



Systematic Reviews Application & Importance

Payam Kabiri, MD. PhD.
Clinical Epidemiologist

انواع مقالات در علوم پزشکی

- Original Article
- Review Article
- Case Reports
- Editorial
- Short Communication
(short papers)
- Letter to Editor
- مقاله پژوهشی اصیل
- مقاله مروری
- مقاله گزارش مورد
- سرمقاله (سخن سردبیر)
- مقاله کوتاه
- نامه به سردبیر

انواع مقالات مروری در علوم پزشکی

- ◆ **Traditional** Review Articles
(Narrative Review)

■ مقالات مروری سنتی
مرور روایتی

- ◆ **Systematic** Review
(Meta-analysis)

■ مقالات مروری نظام‌مند
مرور ساختاردار



Types of Studies

- Primary Studies
- Secondary Studies



Primary Studies

- Experiments
- Clinical trials
- Surveys

Secondary Studies

- Reviews (Overviews)
 - Narrative reviews
 - Systematic reviews & Meta-analyses
- Guidelines
- Decision analyses
- Economic analyses

The Ascent of Evidence (and the exhaustion of Man)

Wissett



fig.1



fig.2



fig.3



fig.4



Medical Publishing

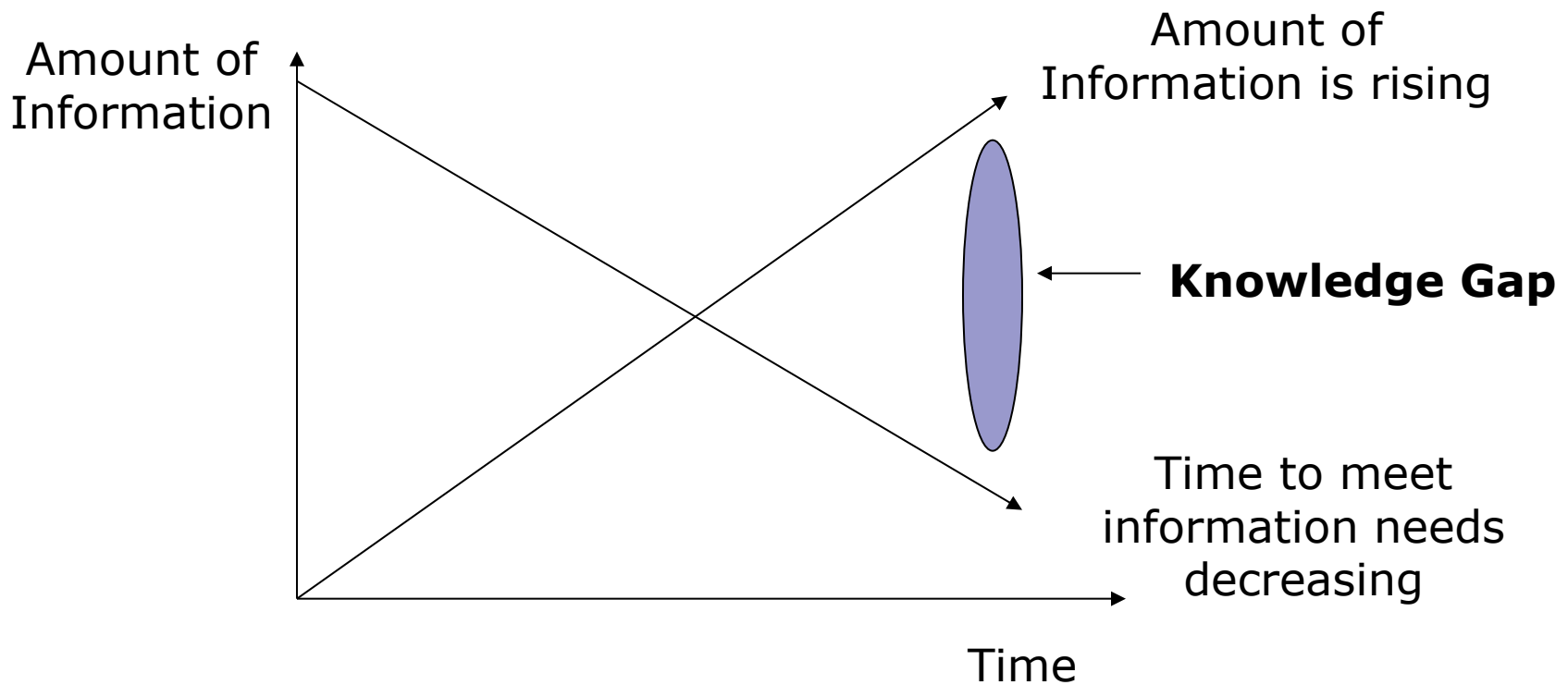
Annually:

- 20,000 journals
- 17,000 new books

MEDLINE:

