EVIDENCE-BASED MEDICINE (EBM) Overview: Notes on Validity, Precision & Contextualization of Results[1,2,3,4,5]

L Regier BSP BA © www.RxFiles.ca Aug 2020

For references/updates/extra info see: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-EBM-Overview.pdf

Critical Appraisal of Drug Studies [6,7]

A) Is the study valid?

1. Were patients **randomized** to treatment (tx) groups & was allocation **concealed** (AC)? {Without concealment, 37% bias in favor of tx. Sealed, opaque envelopes or central registry used to attain AC} [8,9]
2. Was everyone (patients, physicians, investigators, assessors) **blinded** to tx? {Especially important for assessors of subjective outcomes eg. Pain.}
3. Was the study **controlled**? (e.g. inclusion of placebo or active control group/arm; in an "N of 1" trial, patient is own control.)
4. Were treatment & control **groups similar** in prognostic factors for outcome of interest at beginning of study? If not, were adjustments made?
5. Were all patients accounted for at end? {Missing patients addressed?}
6. Was data analyzed based on groups patients were initially randomized to? {Intent to treat or **ITT**; protects integrity of prognostic randomization; per protocol (**PP**) analysis may also be of interest (e.g. non-inferiority trials}
7. Were patient groups treated similarly except for study intervention?
8. How was the study funded (role of funder)? Was study stopped early?
9. Was study type, design & comparator drug & dose a good choice?

B) What are the study results?

1. What was the primary (1°) endpoint? What were the secondary (2°) endpoints? Were endpoints & subgroups pre-specified?[10] Avoid data mining!
2. What was the difference between treatments? (Benefits & Harms)
3. Were the differences statistically significant? Clinically significant? {What were the 95% confidence intervals (**CIs**) or p values? Does the CI cross line of no effect?}
4. What are the absolute and relative risk reductions or increases?
5. What is the number needed to treat (NNT) or harm (NNH)?

C) Does this study matter to my patients?

1. How clinically relevant/important are the outcomes?
2. Were the patients similar to those in my practice? {Consider inclusion & **exclusion** criteria; very sick, old, young, drug interactions & complicated/co-morbid patients often excluded.}
3. Do treatment benefits outweigh the risks, costs & impact on life?

Types of Studies (from low to **high level** of evidence) [11]

- **Case-control study**: a retrospective observational study which selects patients with the outcome of interest (cases) & patients without that outcome (controls); attempts to find exposures linked to the outcome.
- **Cohort study**: an observational study in which 2 groups (cohorts) are observed over time for an outcome. One cohort has exposure to a condition/treatment that the other does not. {Observational studies: association does not prove causation! Strength of association: RR: 1.01-1.5 *weak*; 1.51-3 *moderate*; >3 *strong*.[12]}
- **Crossover study**: a design in which each patient receives both treatments in two phases separated by a washout period. Each patient serves as own control, thus less variability in outcomes, & smaller sample size OK; period effects may limit findings.
- **Randomized controlled trial** (**RCT**): a prospective study in which patients are randomized to treatment or control groups (equal chance at being assigned to any group). Groups are followed for outcome of interest.
- **Systematic Review (SR)**: a systematic collection, review & presentation of available studies addressing a clinical question using specific criteria & methods; may include meta-analysis. e.g. *Cochrane*[13]*/Campbell*[14] *Reviews*

{**Meta-analysis**: the combining of studies meeting prespecified criteria, addressing a clinical question. Results are calculated from each study's data & data is pooled. ↑ sample size & statistical power useful if single trials underpowered or subgroup analysis. Assess appropriateness of a) variables & outcomes; b) studies included; c) study quality & heterogeneity accounted for.}

[**Level of evidence for Tx**: SR>RCT>observational study>expert opinion.[15] Observational studies useful for safety, generalization to different populations, & insights into real world effects, especially when specific RCT not practical.}

Caution: Lots of low quality RCTs may not be better than 1 good quality RCT! A low quality SR, or a SR of low quality trials does not constitute high-level evidence.]

