Evidence based Dental Practice: Systematic Reviews

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Outline

• Background
• Definition and importance of systematic review
• Steps in conducting a systematic review
• Bias in systematic reviews
• Concluding remarks
• Does flossing prevent dental caries?
• Does oral hygiene prevent periodontal diseases?
• Do oxalate treatments improve dentin hypersensitivity?
Where do you get the answers?

- Opinions of teachers and peers
- Expert opinion
- Journals
- Google
- Pubmed
- Cochrane Collaboration
- Evidence based dentistry websites: ADA EBD
- Journals of evidence based dentistry: JEBDP, JEBD
How to be informed?

Published per day in Pubmed:
2000 studies
75 RCTs

Need to be up-to-date

– 1/3 of evidence will eventually be refuted or attenuated
– 1/2 will never be implemented

How would you know what is worth of your time?

Evidence based dental practice

- Best available evidence
- Patient preferences and values
- Patient clinical condition
- Experience and clinical judgement of the health professional
Generate the best evidence

Steps
– Ask
– Access: Exhaustive search
– Detailed appraisal
– Analyze & synthetize
– Apply

Time: 6 months
< 2000 papers
Systematic review

Use the best evidence

Steps
– Ask
– Access: Search
– Appraise
– Apply

Time: 30 minutes
< 20 papers
CAT – critical appraisal tool
Search for a systematic review
Levels of evidence

1. Systematic review of RCTs
2. Randomized trial or (exceptionally) observational studies with dramatic effect
3. Cohort/follow-up study
4. Systematic review of case-control studies, historically controlled studies
5. Opinion without explicit critical appraisal, based on limited/undocumented experience, or based on mechanisms

Oxford Centre for Evidence-based Medicine
What is a systematic review?

A review that attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question using explicit, systematic methods to minimize bias, thus providing more reliable findings from which conclusions can be drawn and decisions made

(Altman 1992, Oxman 1993)
Systematic review

- A clearly stated set of objectives with pre-defined eligibility criteria for studies
- An explicit, reproducible methodology
- A systematic search of studies
- An assessment of the validity of the study findings
- A systematic presentation, and synthesis, of the characteristics and findings of the studies
Meta-analysis

• Estimates an ‘average’ or ‘common’ effect

• Improves the precision of an estimate by using all available data

• Optional part of a systematic review
Meta-analysis of controlled trials of beta-blockers in secondary prevention of mortality after myocardial infarction.

Would any of you have agreed to participate in a placebo controlled trial of **beta-blockers after myocardial infarction** after 1981?
Cumulative meta-analysis of controlled trials of beta-blockers in secondary prevention of mortality after myocardial infarction.
Failure to review the cumulated evidence can lead to unnecessary duplication of research or to trial participants being deprived of effective interventions or exposed to harmful ones.
Trial reports should begin and end with systematic review of evidence

- Only ½ of trial investigators were aware of a relevant existing review when they had designed their trial
- 44% of published trials did not mention a systematic review and only 1 had an updated systematic review integrating the new results

Steps of a systematic review: 5 As

Ask: Define the question and inclusion criteria

Access: Search and select studies meeting inclusion criteria

Appraise: Describe the studies and appraise their quality/risk of bias

Analyze: Extract and synthetize the data

Apply: Report the findings and apply to your practice
Does this treatment help?
Dentin Hypersensitivity and Oxalates: a Systematic Review

J. Cunha-Cruz*, J.R. Stout, L.J. Heaton, and J.C. Wataha
for Northwest

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Systematic review

- Ask
- Access
- Appraise
- Analyze
- Apply
Do oxalate treatments improve dentin hypersensitivity?
In persons with dentin hypersensitivity, does oxalate treatment compared to placebo or no treatment reduce pain?