- +5,000 journals
- +29 Million references
- 10,000,000 new entries yearly

The Problem



The Knowledge Gap



Doubling time of
biomedical science was

about 19 years in 1991

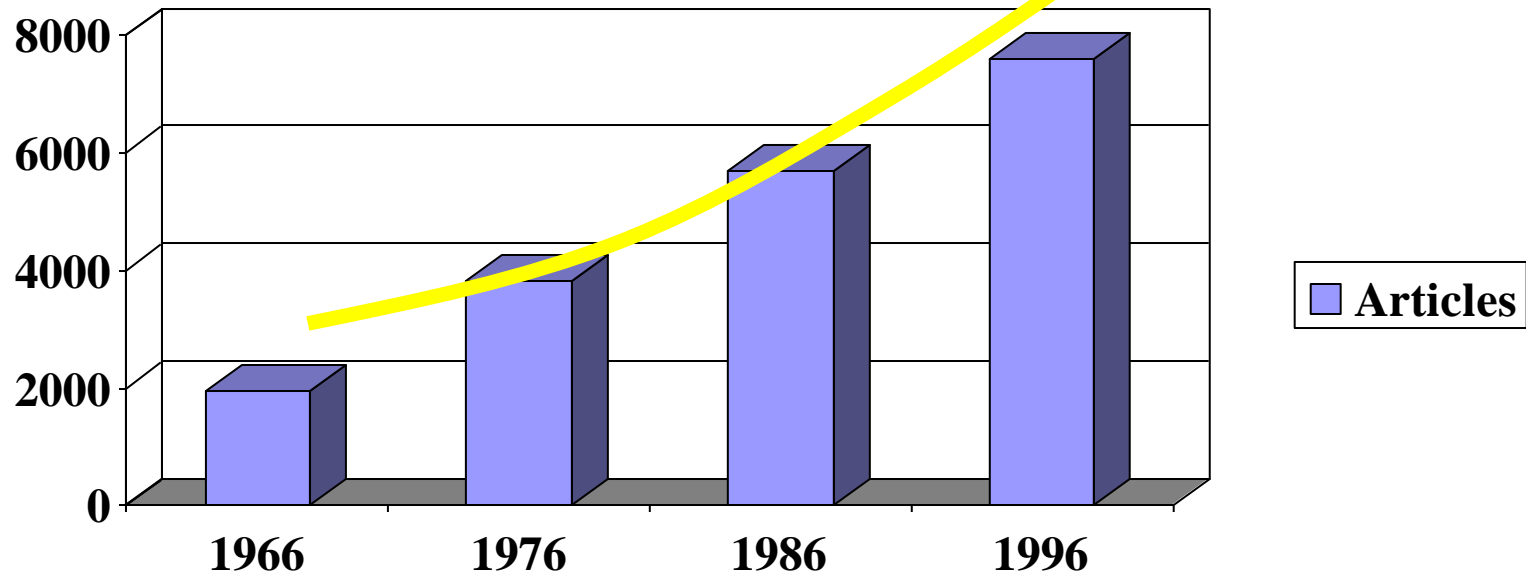


Doubling time of
biomedical science was

about 20 months in 2001

Increasing Knowledge

Number of articles on Hypertension cited in Medline by Year



For General Physicians to **keep current:**

Read 19 new articles per day which appear in medical journals

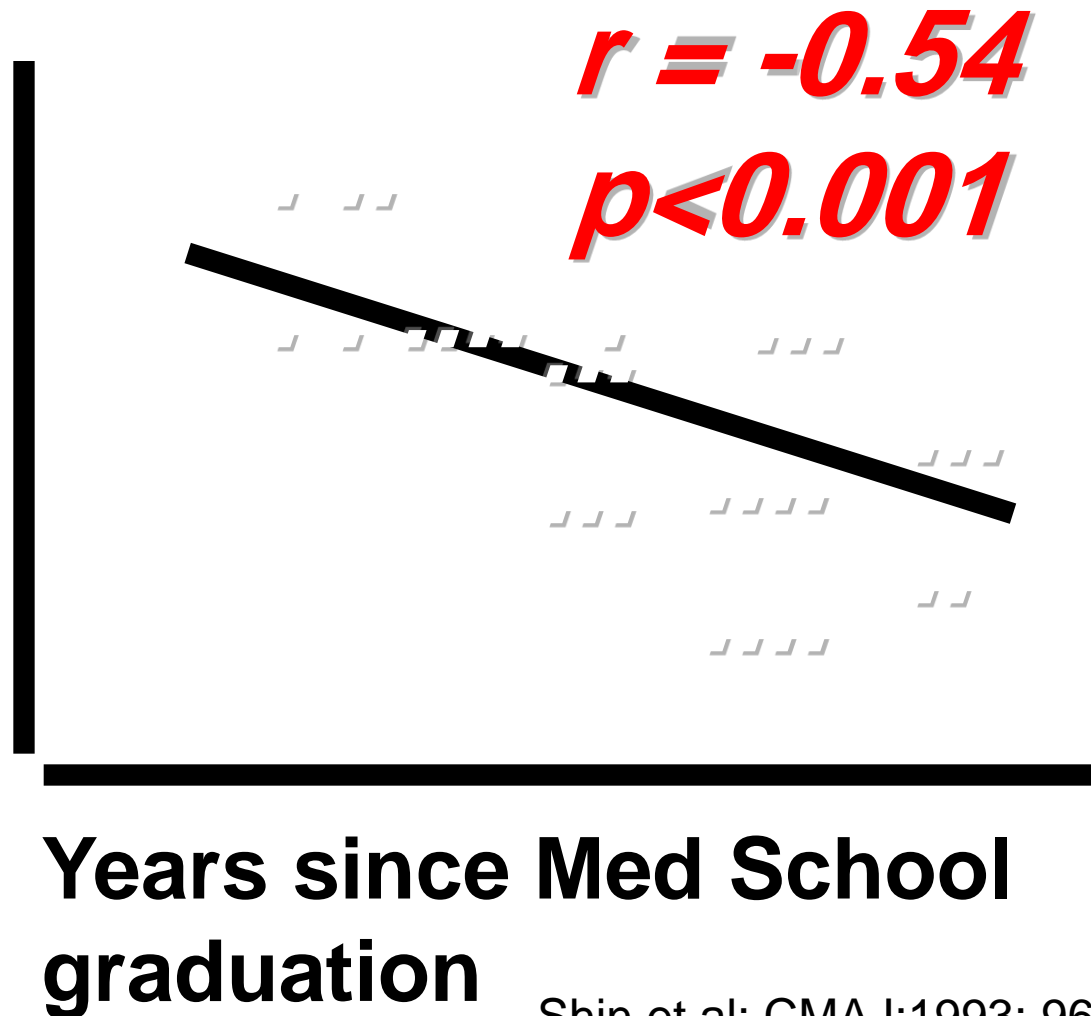
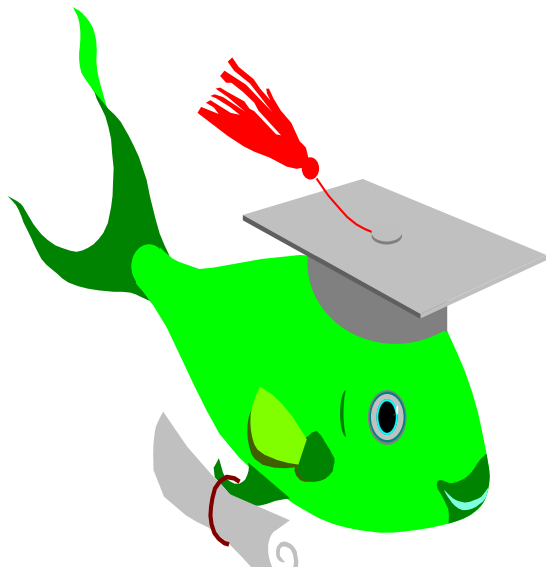
19 x 2 hrs (Critical Appraisal) = **38 hrs per day**

Davidoff F et al. (1995)

EBM; A new journal to help doctors identify the information they need. BMJ 310:1085-86.

The Slippery Slope

Knowledge
of best
current HTN
care



Shin, et al: CMAJ;1993: 969-976

What is 'level of evidence'?

- The extent to which one can be confident that an estimate of **effect** or **association** is **correct (unbiased)**.

Hierarchy of Studies



Evidence Pyramid

Systematic Review

Randomized Controlled Trial

Cohort studies

Case Control studies

Case Series/Case Reports

Animal research

Levels of Evidence


Level of Evidence	Type of Study
1a	Systematic reviews of randomized clinical trials (RCTs)
1b	Individual RCTs
2a	Systematic reviews of cohort studies
2b	Individual cohort studies and low-quality RCTs
3a	Systematic reviews of case-controlled studies
3b	Individual case-controlled studies
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion based on clinical experience

Systematic reviews

- Postdam Consultation on Meta-analysis (Cook et al, 1995) defined a systematic review as
- **"application of scientific strategies that limit bias to the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic"**

Systematic reviews

- **Systematic review** is a method of
 - locating,
 - appraising,
 - and synthesising evidence
 - while making explicit efforts to limit bias
- > a quarter of a century since Gene Glass coined the term "meta-analysis" to refer to the quantitative synthesis of the results of primary studies



A 'systematic review', therefore, aims to be:

- Systematic (e.g. in its identification of literature)
- Explicit (e.g. in its statement of objectives, materials and methods)
- Reproducible (e.g. in its methodology and conclusions)



Systematic Review

*“Scientific tool which can be used to **summaries, appraise, and communicate** the results and implications of otherwise unmanageable quantities of research” (NHS CRD, 1996).*



Systematic Review

- the process by which similar studies, identified from a comprehensive trawl of numerous sources, are summarized in easy-to-read graphical or tabular form and then their collective message or ‘bottom line’ presented, together with implications for practice and future research (Booth & Haines, 1998).

