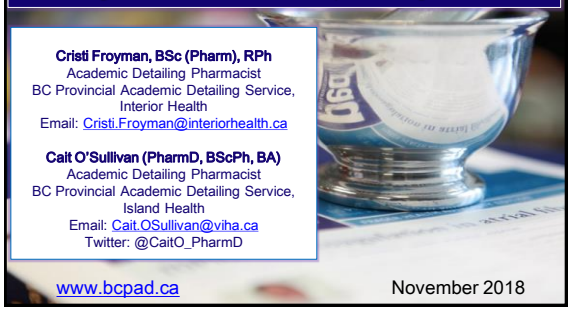
Where Are You Finding the Academic Details?

Using Evidence to Develop Strong Content



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www.bcpad.ca

November 2018

pad BC PROVINCIAL ACADEMIC DETAILING SERVICE
YOUR Rx FOR EVIDENCE-INFORMED PRESCRIBING

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

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- ✓ Employee of Therapeutics Initiative, University of British Columbia
  - Funding provided by the BC Ministry of Health
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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?

Avorn, Jerry. Presentation (2011): Academic detailing: an introduction. https://slideplayer.com/slide/9175351/

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"

https://twitter.com/CochraneCCRG/status/1042081132030910464

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)

What we do in B.C.

1. Needs Assessment

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

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

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

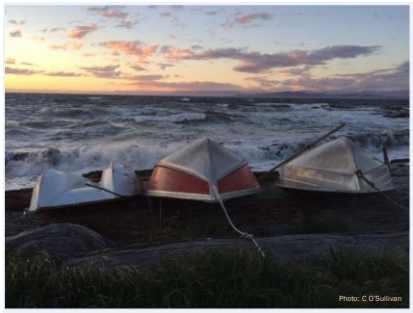
What we do in B.C.

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

What do your Programs do?

Who develops the educational content?

How much input do detailers have?



1. Clinical Practice Guideline Methodology: Trustworthiness
2. Seeking Clear Language: Person Centered Outcomes
3. Newly Approved Medication: Scientific Basis of its Approval

Clinical Practice Guideline Methodology

Systolic Blood Pressure Targets for Adults ≥ 60 Years:

How do you critically appraise guideline methodology?

What is your first step?

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

J Clin Hypertension 2015;17:486-492; https://www.healthquality.va.gov/guidelines/CD/htn/; Hypertension 2016;67:820-825; 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension 2017; epub Nov 13; Ann Int Med 2017;166:430-437; Can J Cardiology 2017;33:557-576

2017 Clinical Practice Guidelines SBP Goals Age ≥ 60

Am College of Physicians / Am Assoc Family Physicians	
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

American College of Physicians and American Academy of Family Physicians: Ann Int Med 2017;166:430-437
Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiology 2017;33:557-576

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

Am Assoc Clinical Endocrinology / Am College Endocrinology	
≤ 6.5% ► "optimal"	"fundamental to the prevention of microvascular complications"
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"

AACE/ACE Endocrine Practice 2018:24:91-120; ADA Diabetes Care 2018:41:S1-S159; Diabetes Canada Can J Diabetes 2018;42:S42-S46; QASEEM Ann Intern Med 2018;168:569-576

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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?

metformin
glyburide
gliclazide
glimepiride
repaglinide
acarbose
rosiglitazone
pioglitazone
sitagliptin
saxagliptin
linagliptin
alogliptin
canagliflozin
dapagliflozin
empagliflozin
ertugflifiozin
liraglutide
exenatide
dulaglutide
albiglutide
lixisenatide
semaglutide

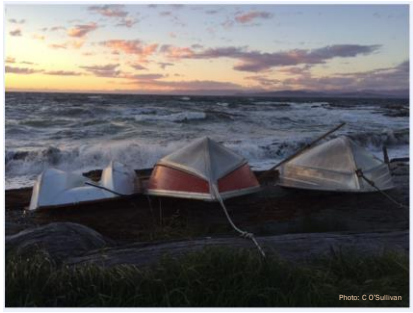
AACE ACP Endocrine Practice 2018;24:91-120

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



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Health and Medicine Division of the National Academies of Sciences

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

tool to assess trustworthiness

http://iom.nationalacademies.org/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

Institute of Medicine: Standards for Developing Trustworthy Clinical Practice Guidelines	
Standards	**Comments**
establishing transparency	process of development and funding should be explicit and publicly accessible
management of COI	members with conflict of interest should not represent more than a minority
guideline development group composition	multidisciplinary, balanced, methodological experts & clinicians, patients & public
clinical practice guideline – SRs	should use systematic reviews of evidence
rating strength of recommendations	clear description of benefits & harms; rating of level of confidence in evidence and strength of recommendations

