Where Are You Finding the Academic Details?
Using Evidence to Develop Strong Content

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Interior Health
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DISCLOSURES – Cristi Froyman
✓ Employee of Interior Health and the British Columbia Provincial Academic Detailing Service
  – Funding provided by the Pharmaceutical Services Division, BC Ministry of Health (Government)
✓ No other financial conflicts of interest to declare

DISCLOSURES – Cait O’Sullivan
✓ Employee of Island Health and the British Columbia Provincial Academic Detailing Service
  – Funding provided by the Pharmaceutical Services Division, BC Ministry of Health (Government)
✓ Employee of Therapeutics Initiative, University of British Columbia
  – Funding provided by the BC Ministry of Health
✓ No other financial conflicts of interest to declare

Goal of Academic Detailing

“Montori: the reason you spend time getting the evidence right is so someone can draw on the evidence to create kind and careful care #CochraneForAll”

Goal of Academic Detailing

“To close the gap between the best available science and actual prescribing practice, so that each prescription is based only on the most current and accurate evidence about efficacy, safety, and cost-effectiveness.”

Is this consistent with your service goals?

Together we will…

1. Consider diverse sources of drug evidence to enrich scientific literacy and knowledge translation.
2. Explore strategies of engaging a team in evidence-informed content development.
3. Identify effective and clear communication skills where evidence is discordant from contemporary clinical practice guideline recommendations.
**Agenda – Content Development**

**Introduction:** (15 minutes) Process (Ours & Yours)

**Examine various sources of drug-evidence:** (45 minutes) 3 examples

**Application:** (15 minutes) Incorporating the team and topic preparation

**Wrap Up:** (15 minutes)

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**What we do in B.C.**

1. Needs Assessment

2. Working Groups
   - Research
   - Critically appraise
   - Assemble content

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**What we do in B.C.**

3. Resources
   a. Guidelines: Local and International
   b. Systematic Reviews: eg, Cochrane Database
   c. Regulatory Reviews: Health Canada Summary Basis of Decision and FDA Medical Reviews
   d. Product Monographs: Indications, dosing, precautions, contraindications, drug interactions
   e. Drug Interaction Tools: Lexi Drugs; CredibleMeds

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**What we do in B.C.**

4. Critical Appraisal
   a. Guidelines: IOM “Guidelines we can Trust” tool, reference check
   b. Systematic Reviews: RCTs, protocols, supplements and editorials, Cochrane Risk of Bias Tool

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**What we do in B.C.**

5. Detailer *Upskilling*
   - WebEx presentations
   - In person 3 day workshop

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**What do your Programs do?**

**Who develops the educational content?**

**How much input do detailers have?**
Clinical Practice Guideline Methodology

Systolic Blood Pressure Targets for Adults ≥ 60 Years:

How do you critically appraise guideline methodology?

What is your first step?

2017 Clinical Practice Guidelines SBP Goals Age ≥ 60

<table>
<thead>
<tr>
<th>Am College of Physicians / Am Assoc Family Physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt; 150 mmHg</td>
</tr>
<tr>
<td>High quality evidence</td>
</tr>
<tr>
<td>Strong recommendation</td>
</tr>
<tr>
<td>SBP &lt; 140 mmHg [high risk]</td>
</tr>
<tr>
<td>Low quality evidence</td>
</tr>
<tr>
<td>Weak recommendation</td>
</tr>
</tbody>
</table>

Hypertension Canada

| SBP < 140 mmHg                                      |
| Grade C Strong recommendation                       |
| SBP ≤ 120 mmHg [high risk]                          |
| Grade B Strong recommendation                       |

 Goals for adults ≥ 60 years ranged from SBP < 150 mm Hg to ≤ 120 mm Hg

2018 Clinical Practice Guidelines HbA1c Goals

<table>
<thead>
<tr>
<th>Am Assoc Clinical Endocrinology / Am College Endocrinology</th>
</tr>
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<tbody>
<tr>
<td>≤ 6.5% ➤ &quot;optimal&quot;</td>
</tr>
<tr>
<td>&quot;fundamental to the prevention of microvascular complications&quot;</td>
</tr>
</tbody>
</table>

American Diabetes Association

| < 7% ➤ "reasonable" |
| < 6.5% ➤ "might"    |
| "shown to reduce microvascular complications"             |

Diabetes Canada

| ≤ 7% ➤ "should be" |
| ≤ 6.5% ➤ "may be"  |
| "strong benefits for microvascular complications"        |

Seeking Clear Language

Intensive Glucose Control for Adults with Type 2 Diabetes:

How would you explain the microvascular effects?