They are **not** conventional Reviews

- Follow a strict methodological and statistical protocol
 - more **comprehensive**
 - **minimising** the chance of **bias**
 - improves **transparency**, **repeatability** and **reliability**



Stages of a systematic review

- **Planning the review** – i.e. identifying the need for a review, and documenting the methodology
- **Conducting the review** – i.e. finding, selecting, appraising, extracting and synthesising primary research studies
- **Reporting and dissemination** – i.e. writing up and disseminating the results of the review

Differences Between **Traditional** and **Systematic** Reviews

(Adapted from Cook, D. J. et. al. (1997). Ann. Intern. Med. 126: 376-380)

Feature	Traditional Review	Systematic Review
Question	Often broad in scope	Focused question
Sources & search	Not usually specified, potentially biased	Comprehensive sources & explicit search strategy
Selection	Rarely specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal, uniformly applied
Synthesis	Often a qualitative summary	Quantitative summary* when appropriate
Inferences	Sometimes evidence-based	Evidence-based

*A quantitative summary that includes a statistical synthesis is a meta-analysis

Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis





Formulating review questions

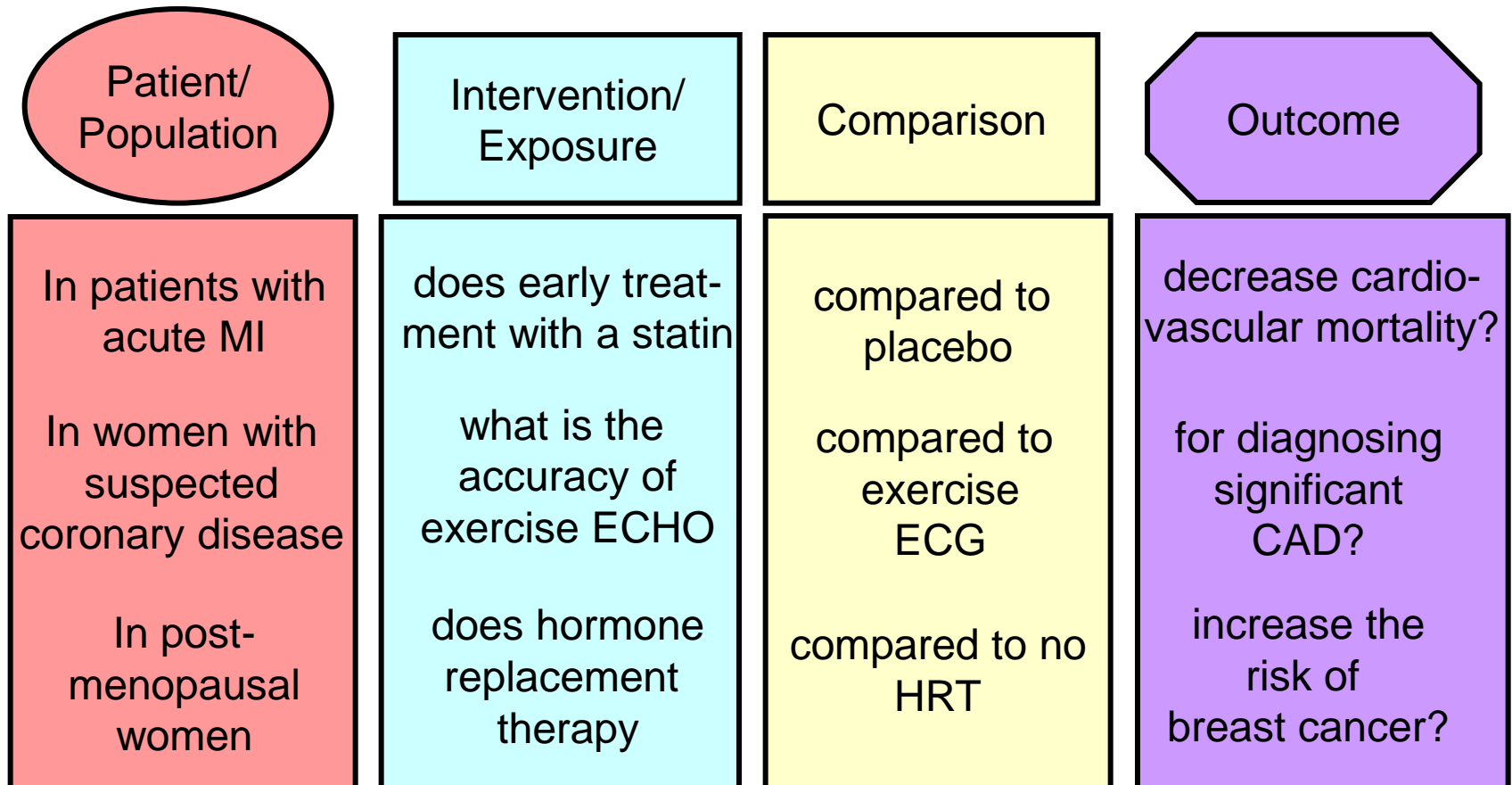
- The first and most important decision in preparing a review is to determine its focus
- This is best done by asking clearly framed questions.
- Define a four part clinical question, breaking the question down into its component parts

Question Components: **PICO**

- What types of **P**atients?
- What types of **I**nterventions?
- What types of **C**omparison?
- What types of **O**utcomes?

Ask Clinical Questions

Components of Clinical Questions





What types of participants?

- Disease or condition of interest
- Potential co-morbidity
- Setting
- Demographic factors



What types of intervention?

- Treatment
- Diagnostic test
- Causative agent
- Prognostic factor
- Exposure to disease
- Risk behavior

What types of outcomes?

- Mortality/Survival
- Risk of disease
- Disease free period
- Quality of life
- Work absenteeism
- Disability/ Duration and severity of illness
- Pain
- Accuracy of diagnose

Rationale for well-formulated questions

- Determining the structure of a review
- Determining Strategies for locating and selecting studies or data,
- Critically appraising the relevance and validity,
- Helping readers in their initial assessments of relevance.

Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis



Selecting studies

- performing **a comprehensive, objective, and reproducible** search of the literature
- selecting studies which meet the original inclusion and exclusion criteria

can be the most time-consuming and challenging task in preparing a systematic review

Data sources for a systematic review

■ **Electronic databases**

- MEDLINE and EMBASE
- The Cochrane Central Register of Controlled Trials (CENTRAL)

■ **Hand searching**

■ **“Grey literature”** (thesis, Internal reports, pharmaceutical industry files)

■ **Checking reference lists**

■ **Unpublished sources** known to experts in the specialty (seek by personal communication)

■ **Raw data** from published trials



Generating a search strategy

- Multiple electronic databases and the internet using a range of Boolean search-terms
- Foreign language searches
- Include grey literature to avoid publication bias (see subsequent slides)
- Search bibliographies and contact experts



Developing a search strategy

- It is always necessary to strike a balance between **comprehensiveness** and **precision** when developing a search strategy.

