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Evidence-based Medicine

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EVIDENCE-BASED MEDICINE

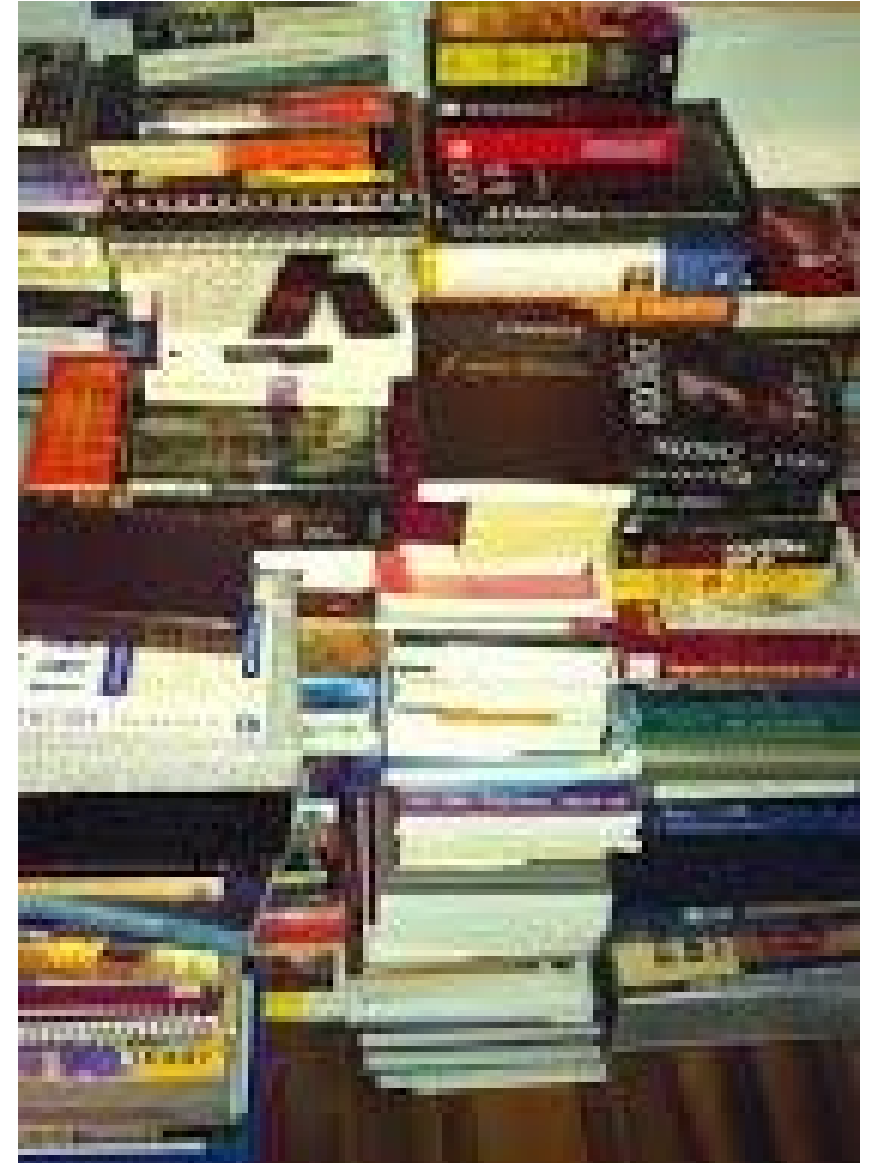
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What is Evidence-based Medicine?

- Start with the patient
- Ask a clinical question
- Search the literature
- Critically appraise the validity of the study process, results and applicability
- Apply back to your patient



Evidence based Medicine

- Integration of:

- Individual Expertise

- With the best available external evidence from systematic research and

- Patient Values and expectations

<http://www.cebm.net/index.asp>

Big Picture

The importance of research synthesis

- Karl Pearson is probably the first medical researcher to use formal techniques to combine data from different studies (1904):
 - He synthesized data from several studies on efficacy of typhoid vaccination
- His rationale for pooling data:
 - “Many of the groups... are far too small to allow of any definite opinion being formed at all, having regard to the size of the probable error involved.”



