Network Meta-Analysis: Case Study using Bariatric Surgery
‘Our’ Learning Objectives

- To better understand issues related to conducting a **rapid network meta-analysis** when an existing systematic review and pair-wise meta-analysis is available.

- To provide an illustration of how to quickly explore whether **expanding a network to include additional treatment nodes** impacts estimates of effect.

- To develop a **hand-on practical example using continuous data** that can be used as an exemplar.
Objective 1

The Cochrane Collaboration
Working together to provide the best evidence for health care

NICE National Institute for Health and Care Excellence

Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé

NCBI
Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed
PubMed comprises more than 22 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.
Objective 2

Smaller homogeneous network using detailed FDA Report information from recent studies

Versus

Larger heterogeneous network using high-level published information spanning decades
Objective 3

Get hands-on practical exercise using continuous outcome and surgical procedure/medical device – most examples have focused on binary outcomes and drugs.

An Introduction to Network Meta-Analysis
A 2-Day Hands-on Workshop

November 6 & 7, 2012 – 9:00 a.m. to 5:00 p.m
Travelodge Ottawa Hotel & Conference Centre
Ottawa, ON

Vancouver – December 2013
Case Study – Bariatric Surgery

• Obesity is a risk factor for chronic disease that leads to morbidity, premature mortality, and impaired quality of life

• The options for the treatment of severe obesity include enhanced physical activity, dietary modification, caloric restriction, use of medications such as orlistat and sibutramine, and bariatric surgery

• Bariatric surgery has become the preferred therapy, at many centres, for severely obese patients who are refractory to medical therapy
Case Study – Bariatric Surgery

- Adjustable gastric band (AGB)
- Sleeve gastrectomy
- Roux-en-Y gastric bypass (RYGB)
- Biliopancreatic diversion with duodenal switch (BPD/DS)
- Banded gastroplasty – Vertical (VBG) Horizontal (HBG)
- Jejunoileal bypass (JB)
Case Study – Bariatric Surgery
### Population, Index Node, Comparators, Outcomes and Study Design

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Adults who fulfill the definition of obesity (i.e., BMI &gt;30), and adolescents who fulfill the definition of obesity for age, sex and height</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index Node</strong></td>
<td>Conventional Treatment</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>Five types of bariatric surgery procedures:</td>
</tr>
<tr>
<td></td>
<td>• Roux-en-Y gastric bypass (RYGB)</td>
</tr>
<tr>
<td></td>
<td>• Vertical banded gastroplasty (VBG)</td>
</tr>
<tr>
<td></td>
<td>• Adjustable gastric banding (AGB)</td>
</tr>
<tr>
<td></td>
<td>• Biliopancreatic diversion with duodenal switch (BPD/DS)</td>
</tr>
<tr>
<td></td>
<td>• Sleeve gastrectomy</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>BMI loss, Percent of excess weight loss (EWL), weight changes (Kg), safety, and resolution of obesity related comorbidities (diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea)</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Network Meta-Analysis of published RCTs</td>
</tr>
</tbody>
</table>

**Rationale:** Less subjective; can be incorporated into HE analyses;
What is a network meta-analysis?
Methods

**Analysis Steps**

- Bayesian Mixed Treatment Comparison NMA using WinBUGS software
- Normal likelihood model allowing for the use of multi-arm trials
- Both fixed and random-effects Bayesian NMA conducted
- Model choice based on assessment of Deviance Information Criterion (DIC) and comparison of residual deviance to number of unconstrained data points
- Compared deviance and DIC statistics in fitted consistency and inconsistency models
- Vague priors assigned for basic parameters throughout Bayesian analyses
- Pair-wise frequentist comparisons (meta-analysis) also conducted
Case Study – Bariatric Surgery

11 RCTs
7 Treatments
N=931

BPD/DS: Biliopancreatic diversion with duodenal switch;
LAGB: Laparoscopic adjustable gastric banding
LRYGB: Laparoscopic Roux-en-Y gastric bypass
LVBG: Laparoscopic vertical banded gastroplasty
VBG: Vertical banded gastroplasty
Results – BMI at 1 year