An electronic search strategy generally has three sets of terms:

- 1) terms to search for the health condition of interest;
- 2) terms to search for the intervention(s) evaluated;
- 3) terms to search for the types of study design to be included (such as randomized trials)



Literature Searching: Search terms

- Key words:

- Reflect the population, intervention and outcome

- Consider synonyms and alternative spellings

- (e.g., colonise and colonize)

- Foreign language translations

Vitamin C for preventing and treating the common cold

- The following electronic databases were searched for reports of trials: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2004); MEDLINE (January 1966 to June 2004); and EMBASE (1990 to June Week 23 2004).
- We ran the following search strings in combination with the search strategy developed by the Cochrane Collaboration for identifying randomised controlled trials ([Dickersin 1994](#))
- MEDLINE and CENTRAL were searched using the following search strategy:

- 1 exp Common Cold/
- 2 common cold\$.mp.
- 3 exp RHINOVIRUS/
- 4 rhinovir\$.mp.
- 5 or/1-4
- 6 exp Ascorbic Acid/
- 7 ascorbic acid.mp.
- 8 vitamin c.mp.
- 9 or/6-8
- 10 5 and 9
- EMBASE search strategy:
- 1 exp Common Cold/
- 2 common cold\$.mp.
- 3 exp Rhinovirus/
- 4 rhinovirus infection\$.mp.
- 5 or/1-4
- 6 exp Ascorbic Acid/
- 7 vitamin c.mp.
- 8 or/6-7
- 9 5 and 8

Documenting a search strategy

The search strategy should be described in sufficient detail in a review that the process could be replicated:

- Title of database searched (e.g. MEDLINE)
- Date search was run (month, day, year)
- Years covered by the search
- Complete search strategy used, including all search terms

Identify potentially relevant citations

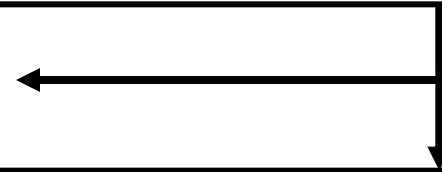
From wide searching of electronic databases & hand searching of other appropriate resources

(n= #)

Exclude irrelevant citations

After screening all **title** & **abstracts**

(n= #)



Retrieve hard copies of all potentially relevant citations

Identified through the above searches plus contact with experts, sifting through reference list & other resources

(n= #)

Exclude irrelevant studies

After detailed assessment of **fulltext**

(n= #)



Include studies in systematic review

(n= #)

Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis



Appraising study quality

- There is no such thing as a perfect study, all studies have **weaknesses, limitations, biases**
- Interpretation of the findings of a study depends on design, conduct and analysis, as well as on the population, interventions, and outcome measures
- The researchers in a primary study did not necessarily set out to answer your review question



What do we do with quality assessment results?

- Determine minimum quality threshold for inclusion
- Explore differences in quality as an explanation for heterogeneity in study results
- To weight individual study results in relation to their validity or the amount of information they contain
- Guide interpretation and overall recommendations

Assessment of study quality

- Assess each study for:
 - eligibility for inclusion
 - study quality
 - reported findings
- Ideally will involve **two independent reviewers**



Assessment of study quality

- **Validity:** the degree to which the trial design, conduct, analysis, and presentation have minimized or avoided systematic biases.

Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis





Collecting data

- Data collection forms

- Methods
- Participants
- Interventions
- Outcome measures and results

Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis

Meta-Analysis

- when an overview incorporates a specific **statistical strategy** for assembling the results of several studies into a **single estimate**

Systematic reviews & Meta-Analysis

- Systematic reviews do **not *have to*** have a meta-analysis
- There are times when it is not appropriate or possible.

Systematic reviews & Meta-Analysis

- The term '**meta-analysis**' is often used interchangeable with '**systematic review**'
- It is actually a statistical technique used to combine the results of several studies addressing the same question into a single summary measure (Khan *et al.*, 2000).



A Venn diagram consisting of two overlapping circles. The left circle is labeled 'Systematic reviews' and the right circle is labeled 'Meta-analyses'. The circles overlap in the center, indicating shared characteristics between the two concepts.