- Reasons to review the literature
- No study is ever considered to provide a definitive result on an exposure/disease relation
 - Why?
 - Random error can explain the association in a perfect study
 - No study is ever perfect-all biases of different kinds
 - The fact that studies are conducted examining the same exposure disease relation is the closest we ever get to repeating studies (From a sampling perspective)

Big Picture

- Literature review in research settings
 - To assess whether a question has been sufficiently answered or whether there is room for further research
 - To develop a new hypothesis, get ideas for new studies
 - To write background sections for grants and manuscripts

Methods for Reviewing the Literature

- Literature review (General, sometimes called a narrative)
- Systematic review
- Meta-analysis

REVIEW

Open Access

Spectrum of lithium induced thyroid abnormalities: a current perspective

Davis Kibirige^{1*}, Kenneth Luzinda² and Richard Ssekitoleko²

Abstract

Background: Lithium is an integral drug used in the management of acute mania, unipolar and bipolar depression and prophylaxis of bipolar disorders. Thyroid abnormalities associated with treatment with lithium have been widely reported in medical literature to date. These include goitre, hypothyroidism, hyperthyroidism and autoimmune thyroiditis. This current review explores the varied thyroid abnormalities frequently encountered among patients on lithium therapy and their management, since lithium is still a fundamental and widely drug used in psychiatry and Internal Medicine.

Methods: PubMed database and Google scholar were used to search for relevant English language articles relating to lithium therapy and thyroid abnormalities up to December 2012. The search terms used were lithium treatment, thyroid abnormalities, thyroid dysfunction, goitre, hypothyroidism, hyperthyroidism, thyrotoxicosis, autoimmune thyroiditis, lithium toxicity, treatment of affective disorders and depression and side effects of antipsychotic drugs. Reference lists of the identified articles were further used to identify other studies.

Results: Lithium affects normal thyroid functioning through multiple mechanisms. At the cellular level, it decreases thyroid hormone synthesis and release. It also decreases peripheral deiodination of tetraiodothyronine (T₄) or thyroxine by decreasing the activity of type I 5' de-iodinase enzyme. Hypothyroidism and goitre (clinically and/ultrasonographically detected) are the most prevalent thyroid abnormalities among patients on long term lithium therapy. Lithium induced hyperthyroidism is very infrequent. Lithium increases the propensity to thyroid autoimmunity in susceptible individuals due to its effect of augmenting the activity of B lymphocytes and reducing the ratio of circulating suppressor to cytotoxic T cells.

Conclusions: Thyroid function tests (serum thyroid stimulating hormone, free thyroid hormones-T₄ and triiodothyronine [T₃] concentrations and thyroid auto-antibodies) and assessment of thyroid size clinically and by thyroid ultrasonography ought to be performed among patients initiating lithium therapy at baseline and later annually. More frequent assessment of thyroid function status and size during the course of therapy is recommended among middle aged females (≥50 years), patients with a family history of thyroid disease and those positive for thyroid auto-antibodies (anti-thyroid peroxidase and TSH receptor antibodies).

Narrative reviews

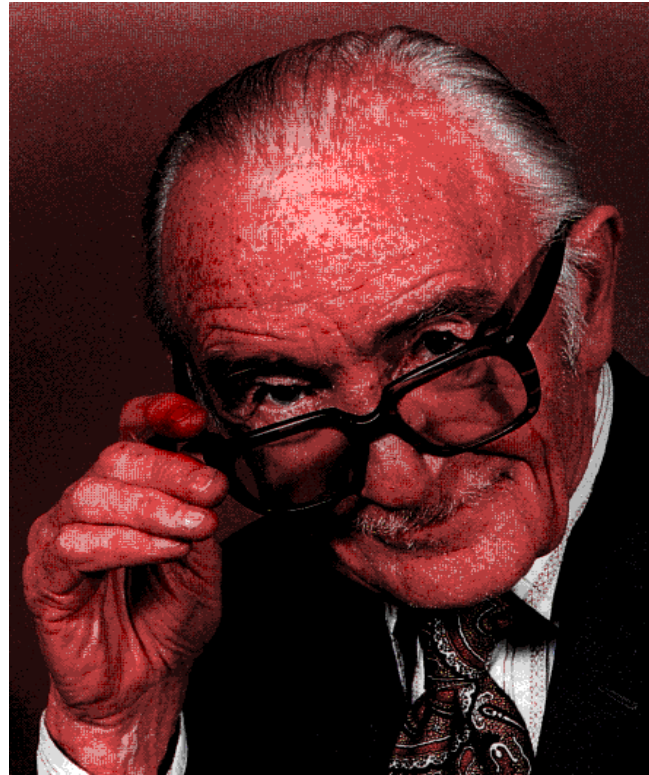
- Most common type of review
- Often produced by individuals considered expert in the field
- Use informal and subjective methods to collect and interpret information
- Attractive to readers because they distill a large amount of information
- Cannot be replicated because they are subjective