- **LRYGB**: -9.7(-11.01,-8.39) vs -8.28(-12.76,-3.29)
- **LAGB**: -2.81(-3.73,1.88) vs -1.96(-6.14,2.57)
- **LVBG**: -7.23(-8.64,5.82) vs -5.93(-11.07,-0.29)
- **Sleeve Gastretomy**: -11.92(-13.5,-10.34) vs -10.53(-16.02,-4.52)
- **BPD/DS**: -15.09(-16.95,-13.22) vs -13.39(-17.89,-8.36)
- **Open VBG**: -6.62(-9.24,-3.98) vs -5.73(-12.55,1.47)

**FE: Resdev=35.2 vs 22; DIC=75.8**

**RE: Resdev=22.4 vs 22; DIC=67.3**

**Definitions:**
- **BPD/DS**: Biliopancreatic diversion with duodenal switch;
- **LAGB**: Laproscopic adjustable gastric banding;
- **LRYGB**: Laproscopic Roux-en-Y gastric bypass;
- **LVBG**: Laproscopic vertical banded gastroplasty;
- **VBG**: Vertical banded gastroplasty.
## Results – Random-effects Model

### BMI at 1 year

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conventional Tx</th>
<th>NA</th>
<th>LRYGB</th>
<th>LAGB</th>
<th>LVBG</th>
<th>Sleeve Gastrectomy</th>
<th>BPD/DS</th>
<th>Open VBG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Tx</strong></td>
<td>NA</td>
<td>-3.10 (4.05, -2.15)</td>
<td>NA</td>
<td>NA</td>
<td>-11.5 (-14.82, -8.18)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>LRYGB</strong></td>
<td>-8.28 (-12.76, -3.29)</td>
<td>5.83 (1.92, 9.74); I²=86%</td>
<td>2.98 (0.49, 5.47); I²=56%</td>
<td>-1.10 (-3.58, 1.38)</td>
<td>-6.40 (-8.17, -4.63)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>LAGB</strong></td>
<td>-1.96 (-6.14, 2.57)</td>
<td>6.32 (3.36, 9.08)</td>
<td>LAGB</td>
<td>-4.90 (-6.19, -3.61)</td>
<td>-9.50 (-10.97, -8.03)</td>
<td>NA</td>
<td>-3.80 (-6.25, -1.3)</td>
<td></td>
</tr>
<tr>
<td><strong>LVBG</strong></td>
<td>-5.93 (-11.07, -0.29)</td>
<td>2.35 (-0.94, 5.63)</td>
<td>-3.97 (-7.48, -0.29)</td>
<td>LVBG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Sleeve Gastrectomy</strong></td>
<td>-10.53 (-16.02, -4.52)</td>
<td>-2.25 (-6.32, 1.86)</td>
<td>-8.57 (-12.47, -4.43)</td>
<td>-4.6 (-9.48, 0.39)</td>
<td>Sleeve Gastrectomy</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>BPD/DS</strong></td>
<td>-13.39 (-17.89, -8.36)</td>
<td>-5.11 (-9.54, -0.61)</td>
<td>-11.44 (-16.12, -6.48)</td>
<td>-7.47 (-12.82, -2.03)</td>
<td>-2.87 (-8.66, 2.99)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Open VBG</strong></td>
<td>-5.73 (-12.55, 1.47)</td>
<td>2.55 (-3.73, 8.73)</td>
<td>-3.77 (-9.3, 1.78)</td>
<td>0.2 (-6.47, 6.73)</td>
<td>4.8 (-2.15, 11.54)</td>
<td>7.66 (0.25, 14.91)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
Results—BMI at 1 year
Results– BMI at 1 year

Conclusion: Weight loss varied across the procedures, with biliopancreatic diversion with duodenal switch achieved the greatest weight loss, followed by sleeve gastrectomy, gastric bypass, followed by vertical banded gastroplasty, and finally adjustable gastric band achieved the least weight loss.
Need to consider ...