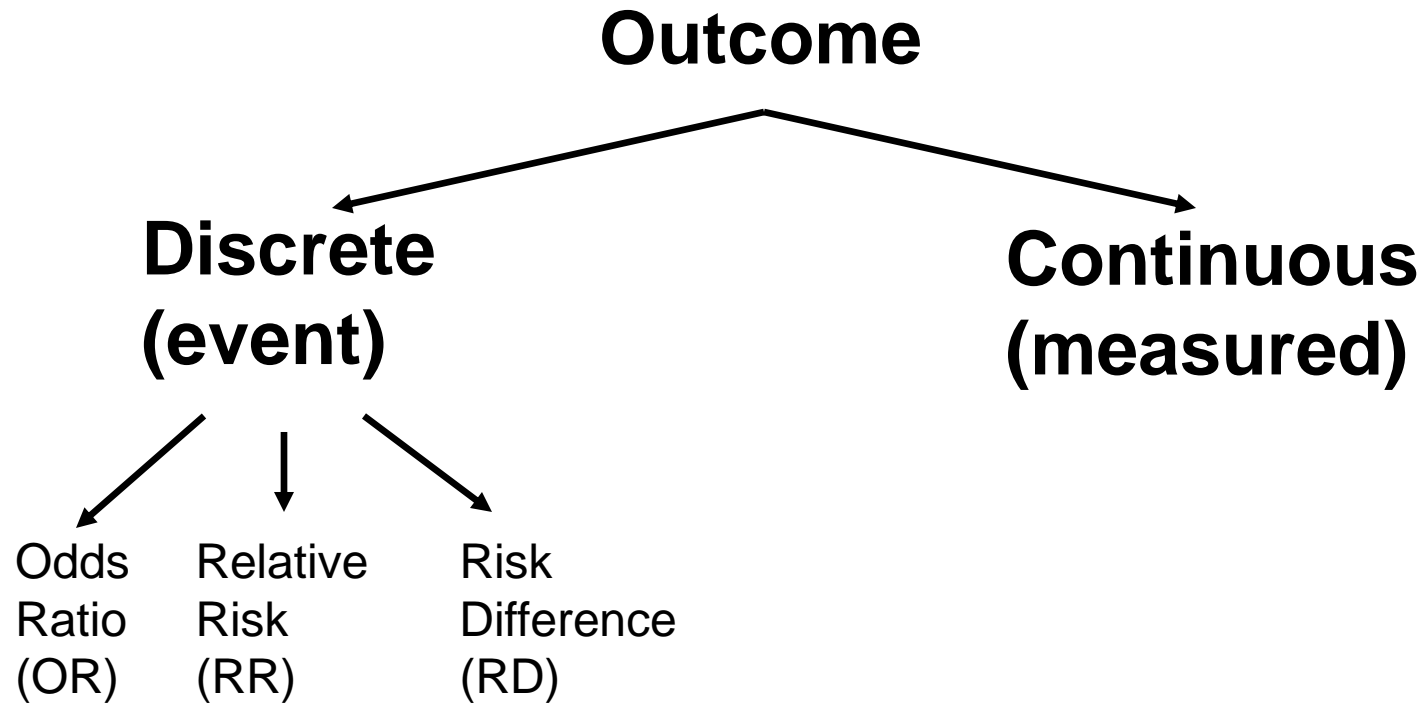
Systematic reviews

Meta-analyses

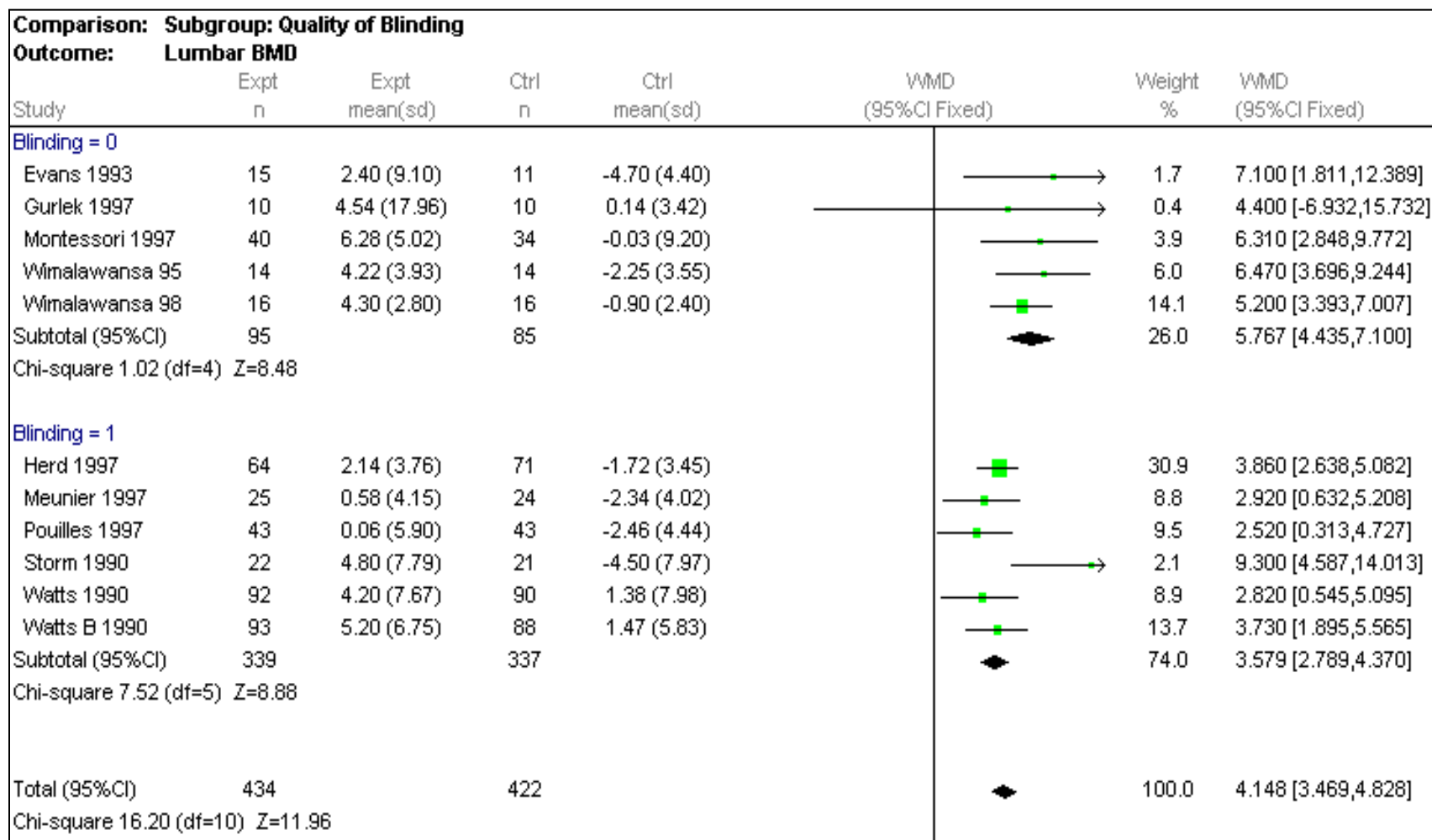
Forest Plot

- ◆ For each trial
 - estimate (square)
 - 95% confidence interval (CI) (line)
 - size (square) indicates weight allocated
- ◆ Solid vertical line of 'no effect'
 - if CI crosses line then effect not significant ($p > 0.05$)
- ◆ Horizontal axis
 - arithmetic: RD, MD, SMD
 - logarithmic: OR, RR
- ◆ Diamond represents combined estimate and 95% CI
- ◆ Dashed line plotted vertically through combined estimate