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clinical practice guideline – SRs	should use systematic reviews of evidence
rating strength of recommendations	clear description of benefits & harms; rating of level of confidence in evidence and strength of recommendations
articulation of recommendations	precise
external review	full spectrum of relevant stakeholders
updating	proposed date for future review

http://iom.nationalacademies.org/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

Institute of Medicine: Standards for Developing Trustworthy Clinical Practice Guidelines		
Standards	**HC 2017**	**ACP 2017**
establishing transparency		
management of COI		
guideline development group composition		
clinical practice guideline – SRs	1 RCT	6 RCTs
rating strength of recommendations		
articulation of recommendations		
external review		
updating		

http://iom.nationalacademies.org/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

BP Targets for Adults ≥ 60 Years

Describe the evidence referenced for treating hypertension in older adults

Search for other Systematic Reviews

https://www.cochranelibrary.com/

http://hypertension.cochrane.org/

145
Cochrane Hypertension
Systematic Reviews

Seeking Clear Language

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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."	

RUOSPO Cochrane Database Syst Rev 2017 CD010137; CONTROL Lancet Diabetes Endocrinol 2017:5:431-437

COCHRANE 2017

RUOSPO Cochrane Database Systematic Reviews 2017, Issue 6. Art. No. CD010137

GRADE Approach

Quality of Evidence or Level of Certainty

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	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
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the estimate of the effect: The true effect is likely to be substantially different from the estimate of effect

http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

CONTROL 2017

kidney outcome

eye outcome

CONTROL Lancet Diabetes Endocrinol 2017:5:431-437

clinically 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

https://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM337268.pdf

Newly Approved Medication

Ertugliflozin for Type 2 Diabetes:

What was the scientific basis for its approval?

What is your first step?

metformin
glyburide
gliclazide
glimepiride
repaglinide
acarbose
rosiglitazone
pioglitazone
sitagliptin
saxagliptin
linagliptin
alogliptin
canagliflozin
dapagliflozin
empagliflozin
ertugliflozin
liraglutide
exenatide
dulaglutide
albiglutide
lixisenatide
semaglutide

AACE ACP Endocrine Practice 2018;24:91-120

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

Tom Jefferson,[1,2] Peter Doshi,[2,3] Isabelle Boutron,[4,5]
Su Golder,[6,7] Carl Heneghan,[1,2] Alex Hodkinson,[8,9]
Mark Jones,[2,10] Carol Lefebvre,[11,12] Lesley A Stewart[9,13]

→ Product new to the market

JEFFERSON BMJ Evidence Based Medicine 2018 Oct 11 [Epub ahead of print]

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

LADANIE BMJ 2018;362:k2815; SEIFE JAMA Intern Med 2015;175:467-77

US FDA Reviews

Drugs@FDA

https://www.accessdata.fda.gov/scripts/cder/daf/

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

Summary Review

"The primary endpoint in all of the phase 3 trials was change from baseline in HbA1c"

"This in turn should result in improved clinical outcomes"

6/7 trials: 26 weeks | 1/7 trials: 52 weeks

3409 people exposed to ertugliflozin

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

LADANIE BMJ 2018;362:k2815

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

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

Demographics

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

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"

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

US FDA Reviews

2016 Meeting Materials, Endocrinologic and Metabolic Drugs Advisory Committee

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm491062.htm

NEJM publication: 15 pages

US FDA Advisory Committee Briefing information: 291 pages

US FDA Advisory Committee Transcript of Meeting: 298 pages

CALVERLY N Engl J Med 2007:356:775-89;
https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#PulmonaryAllergy

GSK Clinical Study Report: 5481 pages

https://www.gsk-clinicalstudyregister.com/search/?study_ids=SCO30003

Health Canada Summary Basis of Decision

https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html

Summary Basis of Decision - Trintellix - Health Canada

11 RCTs
4 "positive"
7 "negative or questionable"

https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html

Role of Guidelines

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

John H. Powers, MD

POWERS Arch Intern Med 2011;171:15-18

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/
GRADE Handbook	https://gdt.gradepro.org/app/handbook/handbook.html
Institute of Medicine: Clinical Practice Guidelines We Can Trust	http://www.nationalacademies.org/hmd/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx
US Food and Drug Administration: FDA Approved Drug Products	https://www.accessdata.fda.gov/scripts/cder/daf/ Drugs@FDA
Ladanie A, Ewald H, Kasenda B, Hemkens L. How to use FDA drug approval documents for evidence synthesis. *BMJ* 2018;362:k2815	https://www.bmj.com/content/bmj/362/bmj.k2815.full.pdf
Turner E. How to access and process FDA drug approval packages for use in research. *BMJ* 2013;347:f5992	https://www.bmj.com/content/347/bmj.f5992.full.print
Health Canada Summary Basis of Decision	https://hpr-rps.hres.ca/reg-content/summary-basis-decision.php
American College of Physicians Clinical Guidelines & Recommendations	https://www.acponline.org/clinical-information/guidelines