BAYESIAN NETWORK META-ANALYSIS: WHAT, HOW, AND WHY?

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Workshop Summary

- Introduction to Bayesian Methods
- Bayesian Approaches to Meta-Analysis
- Gibbs Sampling
- Indirect Comparisons (frequentist)
- Mixed Treatment Comparisons
- Examples

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Bayes' Theorem

- Simple Manipulation of Conditional Probabilities

  P(A and B) = P(A|B)P(B) = P(B|A)P(A)

$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B)}$$

$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B \mid A)P(A) + P(B \mid A')P(A')}$$

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Bayes' Theorem

- Example with diagnostic testing:
- If the prevalence of a disease in a population is 1 in a 1000, and a specific test has a 99% chance of being correct (positive or negative), what is the probability a patient has the disease after testing positive?

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Bayes' Theorem

$$P(D \mid +ve) = \frac{P(+ve \mid D)P(D)}{P(+ve \mid D)P(D) + P(+ve \mid D')P(D')}$$

$$P(D \mid +ve) = \frac{(.99)(.001)}{(.99)(.001) + (.01)(.999)} = 0.09 = 9\%$$

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General Bayesian Formulation

- Want to estimate some parameter θ given data y.
- Frequentist statistical methods do this by using the data to find "best" estimate of θ by some manipulation of the data.
- This estimate will have desirable properties such as unbiasedness and low variance.

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General Bayesian Formulation

$$p(\theta \mid y) = \frac{p(y \mid \theta)p(\theta)}{p(y)}$$

$$p(\theta \mid y) \propto L(y \mid \theta)p(\theta)$$

Posterior $\propto$ Likelihood(Data)*Prior

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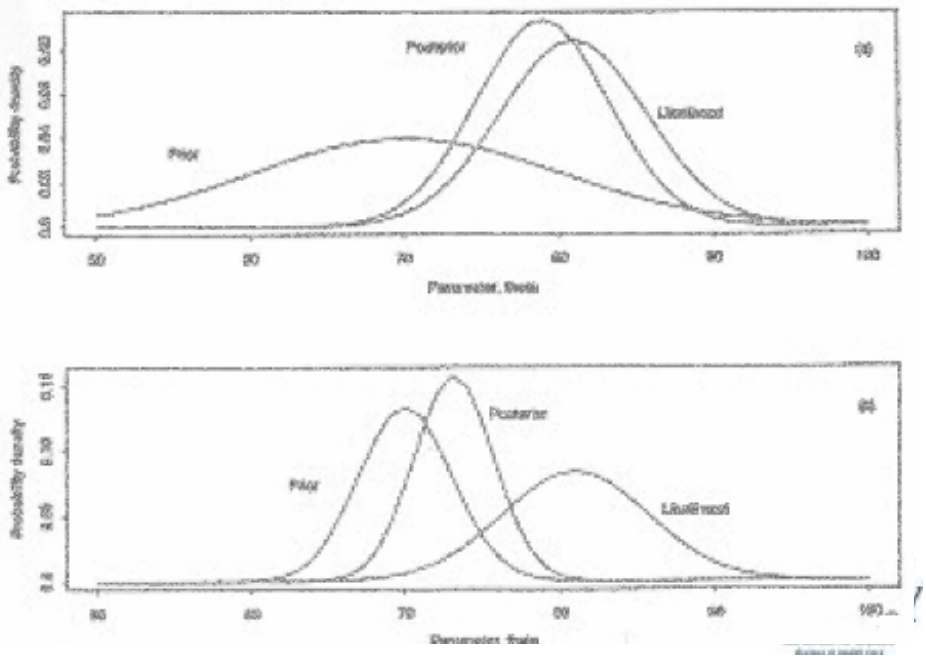

Prior Distributions

- Vague or Non-informative
  - Contain Little Information Relative to Likelihood
- Sceptical
  - Centred at no difference with a specified probability of showing a difference
- Enthusiastic
  - Initially favour one side
- Subjective
  - Elicited from experts or groups
- Based on previous evidence/studies
  - Adjusted and/or down-weighted for potential biases.

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Example of Bayesian Formulation

- Previous experience suggests success rate of an intervention is between 20% and 60%.
- Prior ~ Beta (α=9.2, β=13.8) mean=0.4, SD=0.1.
- Data: Observe 15 successes out of 20.
- Posterior: Beta(α=24.2, β=18.8). Posterior mean = 0.56.