Effect Size Measures



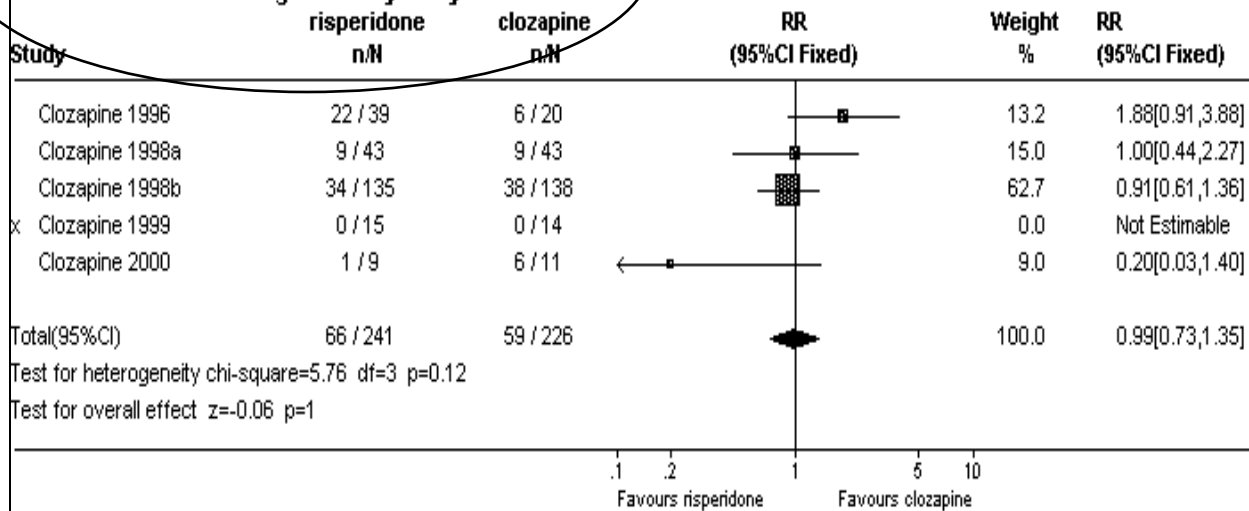
Forest plot



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

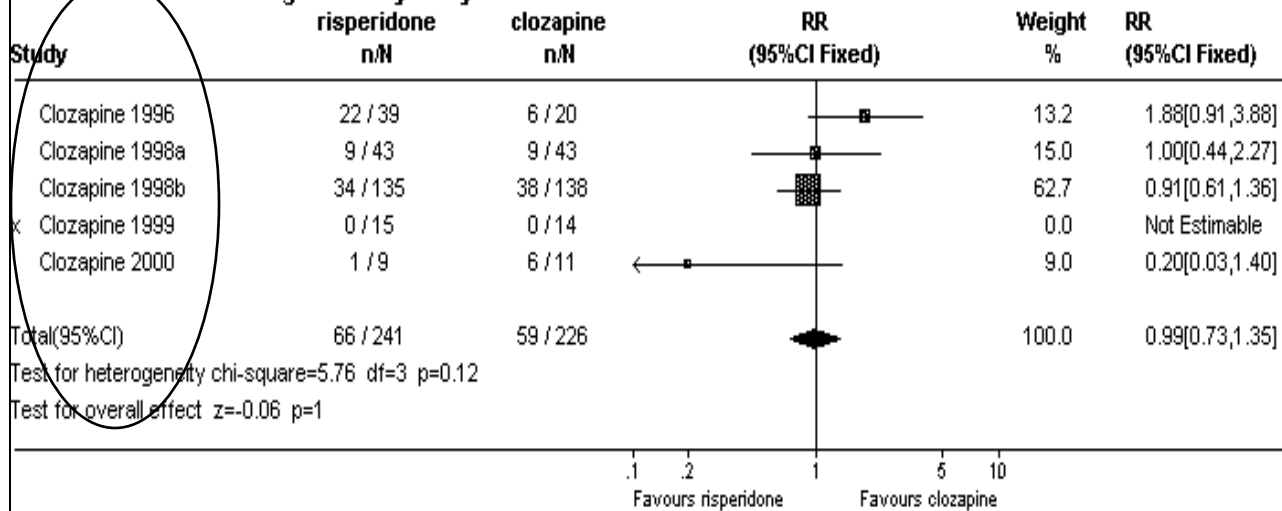
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

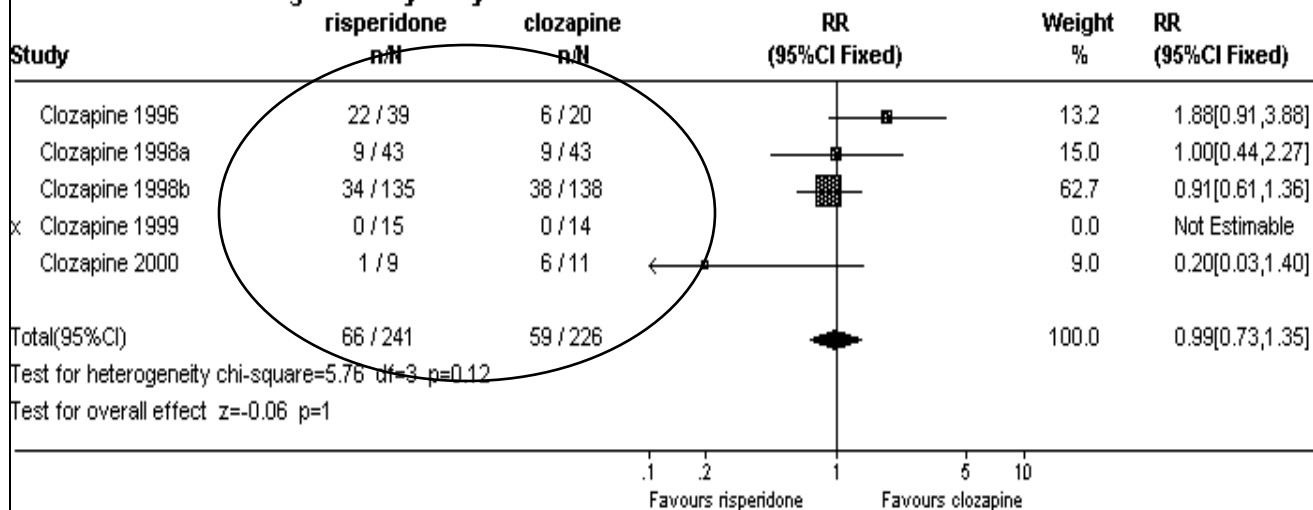
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

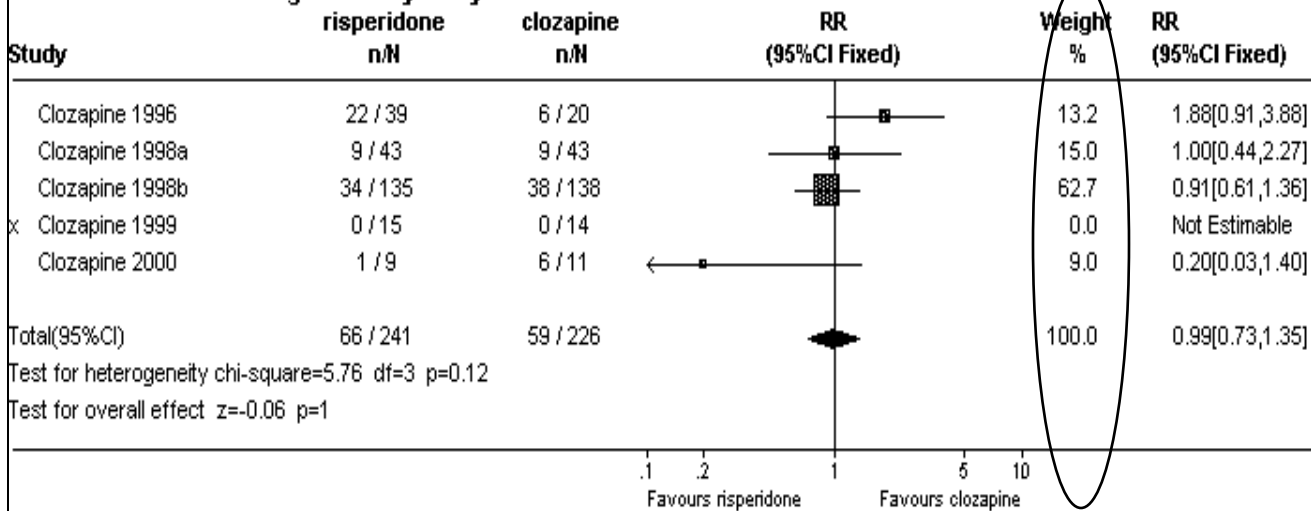
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