Terms: Related To Validity

- **Bias**: design flaws leading to over/underestimation of treatment effect e.g. recall bias, selection bias, publication bias; confounding factors esp observational studies
- **Blinding**: if investigators, patient etc are unaware of who receives tx vs control, they are less likely to inappropriately report better results with tx.

Study Results: Size Of The Treatment Effect [16,17,18,19]

- **Event rate** (**ER**): the number of people experiencing the event as a proportion of total number of people in the population or group
  - -Experimental ER (**EER**): {# events in experimental group / total in exp. group}
  - -Control group ER (**CER**): {# events in control group / total in control group}
- **Relative risk** (**RR**) or **risk ratio**: {EER/CER}
- **Relative risk reduction** (**RRR**): the RR subtracted from 1 {RRR=1–RR} [Whereas ARR varies with type of population treated, RRR is often more constant.]
- **Absolute risk reduction** (**ARR**): the arithmetic difference between the 2 event rates {CER – EER} [If ↑ risk: **ARI**= absolute risk increase]
- **Number needed to treat** (**NNT**): the number of people who would have to be treated with the studied intervention for the studied time period to see 1 extra of them benefit. {NNT= 100 / ARR%}
- **Number needed to harm** (**NNH**): number of people who would have to be treated with the studied intervention for the studied time period for 1 extra person to experience the adverse event. {NNH = 100 / ARI%}
- **Odds ratio** (**OR**): = experimental event odds / control event odds; especially used in case-control studies where baseline risk is not known; also used in meta-analysis. When events are rare, the OR is similar to the RR; however, OR rate exaggerated relative to RR when events more common. {Link www.cebm.net: tool for converting OR to NNT[20]}
- **Point estimate**: the trial result used as best estimate of the true effect
- **Hazard ratio** (**HR**): like RR but more accurate; accounts for the time each participant was in the study before having event or withdrawing.

Study Results: Precision of Treatment Effect [21]

- **Confidence Interval** (**CI**): a 95% CI provides the range of values we are 95% certain that overlaps the true value. CI's indicates the precision of the estimate; where CI's are wide, they indicate less precise estimates of effect (just an estimate of the worst & best case scenario of the outcome; related to p-value)

  {For ratios, a CI that includes 1 means possibility of no difference. For ARR, ARI, NNT, NNH, a CI that includes zero means possibility of no difference between tx. Non-significant results eg. *trends* ~provide clues for future research & uncertainties.}
- **Type 1 (or α) error**: *the false positive*; to find a difference when there is none. **p-value**: reflects type 1 error. A p <0.05 suggests a <1 in 20 probability that any difference is due to chance (statistically significant by convention). The smaller the **p-value**, the less likely that the result is due to chance.
- **Type 2 (or β) error**: *the false negative*; to conclude there is no difference when there really is a difference (e.g. if not enough patients enrolled)
- **Heterogeneity**: when studies within a meta-analysis have more variation than expected; may indicate inappropriate to combine studies.[22] {***Q statistic***: measure of within-study variance; I^2: ratio of variability among studies to total variation.}

Do the study results matter to me & my patients?

- **Clinical significance vs statistical significance**: some studies may detect extremely small statistically significant differences between groups; however magnitude of effect (e.g. NNT) may be too small to change practice. Evaluate both 1) the endpoint, & 2) the NNT or NNH. {e.g. small cognitive score improvement not noticeable to patient.[23,24]}
- **Composite endpoints**: combining endpoints can increase a study's power allowing for smaller or shorter trials. Outcomes should have **similar value**. Examination of individual outcomes can be important in interpretation as one endpoint may be the primary *driver*. {e.g. In DREAM, outcome of diabetes diagnosis the driver **or** death example of unequal endpoints.[25]}
- **Surrogate endpoints**: an endpoint meant to reflect / be correlated with another endpoint (eg. BP/LDL/A1c for CV events; CD4 cell count for HIV mortality). Clinical outcomes are more important since surrogate endpoints assume correlation with an outcome which may or may not always be true.[26] {eg. lower A1C target ≤6% ACCORD: but ↑ death, doxazosin ↓ BP ALLHAT but ↑ HF/stroke, & clofibrate WHO-CLOF ↓ LDL but ↑ death.}
- **Other considerations**: What uncertainties remain? Has drug been studied in enough patients to detect serious rare adverse events? What duration of intervention is studied & what are the potential benefits & risks over a longer term of exposure? Does real-world experience appear to be consistent with clinical trial data? Cost? How benefits & risks are described will also affect decisions.[27]
- **What patient specific and societal values need to be considered?**

