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

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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. RCT: inclusion of placebo or active control group/arm; in an "N of 1" trial, patient is their 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? {Intention 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 $_{95}$ 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 a) with the outcome of interest (cases) & b) 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, like the flip of a coin). Groups are followed for the 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) if 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.

{ **CONSORT Statement**: a checklist of standards for standardized reporting of RCTs intended to reduce bias. http://www.consort-statement.org/ }

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 $_{\leq 6\%}$ 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 & harms over a longer term of exposure? Does real-world experience appear to be consistent with clinical trial data? Cost? How benefits & harms are described e.g. RR vs NNT 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 2004[CPS]: 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 harms 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

- 200 patients in Control group
- 200 patients in Treatment (Tx) group
- Deaths: Control grp: 40. **CER**=40/200=0.2
  Tx grp: 30. **EER**=30/200=0.15

RRR	ARR	NNT	NNH
= (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

For every 20 patients treated for 1yr, there is 1 less *death*; & for every 3 patients treated there will be 1 extra *headache*.

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 tx 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

Online Extras

Guidelines, Evidence and Patients

- Guidelines provide guidance based on evidence, clinical experience and someone's values and preferences.
  - Considerations: Evidence
    - How current? Has level/strength of evidence (evidence quality) been assessed for recommendations? (e.g. May have more confidence if high quality, multiple, trials.)
    - What outcomes are evaluated? Are they patient orientated or surrogate?
    - Has evidence been allowed to inform pre-existing assumptions, biases and beliefs?
    - Is the evidence applicable to your patient(s)?
  - Clinical experience / consensus
    - Is expert opinion, and extent of agreement acknowledged
  - Conflicts of Interest (https://www.cmaj.ca/content/193/2/E49)
    - Are conflicts of interest disclosed
    - Conflicts may be financial or non-financial
    - Methods should be transparent and rigorous to inform objectively on best available evidence
  - Values
    - In what way are values and preferences included?
    - Who's values: Patient? Society? Payer? Professional?
  -
- Overall assessment:
  - Look for transparency, evidence ratings, peer review, conflicts of interest
  - Do the guidelines allow for, and enable, shared decision making with patients?
- If the guidelines don't apply, don't apply them! Almost all guidelines contain a chapter/disclaimer noting that any recommendations must be assessed and individualized for the patient in front of you. Recommendations are often intended to apply to a majority of patients, but may not be suitable for the patient in front of you. If so, document reason for your decision.

EBM	1
Evidence Based Medicine	1
NNH	1
NNT	1
Precision	1
Validity	1

RxFiles: Evidence Based Medicine (EBM) Overview - References

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