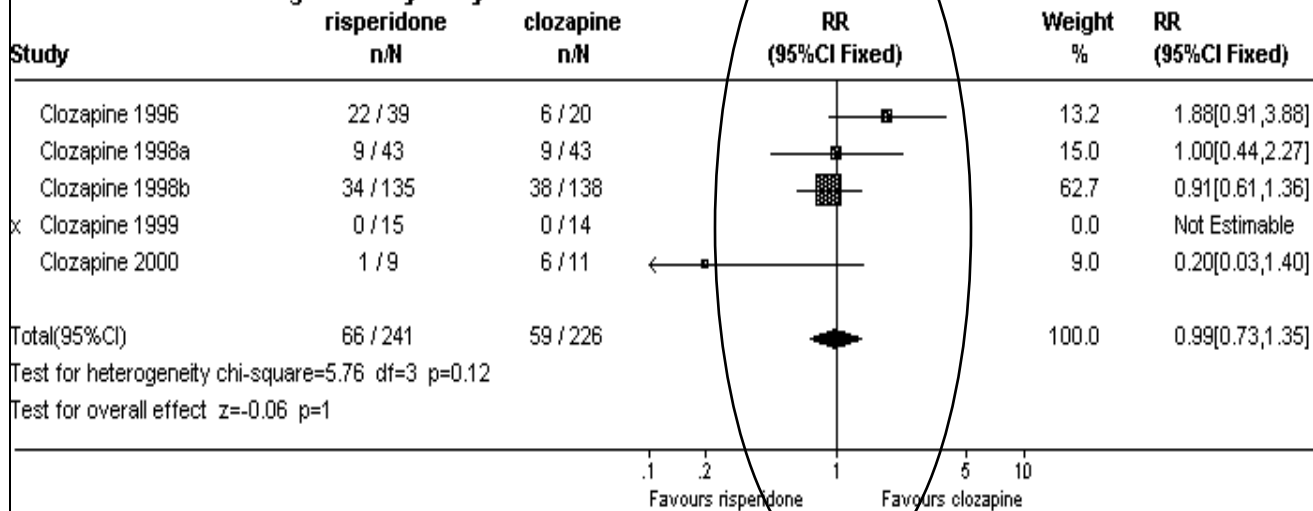
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

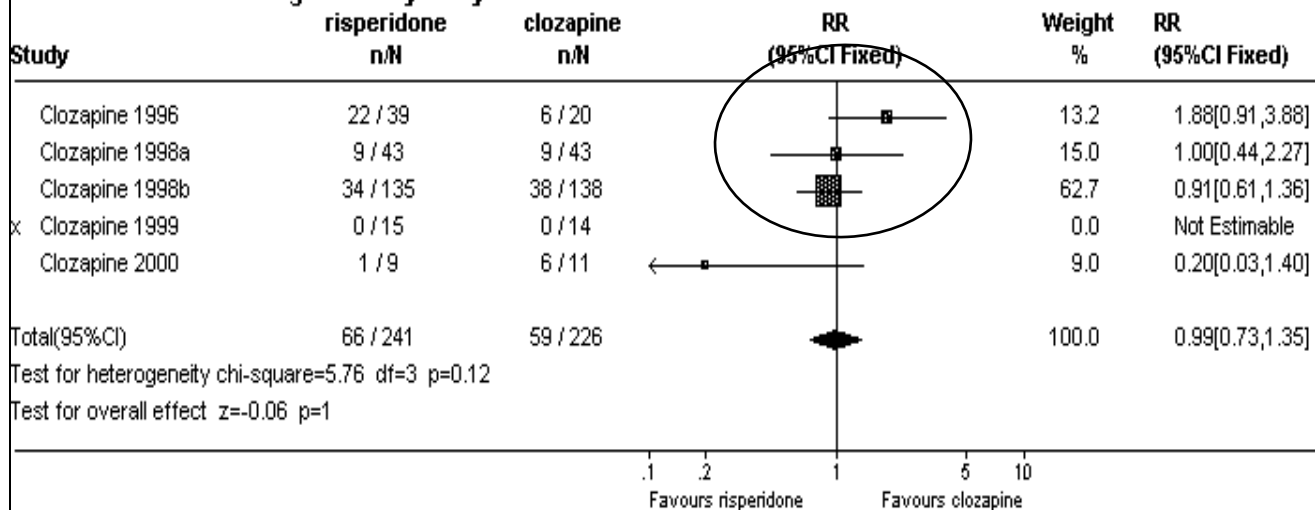
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

Outcome: 02 Leaving the study early



Forest plot

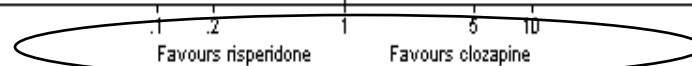
Comparison: 01 RISPERIDONE versus CLOZAPINE

Outcome: 02 Leaving the study early

Study	risperidone n/N	clozapine n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Clozapine 1996	22 / 39	6 / 20		13.2	1.88[0.91,3.88]
Clozapine 1998a	9 / 43	9 / 43		15.0	1.00[0.44,2.27]
Clozapine 1998b	34 / 135	38 / 138		62.7	0.91[0.61,1.36]
Clozapine 1999	0 / 15	0 / 14	Not Estimable	0.0	Not Estimable
Clozapine 2000	1 / 9	6 / 11		9.0	0.20[0.03,1.40]
Total(95%CI)	66 / 241	59 / 226		100.0	0.99[0.73,1.35]