Traditional (narrative) reviews

- Subjective
- Methods not transparent
- Results not reproducible
- No quantitative summary
- Uncertainty remains

Mulrow. *Ann Intern Med* 1987

Archie Cochrane (1979)



“ It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials ”



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Primary prophylaxis for cryptococcal meningitis and impact on mortality in HIV: a systematic review and meta-analysis

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Abstract

Aim—To determine the role of primary antifungal prophylaxis in the prevention of cryptococcal meningitis and all-cause mortality in advanced HIV infection

Materials & methods—This was a systematic review and meta-analysis of randomized trials and observational studies. Google ScholarTM, PubMed and Embase databases were searched for relevant studies. Quality was assessed using different criteria, depending on study type. Publication bias was assessed and subgroup and sensitivity analyses were performed. When the results of the meta-analysis were homogeneous, the fixed-effects model was used; when the results of the meta-analysis were heterogenous, the random effects model was used.

Results—Primary prophylaxis prevented cryptococcal meningitis but did not confer protection against overall mortality, although there was evidence of a reduction in cryptococcal-specific mortality in resource-limited settings.

Conclusion—Primary antifungal prophylaxis should be recommended in patients with advanced HIV infection in resource-limited settings with a high incidence of cryptococcal meningitis.

Systematic reviews



- “A review that has been prepared using a systematic approach to minimise biases and random errors, which is documented in a materials and methods section” (Chalmers and Altman 1994)
- Key features:
 - We aim to locate all relevant information
 - Always include a methods section
- May include meta-analysis

Principles and procedures of systematic reviews

- Formulating the question e.g. What is the association between primary antifungal prophylaxis and prevention of cryptococcal meningitis in advanced HIV?
- Locating and selecting studies (Search engines, Key words, Inclusion and exclusion criteria, language)
- Quality assessment of the studies e.g. Jedad or Newcastle-Ottawa quality assessment scale.
- Analysing and interpreting results

Formulating review question

- Define Inclusion and Exclusion Criteria
 - **Participants:** Patients with advanced HIV
 - **Interventions:** Primary Antifungal prophylaxis
 - **Comparisons:** Placebo or No primary Prophylaxis
 - **Outcome:** Mortality
 - Time and Study designs

Finding studies

- Aim: Collect all available evidence in a replicable way
- Develop search strategy considering data sources e.g. Search engines such as PubMed, Embase, Google scholar, Cochrane database
- Checking references for other studies
- Contact all experts in the given field

Selection of Studies

- Selection should be done independently by >1 reviewer
- Set a clear strategy to resolve disagreements
- Keep record of excluded studies and the reasons for the exclusion
- Quality mark the included studies by use of Quality assessment scores
- Summarize study findings

Jedad Marksheet for Randomized studies

	Gilman et al, 2005	Wald et al, 2011	Pfizer, 2014	Pfizer, 2014(a)	Pfizer, 2015	Anderson et al, 2009	Frazer et al, 2004	Sharp&Corp, 2012
Described as randomized*	1	1	1	1	1	1	1	1
Described as double-blind*	1	0	1	1	1	1 [#]	1 [#]	1
Description of withdrawals*	0	1	1	1	1	1	1	1
Randomization method described and appropriate**	1	0	0	0	0	1	-1	0
Double-blinding method described and appropriate**	0	0	0	0	0	0	1	0
Score	3	2	3	3	3	4	3	3

* A study receives a score of 1 for "yes" and 0 for "no"

** A study receives a score of 0 if no description is given, 1 if the method is described and appropriate, and -1 if the method is described but inappropriate.

[#] The word "double-blind" was not used by the authors. However, according to the description of the blinding of the investigator, investigational site staff, and participants, one point was given for "described as double-blind".