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Fundamental Differences Between Bayesian and Frequentist Formulations

- Prior Distribution
- Bayesian analysis treats unknown parameters as random variables, while frequentist analysis treats them as fixed but unknown quantities. (semantics?).

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Review: Frequentist Methods of Meta-analysis

- Parameters are estimated on the study level first (i.e. parameter estimate with standard error).
- Studies are combined by weighting each by inverse variance (or other method) plus perhaps a function of between study variance (random effects).

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Bayesian Approaches to Meta-Analysis

- Models are created using Bayesian methods.
- Prior distributions are specified for parameters and study results act as data for the likelihood.
- Parameters are defined by joint posterior distributions combined with prior distributions.

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Example: Fixed Effects Model

$Y_i \sim \text{Normal}(d, V_i)$

$d \sim \text{Normal}(0, 10^5)$ (vague prior)

- The distribution of the assumed common mean difference of the studies (d) is derived from a vague prior and the study data.

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Example: Random Effects Model

$Y_i \sim \text{Normal}(\delta_i, V_i)$

$\delta_i \sim \text{Normal}(d, \tau^2)$

$d, \tau^2 \sim$ prior distributions

- Same as fixed effects, except each study is now allowed to have a different mean difference, that is presumably randomly distributed around a common study level mean.
- Note: Watch specification of prior distribution for between studies variance (τ^2).

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Advantages of Bayesian Methods

- Can make direct probability statements.
- All evidence regarding a specific problem can be taken into account.
- Predictive statements can be easily made.
- Elicitation of prior belief forces investigators into more careful consideration.
- RE meta-analyses "borrow strength" from one another.
- Decision theoretic framework allows for easy accounting of cost/utilities in making decisions.

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Disadvantages of Bayesian Methods

- Use of prior beliefs undermines objectivity
- Elicitation of priors is non-trivial with few guidelines.
- Computationally complex to implement and time consuming to perform.
- Software limitations.

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Differences from Frequentist Meta-analysis

- Effects of prior distribution
- Between study variance (τ^2) treated as random variable rather than constant in Bayesian analysis (random effects only).
- Study level estimates are "shrunk" towards overall mean due to borrowing of information across studies.

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Implementation: Gibbs Sampling

- Direct computation of posterior distributions is usually not feasible.
- By sampling from full conditional distributions we can get estimates of marginal (unconditional) distributions.
- This is known as Gibbs sampling—a Markov Chain Monte Carlo simulation.

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Gibbs Sampling

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Indirect Comparisons (Bucher et al)

- When no or little direct evidence is available for comparing two interventions, they can be compared indirectly using the methods of Bucher et al.
- This method preserves the randomisation preserves idea inherent in meta-analysis that we should compare directly only within studies.

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Basic Formulation

- No direct evidence comparing A with B, yet estimate of A-B (d_{AB}) is desired.
- Direct evidence exists comparing A with C (d_{AB}) as well as evidence comparing B with C (d_{BC}).
- $d_{AB} = d_{AC} - d_{BC}$
- $Var(d_{AB}) = Var(d_{AC}) + Var(d_{BC})$

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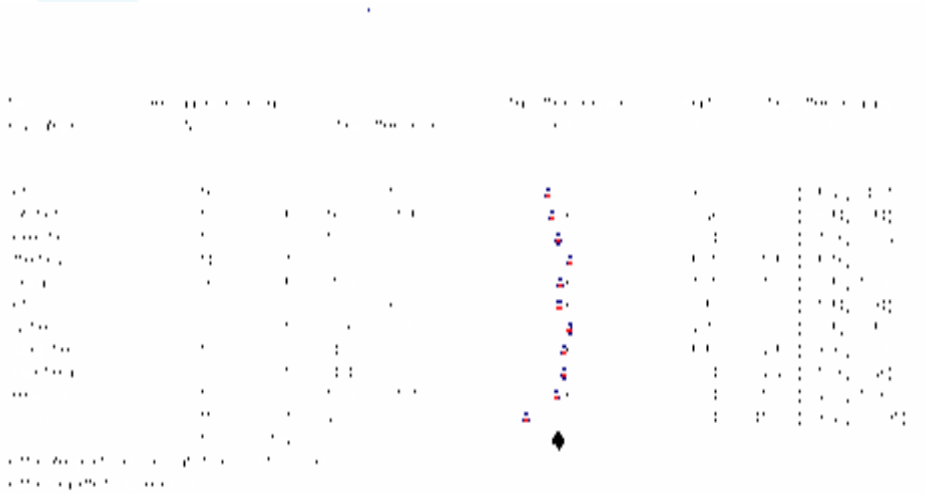
Example