Test for heterogeneity chi-square=5.76 df=3 p=0.12

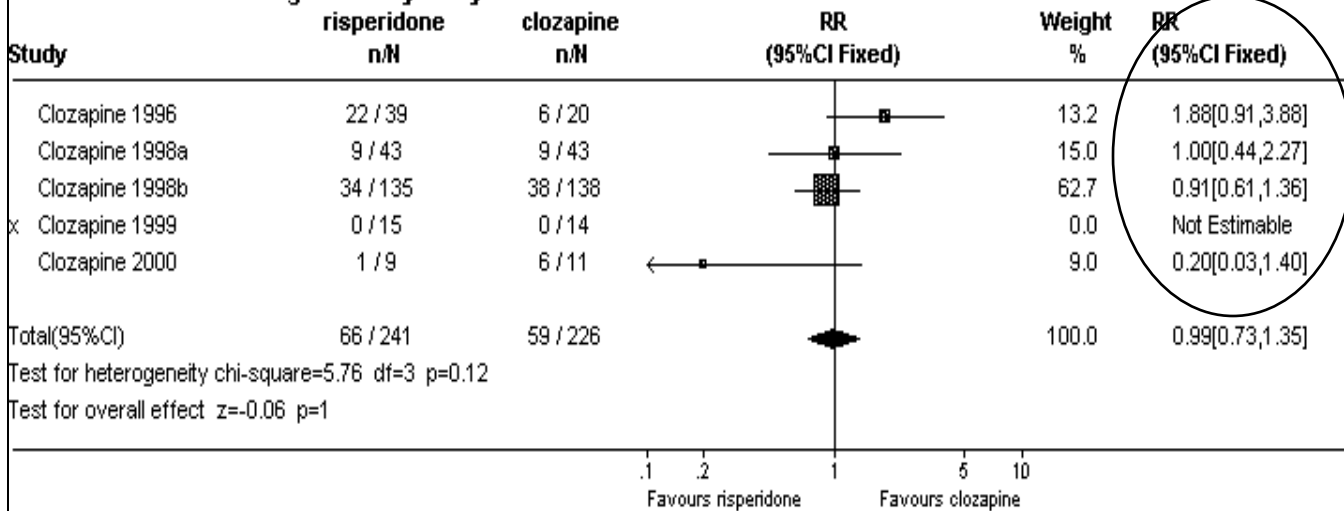
Test for overall effect z=-0.06 p=1



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

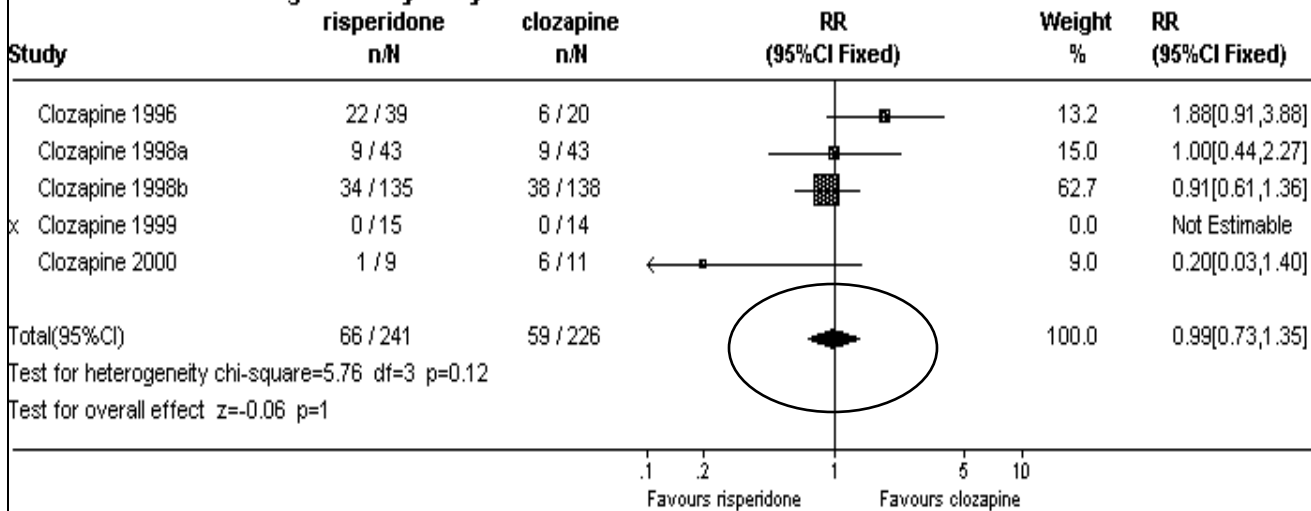
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

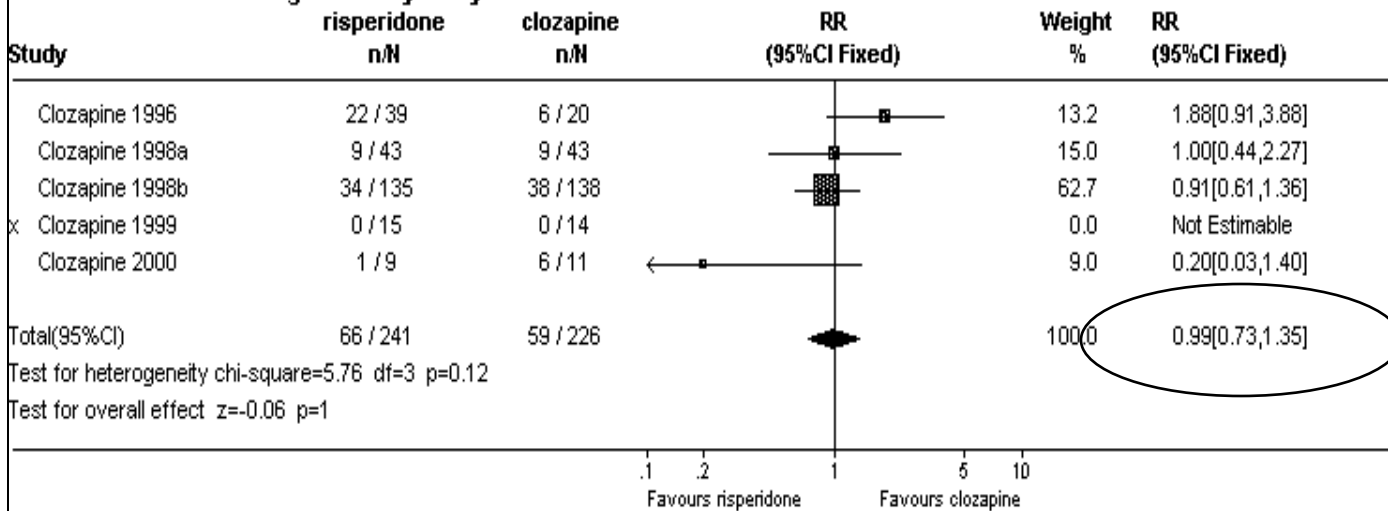
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

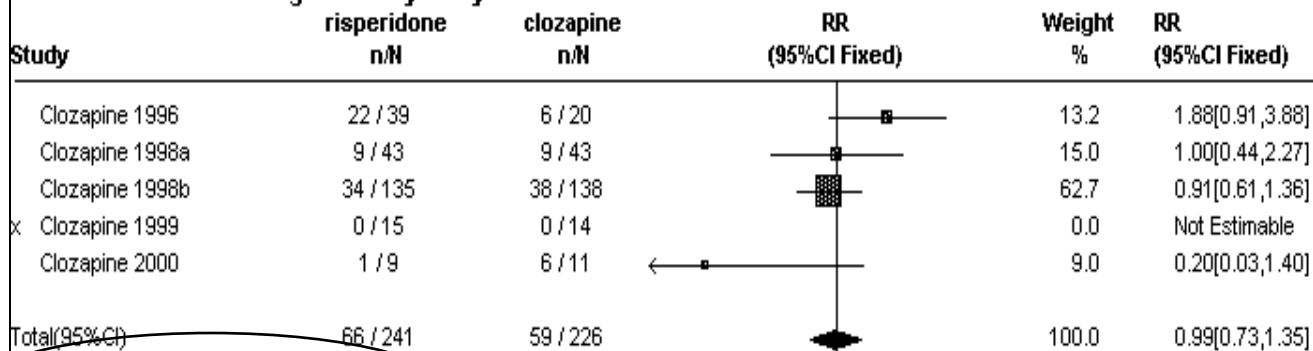
Outcome: 02 Leaving the study early



Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

Outcome: 02 Leaving the study early



Test for heterogeneity chi-square=5.76 df=3 p=0.12

Test for overall effect z=-0.06 p=1

.1 .2 1 5 10
Favours risperidone Favours clozapine



اگر میل داشتید Email بزنید !

kabiri@tums.ac.ir