- Heterogeneity
- Inconsistency
- Convergence
- Prior distributions

Exchangeability Assumption
Inconsistency – How can we assess it?

- Informal approaches – compare direct estimates with those derived from network meta-analytic estimates

- Formal approaches:
  - Bucher method
  - “inconsistency model”
  - node splitting

- While inconsistency must be assessed, tests for inconsistency are inherently underpowered, and will often fail to detect it
Network Meta-Analysis – MTC Model
Mixed Treatment Comparison Model

**Model**

\[
\log \text{it}(p_{jk}) = \mu_{jb} \quad \text{if} \quad k = b; \quad b = A, B, C, \ldots
\]

\[
\mu_{jb} + \delta_{jbk} \quad \text{if} \quad k \text{ after } b
\]

**Probability of event**

Assume \( r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk}) \) where
\( r_{jk} \) number of events in trial j on treatment k
\( n_{jk} \) number of patients in trial j on treatment k

**\( \mu_{jb} \)**

log odds of event on treatment b in trial j (a study specific baseline parameter)

**\( \delta_{jbk} \)**

Trial specific log OR of treatment k relative to treatment b in trial j
(e.g. if trial j compares B and C then B arm provides estimate of \( \logit(p_{jb}) = \mu_{JB} \) and C arm provides estimate of \( \logit(p_{jC}) = \mu_{JB} + \delta_{jBC} \))

Drawn from random effect distribution

\[
\delta_{jbk} \sim N(d_{bk}, \sigma_{bk}^2)
\]

\( d_{bk} \) identifying means of the distributions:

- Treatment effects of B, C, D relative to reference A (basic parameters/contrasts)
- Prior distribution of basic parameters: \( d_{AB}, d_{AC}, d_{AD} \sim N(0, 10000) \)
- Functional parameters expressed in terms of basic parameters (e.g. \( d_{BC} = d_{AC} - d_{AB} \))

\( \sigma_{bk} \) prior distribution for standard deviation: \( \sim \text{Uniform}(0, 2) \)
Inconsistency – Formal Assessment
Comparing Consistency versus ‘Inconsistency’ Model

• In consistency model, basic parameters $d_{AB}$, $d_{AC}$, $d_{AD}$ are given vague priors and consistency equations define other contrasts

\[
\begin{align*}
    d_{BC} &= d_{AC} - d_{AB} \\
    d_{BD} &= d_{AD} - d_{AB} \\
    d_{CD} &= d_{AD} - d_{AC}
\end{align*}
\]

• In inconsistency model, each of the six mean treatment effects ($d_{AB}$, $d_{AC}$, $d_{AD}$, $d_{BC}$, $d_{BD}$, $d_{CD}$) is treated as separate (independent) parameter to be estimated and no consistency is assumed
Inconsistency Plot – BMI at 1 year

Plot of the individual data points posterior mean deviance contributions for the consistency model (horizontal axis) and the inconsistency model (vertical axis) along with the line of equality – BMI, 1 Year

Special thanks to Sofia Dias
Forest Plot – Consistency versus Inconsistency Model

LAGB vs Conventional Tx
BPD/DS vs Conventional Tx
LAGB vs LRYGB
LVBG vs LRYGB
Sleeve Gastretomy vs LRYGB
BPD/DS vs LRYGB
LVBG vs LAGB
Sleeve Gastretomy vs LAGB
Open VBG vs LAGB

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Consistency Model</th>
<th>Inconsistency Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAGB vs Conventional Tx</td>
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<td>-5.11(-9.54,-0.61)</td>
<td>-6.41(-12.8,0.01)</td>
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<td>Sleeve Gastretomy vs LAGB</td>
<td>-8.57(-12.47,-4.43)</td>
<td>-9.49(-15.85,-3.15)</td>
</tr>
<tr>
<td>Open VBG vs LAGB</td>
<td>-3.77(-9.3,1.78)</td>
<td>-3.78(-10.38,2.8)</td>
</tr>
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</table>

Mean Difference in BMI, 1 Year (95% CrI)
Inconsistency – Formal Assessment

Examine Network Diagrams Closely

Simple Network

Yes

Bucher Method or extensions
or compare to an “inconsistency” model in WinBUGS

No

Number of loops? Multi-arm trials?