What is your first step?
## 2018 Clinical Practice Guidelines HbA1c Goals

<table>
<thead>
<tr>
<th>Organization</th>
<th>HbA1c Goals</th>
<th>Comments</th>
</tr>
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<tr>
<td>American College of Physicians</td>
<td>7% - 8%</td>
<td>“aim”</td>
</tr>
<tr>
<td>&lt; 6.5%</td>
<td>“deintensify” main effect of more intensive glycemic control is small absolute risk reductions in the risk for microvascular surrogate events</td>
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**Newly Approved Medication**

**Ertugliflozin for Type 2 Diabetes:**

**What was the scientific basis for its approval?**

What is your first step?

**Small Group Discussions**

Split into 3 groups, you will have 15 minutes

Discuss how each of your services would approach topic content development for the scenario you have been given

We will debrief as a large group for 30 minutes

**Clinical Practice Guideline Methodology**

**Systolic Blood Pressure Targets for Adults ≥ 60 Years:**

How do you critically appraise guideline methodology?

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2017 Clinical Practice Guidelines SBP Goals Age ≥ 60

| SBP < 150 mmHg | High quality evidence | Strong recommendation |
| SBP < 140 mmHg [high risk] | Low quality evidence | Weak recommendation |

Hypertension Canada

| SBP < 140 mmHg | Grade C | Strong recommendation |
| SBP ≤ 120 mmHg [high risk] | Grade B | Strong recommendation |

Institute of Medicine of the National Academies: Clinical Practice Guidelines we can Trust – Standards for Developing Trustworthy Clinical Practice Guidelines

<table>
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<th>Standards</th>
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<tbody>
<tr>
<td>establishing transparency</td>
<td>process of development and funding should be explicit and publicly accessible</td>
</tr>
<tr>
<td>management of COI</td>
<td>members with conflict of interest should not represent more than a minority</td>
</tr>
<tr>
<td>guideline development group composition</td>
<td>multidisciplinary, balanced, methodological experts &amp; clinicians, patients &amp; public</td>
</tr>
<tr>
<td>clinical practice guideline – SRs</td>
<td>should use systematic reviews of evidence</td>
</tr>
<tr>
<td>rating strength of recommendations</td>
<td>clear description of benefits &amp; harms; rating of level of confidence in evidence and strength of recommendations</td>
</tr>
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BP Targets for Adults > 60 Years

Describe the evidence referenced for treating hypertension in older adults

Search for other Systematic Reviews
Seeking Clear Language

Intensive Glucose Control for Adults with Type 2 Diabetes:

How would you explain the microvascular effects?

What is your first step?

2018 Clinical Practice Guidelines HbA1c Goals

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2017: Two Systematic Reviews

Intensive Glucose Control

Cochrane 2017
- 14 RCTs; 29,319 participants
- “Based on absolute treatment effects, the clinical impact of targeting an HbA1c < 7% or blood glucose < 6.6 mmol/L is unclear and the potential harms of this treatment approach are largely unmeasured.”

CONTROL 2017
- 4 RCTs; 27,049 participants
- “More intensive control over 5 years reduced both kidney and eye events. Glucose lowering remains important for the prevention of long-term microvascular complications in adults with type 2 diabetes.”
**GRADE Approach**

<table>
<thead>
<tr>
<th>Quality of Evidence or Level of Certainty</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the estimate of the effect: The true effect is likely to be substantially different from the estimate of the effect</td>
</tr>
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http://gdt.guidelinedevelopment.org/apps/handbook/handbook.html

**Newly Approved Medication**

Ertugliflozin for Type 2 Diabetes:

What was the scientific basis for its approval?