**Participants**  
Persons with dentin hypersensitivity

**Intervention**  
Oxalate treatment

**Comparison**  
Placebo, or no treatment

**Outcomes**  
Improvement on Dentin Hypersensitivity (Pain)
Systematic review

- Ask
- Access
- Appraise
- Analyze
- Apply
Search Strategy

- **Period:** 1966- Jul 2009
- **No language restriction**
- **Electronic search**
  - Pubmed
  - Cochrane Library (CENTRAL)
  - Grey literature (RCT registers, Theses database)
- **Reference lists**

**Electronic search:**
- Boolean operators (OR, AND and NOT)
- Keywords: MeSH terms
- Limits and restrictions [ ]
- Pubmed Clinical Queries
Keywords: MeSH terms
Search Strategy: MeSH terms

Dentin Sensitivity

Year introduced: 1965

PubMed search builder options

Subheadings:
- chemically induced
- classification
- complications
- diagnosis
- diet therapy
- drug therapy
- epidemiology
- ethnology
- etiology
- genetics
- history
- immunology
- metabolism
- microbiology
- pathology
- physiopathology
- prevention and control
- psychology
- radiography
- radiotherapy
- surgery
- therapy

Restrict to MeSH Major Topic.
Do not include MeSH terms found below this term in the MeSH hierarchy.
Boolean operators
(AND, OR and NOT)

Oxalates OR Oxalic acid

Dentin hypersensitivity OR Dentin sensitivity

Oxalates AND Dentin sensitivity

Exclude:
Animals NOT Humans
Restrict your search: Filters

((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
Search Strategy: Cochrane

Current Search History

<table>
<thead>
<tr>
<th>ID</th>
<th>Search</th>
<th>Hits</th>
<th>Edit</th>
<th>Delete</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>MeSH descriptor <strong>Dentin Sensitivity</strong> explode all trees</td>
<td>402</td>
<td>edit</td>
<td>delete</td>
</tr>
<tr>
<td>#2</td>
<td>dentin hypersensitivity</td>
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<td>delete</td>
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<tr>
<td>#3</td>
<td>MeSH descriptor <strong>Oxalic Acid</strong> explode all trees</td>
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<td>edit</td>
<td>delete</td>
</tr>
<tr>
<td>#4</td>
<td>Oxalate</td>
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<td>delete</td>
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<tr>
<td>#5</td>
<td>((( #1 OR #2 ) AND ( #3 OR #4 ))</td>
<td>26</td>
<td>edit</td>
<td>delete</td>
</tr>
</tbody>
</table>

Save Search Strategy  Clear History
• Code all citations and state reason for exclusion
• Pilot test
• Reliability
  – Assessed the agreement of two reviewers
  – Considered adequate (kappa=0.79)
Systematic review

Ask

Access

Appraise

Analyze

Apply
• Designed a data collection form
• Two reviewers collected information independently
Risk-of-Bias Assessment

Recruitment

Allocation

Maintenance

Measurements:

Blind or Objective

GATE: a Graphic Appraisal Tool for Epidemiology
Rod Jackson et al. PMID: 16539343
Risk-of-Bias Assessment

• Biases
  – Recruitment or Selection bias: systematic differences in the baseline characteristics of the comparison groups
  – Allocation: systematic differences in the allocation of participants to intervention and control groups
  – Maintenance:
    • Performance bias: systematic differences in care provided apart from the intervention being evaluated
    • Exclusion/Attrition bias: systematic differences in withdrawals from the trial
  – Measurement or Detection bias: systematic differences in outcome assessment (blind or objective assessment)

• Scales for RCT, cohort and case-control studies
• Methodological quality versus quality of reporting
  – Contact authors
## Risk-of-Bias Assessment

<table>
<thead>
<tr>
<th>Sequence generation</th>
<th>Assignment really random</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>Allocation concealed</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blinding of participants, care providers and outcome assessors</td>
<td>Patient blinded</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Care provider blinded</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Outcome assessor blinded</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Point estimate and measure of variability presented</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Intention to treat analysis</td>
<td>NA</td>
<td>Unclear</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>Free of selective outcome reporting</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Other sources of bias

| Eligibility criteria specified | Yes | Yes |
| Groups similar at baseline | Yes | Yes |
| Split mouth (cross-over design) appropriate | NA | Unclear |

NA: Not applicable
Systematic review

Ask

Access

Appraise

Analyze

Apply
Missing data and estimation
- Need to assess previous publications of the same study
- Contact the authors
- Extract data in the text, tables and figures
- Make assumptions