Complex Network

Yes

Compare to an “inconsistency” model in WinBUGS or Node Splitting Method
Common Issue for rapid network meta-analysis – Exclusion Criteria

- Did not include studies with horizontal banded gastroplasty (HGB) or jejunoileal bypass (JB) – no longer performed

- Did not include comparisons for one procedure using different techniques (e.g., open versus laparoscopic)

- Did not include abstracts

Is there another source of information that can be used to quickly obtain this information and see if inclusion of these studies would impact results?
Other Systematic Reviews

Obesity Treatment

Bariatric surgery: a systematic review and network meta-analysis of randomized trials

R. Padwal\(^1\), S. Klarenbach\(^1\), N. Wiebe\(^1\), D. Birch\(^2\), S. Kamal\(^2\), B. Manna\(^2\), M. Hazel\(^1\), A. M. Sharma\(^1\) and M. Tonelli\(^1\)

\(^1\)Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; \(^2\)Department of Surgery, University of Alberta, Edmonton, Alberta, Canada; \(^3\)Department of Medicine, University of Calgary, Calgary, Alberta, Canada

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Summary
The clinical efficacy and safety of bariatric surgery trials were systematically reviewed. MEDLINE, EMBASE, CENTRAL were searched to February 2009. A basic PubCrawler alert was run until March 2010. Trial registries, HTA websites and systematic reviews were searched. Manufacturers were contacted. Randomized trials comparing bariatric surgeries and/or standard care were selected. Evidence-based items potentially indicating risk of bias were assessed. Network meta-analysis was performed using Bayesian techniques. Of 1838 citations, 31 RCTs involving 2619 patients (mean age 30–48 y; mean BMI levels 42–58 kg/m\(^2\)) met eligibility criteria. As compared with standard care, differences in BMI levels from baseline at year 1 (15 trials; 1103 participants) were as follows: jejunoileal bypass [-11.4 kg/m\(^2\)], mini gastric bypass [-11.3 kg/m\(^2\)], biliopancreatic diversion [-11.2 kg/m\(^2\)], sleeve gastrectomy [-10.1 kg/m\(^2\)], Roux-en-Y gastric bypass [-9.0 kg/m\(^2\)], horizontal stapled gastroplasty [-5.0 kg/m\(^2\)], vertical banded gastroplasty [-6.4 kg/m\(^2\)], and adjustable gastric banding [-2.4 kg/m\(^2\)]. Bariatric surgery appears more efficacious compared to standard care in reducing BMI. Weight losses are greatest with diversionary procedures, intermediate with diversionary/ restrictive procedures, and lowest with those that are purely restrictive. Compared with Roux-en-Y gastric bypass, adjustable gastric banding has lower weight loss efficacy, but also leads to fewer serious adverse effects.

Keywords: Bariatric surgery, obesity, network meta-analysis.

obesity reviews (2011) 12, 602-621

Special thanks to Scott Klarenbach & Natasha Wiebe
<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Severely obese subjects with an accepted indication for bariatric surgery: BMI &gt;40 (or BMI&gt; 35 kg m with at least one obesity-related comorbidity)</th>
</tr>
</thead>
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<tr>
<td><strong>Index Node</strong></td>
<td>Conventional Treatment</td>
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<tr>
<td><strong>Comparators</strong></td>
<td>Five types of bariatric surgery procedures (open or laproscopic):</td>
</tr>
<tr>
<td></td>
<td>• Roux-en-Y gastric bypass (RYGB)</td>
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<td>• Horizontal gastroplasty</td>
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<td></td>
<td>• Jejunoileal bypass</td>
</tr>
<tr>
<td></td>
<td>• Mini GB</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>BMI loss, all-cause mortality, control of comorbidity, hospitalization, reoperations, gastrointestinal disturbances and serious surgical sequelae</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Network Meta-Analysis of published RCTs</td>
</tr>
</tbody>
</table>
Case Study – Bariatric Surgery