What is your first step?


clinical relevant outcome
direct measurement of how a person feels, functions, or survives

surrogate outcome
lab measurement or physical sign that substitutes for clinical outcomes when they are relatively infrequent or occur over long periods of time

metformin
glibizide
gliclazide
repaglinide
acarbose
rosiglitazone
sitagliptin
saxagliptin
linagliptin
alogliptin
canagliflozin
dapagliflozin
empagliflozin
ertugliflozin
lixiagliptide
exenatide
dulaglutide
albiglutide
lixisenatide
semaglutide

When to include clinical study reports and regulatory documents in systematic reviews

Tom Jefferson,1,2* Peter Doshi,1,2* Isabelle Boutron,3* Su Golder,1,2 Carl Heneghan,4* Alex Hodkinson,5* Mark Jones,2,2* Carol Lefebvre,2,2* Lesley A Stewart2,2*
How to use FDA drug approval documents for evidence synthesis

► minimize impact of reporting biases
► obtain information not disclosed in clinical trials reports
► identify unpublished clinical trials
► assessment quality of evidence (risks of bias)

Research misconduct identified by the US FDA:
Out of sight, out of mind, out of the peer-reviewed literature

► departures from good clinical practice
► not reported in 96% of published trials

US FDA Reviews: Ertugliflozin

Summary 27 pages
Medical 299 pages
Pharmacology 805 pages
Statistical 146 pages

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209803,209805,209806Orig1s000SumR.pdf

US FDA Reviews

Search for FDA Guidance Documents

https://www.fda.gov/RegulatoryInformation/Guidances/

Summary Review

“One concern is the analysis population. Dr. Cambon believes that the analysis populations should include all randomized subjects … He does not believe that it adequately addresses missing data”

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209803,209805,209806Orig1s000SumR.pdf
Executive Summary
Therapeutic Context
Regulatory Background
Issues from other review disciplines
Sources of clinical data
Review of efficacy trials
Efficacy review
Safety review
Advisory committee meeting
Labelling recommendations
Risk evaluation and mitigation strategies
Postmarketing requirements

Postmarketing Requirements
- Cardiovascular outcomes study
- FDA 2008 guidance to industry
- Adverse events of special interest
- Renal function
- Amputations
- Complicated urinary tract infections
- Fractures
- Pancreatitis
- Serious hypersensitivity events
- Malignancy

Demographics

Dose Response

15 mg ▼ HbA1c: 0.713%
5 mg ▼ HbA1c: 0.625%
difference < 0.1%

FDA medical reviewer

“Clinical relevance of these nominal changes is uncertain”

US FDA Reviews

2016 Meeting Materials, Endocrinologic and Metabolic Drugs Advisory Committee

US FDA Advisory Committee Briefing information: 291 pages
US FDA Advisory Committee Transcript of Meeting: 298 pages

Calverly N. Engl J Med 2007;356:775-81
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugAdvisoryCommittee/ucm491062.htm

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209803,209805,209806Orig1s000MedR.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209803,209805,209806Orig1s000MedR.pdf

NEJM publication: 15 pages
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugAdvisoryCommittee/ucm491062.htm

Ray B. Circulation 2007;115:2222-30
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugAdvisoryCommittee/ucm491062.htm
GSK Clinical Study Report: 5481 pages

https://www.gsk-clinicaltrialsregister.com/search/?study_id=SCO30003

Health Canada Summary Basis of Decision


Role of Guidelines

"guidelines may provide a starting point for searching for information, but they are not the finish line"

John H. Powers, MD

Incorporating the Team (15 min)

How can each member of your team contribute to topic content development and preparation?

How can we advance academic detailers' scientific literacy with each topic?

Wrap-up

What do you do when you identify that “strong recommendations” in contemporary clinical practice guidelines have no or low quality evidence to support them?

How do we communicate evidence that is practical and scientific?

How can detailers improve the participants’ scientific literacy with each topic?
Practice Change?

Is there one thing you will change tomorrow as a result of this session?

Resources

- Cochrane Handbook for Systematic Reviews of Interventions: https://training.cochrane.org/handbook
- Cochrane Library: Cochrane Reviews: https://www.cochranelibrary.com/
- GRADE Welcome to the GRADE working group: http://www.gradeworkinggroup.org/
- Turner E. How to access and process FDA drug approval packages for use in research. BMJ 2013;347:f5992
- American College of Physicians Clinical Guidelines & Recommendations: https://www.acponline.org/clinical-information-guidelines