cochrane Collaboration has provided guidance on how to report potential biases which allows the reader to assess the type of bias associated with each study.[6] This is important so the reader can assess the validity of the review's results. Specific information and results are abstracted from individual studies; again, more than one investigator should ideally conduct abstraction in order to minimize bias.[4]

Methods of a Meta-analysis

A meta-analysis adds to a systematic review by calculating a pooled estimate of the effect size between the intervention and comparison arms across all included studies. One benefit to meta-analyses is greater power from the larger sample size obtained when combining multiple trials.[3] The results of a meta-analysis are often graphically depicted in a forest plot as seen in Figure 1. The squares represent point estimates (i.e., the difference between two study groups) from each included study, with the horizontal lines depicting the 95% confidence intervals. The point estimate can be the difference between the means of two arms for a continuous outcome variable or the relative risk, odds ratio, or hazard ratio for a binomial outcome variable. The diamond at the bottom of the plot represents the pooled estimate of the results. The vertical points of the pooled estimate diamond represent the point estimate of the pooled results. The horizontal points of the diamond represent the 95% confidence interval of the pooled estimate.[4]

The pooled estimate of a meta-analysis provides a weighted average of all the analyzed studies, where studies with more precise estimates (i.e., narrower confidence intervals) or larger sample sizes will typically have greater influence on the pooled estimate of the results.[1] More precise studies also tend to have the largest sample sizes. Some studies will report the percent weight each study contributed to the pooled estimate, but often the size of the square indicates the weight of the study, with larger boxes indicating a greater weight in the pooled estimate.[4]

FIGURE 1. Example of a Forest Plot

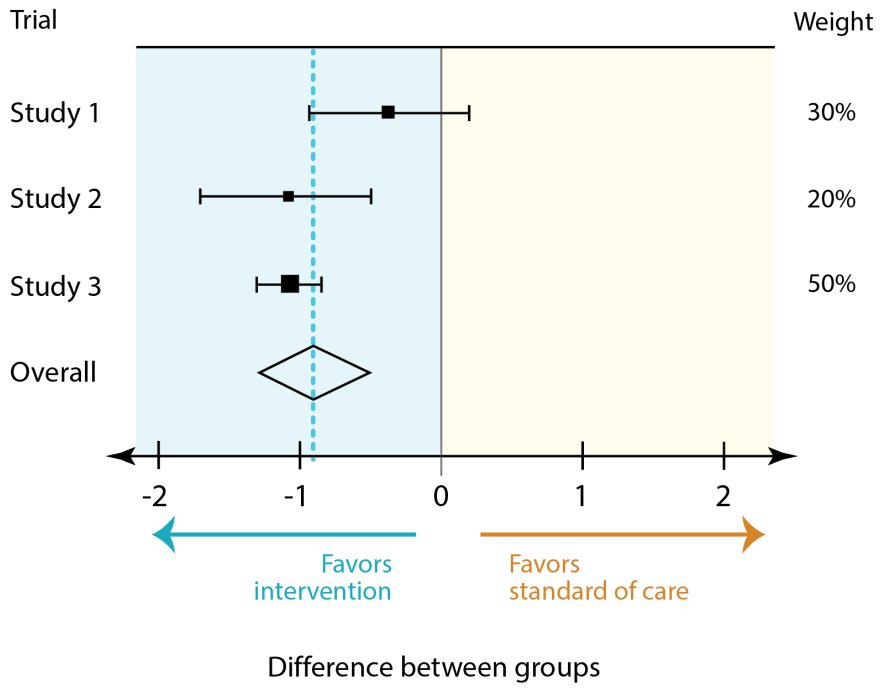
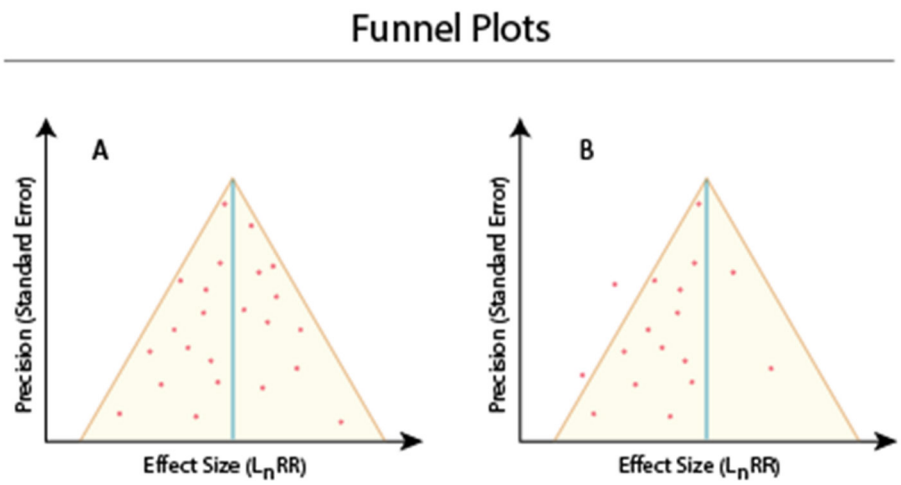