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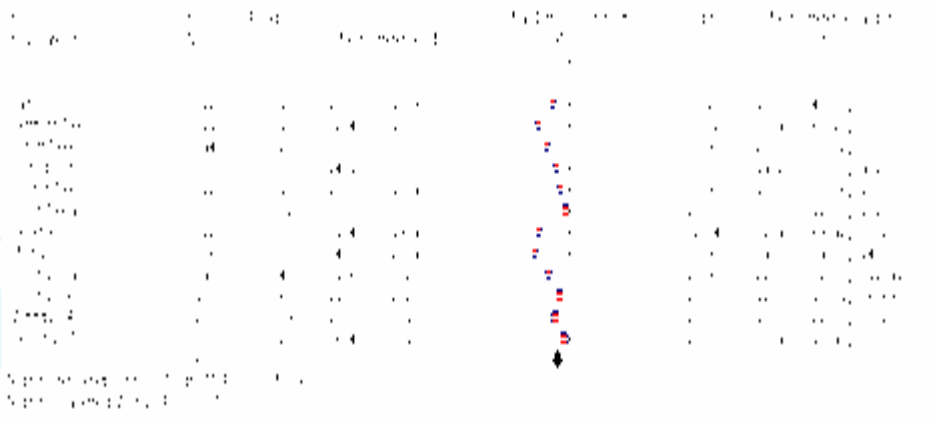
Example



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Example

- Indirect estimate of benzos versus non-benzos can be obtained through their respective direct comparisons with placebo:
- diff = 2.81 (-4.91, 10.52) (using variance formula to compute 95% CI).
- Confidence interval wider than either direct comparison.

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Combining

- Indirect evidence can also be combined with direct evidence.

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Bayesian Network Meta-Analysis (or Mixed Treatment Comparison)

- Also known as mixed treatment comparison (MTC).
- What is it?
- When can/should it be used?
- How do we perform it?

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What is MTC?

- Generalisation of meta-analysis.
- Direct and indirect evidence are combined using Bayesian meta-analysis formulations.
- Accommodates any number of interventions as long as all interventions are connected in a network of studies.

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When Can It Be Used?

- When all interventions are connected in network of studies:

Eg. if we have 7 interventions (A, B, C, D, E, F, G) and we have the following sets of pairwise studies: AB, AC, BC, CD, EF, EG, FG; we can only do an MTC on the A, B, C, D group and E, F, G groups separately, since there is no connecting link

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How is it performed?

- Method sets one treatment as a reference and compares all other treatments to this reference. These are basic parameters and are given prior distributions.
- All other contrasts can be defined as functional parameters of the base parameters.

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Formulation

Four treatments A, B, C, and D. A is baseline treatment:

d_{AB}, d_{AC}, d_{AD} ~N(0,10000)

$d_{BC}=d_{AC}-d_{AB}$
$d_{BD}=d_{AD}-d_{AB}$
$d_{CD}=d_{AD}-d_{AC}$

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Advantages

- Easily incorporates multi-arm trials.
- Easy to incorporate cost-effectiveness into analysis.
- Easy to compute rank statistics.

Disadvantages

- More assumptions required.
- Between studies variance can be difficult to prioritize (random effects only).

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Example: Procedural Sedation

- Four interventions: Midazolam, Etomidate, Propofol and Ketofol.
- 6 trials: M vs E (2 trials)
  M vs E vs P
  M vs P
  E vs P
  P vs K

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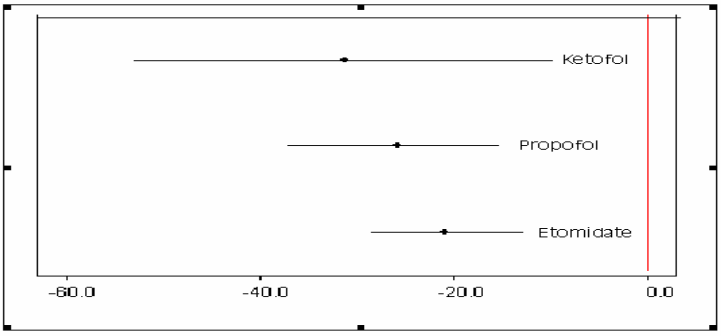
Procedure Time compared to Midazolam (standard care) (minutes)