17 RCTs
12 Treatments
N=1203

BPD/DS: Biliopancreatic diversion with duodenal switch;
LAGB: Laparoscopic adjustable gastric banding
LRYGB: Laparoscopic Roux-en-Y gastric bypass
LVBG: Laparoscopic vertical banded gastroplasty
VBG: Vertical banded gastroplasty
JB: Jejunoileal bypass
HG: Horizontal gastroplasty
Common Issue for rapid network meta-analysis – Exclusion Criteria

• Added 6 studies to network original network

• Majority were older smaller studies – 5 of 6 studies from 1980’s using open surgery (versus laprospopic surgery)

• One study from 2005 comparing LRYGB vs Laproscopic mini-GB

• Did not have a significant impact on estimates of effect
Results—BMI at 1 year, Common Treatments in Expanded vs. Original network
Limitations

• Only considered 1 outcome – BMI

• Only considered 1 time point (e.g., 1 year BMI versus 2 years)

• May have missed studies due to slightly different patient populations

• Did not assess impact of heterogeneity across trials in significant detail

• Need to update search dates beyond 2011
Moving Forward – Rapid Network Meta-Analysis for Atypical Antipsychotics

Antipsychotics in Adults With Schizophrenia: Comparative Effectiveness of First-Generation Versus Second-Generation Medications

A Systematic Review and Meta-analysis

Lisa Hartling, PhD; Ahmed Al Abor-Setta, MD, PhD; Serdar Dursun, MD, PhD; Shima S. Mozavi, MD; Dior Pasichnyk, BSc; and Amanda S. Newton, RN, PhD

Background: Debate continues about the comparative benefits and harms of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in treating schizophrenia.

Purpose: To compare the effects of FGAs with those of SGAs in the treatment of adults aged 18 to 64 years with schizophrenia and related psychosis on illness symptoms, diabetes mellitus, mortality, tardive dyskinesia, and a major metabolic syndrome.

Data Sources: English-language studies from 10 electronic databases to March 2012, including PubMed, Embase, and others.

Methods: A comprehensive search was conducted to identify relevant studies. Data were extracted, and a meta-analysis was performed using both fixed- and random-effects models.

Key Outcomes: The results showed a lower risk of extrapyramidal symptoms and a lower risk of tardive dyskinesia with SGAs compared to FGAs. The risk of diabetes mellitus was higher with SGAs, and the risk of mortality was similar between the two groups.

Conclusion: SGAs are associated with improved extrapyramidal symptoms and lower risk of tardive dyskinesia compared to FGAs, but may have a higher risk of diabetes mellitus.

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

A systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for the treatment of adult patients with schizophrenia

Leslie Citrome
New York Medical College, Valhalla, NY, USA

Introduction: Meta-analyses are a convenient way for clinicians and researchers to review data regarding different interventions. Meta-analyses can overcome many of the limitations of individual studies, namely the power to detect differences, and help resolve the results of inconsistent studies.

Areas covered: This paper is a review of meta-analyses of oral atypical antipsychotics for the treatment of schizophrenia, located through PubMed and the Cochrane Database of Systematic Reviews. A total of 81 meta-analyses were identified that included efficacy outcome data for the 10 atypical antipsychotics available in the USA (11 focused on clozapine, 17 for risperidone, 8 for olanzapine, 5 for quetiapine, 3 for ziprasidone, 10 for aripiprazole, 5 for...
Questions or Thoughts?