FIGURE 2. Example of Funnel Plots



Limitations

Review articles answer clinical questions by evaluating all available literature, which has the potential to provide the highest strength of clinical evidence.[1] Although reviews have the potential to provide great insight into a variety of clinical questions, they also have limitations. The main limitation of review articles is that the estimates are only as accurate and reliable as the studies reviewed. In order for a review article to be accurate and beneficial, there must be high quality research available.[7]

Additional limitations of review articles are selection bias and reporting bias. Selection bias in the setting of a review refers to researchers preferentially picking literature, whether it is due to only selecting published studies or those with positive results (those studies with statistically significant results). In order for researchers to minimize the risk of selection bias in reviews, it is crucial that reviews utilize a complete and representative sample of all eligible studies. Furthermore, the reason the protocol must be established *a priori* is to ensure that studies are not included based on preconceived notions of the outcome.

Reviews with limited selection bias are conducted utilizing many different search databases. Additionally, in order for reviews to minimize the risk of selection bias and subjectivity of the study, it is recommended that more than one reviewer participates in the selection and review process.[2]

Reporting bias (or publication bias) can also impact the results of a review article. That is, studies with statistically significant findings are more likely to be published than studies without a statistically significant outcome.[4] This may bias the conclusions made when summarizing literature in a review article if only those published studies with statistically significant findings are included. A tool to assess the potential for reporting bias is a funnel plot. A funnel plot is a comparison of the effect size compared to the precision (standard error) of the studies included in the review.[4] Smaller studies typically have larger standard errors and are at the base of the funnel. In a meta-analysis with little reporting bias, the larger studies will be plotted near the center of the funnel with symmetry noted around the combined effect, creating a funnel shape. In a meta-analysis with significant reporting bias, there will be deviation from the funnel plot shape. In addition to the concern of reporting bias, asymmetry in the funnel plot may also be associated with poor study design or low quality of the trials.[8] Figure 2 represents two different funnel plots, with funnel plot A representing little risk for bias as seen with a symmetrical distribution of studies throughout the plot, and funnel plot B representing significant risk for bias in the meta-analysis given the asymmetry in the funnel plot. A statistically significant Egger's test is also an indicator for asymmetry in a funnel plot, but is often underpowered.[9] When evaluating a funnel plot where asymmetry is present, it can be difficult to tell if it is due to publication bias or to poor quality of the studies included in the review. Either way, an unsymmetrical funnel plot is an indicator of bias in the review.[4]

Heterogeneity in Meta-Analyses

Another limitation of meta-analyses is significant heterogeneity (or variation) between studies. It is crucial that readers assess the similarities and differences between each study included in the meta-analysis in order to determine if there is true heterogeneity or if differences are due to chance. If significant heterogeneity is noted, combination of the studies into a meta-analysis may be inappropriate.[9] Readers of a meta-analysis should consider both clinical and statistical evaluations of heterogeneity. Evaluations of heterogeneity include thorough reviews of the evidence table and forest plot. When reviewing the evidence table, consider if the study design, interventions, and populations are similar enough that it seems reasonable to combine study results.[4] When reviewing the forest plot, consider how similar the results are across studies. Clinicians can have a higher level of trust in meta-analyses that combine multiple studies with similar designs and results.