Newcastle-Ottawa quality assessment scale

Study	Is the case definition adequate? (one point)	Representativeness of the cases (one point)	Selection of controls (one point)	Definition of controls (one point)	Comparability of cases and controls on the basis of the design or analysis (two points)	Assessment of outcome (one point)	Was follow-up long enough for outcomes to occur? (one point)	Adequacy of cohort follow-up (one point)	Total score (nine points)
Arora 2007	1	1	1	1	2	1	1	1	9
Lawson 1992	1	1	1	1	2	1	1	1	9
Masuda 2001	1	1	1	1	2	1	1	1	9
Michaels 2002	1	1	1	1	2	1	0	1	8
Michaels 2005	1	1	1	1	2	1	1	1	9
Tartaglia 2003	1	1	1	1	2	1	1	1	9

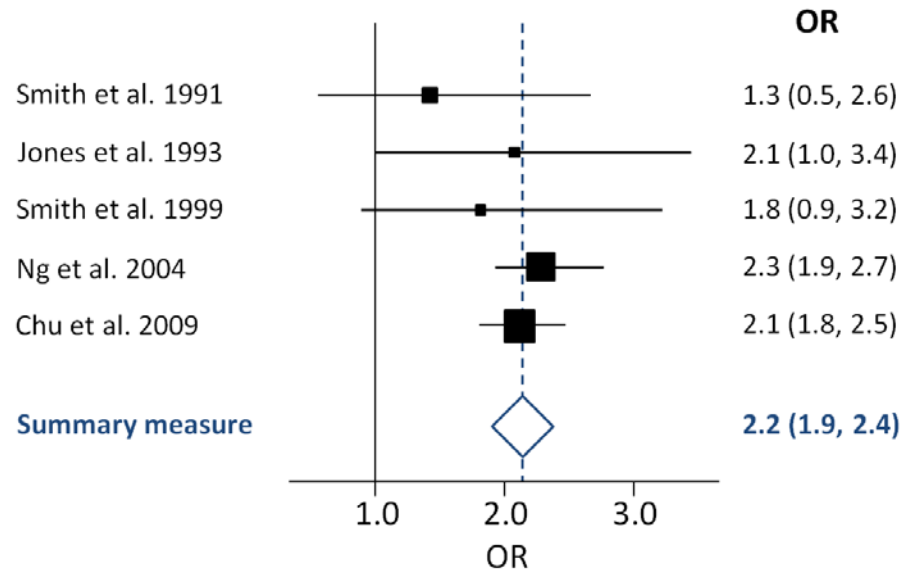
Interpreting results

- Consider limitations of each study
- Consider limitations of the systematic review e.g. Sources of Bias
- Consider strength of evidence
- Consider applicability to your patient, Clinical or public health practice.

Meta-analysis

- A review, where results of included studies are pooled statistically to produce one measure of association
- A quantitative approach for systematically assessing the results of previous research in order to arrive at conclusions about a body of research
- Goal is to increase precision of measures of association by increasing sample size- this is done by pooling samples of multiple studies.

Forest plots



- Box sizes draw attention to the weight of included studies
- Box area is proportional to the weight of the study
- The diamond (and broken vertical line) represent the overall summary estimate and the confidence intervals are represented by its width
- Unbroken vertical line is the null value

Meta-analysis

- Systematic reviews \neq Meta-analysis
- Systematic reviews do not combine/pool data
 - Systematic =qualitative
 - Meta-analysis=Quantitative
- Technically, a meta-analysis can be done without a systematic review- that is studies are selected non systematically and results pooled.

Limitations

- Most time consuming
- Always requires a team
- Biases of individual studies are combined and there is no way to know the effect of the study bias combination
- Most appropriate for RCTS or other types of trials on similar populations
- A major issue of concern is heterogeneity



The dissemination of evidence ...

unavailable

(unpublished)

available in principle

(e.g. thesis, obscure journal)

easily available

(Medline-indexed)

actively
disseminated

*(e.g. reprint from
drug company)*

Type of reporting bias	Definition
Publication bias	The <i>publication</i> or <i>non-publication</i> of research findings, depending on the nature and direction of the results
Time lag bias	The <i>rapid</i> or <i>delayed</i> publication of research findings, depending on the nature and direction of the results
Multiple (duplicate) publication bias	The <i>multiple</i> or <i>singular</i> publication of research findings, depending on the nature and direction of the results
Citation bias	The <i>citation</i> or <i>non-citation</i> of research findings, depending on the nature and direction of the results
Language bias	The publication of research findings <i>in a particular language</i> , depending on the nature and direction of the results
Outcome reporting bias	The <i>selective reporting</i> of some outcomes but not others, depending on the nature and direction of the results

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