*Fig. 3.* Gingival status. Frequency of tooth surfaces scored 0 and 2+3 according to Gingival Index. Registrations are baseline, 3 and 30 months after oral hygiene education. Teeth examined are 16, 15, 13, 46, 45 and 43 (24 surfaces/individual).
• Heterogeneity
  – Proportion of variation not due to chance: $I^2$
  – Test of “Null hypothesis” of no variation (p-value)

• Meta-analysis
  – If $I^2 < 70\%$
  – Summary estimate: standardized mean differences

• Analyses planned but not performed
  – Publication Bias Analysis
  – Sensitivity Analysis
  – Meta-regression
### Results

**3% monohydrogen monopotassium oxalate**
- **Muzzin, 1989**: SMD = -0.71 (95% CI = -1.48, 0.06, p = 0.07)

**Other treatments** not associated with decreased dentin hypersensitivity when compared to placebo.

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**ANALYZE**

**Study**
- 3% monohydrogen monopotassium oxalate
  - Muzzin, 1989: SMD = -0.13 (95% CI = -0.81, 0.55)
  - Cuenin, 1991: SMD = 0.94 (95% CI = -0.23, 2.11)
  - Holborow, 1994: SMD = -0.88 (95% CI = -1.41, -0.35)
  - Gillam, 1997: Not estimable
  - Pereira, 2001: SMD = 0.42 (95% CI = -0.08, 0.92)
  - Camps, 2003: SMD = -1.10 (95% CI = -1.94, -0.26)
  - Pillon, 2004: SMD = -3.36 (95% CI = -4.52, -2.20)
  - Pamir, 2007: SMD = -0.71 (95% CI = -1.48, 0.06)
- 30% dipotassium oxalate
  - Muzzin, 1989: SMD = 0.13 (95% CI = -0.54, 0.80)
- 3% monohydrogen monopotassium oxalate + 30% dipotassium oxalate
  - Hansson, 1987: SMD = -0.85 (95% CI = -1.20, -0.50)
  - Cooley, 1989: SMD = 0.73 (95% CI = 0.19, 1.27)
  - Muzzin, 1989: SMD = 0.17 (95% CI = -0.50, 0.84)
- 6% monohydrogen monopotassium oxalate
  - Pereira, 2001: SMD = 0.17 (95% CI = -0.45, 0.79)
- 6.8% ferric oxalate
  - Gillam, 2004: SMD = -0.27 (95% CI = -0.72, 0.18)
- Oxalate pre-polymerized resin
  - Morris, 1999: SMD = 0.28 (95% CI = -0.20, 0.76)

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**Risk of bias**
- **3% monohydrogen monopotassium oxalate**
  - Muzzin, 1989: ++ + + + +
  - Cuenin, 1991: -- + + ?
  - Holborow, 1994: ? - - - -
  - Gillam, 1997: ? - - + -
  - Pereira, 2001: -- - + -
  - Camps, 2003: -- + + -
  - Pillon, 2004: +++ + + +
  - Pamir, 2007: ++ + + + +
  - Total (p = 0.07; I² = 88%)