Two common tests to assess statistical heterogeneity in meta-analyses are the Cochran Q test and the I^2 statistic. The Cochran Q test has a null hypothesis of: there is no difference in the effect of each of the trials (i.e., no major heterogeneity).[4] A statistically significant p-value indicates that random error is an unlikely explanation for differences in effect results (i.e., statistically significant heterogeneity).[9] However, the Cochran Q test is limited in that it is often underpowered and cannot be compared across meta-analyses. Due to these limitations, the Cochran Q test is losing favor as a test for heterogeneity to the I^2 statistic.[9]

The I^2 statistic indicates the proportion of variation among studies that can be considered due to heterogeneity and not due to random chance. An I^2 of 0% suggests that chance alone explains any variability, an I^2 of 25% suggests low heterogeneity, an I^2 of 50% suggest moderate heterogeneity, and an I^2 of 75% suggests high heterogeneity.[9] While these cutoffs are suggestions, different methodologists have suggested variable cutoffs for situations where a meta-analysis is not appropriate due to high heterogeneity. During the assessment of heterogeneity, it is important to note that a lack of heterogeneity does not mean homogeneity, so it is crucial to critically analyze all published assessments of heterogeneity within the systematic review.[4,9]

Importance of Critical Assessment

Since review articles serve as a great source to answer clinical questions by assessing all available trials but have potential limitations, it is crucial for pharmacists to know how to critically evaluate the literature. Firstly, it is crucial that the reviewer analyzes the credibility of the methods utilized in the systematic review. The validity of the results must be assessed using the sensibility of the clinical question, the search parameters, and by evaluating the quality of the individual studies. Secondly, a reader must critically interpret the results. The size and precision of the treatment effect should be assessed and the results of the meta-analysis should be compared to the results of the individual studies. Finally, after the validity and magnitude of the study have been determined, the reader must assess if the study is applicable to his or her patient population.[4] A tool for clinicians to critically analyze the appropriateness of a systematic review is the PRISMA checklist. This checklist consists of 27 items deemed necessary for appropriate reporting of a systematic review and includes components such as title, abstract, introduction, methods, results, discussion, and source of funding.[5]

Summary

This article reviewed key concepts necessary for the critical review of systematic reviews and meta-analyses. Systematic reviews answer clinical questions by summarizing all available research. Meta-analyses are a subset of systematic reviews that utilize statistical analyses to form a pooled estimate of the effect sizes across all included studies. Systematic reviews and meta-analyses are powerful tools that can help answer important clinical questions, but should be critically assessed for appropriate methods and reporting.

Practice Questions

1. What does the diamond on a forest plot graphically represent?
   a. Confidence interval of an individual study
   b. Indicator of heterogeneity of the included studies
   c. Pooled estimate of all included

studies
d. Point estimate of an individual study

2. Which of the following I^2 statistics best represents the variability in the pooled point estimate from a meta-analysis being due to chance?
   a. 0%
   b. 25%
   c. 66%
   d. 90%

3. What all needs to be included when considering a clinical question for a systematic review?
   a. The population, intervention, comparison, and outcome
   b. The population, intervention, comparison, outcome, and study design
   c. The intervention, comparison, outcome, and study design
   d. The population, intervention, comparison, and study design

Answers:

1. **c** The diamond at the bottom of the plot represents the pooled estimate of the results, which is a weighted average of all the analyzed studies.

2. **a** The I^2 statistic suggests the proportion of variation among studies that can be considered due to heterogeneity versus due to random chance. An I^2 of 0% suggests that variability may be due to chance alone.

3. **b** The therapeutic question of a systematic review should include the following elements: a specific population, intervention, comparison, outcome, and study design (PICOS).

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References and suggestions for further review

1. Pai M, McCulloch M, Gorman JD, et al. Systematic reviews and meta-analyses: an illustrated, step-by-step guide. Natl Med J India. 2004;17(2):86-95.
2. DiCenzo R. Interpreting results from clinical trials. In: DiCenzo E. Clinical Pharmacist's Guide to Biostatistics and Literature Evaluation. Lenexa, KS: American College of Clinical Pharmacy, 2011:69-72.
3. Feldstein DA. Clinician's guide to systematic reviews and meta-analyses. Wisc Med J. 2005;104(3):25-29.
4. Murad MH, Montori VM, Ionnidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literatures. JAMA. 2014;312(2):171-179.
5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W65-94.
6. The Cochrane Collaboration. Available at: http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm. Accessed May 1, 2015.
7. Sedgwick P. Meta-analysis: testing for reporting bias. Brit Med J. 2015;350:g7857.
8. Sedgwick P. Meta-analysis: how to read a funnel plot. Brit Med J. 2013;346:f1342.
9. Ioannidis J, Patsopoulos N, Evangelos E. Uncertainty in heterogeneity estimates in meta-analyses. Brit Med J. 2007;335(7626):914-916.