GRADE, EBM and Deprescribing

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“Research is like turning on the light before you clean up the room: it doesn’t clean it for you but does tell you where the problems are”

(Frank Davidoff, Annals of Internal Medicine)
GRADE Walkthrough
GRADE

- GRADE emerged from an informal meeting in Oslo, Norway in 2000.
- Led to a GRADE series in BMJ in 2008
- 26 GRADE methods series began in J Clin Epi 2012
- Leading WHO methods and Canadian Task Force, IOM Standards and over 100 guidelines organizations
- Over 400 international GRADE members, debate science evidence and guidelines and apply this across diverse fields
Examples of GRADE Recommendations

• PPI - Strong for deprescribing (low quality evidence) (Farrell CFP 2017)

• BZRA for insomnia- Weak for deprescribing (low quality evidence) Strong for elderly (low quality of evidence) (Pottie CFP in press)

• Antipsychotics in dementia: Taper and stop antipsychotics slowly in collaboration with the patient and caregivers (strong recommendation, moderate-quality evidence) (Bjerre 2018)
Strong and Weak Recommendations

• A strong recommendation implies that all patients in the given situation would want the recommended course of action, and only a small proportion would not.

• A weak recommendation implies that most patients would wish to follow the recommendation, but some patients would not. (more shared decision making)
Deprescribing can include stopping, stepping down, or reducing doses

- Stopping can be done either via abrupt discontinuation or a tapering regimen

- Stepping down involves abrupt discontinuation or tapering

- Reducing dose
**Unique elements of GRADE: Patient Important Outcomes**

**Primary outcomes: GRADE lingo: critical outcomes**
- Quality of life
- **Sleep quality**
- Effect on cognition
- Effect on anxiety
- Adverse drug withdrawal events
- **Cessation rate**
- Harms

**Secondary outcome: GRADE lingo: Important outcomes**
- Patient satisfaction
- aBZRA pill burden
### Sleep Latency at 1 Year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CBT+taper</th>
<th>Taper</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Lichstein 2013</td>
<td>24.1</td>
<td>16.7</td>
<td>24</td>
</tr>
<tr>
<td>Morin 2004</td>
<td>23.82</td>
<td>4.77</td>
<td>27</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>51</td>
<td>47</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 243.41; Chi² = 13.35, df = 1 (P = 0.0003); I² = 93%

Test for overall effect: Z = 1.02 (P = 0.31)
Sleep Efficiency

Post-treatment

At 1 year follow-up
Role of logic models

• Logic models demonstrate a chain of logic between inputs and outcomes and to capture possible alternative explanations

• Logic models can be used at different stages of a systematic review, for example,
  – scoping the review,
  – refining and conducting the review,
  – and making the review relevant to policy and practice
Figure 1. Analytic Framework and Key Questions

1. Screening
   Tuberculin skin test or interferon-gamma release assay

2. Latent tuberculosis infection

3. Treatment
   - Reduced incidence of active tuberculosis disease
   - Reduced tuberculosis transmission
   - Improved quality of life
   - Reduced tuberculosis disease or overall mortality

4. Harms of screening

5. Harms of treatment

Asymptomatic adults belonging to populations at increased risk
Key questions

1. Is there direct evidence that targeted screening for latent tuberculosis infection (LTBI) in primary care settings in asymptomatic adults at increased risk for developing active tuberculosis disease (eg, individuals in populations with a high prevalence of active TB disease or with documented increased risk for progression from LTBI to active TB disease) improves quality of life, or reduces active TB disease incidence, or reduces transmission of TB, or reduces disease-specific or overall mortality?

2. a. What is the accuracy and reliability of the TST or the interferon-gamma release assay (IGRA) for screening asymptomatic adults who are at increased risk for developing active TB disease?
   b. What is the accuracy and reliability of sequential screening strategies that include both TST and IGRA testing in asymptomatic adults who are at increased risk for developing active TB disease?

3. Does treatment of LTBI with CDC-recommended pharmacotherapy regimens improve quality of life or reduce progression to active TB disease, or reduce transmission of TB, or reduce disease-specific or overall mortality?

4. Are there harms associated with screening for LTBI?
   a. Do these harms differ by screening method or strategy?
   b. Do these harms differ by population?

