Randomized trials are not black boxes

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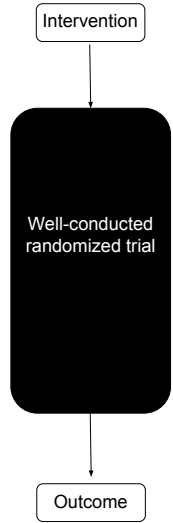
Randomized trials as a black box

Randomized trials provide a way to assess an intervention in terms of the outcomes in generates without being concerned about the details of the mechanisms by which the intervention produces the outcomes



Oxford Centre for Evidence-based Medicines Levels of Evidence (2011)

Level	Benefits	Harms
1	Systematic review of RCTs, n-of-1 studies	*Common*: Systematic review of RCTs, nested case-control studies, n-of-1 studies or observational study with large effect *Rare*: Systematic review of RCTs or n-of-1 study
2	RCT or observational studies with dramatic effect	Individual RCTs or (exceptionally) an observational study with dramatic effect
3	Non-randomized controlled cohort or follow-up study with sufficient numbers	
4	Case-series, case control, or historically controlled studies	
5	Mechanism-based reasoning	

Table: This is a summary of Oxford Center for Evidence-based Medicine's (2011) levels of evidence for assessing drug benefits and harms. The document provides guidance for grading evidence higher or lower based on methodological considerations and effect sizes.

EBM and black boxes

Howick, Glasziou, and Jeffrey K Aronson (2010, 2013)

The prediction of patient outcomes on the basis of evidence of mechanisms is typically not possible because:

1. The mechanisms that can influence patient outcomes are many and complex
2. Our knowledge of the relevant mechanisms is almost always incomplete

EBM's standard guidance for assessing external validity

> *If the patient would have been enrolled in the study had she been there . . . there is little question that the results are applicable. . . .*
>
> *If this is not the case . . . judgment is required. . . .*
>
> *A better approach than rigidly applying the study's inclusion and exclusion criteria is to ask whether there is some compelling reason why the results should not be applied to the patient.*
>
> *A compelling reason usually won't be found, and most often you can generalize the results to your patient with confidence.*

Guyatt, Sackett, et al. (1994, p. 20)[1]

[1] See also Guyatt, Rennie, et al. (2014), Moher et al. (2010), and Schunemann et al. (2017)

Aims

Randomized trials are not a black box: mechanisms are important to the design, interpretation and application of randomized trials

1. Characterise the key types of mechanistic evidence that are important to the design, interpretation and application of randomized trials
2. Argue that the status of this mechanistic evidence is important to the warrant provided by a successful randomized trial

Mechanisms/evidence of mechanisms/mechanistic reasoning

> *A mechanism for a phenomenon consists of entities and activities organized in such a way that they are responsible for the phenomenon.*

Illari and Williamson (2012, p. 120)

Mechanisms/evidence of mechanisms/mechanistic reasoning

Evidence of mechanisms specific, objective, assessable evidence of the mechanism—its entities, activities, organization and/or existence.

Mechanistic reasoning "an inference about an intervention's clinical effect from alleged knowledge of relevant mechanisms and how they relate to one another" (Howick, Glasziou, and Jeffrey K. Aronson 2013, p. 279)

Outline

EBM's approach to mechanisms is a consequence of its approach to evidence

1. EBM ranks methods to address a specific question:
2. *Which methods provide the most reliable estimate of the effects of a treatment on patient-relevant outcomes?*

Causal assessment

1. *What evidence do we have to support the causal claim (efficacy, effectiveness, harm,...)?*
2. How do we best amalgamate the available evidence to address the claim?

Causal assessment

- The approach to evidence and evaluation of mechanisms developed around the Russo-Williamson Thesis (Parkkinen et al. 2018, Williamson 2018)
- Julian Reiss's (2015) Pragmatist Theory of Evidence provides an account of evidential support and warrant
- Nancy Cartwright's (2011, 2012) work on evaluating effectiveness claims

EBM v Casual Assessment

Approach to evidence	Evidence-based medicine	Causal assessment
Guiding heuristic	Use best evidence to assess the claim	Evaluate evidence of mechanisms and evidence of correlations to assess the claim (RWT)
Evaluating evidence	Where does the evidence sit in the hierarchy of evidence?	To what degree does the body of evidence support the claim and relevant alternative accounts of the evidence are ruled out? (Reiss)
Assessing external validity	“Simple extrapolation, unless”	Are the support factors necessary for the intervention present? (Cartwright)

Table: Comparing the EBM and Causal Assessment approaches to evidence

Outline

Ertugliflozin

- One of a new class of antihyperglycaemic agents: sodium-glucose transport protein 2 inhibitor (SGLT2i)
- SGLT2 is responsible for $\approx$ 90% of glucose resabsorption in the kidneys
- Inhibiting SGLT2 is expected to lead to:
  - increased urinary glucose excretion
  - reduced blood glucose levels
  - reduced blood volume
  - reduced blood pressure
  - weight loss
  - increased glucose in the urine (genitourinary infections)