Intervention	Point Estimate	95% Credible Interval	Probability of "best"
Ketofol	-31.4	-52.9, -9.8	73%
Propofol	-25.7	-36.9, -15.5	24%
Etomidate	-21.2	-28.6, -12.8	3%



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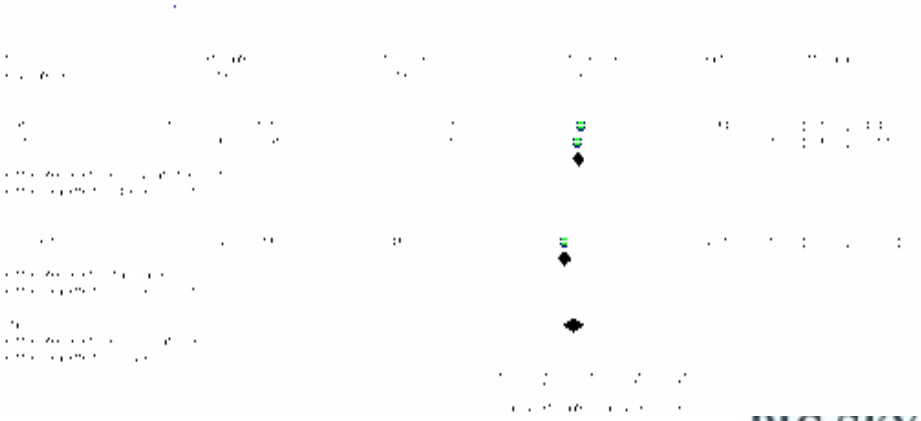
Compare to Frequentist Results



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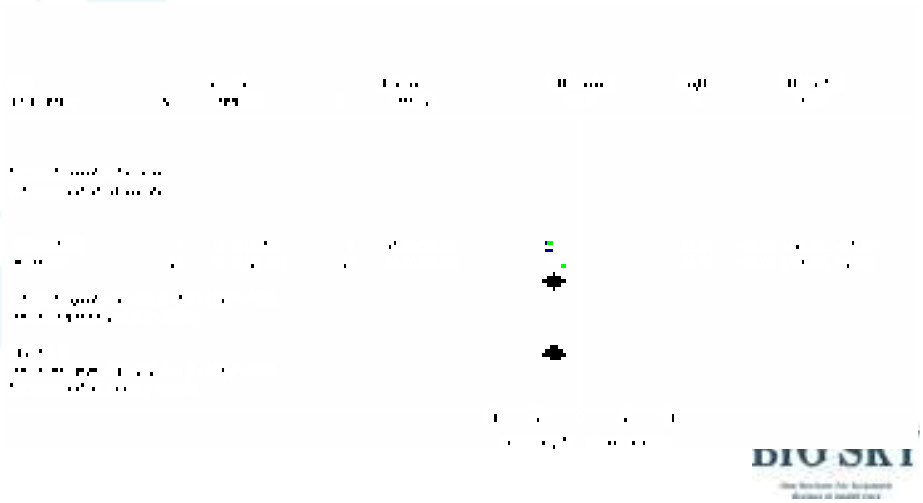

Example 2 Meditation Review

15 interventions:

1. No Intevention
2. Education
3. Yoga
4. Relaxation Response
5. Transcendental Meditation
6. Buddhist Meditation
7. Biofeedback
8. PMR
9. Tai Chi
10. MBCT
11. Mantra Meditation
12. Rest/Relaxation
13. Yoga + Biofeedback
14. Waiting List
15. Qi Gong

23 studies

- 1 vs 3
- 1 vs 3 vs 6
- 1 vs 3 vs 8
- 1 vs 3 vs 13
- 1 vs 5
- 1 vs 9
- 1 vs 10
- 1 vs 11
- 2 vs 3 (2 studies)
- 2 vs 4
- 2 vs 5 (3 studies)
- 2 vs 5 vs 8 (2 studies)
- 3 vs 12
- 4 vs 7 (2 studies)
- 4 vs 7 vs 14
- 12 vs 13
- 14 vs 15 (2 studies)

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Practical Example