Heads Up! Know what the numbers are telling you.

⇨ *You double your chance of winning a lottery if you buy a 2nd ticket; however your chance of winning is impacted more by whether 2 tickets or 2 million tickets are sold!*

- ***Beware of the Relatives*** ☺
  - Benefits are often given as **relative** numbers, whereas harms are often given as **absolute** numbers. This tends to exaggerate benefits & minimize the harms. ⇨Look for NNTs & NNHs.
    {e.g. Vioxx monograph 2004CPS: reported ~ 50% ↓ in GI complications with Vioxx 50mg/day vs naproxen 500mg BID & a thrombotic event rate of 1.8% (Vioxx) vs 0.6% (naproxen). Actual GI complications reductions 0.59% vs 1.37% (ARR=0.78; NNT=**129**); whereas thrombotic risk was worse (NNH=**83**).}
    {e.g. Oral contraceptives: risk of DVT in a younger, non-smoking ♀ may be ↑300% but absolute risk is <1.5/10,000 /yr & lower than risk in pregnancy}
- ***Non-Equivalent Durations & Risk/Benefit Perception***
  - Benefits are often given for total duration of trial which may be several years, whereas harms are often given per year.
    {e.g. UKPDS-33: aggressive glucose control benefit on microvascular endpoints given per **10 years**; risks of hypoglycemia were given **per year**.[28]}
- ***Analysis: Pooling Together or Dividing Out***
  - Discussing the multiple benefits of a composite endpoint while individually sorting out risks may minimize risk perception.
    {e.g. In WHI, risk of just breast CA with HRT was **8/10,000 pt-years**; yet risk of any harm (DVT, CHD, stroke, PE & breast cancer) was **1/66** over 5.2yrs.[29] }

Calculations Example: 1 yr trial	RRR	ARR	NNT	NNH
◆200 patients in Control group ◆200 patients in Treatment (Tx) group ◆Deaths: Control grp: 40. **CER**=40/200=0.2	= (0.20 - 0.15)/0.20 X 100 = 25% {risk of event is reduced by 25%}	20% - 15% = 5% {absolute risk of event is reduced by 5%}	= 100 / 5% = 20	if 60% of patients in Tx group experienced *headaches* compared with 27% in control group (ARI=33%) NNH= 100 / 33% = 3

A few NNTs / NNHs of interest	NNT
↓ mortality with simvastatin 20-40mg/day over 5.4yrs vs placebo in patients with CHD 4S	**30** / 5.4yrs
↓ mortality with metformin 2550mg/day over 10 years vs non-intensive in obese T2DM patients UKPDS-34	**14** / 10 yrs
↓ CV death/MI/stroke; clopidogrel 75mg/day + ASA vs ASA alone in ACS pts (↑ bleeding: NNH=**99**) CURE	**48** / 9mo
↓ pain by ≥50% with TCAs (e.g. amiltriptyline 100mg/day) vs placebo in neuropathic pain (short term trials)	**4**

What makes for a good NNT? *It all depends!!!* NNTs will vary greatly with variations in baseline population risk, duration of tx, & type & number of endpoints included in composite. The value of the endpoint also varies from patient to patient.