5. Are there harms associated with treatment for LTBI with CDC-recommended pharmacotherapy regimens?
Patients’ perspective
- Patients’ perceptions, concerns about medication use and deprescribing
- Shared decision-making
- Cost (financial, other)

People at risk
- Elderly (over age 65); differentiate robust vs. frail?

Deprescribe
- Does reducing the dose/or stopping this drug (class) do more good than harm?
- Subquestion for which we use existing materials: What evidence is there for effectiveness or harm in continuing the drug/drug class?

Short term outcomes
- Evidence for benefit of deprescribing
- Evidence for safety of deprescribing
- Evidence for harm of deprescribing

Long-term outcomes
- Quality of life
- Self-reported health
- Reduced morbidity
- Reduced mortality

Balance benefits vs. harms model

Patient important outcomes (examples provided; content and relevance to be determined):
*Critical*: Fractures related to falls, mortality, admission to Long-term care
*Important*: Emergency room visits, falls
*Possibly important*: Creatinine, blood pressure, orthostatic hypotension, blood sugar, general practitioner visits, number of medications taken, symptom control, reduced risk of drug interactions, increased chance of adherence, decreased cost, caregiver stress, dizziness, confusion
Logic models

- Scoping the review
  - Refining review question
  - Deciding on lumping or splitting a review topic
  - Identifying intervention components

- Defining and conducting the review
  - Identifying relevant study inclusion/exclusion criteria
  - Guiding the literature search strategy
  - Explaining the rationale behind surrogate outcomes used in the review
  - Justifying need for subgroup analyses (e.g., age, sex/gender, socioeconomic status)

- Making the review relevant to policy and practice
  - Structuring reporting of results
  - Illustrating how harms and feasibility are connected with interventions
  - Interpreting results based on intervention theory and systems thinking
Evidence to Decision Framework

• GRADE approach used to select, appraise, and synthesize best available evidence
• SOF tables show pooled estimates of effect and rate certainty of recommendations
• Transparently weigh effectiveness, harms, cost requirements, and values and preferences to determine recommendations

• GRADE: Grading of Recommendations Assessment, Development and Evaluation
• GRADE Evidence to Decision Frameworks, BMJ 2016.
VALUES

GOALS

Benefit

Risk

Evidence for ongoing indication (diagnosis, risk)

Known adverse effect(s) or risk of adverse effect(s)

Evidence for effectiveness

Age-related changes

More comorbidities and medications

Frailty
Methods Discussions (workshop)

A. Deprescribing Methods and Guidelines – “inside or outside GRADE Working Group”

B. Deprescribing Methods – “inside or outside general therapeutic guidelines”

- Guide research and methods
- Debates and inform strong versus weak and certainty of evidence
- Use methods that engage stakeholders across countries; ie GRADE recommendation and KT tools/ algorithms
GRADE FACE Survey (GRADE Stakeholder Engagement special interest group)

• The GRADE Feasibility, Accessibility, Cost and Equity (FACE) Survey efficiently engages stakeholders to improve the quality and meaningfulness of implementation.
What are Recommendations?

• For the purposes of FACE, we define:
  - **Recommendation** as a statement that includes the direction and strength based on: 1) the balance between desirable and undesirable outcomes; 2) certainty in the estimates of effect on the patient important outcomes; 3) variability in patient values and preferences; 3) variability in resource use.

• **Implementation considerations** are knowledge translation strategies to address any concerns about the feasibility, acceptability, cost and equity of the recommendation.
Canadian Task Force Hep C screening recommendations CMAJ (2017)
FACE Spider stakeholder graphs

FACE Values and Level of Priority for Hepatitis C by Professional Role

- Priority
- Feasibility
- Affordability
- Acceptability
- Health Equity

- Blue: Other healthcare professional
- Orange: Public health/surveillance professional
- Pink: Policy Analyst
- Yellow: Physician
- Green: Other (mostly governmental organizations)
Conclusions

• GRADE is a series of methods from panel formation to guideline implementation
• Highest quality methods will support international and national knowledge mobilization
• GRADE has track record transforming WHO guidelines, and we have an opportunity through GRADE to be part of ongoing Deprescribing methods
Acknowledgments

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