---

**Duration**
- 4 wk
- 3 mo
- 1 yr

---

**Summary estimate and 95% Confidence interval**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias</th>
<th>Duration</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muzzin, 1989</td>
<td>++ + + + +</td>
<td>4 wk</td>
<td>-0.13 [-0.81, 0.55]</td>
<td>-0.13 [-0.81, 0.55]</td>
</tr>
<tr>
<td>Cuenin, 1991</td>
<td>-- + + ?</td>
<td>1 yr</td>
<td>0.94 [-0.23, 2.11]</td>
<td>0.94 [-0.23, 2.11]</td>
</tr>
<tr>
<td>Holborow, 1994</td>
<td>? - - - -</td>
<td>3 mo</td>
<td>-0.88 [-1.41, -0.35]</td>
<td>-0.88 [-1.41, -0.35]</td>
</tr>
<tr>
<td>Gillam, 1997</td>
<td>? - - + -</td>
<td>1 yr</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Pereira, 2001</td>
<td>-- - + -</td>
<td>1 yr</td>
<td>0.42 [-0.08, 0.92]</td>
<td>0.42 [-0.08, 0.92]</td>
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<tr>
<td>Camps, 2003</td>
<td>-- + + -</td>
<td>1 yr</td>
<td>-1.10 [-1.94, -0.26]</td>
<td>-1.10 [-1.94, -0.26]</td>
</tr>
<tr>
<td>Pamir, 2007</td>
<td>++ + + +</td>
<td>4 wk</td>
<td>-1.10 [-1.65, -0.55]</td>
<td>-1.10 [-1.65, -0.55]</td>
</tr>
<tr>
<td>Total (p = 0.07; I² = 88%)</td>
<td></td>
<td></td>
<td>-0.71 [-1.48, 0.06]</td>
<td>-0.71 [-1.48, 0.06]</td>
</tr>
</tbody>
</table>
Systematic review: 5 As

- Ask
- Access
- Appraise
- Analyze
- Apply
Bias in systematic reviews

Garbage in, garbage out?

- Meta-analysis without a systematic review
- Poor quality of studies or quality issues ignored
- Heterogeneity of studies not considered
- Indiscriminate data aggregation
- Reporting biases

Attention: small biases may be interpreted as real effects

### Reporting biases

<table>
<thead>
<tr>
<th>Statistically significant, “positive” results are more likely to be published:</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>rapidly</td>
<td>Time lag bias</td>
</tr>
<tr>
<td>in English</td>
<td>Language bias</td>
</tr>
<tr>
<td>more than once, and</td>
<td>Duplicate publication bias</td>
</tr>
<tr>
<td>more likely to be cited more than once</td>
<td>Outcome reporting bias</td>
</tr>
</tbody>
</table>

Fig 2. Results from discordant pairs of meta-analyses of small trials and single large trials.
Beta-carotene intake and cardiovascular mortality

Cohorts

- Male health workers, USA
- Social insurance, men, Finland
- Social insurance, women, Finland
- Male chemical workers, Switzerland
- Hyperlipidaemic men, USA
- Nursing home residents, USA

Relative risk (95% CI)
Concluding remarks: a systematic review can

- Refine unmanageable amounts of information
- Shorten the time between research discoveries and clinical implementation
- Investigate generalisability, consistency and inconsistency of studies
- Increase power and precision
Concluding remarks

• Motivation: time consuming tasks
• Focus: a clearly formulated question and a protocol
• Multidisciplinary review team
  – Content Specialist, epidemiologist, biostatistician, librarian
• Training
  – Methods: Cochrane handbook, books, etc
  – Software: Reference Manager, RevMan, Stata, etc
Resources

- Cochrane Collaboration: http://www.cochrane.org/
- Cochrane handbook: http://www.cochrane-handbook.org

• Do oxalate treatments improve dentin hypersensitivity?
• Does flossing prevent interproximal dental caries?
• Does personal oral hygiene prevent periodontal diseases?
Does flossing prevent interproximal dental caries?

• Weak evidence from 6 RCTs with children 4 – 13 years old
  • Flossing
    – performed by professionals in school days for 1.7 years: 40% reduction in dental caries (RR=0.6; 95%CI=0.48-0.76)
    – performed by professionals every 3 months for 3 years: no caries reduction (RR=0.93; 95%CI=0.73-1.19)
    – Self-performed by young adolescents for 2 years: no caries reduction (RR=1.01; 95%CI=0.85-1.20)
  • No RCT in adults or unsupervised

Does personal oral hygiene prevent periodontal diseases?

- Weak evidence from 3 RCT
- Oral hygiene did not prevent periodontal disease progression
  - Non-significant increase in alveolar bone loss in 13-yr children after 3 years (0.05 mm)
  - Not associated with tooth loss, probing depth or attachment loss in 60-90 yr seniors after 3 years
  - Not associated with periodontal index and attachment loss (0.09 mm) in 18 yr men after 46 months

Absence of evidence is not evidence of absence of effect

Systematic reviews also demonstrates where available evidence is insufficient and new trials are needed
Thank you

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