Other Online EBM Resources/Links:

EBM Portal Links (SK): http://web.mac.com/malees/Primary_Care_Portal/EBM.html; Evidence Updates service: http://plus.mcmaster.ca/EvidenceUpdates/Default.aspx

General: U of T: http://www.cebm.utoronto.ca/; Oxford: http://www.cebm.net/?o=1011; McMasters: How to teach evidence based clinical practice – Links: http://hsl.mcmaster.ca/ebcp/. Dynamed: *www.ebscohost.com/dynamed/*

User's Guide: UofA, Centre for Health Evidence: http://www.cche.net/usersguides/main.asp; UBC: http://www.ti.ubc.ca/; Grey Literature Searching: http://www.cadth.ca/index.php/en/cadth/products/grey-matters

ScHARR Intro to Evidence Based Practice (Sheffield, UK) http://www.shef.ac.uk/scharr/ir/netting/; BMJ – Clinical Evidence Links: http://clinicalevidence.bmj.com/ceweb/resources/useful_links.jsp; NNTs http://www.thennt.com/

Clinical significance CALCULATORS: UBC: http://spph.ubc.ca/sites/healthcare/files/calc/clinsig.html; Wisconsin: http://intsmain.is.mcw.edu/clincalc/bayes.html. Essential Evidence Plus: http://www.essentialevidenceplus.com/

Dalhousie Katie Clinical Significance Calculator*: http://ktcalc.cme.dal.ca/site/login.php Z-score: http://www.socscistatistics.com/pvalues/normaldistribution.aspx Teaching EBM Videos: McMaster Guyatt: http://ebm.mcmaster.ca/materials_videos.htm

RxFiles – Select Trial Summaries (more available online at www.RxFiles.ca)

Anemia: Trials Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Anemia-Key-Trials.pdf

Dementia: CATIE-AD: http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf

Diabetes: Landmark Trials Summary: Glucose: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

Landmark Trials Summary: NON-Glucose: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-DIABETES-Landmark-Trials-Non-Glucose.pdf

ACCORD-ADVANCE Comparison: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-A1C-ACCORD-vs-ADVANCE-COMPARISON.pdf

ACCORD-BP & LIPID: http://www.rxfiles.ca/rxfiles/uploads/documents/ACCORD-BP-Lipid-Trial-Overview.pdf

ACCORD: Glucose http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf

ADVANCE: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-ADVANCE-trial.pdf

AVANDIA & CV risk – Meta-analysis: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Avandia-CV-Meta-Comments.pdf

DREAM: http://www.rxfiles.ca/rxfiles/uploads/documents/Dream-QandA.pdf

ELIXA: Lixisenatide : http://www.rxfiles.ca/rxfiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf 2016

EMPA-REG: http://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf 2016

LEADER: Liraglutide: http://www.rxfiles.ca/rxfiles/uploads/documents/Leader-Liraglutide%20VICTOZA%20and%20Cardiovascular%20Outcomes%20in%20Type%202%20Diabetes.pdf 2016

RECORD:http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-RECORD-Trial-Summary.pdf

SAVOR-TIMI 53: http://www.rxfiles.ca/rxfiles/uploads/documents/SAVOR-TIMI-53-Saxagliptin-CV-Outcomes-Trial-Summary.pdf

TECOS: Sitagliptin CV outcomes: http://www.rxfiles.ca/rxfiles/uploads/documents/TECOS-Trial-Summary.pdf 2016

Hypertension: Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/HTNLandmarkHypertensionTrials.pdf

ACCOMPLISH: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-Accomplish.pdf

ALLHAT: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-Update-2003-Final.pdf

ANBP2: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-ANBP2.pdf

ASCOT-BPLA: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-ASCOT.pdf

SPRINT: http://www.rxfiles.ca/rxfiles/uploads/documents/SPRINT-BP-Trial-Overview.pdf 2015

Trial Summary table - abridged: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf

HF: CHARM: http://www.rxfiles.ca/rxfiles/uploads/documents/CHARM-Comments.pdf

PARADIGM-HF: http://www.rxfiles.ca/rxfiles/uploads/documents/PARADIGM-HF-Trial-Sacubitril.pdf 2015

Hirsutism: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Hirsutism%20Trial%20Summary.pdf