Ertugliflozin clinical drug development

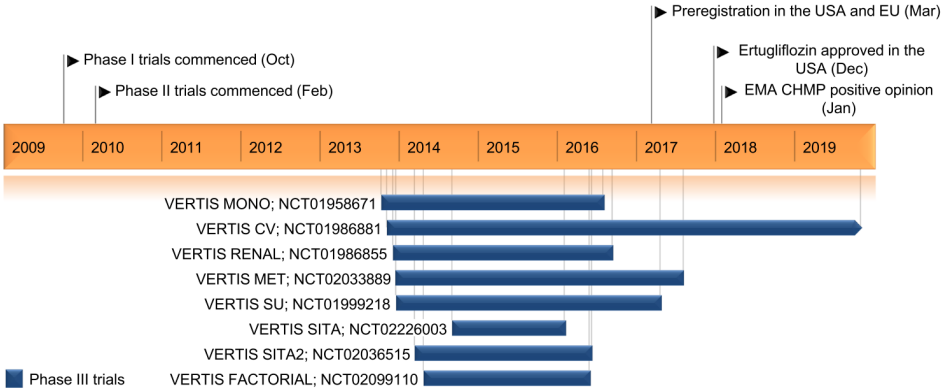


Figure: Clinical drug development of ertugliflozin (Markham 2018)

Context: What is wrong and what has been shown to work

- Poor control of T2DM leads to microvascular (eyes, kidneys, nerves) and macrovascular disease (heart attack, stroke, heart failure)
- There are currently 8 classes of drugs used in the treatment of T2DM
- All lower blood glucose: tight control reduces microvascular disease (too tight control leads to worse outcomes)
- The available agents vary considerably in terms of risk of cardiovascular disease: some reduce risk, others increase risk
  - FDA requires cardiovascular outcome trials in T2DM (since 2008)

Phase I & II studies: pharmacokinetics and pharmacodynamics I

Amin et al. (2015), Dawra et al. (2019), Markham (2018), and Sahasrabudhe et al. (2018)

- Oral bioavailability (absorption) is close to 100%
- Cleared from the body via liver (gastrointestinal tract) and kidneys
- Elimination half-life is approximately 16 hours in patients with T2DM without renal impairment
- Exposure is not significantly effected by food, rifampicin, metformin, sitagliptin, or renal impairment

Phase I & II studies: pharmacokinetics and pharmacodynamics II

Amin et al. (2015), Dawra et al. (2019), Markham (2018), and Sahasrabudhe et al. (2018)

- Dose-response curve characterised
  - 50% maximum effective dose (EC50) $\approx$ 2.5–3 mg
  - Oral doses of 5mg and 15mg provide maximal effect on glucose excretion
- In short-term studies in 'healthy' patients, ertugliflozin reduced: blood glucose compared to placebo and reduced blood pressure and weight compared to active control

SGLT2i and cardiovascular outcomes (empagliflozin, canagliflozin, dapagliflozin)

Chin et al. (2019), Hupfeld and Mudaliar (2019), Zelniker et al. (2019), and Zinman et al. (2015)

Meta-analysis results:

- Reduction in hospitalisation for heart failure in patients with and without existing cardiovascular disease
- Reduction in major adverse cardiovascular events (CV-death, nonfatal myocardial infarction, nonfatal stroke) in patients with established cardiovascular disease
- Reduction in myocardial infarction in patients with established cardiovascular disease

Types of mechanisms and clinical drug development

1. What is wrong and what works
   - Pathophysiology and details regarding the existing interventions
2. Mechanism of action
   - How the drug works
3. Mechanisms relating to exposure
   - ADME: absorption, distribution, metabolism, elimination (pharmacokinetics)
4. Mechanisms linking exposure and outcome
   - How differences in exposure influence the actions of the drug (pharmacodynamics)

Outline

Evidence of mechanisms and warrant

- Type of mechanisms that support the warrant of randomized trials
- Types of evidence for mechanisms (Illari 2011)

Types of evidence for mechanisms	Ranking
Evidence of *what the mechanism is* in detail	$+++$
Evidence *that there is* a mechanism of the postulated kind	$++$
Postulated mechanism, based on evidence of analogous mechanisms	$+$
Evidence that there is *no* mechanism	$-$

Randomized trials in different contexts

- Clinical drug development (e.g. ertugliflozin)
- Homeopathy: EBM tends to rely on results from systematic reviews and meta-analyses rather than highlight problems with the mechanisms
- Pragmatic trials in contexts in which there is considerable heterogeneity (e.g. POISE trials to reduce major adverse cardiac events following non-cardiac surgery)
- Policy trials in education, public health (e.g. class sizes in early education, integrated nutrition projects)

Evaluating warrant of randomized trials based on mechanistic evidence

Type of mechanism	Ertugliflozin	Homeopathy	Pragmatic trials	Policy trials
What is wrong/works?	+++	−	+	+
MOA	+++	−	+	++
Exposure	+++	−	+++	++
Exposure-Outcome	+++	−	+	+

Outline

Conclusion

1. Recognising clinical drug development as a paradigmatic context for assessing approaches to evaluating evidence
2. Contribute to the causal assessment approach to evaluating medical evidence
   - The end-goal is supporting decision-makers—clinicians making therapeutic decisions, researchers conducting systematic reviews, guideline developers

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