HRT: WHI: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT Post-WHI-2002-Header.pdf

WHI & Age: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-Age-and-the-WHI.pdf ;

WHI & Extras/Perspectives on NNTs, NNHs: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-WHI-Extras-Perspectives.pdf

Lipid: Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid agents-major trials.pdf

& Q&A 2004: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Update-Oct04.pdf

AIM-HIGH: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-AIM-HIGH-nicotinic-acid-Niaspan-trial.pdf

ASCOT-LLA: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-ASCOT.pdf

CARDS: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-CARDS.pdf

ENHANCE: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-ENHANCE trial overview.pdf

FIELD Substudy: http://www.rxfiles.ca/rxfiles/uploads/documents/FIELD-Sub-Analysis-Women-Trial-Summary.pdf 2015

IDEAL: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-IDEAL.pdf

IMPROVE-IT: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-IMPROVE-IT-Trial-Summary-QandA.pdf 2014

JUPITER: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Jupiter-trial-overview.pdf

PROVE-IT: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Prove-It.pdf

SHARP: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Sharp-CKD-trial.pdf

SPARCL: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-SPARCL.pdf

Thrombotic (antithrombotics: ASA, clopidogrel, anticoagulants: warfarin) :

ACTIVE-A & ACTIVE-W trials http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf

Antithrombotics Summary Chart:: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf

ARISTOTLE: Apixaban vs warfarin in A Fib: http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf

CHARISMA: http://www.rxfiles.ca/rxfiles/uploads/documents/Charisma-QandA.pdf

Clopidogrel-PPI drug interaction: http://www.rxfiles.ca/rxfiles/uploads/documents/Clopidogrel-PPI-interaction-QandA.pdf

DAPT: 12 vs 30months http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT-Trial-12vs30months.pdf

PCI-Clarity: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf 2016

PCI-CURE: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf 2016

PEGASUS-TIMI 54: Ticagrelor vs Pl, prior-MI: http://www.rxfiles.ca/rxfiles/uploads/documents/PEGASUS%20Trial%20Summary.pdf 2016

PLATO: Ticagrelor vs clopidogrel ACS: http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf 2016

RE-LY: Dabigatran vs warfarin in Atrial Fibrillation http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf

ROCKET-AF: Rivaroxaban vs warfarin in A Fib: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf

TRITON-TIMI 38: Prasugrel vs clopidogrel, ACS: http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf 2016

MISC.:

Catie-AD: Atypical Antipsychotics in Patients with Alzheimer's http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf

FLAME*: Indacaterol+Glycopyrronium vs Salmeterol+Fluticasone for COPD:http://www.rxfiles.ca/rxfiles/uploads/documents/FLAME-Trial-Summary.pdf* 2016

Meloxicam: SELECT, MELISSA; *celecoxib* CLASS, *rofecoxib* VIGOR,: http://www.rxfiles.ca/rxfiles/uploads/documents/QandA-Meloxicam-2.pdf

OAB: Darifenacin-Oxybutynin Memory Trial : http://www.rxfiles.ca/rxfiles/uploads/documents/UI-Darifenacin-Kay-Trial-QandA.pdf

SENIOR: http://www.rxfiles.ca/rxfiles/uploads/documents/Senior-Trial-Oxybutynin-Solifenacin-Elderly-Cognitive-Impairment.pdf

WARFASA: http://www.rxfiles.ca/rxfiles/uploads/documents/Aspirin-warfarin-trial-summary-WarfASA.pdf

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[23] Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. 2005 Aug 6;331(7512):321-7. http://www.bmj.com/cgi/reprint/331/7512/321 {A systematic review by Kaduszkiewicz and colleagues (p 321) included 22 double blind randomised controlled trials with the follow-up ranging from six weeks to three years, but the trials scored poorly on a predefined checklist of criteria of methodological quality. Further, the outcomes measuring cognition did show beneficial effects of cholinesterase inhibitors, but these effects were minimal (ranging from 1.5 points to 3.9 points on a 70 point Alzheimer's disease assessment scale).}

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